EU Risk Management Plan for Ruconest (conestat alfa, recombinant human C1 esterase inhibitor)

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Completion of the clinical development program.

Termination of the EU Registry

Summary of significant changes in this RMP:

- Cumulative review and update of important identified and potential risks
- Completion of data of the clinical development program
- Analysis of the data from the EU Registry

Other RMP versions under evaluation:

Not applicable

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PART I: PRODUCT OVERVIEW

Table I.1: Product overview

Active substance(s) (INN or common name)	INN: conestat alfa Common name: recombinant human C1 esterase inhibitor or rhC1-INH
Pharmacotherapeutic group(s) (ATC code)	Other hematological agents, drugs used in hereditary angioedema (B06AC04)
Marketing Authorization Holder	Pharming Group N.V. Darwinweg 24 2333 CR Leiden The Netherlands
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Ruconest
Marketing authorization procedure	Centralized
Brief description of the product	*Chemical class* Recombinant human C1 esterase inhibitor (conestat alfa) (INN: conestat alfa) is obtained from the milk of rabbits expressing the gene coding for human C1 esterase inhibitor. The amino acid sequence of the recombinant form is identical to human C1 esterase inhibitor (van Veen , 2012).
	Summary of mode of action C1 esterase inhibitor (C1-INH) is the only known inhibitor of activated subcomponents C1s (C1 esterase) and C1r of complement component 1 (C1) of the classical pathway of the complement system. In addition, C1-INH inhibits the mannan binding protein (MBP)-associated proteases (MASPs) of the lectin pathway of complement. Furthermore, it is the major inhibitor of activated factor XII, activated factor XI and kallikrein of the contact system in plasma. From the spectrum of its target proteases C1-INH is concluded to be of major importance in regulating the activation of both the classical and lectin pathway of complement and the contact system (Davis, 2004). In hereditary angioedema (HAE), a rare autosomal dominant condition, plasma C1-INH activity levels are reduced due to a gene defect. In patients with HAE, who suffer from recurrent angioedema attacks, the complement and contact systems are not appropriately regulated, leading to local release of the vasoactive peptides bradykinin and C2-kinin and subsequent increase of vascular permeability, which ultimately results in angioedema. Administration of functional C1-INH, i.e. C1-INH activity, restores the control of complement and contact systems and leads to the resolution of symptoms (Agostoni , 2004; Zuraw, 2008). The inhibitory potency of conestat alfa towards the target proteases C1 esterase, kallikrein, factor XIa and factor XIIa was found to be comparable

	with the inhibitory potency of endogenous human C1-INH (van Veen , 2012).
	Important information about its composition Endogenous C1-INH is primarily synthesized in the liver and its level in normal plasma is 150-200 µg/mL. C1-INH is a single-chain plasma glycoprotein with a molecular mass of 73,650 Da that belongs to the superfamily of serine proteinase inhibitors (serpins) in plasma.
Hyperlink to the Product Information	Product Information for Ruconest
Indication(s) in the EEA	*Current:* Ruconest is indicated for treatment of acute angioedema attacks in adults, adolescents, and children (aged 2 years and above) with hereditary angioedema (HAE) due to C1 esterase inhibitor deficiency.
	Proposed: Not applicable.
Dosage in the EEA	*Current:* Posology: *Body weight up to 84 kg* One intravenous injection of 50 U/kg body weight. *Body weight of 84 kg or greater* One intravenous injection of 4200 U (two vials). In the majority of cases a single dose of Ruconest is sufficient to treat an acute angioedema attack. In case of an insufficient clinical response, an additional dose (50 U/kg body weight up to 4200 U) can be administered. Not more than two doses should be administered within 24 hours.
	Proposed: Not applicable

Pharmaceutical form(s) and strengths	*Current:* Ruconest 2100 U powder for solution for injection. One vial contains 2100 units of conestat alfa, corresponding to 2100 units per 14 mL after reconstitution, or a concentration of 150 units/mL. 1 unit of conestat alfa is defined as the C1 esterase inhibiting activity present in 1 ml of pooled normal plasma. Ruconest 2100 U powder and solvent for solution for injection. <u>Powder vial:</u> One vial contains 2100 units of conestat alfa, corresponding to 2100 units per 14 mL after reconstitution, or a concentration of 150 units/mL. 1 unit of conestat alfa is defined as the C1 esterase inhibiting activity present in 1 ml of pooled normal plasma. <u>Solvent vial:</u> One solvent vial contains 20 mL of water for injections.
	Proposed: Not applicable
Is the product subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI – EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Hereditary angioedema

Hereditary angioedema (HAE) is a rare condition caused by deficiency in functional C1 esterase inhibitor (C1-INH), a plasma protease inhibitor known to regulate the inflammatory pathways (Zuraw, 2008; Morgan, 2010; Cicardi, 2012). It is inherited in an autosomal dominant fashion, with a percentage of spontaneous mutations of about 20% (Bork, 2019). HAE is associated with acute recurrent attacks which manifest as localized subcutaneous and/or mucosal tissue swelling that can affect any part of the body. However, it most frequently impacts the skin, gastrointestinal (GI), genitourinary and respiratory tract, the latter being potentially life-threatening. HAE attacks are unpredictable and the severity of HAE depends on the location and frequency of the attacks (Davis, 2005; Longhurst, 2010; Nordenfelt, 2016). Bradykinin has been identified as one of the key mediators of angioedema and HAE can be classified into 3 subtypes based on the mechanisms that trigger elevated plasma bradykinin levels. Type I and II HAE involve genetic defects in the gene coding for C1-INH resulting in reduced C1-INH activity levels which make the kallikrein-kinin cascade subject to over-activation leading to excess bradykinin production. Specifically, type I defects are characterized by reduced antigenic and therefore, functional levels of C1-INH and type II defects are characterized by normal or high concentrations of dysfunctional C1-INH. In most patients, the HAE clinical symptoms are first observed during childhood or adolescence and thereafter HAE attacks continue occurring throughout patients' lifetime, with only a small minority having long symptoms-free periods in case no preventive treatment is administered (Bork, 2006b).

Up to date, over 700 different mutations in C1-INH have been identified (Ponard, 2020). For the majority of patients, first symptoms of angioedema occur in later childhood (Agostoni, 1992). Among the different types of HAE identified, type I is the most common, representing approximately 85% of all cases. About 15% of HAE is type II (Zuraw, 2008; Zanichelli, 2015).

Incidence

In hereditary diseases, like HAE, the incidence (the number of cases per number of inhabitants per time period) and the prevalence (the total number of cases registered for a population expressed in number of cases per number of inhabitants) is identical, as the disease is present from birth.

Prevalence

The rarity of HAE and the challenging diagnosis make it difficult to accurately estimate its prevalence. Often, an estimated prevalence of about 1 per 50,000 persons is presented globally (Maurer, 2018). Orphanet estimates the prevalence to be 1:100,000 persons on their website (Orphanet 2024). The estimation of Aygören-Pürsün et al. is 1: 67.000 persons, based upon data from Spain, Norway, Denmark, Sweden, Italy and Greece (Aygören-Pürsün et al., 2018). Males and females, and all ethnicities, are almost equally affected by HAE (Zanichelli, 2015).

The total population in the EU/EEA is about 450 million (Eurostat, 2023). Consequently, based on

the estimated prevalence, it can be assumed that there are about 4500-9000 patients with HAE in the EU/EEA. The total population in the US is about 336 million (US Census Bureau), resulting in an estimate of 3360-6720 patients.

Demographics of the population in the authorized indication and risk factors for the disease

HAE is a genetic disorder with an equal geographical, ethnic and gender distribution. Symptoms typically begin in childhood (often as early as 2 or 3 years of age), worsen around puberty, and persist throughout life, with unpredictable severity (Zuraw, 2008).

Results of observational studies suggest that minor trauma and stress are frequent precipitants of episodes of swelling, but many attacks occur without an apparent trigger. Pregnancy has a variable effect on disease severity, but attacks are rare at the time of delivery (Zuraw, 2008).

A variety of risk factors are known to trigger HAE attacks, such as trauma, dental, medical, or surgical procedures, the use of estrogen-containing oral contraceptives or hormonal replacement therapies. Other reported trigger factors include stress, fatigue, febrile illness, and menstrual cycle.

The demographics and risk factors in children are similar to those in adults. Although C1-INH deficiency is present at birth, clinical symptoms are rare during infancy. Symptoms typically begin in childhood, worsen around puberty, and persist throughout life, without predictable severity (Agostoni , 2004; Zuraw, 2008). Like in adults, clinical events in pediatric patients characterized by recurrent subcutaneous edematous episodes without wheals or pruritus are the most common and the earliest symptoms. If untreated, the edema may persist as well for 1-5 days before resolving spontaneously. Abdominal symptoms may be unrecognized and mistaken for other gastrointestinal diseases, leading in many cases to unnecessary exploratory abdominal surgeries.

The main existing treatment options for the treatment of acute attacks

Initially, the only specific treatment for acute angioedema attacks was a C1-INH preparation purified from pooled human plasma. This replacement therapy was shown to be highly effective and well tolerated without serious adverse effects. Previously, this was available on a limited basis. In 2008, Berinert®, a plasma-derived C1-INH, was granted a license, but it has been marketed since 1979 (Berinert, EPAR) and is currently approved for the treatment and pre-procedure prevention of acute episodes in patients with HAE type I and II in several European countries. In 2010, Ruconest® (conestat alfa), a recombinant human C1-INH, was granted marketing authorization in Europe and is now approved for treatment of acute angioedema attacks in adults and adolescents with HAE due to C1-INH deficiency. In 2011, another plasma-derived C1-INH (Cinryze®) was granted marketing authorization via the CP in Europe and is now approved for treatment and pre-procedure prevention of angioedema attacks in adults, adolescents and children (2 years old and above) with HAE and routine prevention of angioedema attacks in adults, adolescents and children (6 years old and above) with severe and recurrent HAE attacks, who are intolerant to or insufficiently protected by oral prevention treatments, or patients who are inadequately managed with repeat acute attack treatment.

In addition to these C1-INH products, Firazyr® (icatibant), a bradykinin B2-receptor antagonist was

approved in Europe for treatment of acute HAE attacks in the EU in 2008. Firazyr is currently indicated for symptomatic treatment of acute HAE attacks in adults, adolescents and children aged 2 years and older, with C1-INH deficiency.

Historically, various other non-licensed interventions have been suggested and used, such as fresh-frozen plasma. Clinical experience indicates that epinephrine may provide a transient benefit, occasionally (but not predictably) obviating the need for intubation. Neither corticosteroids nor antihistamines have been shown to provide a meaningful benefit during HAE attacks. Although 17α-alkylated androgens are efficacious in preventing HAE attacks, they do not become effective for several days, making them unsuitable for acute attack treatment. The same generally also applies for antifibrinolytics (Agostoni , 2004; Zuraw, 2008). The most current World Allergy Organization (WAO) international guideline recommends that HAE attacks are treated with either C1-INH, ecallantide (only approved in the United States of America [US]), or icatibant in adults and C1-INH as first line therapy in children (<12 years) (Maurer, 2018, Maurer, 2023; Branco Ferreira , 2023).

Besides treatment of acute attacks, some treatments are approved for short-term prophylaxis (STP, e.g., treatment just before undergoing a medical or dental procedure) or for long-term prophylaxis (LTP, systematic prophylactic treatment in order to prevent the occurrence of attacks as much as possible). An overview of the approved treatment is presented in **Table SI.1**.

Table SI.1: Overview of available targeted treatment options for HAE

Product	INN	1st approval	Availability	Indication		
				Attacks	STP	LTP
Berinert	pdC1-INH	1979*	EU US	Yes	Yes	Yes (sc)
Cinryze	pdC1-INH	2011	EU US	Yes	Yes	Yes
RuconestRuconest	Conestat alfa rhC1INH	2010	EU US	Yes	No	No
Firazyr	Icatibant	2008	EU US	Yes	Yes	Yes
Kalbitor	Ecallatide	2009	US	Yes	No	No
Takhzyro	Lanadelumab	2018	US	No	No	Yes
Orladeyo	Berotralstat	2020	EU US	No	No	Yes

*First pdC1-INH, has undergone several formulation changes and is available as pasteurized, nano-filtered formulation since 2011

Natural history of the indicated condition in the population, including mortality and morbidity

Prodromal signs and symptoms

Attacks are often preceded by prodromal signs (Aberer, 2023; Bork, 2019), such as:

- Erythema marginatum
- Prickling sensation of the skin
- Fatigue, exhaustion and irritability, aggressiveness or depressed mood
- Abdominal discomfort or feelings of hunger

- Changes in voice, like dysphonia

HAE localizations

HAE can seriously affect patients' day-to-day life. Patients with HAE experience angioedema attacks episodically. These attacks result in swelling of the skin, hands, feet, arms, legs, the GI and genitourinary tract and (less often, but life-threatening) the airways. Some symptoms may precede HAE episodes, such as increased thirst, fatigue and/or exhaustion, aggressive temper and depressive disposition, and erythema marginatum. Such symptoms are referred to as prodromal symptoms (Longhurst, 2006). The different types of HAE have similar symptoms. The disease has a strong negative impact on the quality of life of the patients. The attacks can be very painful and cause functional problems. Moreover, the attacks can temporarily but substantially affect physical appearance. Every organ can be involved, but extremities and gastro-intestinal tract are most frequently involved. Up to 50% of patient have reported at least one life-threatening throat swelling (Aberer, 2023). Table SI.2 provides a description of the symptoms of an attack.

Table SI.2: Manifestations of Hereditary Angioedema Attacks

HAE manifestations	Main characteristic/consequences
Skin swelling	Swellings may occur in the subcutaneous tissues of the limbs, the genitals and the trunk. Most swellings occur in the extremities, i.e. hands and/or arms (53%) and feet and/or legs (30%) (Longhurst, 2006; Bork, 2008; Bork, 2019). The skin swellings, which are pale or skin colored, are commonly tense, but they can also feel soft. They are not associated with pruritus. If swellings advance, they can become very painful. Without treatment, the swellings usually last 1 to 3 days on average, but they can also decrease after just a few hours or after as long as 7 days. Swellings of the face usually last longer than swellings of the extremities.
Gastrointestinal attacks	Many patients experience GI attacks (Bork, 2006a; Bork, 2019; Longhurst, 2006). These attacks can cause severe cramp-like abdominal pain and nausea and often include vomiting. During a GI attack, which usually lasts 2 to 7 days, patients sometimes develop ascites which resolves fully in a few days. Patients can also experience watery diarrhea due to fluid accumulation in the lumen of the edematous intestine which, combined with the related ascites, can cause dehydration. This could result in hemoconcentration with risk of shock. Some patients experience only abdominal attacks. In other patients, abdominal attacks can precede the start of skin symptoms by several years. Because patients may experience a strong pain during an abdominal attack, some patients have had unnecessary exploratory laparotomies due to suspicion of "acute abdomen" or appendicitis.
Laryngeal attacks	Laryngeal attacks (more precisely, supraglottic edema) occur less frequently than attacks of the skin and GI attacks but can be life threatening. Indeed, the most common cause of HAE-related death is asphyxiation during laryngeal attacks. Although they occur sporadically, the risk of a laryngeal attack is increased after trauma to the oral cavity or the pharynx, especially after dental surgery, tooth extraction or tonsillectomy. Laryngeal edema can also occur up to 24 h following the intervention (Bork, 2003; Bork, 2019). There have been repeated reports of death from asphyxiation (Bork, 2019). Mostly these deaths occurred in patients who were not diagnosed and unaware of the disease and its associated risks. However, there are also cases in which the diagnosis and the necessary treatment were recognized but, for different reasons, asphyxiation still occurred. As such, it is critical that patients with possible edema of the pharynx or larynx are hospitalized immediately, so they can be monitored and if needed, intubated or have a tracheotomy performed. Moreover, immediate treatment with a C1-INH concentrate or Firazyr is recommended (Bork, 2000; Branco Ferreira , 2023; Maurer, 2023).

HAE manifestations	Main characteristic/consequences
Other organs	HAE can also cause swellings in other organs, such as the hypopharynx, oropharynx with soft palate and uvula, or the tongue (Longhurst, 2006; Zuraw, 2010; Bork, 2019). Swelling in the efferent urinary tract, which can cause symptoms similar to a urinary tract infection may also occur. Swellings in other organs occur less often than abdominal swellings or swellings in the extremities.

C1-INH = C1 esterase inhibitor; GI = gastrointestinal; HAE = hereditary angioedema

Acute HAE attacks, especially acute laryngeal attacks, can be fatal. About 50% of patients with HAE experience one or more laryngeal edema attacks in their lifetime (Agostoni, 1992). Laryngeal attacks are less common compared to attacks with skin or abdominal involvement. To illustrate, in an ongoing, prospective, international, observational study monitoring the safety and effectiveness of an HAE-approved drug during long-term treatment in real-world settings, 4.4% of the 3,228 HAE attacks consisted of laryngeal attacks, of which 63.6% attacks were severe to very severe (Caballero, 2017). Such attacks are the primary cause of deaths associated with HAE and if undiagnosed, mortality due to laryngeal attacks can be as high as 30% to 40% (Ghazi, 2013). A cohort study on 782 patients from 182 families with C1-INH-HAE showed that 70 (32.7%) of 214 deaths reported among these 782 patients were caused by laryngeal attacks (Bork, 2012).

Attack frequency and burden of disease

In previous versions of the RMP an estimated attack frequency of 5 attacks per year was mentioned. Recent literature showed that the attack frequency is very variable: some patients with a positive family history have been diagnosed with HAE but are asymptomatic. Other patients can have sporadic attacks that do not require treatment. But other patients can have up to 200 attacks per year and episodes of daily attacks.

Burton reports a mean of 3.62 attacks per month, with a range of 0-36, and a mean of 0.73 hospital admissions over the last 12 months with a range of 0-20 admission (Burton, 2023). Christiansen observed that most patients with HAE had between 1 attack per month and 1 per week, with between 5 and 10% more than 1/week (Christiansen, 2023). Longhurst reported a mean of 17.9 attacks during the 3 months prior to start of the study (range, 12–33) and a mean attack frequency of 7.2 during the 4-week placebo treatment period. Significant decrease of attack frequency with long-term prophylaxis (Longhurst , 2023). Iwamoto described that Japanese patients reported an average of 15.7 (0-100) attacks per year, but only 53.1% of attacks were treated. The days of hospitalization due to severe attacks was 14.3 (0-200) before diagnosis, but these declined to 4.3 (0-50) after diagnosis (Iwamoto, 2021).

Johnson describes the phenomenon of **cluster attacks**. Clinicians are occasionally confronted with patients who have recurrent attacks despite treatment with C1-INH concentrate or β_2-receptor antagonists. The goal of this study was to investigate repeated attacks that occur 48 hours to 7 days ("cluster attacks") after treatment. 12/132 patients had a total of 48 cluster attacks. Approximately 72% of all the cluster attacks were caused by exogenous stimuli (41% due to psychological stress, 29% due to physical stimuli, and 2% due to menstruation). Cluster attacks occurred in 7% of the patients who received prophylactic therapy in comparison with 12.5% of patients who received on-demand therapy. Cluster attacks comprised 48.4% of all the attacks that patients with cluster-attacks (n= 9) experienced. In addition, the patients who were underdosing their C1 INH treatment had cluster

attacks more often. A lower "time to repeated attack" was seen in the patients who received on-demand therapy compared with those who received prophylactic therapy (Johnson, 2021). Strassen had 15 patients who had a total of 126 cluster attacks. In these patients, 66% of all cluster-attacks were caused by exogenous stimuli (36% due to psychological stress, 27% due to physical stimuli, and 4% due to menstruation, 1% due to infections). The rate of cluster attacks was lower for patients receiving prophylactic therapy than for patients receiving on-demand therapy (7 versus 14%) (Strassen 2020).

Bernstein also underlines that the severity and frequency of swelling in patients with HAE is highly variable. Swelling is characteristically episodic rather than continuous, with many patients experiencing swelling episodes every 10 to 20 days if not treated. However, when examining individual patient experiences, the incidence of swelling can vary from more than 1 swelling per week to fewer than 1 per year (Bernstein, 2018).

Important co-morbidities

After a series of anecdotal reports that HAE patients have a markedly increased incidence of autoimmune disease, Brickman and co-workers performed a systematic review of a relatively large cohort of 157 HAE patients for manifestations of autoimmunity (Brickman, 1986a). Nineteen of these patients (12%) had clinical immune-regulatory diseases including glomerulonephritis (5 patients), Sjögren's syndrome (3), inflammatory bowel disease (3) thyroiditis (2), systemic lupus erythematosus (1), drug-induced lupus (1), rheumatoid arthritis (1), juvenile rheumatoid arthritis with IgA deficiency (1), incipient pernicious anemia (1), and sicca syndrome (1). Furthermore, Brickman et al. report that a vast majority of patients with uncomplicated HAE from the same cohort as studies in the previous publication, have statistically significant cellular immune abnormalities, although the authors concluded that, in addition to cellular immune abnormalities, additional precipitating factors (e.g. genetic, viral, environmental) appear to be necessary for the development of a particular autoimmune disorder in hypocomplementemia patients (Brickman, 1986b).

A retrospective cohort study of HAE patients versus the general population was performed by Zanichelli et al. A total of 446 patients were studied. A greater prevalence among patients was found for heart diseases (9.6% vs 4.8%), acute myocardial infarction (5.6% vs 1.4%), hepatitis C virus infection (10.5% vs 2.5%), and appendectomy (15.9% vs 4.3%) (Zanichelli, 2024).

PART II: MODULE SII – NON-CLINICAL PART OF THE SAFETY SPECIFICATION

A nonclinical program consisting of pharmacology, pharmacokinetic and toxicology studies has been performed with intravenously administered conestat alfa to support the clinical use of Ruconest, for the intermittent treatment of acute angioedema attacks, in the Marketing Authorization Application (MAA). These nonclinical studies have been performed in Sprague Dawley rats, Beagle dogs, cynomolgus monkeys and New Zealand White (NZW) rabbits.

The recommended clinical dose proposed for the treatment of acute angioedema attacks in patients with HAE is 50 U/kg body weight. In case of an insufficient clinical response, a second dose of 50 U/kg body weight can be administered. The highest daily doses tested in these nonclinical studies were 6.25 to 40 times the highest recommended clinical dose (100 U/kg).

Table SII.1 summarizes the potential safety concerns as addressed in the nonclinical studies and provides and evaluation of the relevance of the results of these studies for the usage of Ruconest in a clinical setting.

Table SII.1: Safety concerns from non-clinical studies and human relevance

Key safety findings	Relevance to human usage
Single-dose toxicity studies Single-dose (acute) toxicity of conestat alfa was assessed in Sprague Dawley **rats** and Beagle **dogs**. Except for piloerection in rats at the highest dose given, no treatment-related findings were observed for a dose range from 25 to 1250 U/kg body weight.	No special hazard for humans identified.
Safety pharmacology studies **Cardiovascular/Respiratory study** In a cardiovascular and respiratory safety cross-over pharmacology study performed in anaesthetized Beagle dogs under GLP, with intravenous administration of 625 U/kg conestat alfa, no consistent overt effects on arterial blood pressure, heart rate, left ventricular systolic pressure, electrocardiogram (lead II) waveforms, cardiac output and total peripheral resistance were observed in any of the animals tested when compared to effects recorded following vehicle administration. In addition, respiratory and blood gas parameters remained normal.	No special hazard for humans identified.
Repeat-dose toxicity studies Repeat-dose toxicity studies performed with intravenously administered conestat alfa for 4 days in rats (625 to 2500 U/kg/day), 14 days continuous infusion in rats (25 to 625 U/kg/day) and 5 days in dogs (625 U/kg/day), did not reveal any mortality, clinical signs and macroscopic or microscopic findings indicative of test substance-induced toxicity. Clinical laboratory investigations in rats revealed a dose-dependent increase in total cholesterol (at 2500 U/kg: 33.8% in males, 15.4% in females), a decrease in albumin in females in the 2500 U/kg group (-6.3%), and a slight decrease in body weight gain in	No special hazard for humans identified.

Key safety findings	Relevance to human usage
females, accompanied by reduced food consumption (-13.6%). Clinical laboratory investigation in dogs revealed that the relative number of neutrophils was decreased (males -19.9%; females -40.6%), lymphocytes were increased (males 97.1%; females 163.2%) and total white blood cell count (males -15.1%; females 15.3%) and platelet count (males -14.9%; females -31.2%) were decreased. These effects are attributed to a mild immune response towards conestat alfa which is not unexpected as conestat alfa is a heterologous protein for dogs. In a 14-day toxicity study in Sprague-Dawley rats, with continuous intravenous infusion of conestat alfa at doses of 25, 125 or 625 U/kg/day, followed by a 14-day observation period, no significant treatment-related findings were noted with regard to vital signs, hematology and clinical chemistry, macroscopic and microscopic pathology and immunogenicity. In male rats, urinalysis revealed reversible low sodium concentration at the 625 U/kg/day dose level. The NOAEL was estimated to be 625 U/kg. In a 14-day toxicity study performed in cynomolgus monkeys, doses of conestat alfa of 250, 500, 1000 and 2000 U/kg/administration were administered intravenously BID. The NOAEL was estimated to be 1000 U/kg/administration. An MTD was not established. Observations in the study included clinical signs, ophthalmology, body weight, food consumption, cardiovascular examinations, clinical chemistry and hematology, pharmacokinetics/toxicokinetics, immunogenicity, specific antibody formation against C1-INH and full histopathology. Dose-related histopathological changes (microvacuoles in epithelial cells lining the renal tubes) were noted in the kidneys at 500 to 2000 U/kg/administration. The effects were minimal at 500 U/kg/administration but increased in severity and frequency at doses up to 2000 U/kg/administration.	
Local tolerance studies Local tolerance of conestat alfa was studied in New Zealand White rabbits using the proposed clinical route of administration, i.e. intravenous injection. Neither edema, nor macroscopic or microscopic findings were noted at the injection sites. Very slight erythema was noted for all doses at nearly all injection sites, which resolved after 3 days at the intravenous injection sites and 4 and 5 days for the perivenous and intra-arterial injection sites. Absence of local effects at the injection site has been confirmed in all acute and repeat-dose toxicity studies using reconstituted lyophilized Drug Product, the intended pharmaceutical formulation.	No special hazard for humans identified.

Key safety findings	Relevance to human usage
Reproduction toxicity studies An embryo-fetal development study in Sprague Dawley rats, in which repeat doses of conestat alfa were administered by intravenous infusion from Day 6 (G6) to Day 17 (G17) of gestation at a dose of 625 U/kg, revealed no adverse influences of conestat alfa on the course and outcome of pregnancy nor did necropsy examinations of the fetuses show any abnormalities in either the conestat alfa group or the control group. Toxicokinetic analysis did not show any accumulation of conestat alfa after 12 consecutive daily doses to pregnant rats. An embryo-fetal development study in New Zealand White rabbits, in which repeat doses of conestat alfa were administered by intravenous infusion from Day 6 (G6) to Day 19 (G19) of gestation at a dose of 625 U/kg, revealed a slight decrease in food consumption during the treatment period and first 4 days of post-treatment period, accompanied by decreased body weight gain in treated dams (-5.7% on G29). No adverse influences of conestat alfa on the course and outcome of pregnancy were observed. Necropsy examinations of the fetuses indicate a possible increase in the incidence of cardiac vessel defects (1.12% in treated animals versus 0.03% in historical controls) in animals that were administered conestat alfa. Delayed ossification of the bones of the paws was observed. The severity was not considered sufficient to result in any lasting effects. An association between reduced maternal body weights at term and delayed ossification is considered likely. Toxicokinetic analysis did not show any accumulation of conestat alfa after 14 consecutive daily doses to pregnant rabbits.	A special hazard for humans cannot be excluded. Results of one of the reproductive toxicity studies indicates a possible small increase in the incidence of cardiac vessel defects. Potential effects on fertility and on peri- and postnatal development were not studied and no data of transfer into milk are available. This is mentioned in the Summary of Product Characteristics (SmPC) in section 4.6.
Immunogenicity studies The IgG antibody titer was measured in samples collected from all toxicity studies in rats, rabbits and monkeys. As expected, following administration of a human protein to rats, rabbits and monkeys, elevated IgG titers were found in all animal species. There was no evidence for the generation of neutralizing antibodies as evaluated in the single rat study. Immunogenicity of conestat alfa was evaluated in transgenic rabbits for conestat alfa, which are immune tolerant to human conestat alfa. Rabbits were injected intravenously with conestat alfa with low (≤1.4%) or high (14%, i.e. 10 times more than acceptable for release) content of aggregates at a dose of 15 mg/kg (90 U/kg) on Days 1, 2, 3, 4, 17, 31 and 45; plasma samples were taken for up to 88 days. No clinical signs or symptoms indicative of adverse effects were observed. No measurable IgG antibody response occurred in the conestat alfa-transgenic rabbits. A control group consisting of non-transgenic wild-type rabbits developed a marked increase in the IgG antibody titers following administration with conestat alfa (with low as well as high content of aggregates).	The induction of antibody formation in animals is not predictive of a potential for antibody formations in humans. It is widely considered that the presence of aggregates enhances immunogenic potential of therapeutic proteins. Results show that conestat alfa, even when containing increased amounts of aggregates, does not elicit antibody responses in a host that is tolerant to human C1-INH. Notably, HAE patients are tolerant to exogenous C1-INH since they suffer from a heterozygous deficiency of C1-INH. Hence, the data from the transgenic rabbit study supports the lack of immunogenic potential of conestat alfa in HAE patients.

Key safety findings	Relevance to human usage
Other toxicity-related information or data	Pre-clinical data do not indicate safety concerns (see Toxicity studies). Genotoxic and carcinogenic potential is not expected.

Conclusions on non-clinical data

No special hazards for humans have been identified in toxicity (single- and repeat-dose, reproduction), pharmacology, local tolerance and immunogenicity studies. Apart from the expected interaction with tissue-type plasminogen activator (tPA), no interactions with drugs used in the clinical indication and small molecule drugs are expected.

Results of one of the reproductive toxicity studies indicate a possible small increase in the incidence of cardiac vessel defects, as observed in the rabbit embryotoxicity study (as described in SmPC section 5.3).

Case reports on human exposure to conestat alfa during pregnancy are described in Module SIV.3. Cardiac vessel defects in newborns have not been reported.

PART II: MODULE SIII – CLINICAL TRIAL EXPOSURE

The approved indication for Ruconest in the EU is the treatment of acute angioedema attacks in adults, adolescents and children (aged 2 years and above) with HAE due to C1-INH deficiency. Additionally, the prophylactic use of conestat alfa has been investigated in Studies C1 1207 and C1 3201.

An overview of the clinical studies constituting the clinical development program of conestat alfa is given in **Table SIII.1**. In the completed clinical studies for the indication HAE, a total of 375 clinical trial subjects (268 unique subjects) have been exposed to 1594 administrations. In addition, 22 patients received Ruconest in study C1 5201 for prevention of acute kidney injury (AKI) after non-ST elevation myocardial infarction (NSTEMI) and 27 patients received Ruconest in study C1 6201 for prevention of severe SARS-CoV-2 infection in hospitalized patients with COVID-19. Special populations, such as pregnant or breastfeeding women were excluded from study participation in all clinical trials. The clinical development is completed after completion of studies C1 5201 and C1 6201.

Table SIII.1: Cumulative patient exposure in completed trials

Clinical Trial	Number of Subjects (Number of Administrations)		
	Conestat alfa	**Placebo (saline)**	**Naïve Subjects at Start Trial[a]**
Indication HAE **Symptomatic patients with HAE**			
C1 1202/03	14 (21)	-	13
C1 1304 RCT	16 (16)	16	16
C1 1304 OLE	57 (194)	-	50
C1 1205 RCT	25 (25)	13	25
C1 1205 OLE	62 (168)	-	50
C1 1310 RCT [b]	56 (56)	31	46
C1 1310 OLE	44 (224)	-	
C1 1209	20 (73)	-	20
Subtotal	**294 (777)**	**60**	**220**
Asymptomatic patients with HAE			
C1 1101	12 (24)	-	12
C1 1207	25 (207)	-	10
C1 3201	30 (527)	28	12
Subtotal	**67 (758)**	**28**	**34**
Healthy volunteers			
C1 1106	14 (59)	-	14
Total HAE	**375 (1,594)**	**88**	**268**
Indication COVID-19			
C1 6201	27	11	27
Total COVID-19	**27**	**11**	**27**
Indication Acute kidney injury			
C1 5201	22	7	22
Total Acute kidney injury	**22**	**7**	**22**

HAE: hereditary angioedema; OLE: open-label extension; RCT: randomized, controlled trial.
[a] Naïve indicates that the HAE patient has not been exposed to conestat alfa before the trial. The sum of this column provides the number of unique patients exposed to conestat alfa during clinical development.
[b] In the RCT phase of Study C1 1310, 13 patients randomized to placebo (saline) treatment also received conestat alfa as rescue medication; these 13 patients are included in the conestat alfa column (in total 56 patients).

The following tabulations provide a detailed overview of patient numbers, stratified for relevant population categories and other relevant variables. Given that conestat alfa is not indicated for chronic use but rather for intermittent treatment of acute HAE attacks, a breakdown according to patient time is not considered relevant and has not been provided. However, as the number of repeat administrations of conestat alfa is of relevance for the evaluation of safety and immunogenicity, the total number of administrations per subject is presented in the tabulations below (Table SIII.1 to Table SIII.3: Cumulative subject exposure to conestat alfa from completed clinical studies by racial group (unique patients only)).

Table SIII.1: Cumulative subject exposure to conestat alfa from completed clinical trials by age and sex

Study	Age group (years)				Gender	
	2 up to and including 13	**14 up to and including 17**	**18-65**	**≥65**	**Male**	**Female**
Indication HAE						
C1 1101	0	0	12	0	8	4
C1 1106	0	0	14	0	4	10
C1 1202/03 [a]	0	0	14	0	4	10
C1 1205 RCT	0	1	23	1	9	16
C1 1205 OLE [b]	0	9	53	0	24	38
C1 1304 RCT	0	0	14	2	8	8
C1 1304 OLE [c]	0	7	46	4	20	37
C1 1207 [d]	0	0	25	0	5	20
C1 1310 RCT	0	1	54	1	22	34
C1 1310 OLE	0	1	41	2	18	26
C1 3201	0	1	26	3	6	24
C1 1209	20		0	0	11	9
Total HAE[e]	**20**	**20**	**322**	**13**	**139**	**236**
Indication COVID 19						
C1 6201	0	0	27	0	14	13
Indication AKI						
C1 5201	0	0	1	21	10	12
Grand total	**20**	**20**	**350**	**34**	**163**	**261**

OLE = open-label extension; RCT = randomized controlled trial.

[a]: One HAE patient has participated previously in Study C1 1101.

[b]: 12 HAE patients have participated previously in RCT phase of Study C1 1205.

[c]: 7 HAE patients have participated previously in RCT phase of Study C1 1304.

[d]: 15 patients participated in Study C1 1304 or Study C1 1203.

[e]: Total is not corrected for exposure in multiple trials.

Table SIII.2: Exposure by dose for the indication HAE

Dose of exposure to conestat alfa	Patients	Number of administrations
100 U/kg (single dose)	57	109
50 U/kg (single dose / single plus additional dose)	249 [a]	1267
Two increasing doses in Study C1 1101 [b]	12	24
2100 U (single dose / single plus additional dose)	57	194
Total	**375**	**1594**

[a]: Including 13 patients randomized to placebo group receiving rescue medication in Study C1 1310 RCT.

[b]: In Study C1 1101 patients received increasing doses conestat alfa (starting from 6,25 U/kg to 100 U/kg).

Table SIII.3: Cumulative subject exposure to conestat alfa from completed clinical studies by racial group (unique patients only)

Racial group	Number of subjects (% of total) [a]
Indication HAE	
Asian	3 (1)
African American / Black	7 (3)
Caucasian	239 (94)
Other	5 (2)
Indication COVID-19	
African American / Black	1 (3.7)
Caucasian	25 (92.6)
Other	1 (3.7)
Indication AKI	
Asian	0
African American/Black	1 (4.5)
Caucasian	21 (95.5)
Other	0

[a] Including the completed clinical studies in symptomatic patients with HAE (Studies C1 1202/03, C1 1209, and the RCT and OLE phases of Studies C1 1205, C1 1304, and C1 1310) and asymptomatic patients with HAE (Studies C1 1101, C1 1207 and C1 3201).

Use of Ruconest for acute attack treatment in pediatric patients with HAE

Adolescent patients (aged between 14 up to and including 17 years of age) who took part in Studies C1 1205 and C1 1304 (RCT and OLE) were included in a separate analysis. A total of 16 patients, 8 male and 8 female, received conestat alfa treatment for a total of 50 HAE attacks at a dose of 50 or 100 U/kg body weight in the RCT phases and an initial dose of either 2100 U or 50 U/kg body weight (with the possibility of an additional dose depending upon the patient's clinical response) in the OLE phases.

In Study C1 1209, pediatric patients (aged between 5 and including 13 years of age) received conestat alfa at a dose of 50 U/kg body weight up to a maximum of 4200 U. A total of 20 patients, 11 male and 9 female, received conestat alfa treatment for a total of 73 HAE attacks.

Repeat treatment with conestat alfa appeared generally safe and well tolerated in pediatric HAE patients. The results in pediatric subjects are consistent with the findings for the overall study population and support the efficacy of conestat alfa for treatment of acute HAE attacks in children

and adolescents.

Use of Ruconest in the prophylactic treatment of HAE

Study C1 1207 was an exploratory trial to study the application of Ruconest in prophylactic treatment of HAE patients. In this open-label study, patients received conestat alfa 50 U/kg, once a week over an 8-week period. Breakthrough attacks were also treated with conestat alfa at 50 U/kg, with the provision for a second dose. All 25 patients listed in the table received at least one dose of conestat alfa.

Study C1 3201 was an interventional trial to study the efficacy, safety and immunogenicity of conestat alfa in prophylactic treatment of HAE patients. Patient medical history specific to HAE attacks was collected to assess eligibility. Eligible patients with a history of frequent HAE attacks (>4 attacks per month) were enrolled and randomized to 1 of 6 treatment sequences. Each patient received three 4-week periods of treatment twice weekly, with a one-week washout between treatment periods. Treatment during the 3 treatment periods consisted of 50 U/kg Ruconest and placebo, each once-weekly, 50 U/kg Ruconest twice weekly, or placebo twice weekly. Of the 28 patients who received placebo, one patient dropped out before receiving conestat alfa. All other patients received at least one dose of conestat alfa, either as randomized treatment, or as open-label treatment in case of a breakthrough attack. The total number of randomized patients was 32; 31/32 patients were exposed to blinded treatment, 30/32 patients were exposed to conestat alfa (randomized or open-label), 28/32 patients received placebo (randomized) and 1/32 patients withdrew consent prior to receiving any blinded study medication.

Skin prick study

In addition to these studies, Study C1 1113 was conducted to estimate the negative predictive value of a skin prick protocol for HAE patients with rabbit or cow milk allergy. Given that doses were administered through a different route of administration and doses were smaller than those used in the other clinical studies, the data for Study C1 1113 are summarized separately and therefore not included in any of the tables listed above. Healthy volunteers with a documented clinical allergy to rabbits or cow milk were eligible if the skin prick test with cow's milk and/or rabbit dander was positive. Subjects were exposed to small amounts of Ruconest solution via a percutaneous skin prick test, or via intradermal or subcutaneous administration. A total of 26 subjects, 9 male and 17 female, received at least one dose of Ruconest, with a total of 48 exposures. On average, the subjects were 33.7 years of age (SD: 11.4, range: 19-54). Twenty-three subjects were Caucasian and 3 were Asian. The skin test protocol used in this study had a high negative predictive value to rule out systemic hypersensitivity to Ruconest in subjects with an allergy to rabbits or cow milk.

Use of Ruconest in non-HAE indications

Ruconest has been investigated in study C1 5201 for prevention of acute kidney injury after non-ST elevation myocardial infarction (n=22) and C1 6201 for the prevention of severe SARS-CoV-2 infection in hospitalized patients with COVID-19 (n=27) and in study.

In study C1 5201, the 22 patients treated with Ruconest reported 8 SAE cases (8 events), of which 7 were assessed as not related/not related by the reporter and the company. The 8th case reported cardiac arrest with fatal outcome in a patient with advanced coronary artery disease who was

undergoing PCI following NSTEMI. Patient died during coronarography where they observed that essentially, the whole heart was supplied by only one very small vessel. Patient developed ventricular fibrillation after balloon dilation and died of cardiac arrest. The investigator assessed causality as possibly related, the company considers the event not related to Ruconest. During FU, the investigator changed the causality to “unlikely”.

In study C1 6201 the 27 patients treated with Ruconest reported 3 SAE cases (11 events), which all were assessed as not related/not related by the reporter and the company.

As these indications were not pursued, no further details are provided in this RMP.

Patient registries

EU Registry

A Post Approval Safety Study (PASS) including patients treated with Ruconest for acute attacks is ongoing in Europe. In this EU registry (Study C1 1412), 92 patients received a total of 4045 treatments with Ruconest up to DLP of 28 April 2024.

Results up to 28 April 2024:

Patient and treatment information

70 patients treated with Ruconest only, 7 with pdC1-INH only and 38 patients received different treatments during the study.

92 patients (37 male/55 female, ages 19-83 years) were treated with rhC1INH in the registry for 4045 attacks in 9 European countries. Sixty-seven (67) of these patients were treated 3 times or more.

199 attacks were treated with pdC1-INH, 595 attacks were treated with Firazyr (icatibant) and 7 with other approved medication. The treatments with rhC1INH, pdC1-INH and Firazyr (icatibant) are described below:

Patients were treated for up to 520 attacks and followed for a period of up to 11.3 years.

98 patients received up to 100 treatments, 15 patients up to 200 treatments.

1 patient received 287 Ruconest treatments for 5 years and 1 patient received a total of 520 different treatments (318 Ruconest, 5 pdC1-INH and 197 Firazyr) during 10.8 years.

One patient has been followed for 11.3 years in which they received 144 treatments (59 Ruconest and 85 Firazyr).

The average age at diagnosis for Ruconest treated patients was 27 years (range 3-78). Prior to entry in the registry, these patients experienced an average of 30 HAE attacks in the preceding year. Of the Ruconest treated patients, 28,3% (26/92) were on maintenance therapy/prophylaxis at enrollment.

There were, in the Ruconest treated attacks, 1685 (41,7%) abdominal, 1431 (35,4%) peripheral, 554 (13,7%) facial, 289 (7,1%) urogenital and 235 (5,8%) laryngeal attacks, including 135 attacks that involved more than one location and 7 attacks that included three locations.

Of the 199 pd-C1INH treated attacks there were 80 (40,2%) abdominal, 76 (38,2%) peripheral, 26 (13,1%) facial, 12 (6,0%) urogenital and 20 (10,1%) laryngeal attacks, including 15 attacks that involved more than one location.

Of the 595 attacks treated with Firazyr (icatibant) there were 382 (64,2%) abdominal, 184 (30,9%) peripheral, 65 (10,9%) facial, 17 (2,9%) urogenital and 64 (10,8%) laryngeal attacks, including 98 attacks that involved more than one location, 8 attacks that included three locations and 1 attack that included 4 locations.

Efficacy information

Patients reported relief within 4 hours in 98,0% (3966/4045) of the Ruconest treated attacks, 90,5% (180/199) of the pdC1-INH treated attacks and 97% (577/595) of the Firazyr/Icatibant treatments.

Almost all Ruconest-treated attacks (4039/4045) were treated with a single dose of Ruconest. Six attacks were reported as treated with a second dose with 4200 U administered in total.

Safety information

Review of cumulative safety data received for Study C1 1412 showed that a total of 57 events were reported in 42 case reports. Among those 57 events, 12 were serious including (PT level) COVID-19, Caesarean section, Clavicle fracture, Acute vestibular syndrome, Chest injury, Accident, Pelvic fracture, Traumatic lung injury, Pyelonephritis acute, Invasive ductal breast carcinoma, Hospitalization, and Laryngeal oedema (all reported once). The most frequently reported non-serious events (PT level) were Headache (n=23), Nausea (n=3), Maternal exposure during pregnancy (n=3), Erythema (n=3) and product use in unapproved indication (n=3).

No hypersensitivity or thrombotic/thromboembolic events were reported for any of the treatments. No patients had any related serious adverse events.

Overview of the pregnancy cases:

1 patient received 41 doses of Ruconest and had a live delivery at full term. 1 patient received 9 doses of Ruconest and had a live delivery with no complications and the third patient received 8 doses of Ruconest and delivered at full term through a caesarian section.

US Registry

In addition, a post-approval observational registry study has been performed in the US:

Study C1 1414: An observational patient registry to evaluate the real-world safety of commercially prescribed Ruconest (C1 esterase inhibitor [recombinant]) for the treatment of hereditary angioedema.

This USA registry was initiated in 2018. In this registry, 152 patients were enrolled, of which 21 patients were treated and received a total of 111 treatments for acute HAE attacks. Seven of these 21 patients also received Ruconest for prophylaxis. Only limited information was recorded for these patients, therefore the number of treatments provided for prophylaxis was unknown. In this study, 4 patients have withdrawn consent before treatment with Ruconest was initiated. Study C1 1414 enrollment was completed on 30-Jun-2021. The final study report was submitted to the FDA on 30-Jun-2022 and to EMA and MHRA on 01-Nov-2022.

PART II: MODULE SIV – POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

The EU pivotal studies for the initial marketing authorization for the treatment of acute attacks in HAE patients in the EU were Studies C1 1205 and C1 1304. Patients with a "history of anaphylaxis, or severe allergies (i.e. requiring medication) to food, proteins and/or drugs" were excluded from the pivotal trials, i.e., Studies C1 1205 and C1 1304. Because of limited available knowledge at the start of these studies, this stringent exclusion criterion was added merely as a safety precaution. This exclusion criterion was considered irrelevant in view of the available data and knowledge on hypersensitivity-related events in relation to treatment with conestat alfa. It was therefore no longer listed in the exclusion criteria for the subsequent studies.

The main exclusion criteria from all the clinical trials are listed in Table SIV.1.

Table SIV.1: Main exclusion criteria in clinical trials with conestat alfa

Criterion 1	**Known or suspected allergy to rabbits or rabbit-derived products**
Reason for exclusion	An allergy to rabbits or a history of administration of rabbit-derived pharmaceutical products (with evidence of an allergic reaction) may result in an allergic reaction after exposure to conestat alfa.
Is it considered to be included as missing information?	No
Rationale	Conestat alfa is derived from milk of transgenic rabbits and contains traces of rabbit protein. Before initiating treatment with conestat alfa, patients should be queried about prior exposure to rabbits and signs and symptoms suggestive of an allergic reaction. Patients with known or suspected allergy to rabbits are excluded from treatment with Ruconest as is stated in the SmPC.
Criterion 2	**Hypersensitivity to the active substance or to any of the excipients**
Reason for exclusion	Patients with hypersensitivity to the active substance or any of the excipients are excluded from clinical trial participation in order to avoid having a hypersensitivity reaction.
Is it considered to be included as missing information?	No
Rationale	Hypersensitivity reactions cannot be excluded. Patients with hypersensitivity to the active substance or any of the excipients are excluded from treatment with Ruconest as is stated in the SmPC.
Criterion 3	**Diagnosis of acquired angioedema (AAE)**
Reason for exclusion	AAE is different from HAE, it is another indication.
Is it considered to be included as missing information?	No
Rationale	AAE is different from HAE. The approved indication is clearly stated to be for treatment of acute angioedema attacks in patients with HAE.
Criterion 4	**Pregnant or breastfeeding women**
Reason for exclusion	Lack of relevant data on pregnant and breastfeeding women
Is it considered to be included as missing information?	Yes
Rationale	There are no adequate clinical data from the use of conestat alfa in pregnant and breastfeeding women. Limited post-marketing data are available (see Table SIV.1).

Pediatric subjects

In the pivotal Studies C1 1205 and C1 1304, pediatric patients below the age of 12 and 16 years, respectively, were excluded. In line with the Paediatric Investigation Plan (EMEA-000367-PIP01-08), the safety and efficacy of conestat alfa in pediatric subjects younger than 2 years has not been established; studies in pediatric subjects of 2 years or older (adolescents and children) were deferred after approval of Ruconest in 2010.

- Pre-term newborns, neonates, infants and toddlers: For pre-term new-born infants, and neonates (from birth to 27 days), infants and toddlers (from 28 days to 2 years) the European Medicines Agency has granted a waiver on grounds that the specific medicinal product does not represent a significant therapeutic benefit as clinical studies are not feasible.
- Children: The safety, immunogenicity, pharmacokinetics and efficacy of conestat alfa for the treatment of acute attacks in pediatric patients with HAE was investigated in Study C1 1209. In this open-label, phase II, single arm study, children from 2 up to and including 13 years of age were enrolled. Treatment with conestat alfa was effective and well-tolerated in pediatric patients aged 4 years and 9 months up to over 13 years at the time of the first dose in the study. On 28 April 2020, the indication for Ruconest was extended to include treatment of children aged 2 years and above (procedure EMEA/H/C/001223/II/0053/G).
- Adolescents: In the clinical development program 9 HAE patients (aged 14 to 17 years) were treated with 50 U/kg for 26 acute angioedema attacks (derived from Study C1 1205), 7 (aged 16 to 17 years) with 2100 U for 24 acute angioedema attacks (derived from Study C1 1304). The data from the adolescent patients in the RCT phases of Studies C1 1205 and C1 1304 and the integrated results from these adolescent patients support the efficacy and safety of conestat alfa for the treatment of HAE attacks in adolescent patients. Repeat treatment with conestat alfa appeared generally safe and well tolerated in adolescent HAE patients. Additionally, there was one 17-year old adolescent with HAE treated for 2 attacks in Study C1 1310, once in each phase (RCT and OLE). Because Study C1 1310 was only completed after finalization of the integrated analysis report on adolescents this patient was not included in this integrated analysis. In 2016, the indication for Ruconest was extended to include treatment of adolescents (procedure EMEA/H/C/001223/II/0031).

SIV.2 Limitations to detect adverse reactions in clinical trial development programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions or adverse reactions with a long latency.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programs

Table SIV.1: Exposure of special populations included or not in the clinical trial development programme

Type of special population	Exposure
Pregnant women	Not included in the clinical development program for HAE indication.

Type of special population	Exposure
Breastfeeding women	There is significant experience with the use of conestat alfa in pregnant and breastfeeding women, given the rarity of the disease. Up till the DLP 28 April 2024 there were 193 reports of use during pregnancy. No safety concerns were observed. Three patients got pregnant in the Ruconest Registry study, all delivered of a full-term healthy baby. HAE guidelines mention rhC1INH as treatment option during pregnancy and lactation if no pdC1-INH is available. Pregnancy and breastfeeding are addressed in SmPC section 4.6.
Patients with relevant comorbidities: Patients with hepatic impairment Patients with renal impairment Patients with cardiovascular impairment Immunocompromised patients	Patients with co-morbidity such as hepatic, renal or cardiovascular impairment have not been included in the clinical development program. 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 for patients with hepatic impairment. In patients with renal impairment no dose adjustment is necessary since conestat alfa does not undergo renal clearance. Cardiovascular impairment might affect plasma half-life of conestat alfa, but this is not thought to be of clinical concern. The interaction of C1-INH with its target proteases is not expected to be affected in patients with HAE and other immunological conditions, including immunocompromised patients. As treatment involves replacement therapy with C1-INH using a recombinant analogue of the human plasma protein C1-INH, it is unlikely that administration of conestat alfa will involve any particular risk for patients with co-morbidity such as renal, hepatic or cardiac impairment or immunocompromised patients. Therefore, patients with co-morbidity have not been included in the clinical program but are not excluded from treatment in the SmPC.
Patients with disease severity different from inclusion criteria in clinical trials	Not applicable
Population with relevant different ethnic origin	Most patients included in the clinical development program were Caucasian. In addition, 5 Asian patients, 8 black patients and 4 patients of other/mixed ethnic origin were included in the HAE studies. There is no reason to assume that safety and efficacy of conestat alfa differs according to ethnic origin.
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Other: pediatrics	For pre-term new-born infants, and neonates (from birth to 27 days), infants and toddlers (from 28 days up to 2 years) a waiver has been granted on grounds that the specific medicinal product does not represent a significant therapeutic benefit as clinical studies are not feasible. Study C1 1209 investigated the safety and efficacy of conestat alfa in children (from 2 years up to and including 13 years of age), and 6 children in the age group of 2 up to 5 years old were treated. None of these children experienced any adverse events considered related to conestat alfa. Adolescents participated in Studies C1 1205, 1304 and 1310 (RCT and OLE). Based on the cumulative review of the AEs reported in children aged 2-5 years (n=12, see also Section SVII.3.2 for details), there is no evidence for an increased risk associated with use of Ruconest for HAE, but the number of patients exposed to Ruconest for this orphan

Type of special population	Exposure
	disease, with the onset of symptoms usually starting between the ages of 5 and 11 years of age (Campos, 2021) is unavoidably low. This is addressed in SmPC section 4.2, 4.4, 4.8 and 5.1.
Other: elderly	Not included in the clinical development program. The age limit was 65 and 70 years in Study C1 1202 and C1 1203, respectively. In the pivotal trials (C1 1205 and C1 1304) and in C1 1310 there was no upper age limit. Nine unique patients aged 65 years of age or older have been included in the clinical studies. There is no reason to assume that patients aged 65 years and older will react differently to this therapy. Therefore, they are not excluded from treatment. At the DLP of 28 April 2024, 247 case reports with 429 events concerning elderly patients have been received. Of these, 112 cases reported at least 1 SAE. Of the 429 events, 49 were assessed as possibly related by the medical assessor (19 serious). The distribution of adverse events over the SOC was not different compared to patients of younger age groups. A number of not related SAEs originated from sponsored and unsponsored clinical studies in patients with COVID-19, or participating in the prevention of CVA and renal events after TAVI or prevention of AKI after NSTEMI studies. There are no safety concerns specific for the elderly population. This is addressed in SmPC section 4.2.
Other: patients with Acquired Angioedema (AAE)	Not included in the clinical development program. Neutralizing antibodies against endogenous C1-INH may cross-react with therapeutically administered C1-INH. In contrast to HAE, which is a genetic disease, AAE is an acquired disease with neutralizing auto-antibodies to endogenous C1-INH. As a result, like HAE patients, AAE patients have a deficiency in C1-INH function. At the DLP of 28 April 2024, 3 cases of use of Ruconest for AAE were received. The first patient obtained relief for a short period of about 20 minutes before getting worse again, which was reported as LoE in an unapproved indication. The second patient had resistant or frequent attacks and poor response on pdC1-INH. The patient tolerated Ruconest treatment without immediate side effects and noted complete resolution within one hour of taking Ruconest but his symptoms returned after 7 hours (Manson, 2014). The third patient successfully received Ruconest as STP prior to cataract surgery (Farkas, 2014).

PART II: MODULE SV – POST-AUTHORIZATION EXPERIENCE

SV.1 Post-authorization exposure

SV.1.1 Method used to calculate exposure

Given that limited details are available on the number and demographics of patients using Ruconest, the number of patients being exposed to Ruconest was estimated. In the EU, the distribution of a self-administration kit has been initiated but use to date has been limited.

For every country, the total vial sale for every year was identified and that number of vials was converted to an estimated number of exposed patients using the following assumptions:

- Patients who start using Ruconest continue to use it for some time.
- All patients weighed more than 42 kg and 2 vials were used per HAE attack (with the recommended dose of Ruconest being 50 U/kg body weight up to 4200 U and each vial containing 2100 U, 2 vials would always be sufficient to treat a patient of more than 42 kg in weight.
- The attack frequency is 5 attacks per year. The number of attacks per time frame varies widely by patient. In a publication by Agostoni et al.1, attack frequencies ranged from less than one attack per year to more than 12 attacks per year (Agostoni , 2004). Based on this publication a conservative estimate of the attack frequency of 5 attacks per year was deducted.
- All vials sold during a reporting interval were used over the course of that reporting interval. In sporadic cases vials were returned upon expiration and these vials were subtracted from the number of vials sold in that country in that reporting interval.

Combined, the estimated number of patients treated per country would equal the yearly peak sales over the full post-marketing period, divided by 2 vials per treatment, divided by 5 attacks per 1-year period.

SV.1.2 Exposure

Cumulatively, 336,754 vials were sold, of which 242,054 in the US and 94,700 in the EEA and in other countries.

The calculation of estimated cumulative exposure is based on the assumption that HAE patients will remain on Ruconest once they have started using it. Based on this assumption, an estimated 6,484 patients were exposed to Ruconest post-marketing. This excludes USA patients, known to amount to cumulatively 1,983 patients having been exposed to at least 1 treatment of Ruconest. The estimated combined worldwide exposure would therefore be approximately 8,467 patients.

In the US, shipment data show that cumulatively 1,996 patients having been exposed to at least one treatment of Ruconest. The number of exposed patients in the EU/EEA and rest of the world is an estimation (EU/EEA 5,192 and RoW 1,292). The assumptions that patients will continue to use Ruconest could result in an underestimation of the actual number of patients exposed, because patients may switch treatment after some time. However, there are other unknown factors that could

affect the actual numbers, including that some patients may receive a dose lower than 50 U/kg in case they respond well to lower doses, and patients may have more or less frequent attacks than 5 per year. Hence the provided numbers are considered to be a reasonable estimate of the actual number of exposed patients. In the absence of more specific data on post-marketing exposure, more accurate estimates of the number of treated patients up to the DLP cannot be made.

Table SV.1: Cumulative exposure

Region	**Cumulative Number of vials**	**Cumulative Number of treatments**	**Estimated Cumulative Number of patients**
USA	242,054	121,027	1,983
EU/EEA + RoW countries	94,700	47,350	6,484
Total	**336,754**	**168,377**	**8,467**

PART II: MODULE SVI – ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

The product has no properties which would attract misuse for illegal purposes.

PART II: MODULE SVII – IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

At the time of approval of Ruconest the approved RMP (V6.0) dated 10 October 2010 contained the following summary of safety concerns:

Table SVII.1: Summary of initial safety concerns

Important identified risks	Allergic reaction due to pre-existing anti-rabbit allergen IgE antibodies reacting with Host Related Impurities
Important potential risks	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
Important missing information	Data on paediatric patients are limited Data on pregnant and breast-feeding women are missing

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Table SVII.2: Summary of actual safety concerns

Important identified risks	• Allergic reaction 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 events with self or home administration
Important missing information	Data on paediatric patients aged 2 up to 5 years Data on pregnant and breast-feeding women

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Since the data lock point of the previous update of the RMP (V19.2) of 28-Oct-2018, almost 6 years have passed. Therefore, a cumulative review has been performed of all important identified and

potential risks to determine whether the risks have changed or whether there are changes to the risk-benefit balance of the product, in line with the GVP guideline on Risk Management Systems, Module V (Rev 2), section V.B.2.

The MAH considers there is sufficient cumulative evidence to remove the important identified and potential risks of Off-label use and of Thromboembolic complications from the safety specification, as accumulating scientific and clinical data retrieved in the almost 14 years since the IBD in Europe do not support the initial supposition.

Justification of the reclassification is provided in Section SVII.2.1 through SVII.2.2.

SVII.2.1 Important Identified Risk: Off-label use

<table>
<tr><th>Name of the risk</th><th>Off-label use</th></tr>
<tr><td>Reclassification as</td><td>Identified risk not considered important for inclusion in the list of safety concerns</td></tr>
<tr><td>Background</td><td>The large majority of off-label use concerns prophylactic use of Ruconest to prevent HAE attacks.RuconestRuconest</td></tr>
<tr><td>Cumulative clinical trial data</td><td>Studies C1 1207 and C1 3201, in which the prophylactic use of Ruconest to treat HAE attacks was evaluated, suggest that there are no new safety concerns related to prophylactic use of Ruconest. Prophylactic use of Ruconest could result in breakthrough attacks; breakthrough attacks can be treated using the approved products for treatment of HAE attacks. Study C1 1207 was an exploratory study of prophylactic use. In Study C1 3201, the safety and efficacy of prophylactic use of Ruconest to treat HAE attacks was further evaluated. Treatment with conestat alfa 50 U/kg once-weekly and twice-weekly resulted in statistically and clinically significant reductions in the number of angioedema attacks and was generally well-tolerated. The results of these studies suggest that there are no new safety concerns related to prophylactic use of Ruconest.</td></tr>
<tr><td>Registry data</td><td>In accordance with the protocol, patients were included for treatment of HAE attacks. No off-label use was reported.</td></tr>
<tr><td>Cumulative post-marketing data</td><td>Cumulatively, 723 events have been reported in the HLGT Off label uses and intentional product misuses/use issues. In 186 cases, no other events were reported. When other events were reported, they were not the consequence of OLU.

Cumulative overview of off-label use
<table>
<tr><th>PT</th><th>N</th><th>RR*</th><th>Comment</th></tr>
<tr><td>Intentional dose omission</td><td>7</td><td>0.042</td><td>Insurance issue, missed prophylactic dose, or nurse did not show up</td></tr>
<tr><td>Intentional product misuse</td><td>8</td><td>0.048</td><td>Prophylactic use or use of 8400 IU</td></tr>
<tr><td>Intentional product use issues</td><td>545</td><td>3.237</td><td>Mainly prophylactic use</td></tr>
<tr><td>Off label use</td><td>163</td><td>0.968</td><td>Mainly prophylactic use (both short-term and long-term)</td></tr>
<tr><td>Total</td><td>723</td><td>4.294</td><td></td></tr>
</table>
*RR: relative risk per 1000 treatments</td></tr>
<tr><td>Literature data</td><td>Ruconest is not approved for prophylactic use.
Actual treatment recommendations in treatment guidelines [Branco Ferreira , 2023]:
• Treat any angioedema attack regardless of the location and as early as possible [US HAEA, 2013; WAO/EACCI guidelines, 2022]. Ruconest is a first-line therapeutic option.
• Short-term prophylaxis is preventive treatment administered before medical or surgical procedures to prevent HAE episodes. This is now extended to preventive treatment in case of life events as well. RUNONEST is a therapeutic option when pd-C1INH is not available.
• Long-term prophylaxis: scheduled therapy to reduce the frequency and/or severity and/or duration of attacks and improve patients' QOL when they are unable to meet their</td></tr>
</table>

	treatment goals with on-demand therapy alone. Ruconest not mentioned as therapeutic option. In addition, Valerieva et al. have published the results of a retrospective cohort of 70 patients using Ruconest for the short-term prophylaxis to prevent attacks in adult and adolescent patients with HAE. In 97.1% of procedures for which prophylactic Ruconest was administered, HAE attacks were prevented. The attack rate in the self-control group (n=26) was 76.9% (so only 23.1% had no attacks) (Valerieva et al., 2020).
Justification of reclassification	Identified risk not considered important for inclusion in the list of safety concerns. Cumulative data received since the IBD show that OLU does occur, with an estimated frequency of OLU of 4.3 per 1000 treatments (0.43%). Most cases concern prophylactic use and are not associated with safety concerns. In most instances there is also no report of associated lack of effect. The company considers the important identified risk of OLU can be removed from the safety specification in the RMP as the impact on the individual has been shown less than anticipated. The risk is also fully characterized and the specific clinical measures to address the risk have become fully integrated into standard clinical practice, as the clinical guidelines recommend to use Ruconest of STP only if no other treatment is available and do not indicate Ruconest for LTP (Branco Ferreira , 2023; Maurer, 2022; Bork 2018; Bork, 2019). Even if OLU is removed from the summary of safety concerns, OLU will continue to be monitored and reported in the PSUR in the Section 5.2.3 Other Post-authorization use (5.2.3.3 Off label use).

SVII.2.2 Important Identified Risk: Thromboembolic complications

Name of the risk	**Thromboembolic complications**
Reclassification as	No safety concern.
Background	It has been hypothesized that the inhibitory effects of C1-INH on the activity of fibrinolytic proteases may cause thromboembolic side effects. However, a review of the biochemical properties of C1-INH indicates that the inhibitory effect of C1-INH on fibrinolytic proteases is at the best weak and of doubtful physiological relevance. This important potential risk is based on thrombogenicity position paper and post-marketing safety data. 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 whether the thromboembolic complications observed in these cases are caused by C1-INH as C1-INH influences the fibrinolytic system. Based on the observations on coagulation and fibrinolytic parameters in HAE patients treated with conestat alfa, the position paper concluded that conestat alfa had no effect on activation of coagulation and fibrinolysis in HAE patients at the doses administered. To further support the MAH's position that the thromboembolic risk of Ruconest is negligible, a study was undertaken to assess the effects of Ruconest on activation of coagulation and of fibrinolysis in HAE patients 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, conestat alfa had no effect on coagulation and fibrinolysis parameters. <u>Background frequency</u> The prevalence of venous thromboembolic events in the US population was estimated to be 100:100,000 persons (1:1,000) per year (White, 2003).

Cumulative clinical trial data	There has been one event of myocardial infarction in a [redacted] patient participating in Study C1 1304 OLE. The event occurred more than 2 months following a single administration of 100 U/kg conestat alfa and was unlikely related to the administration of conestat alfa according to the Investigator.
Registry data	No thromboembolic events (TEEs) were reported in the EU and US Registry studies.
Cumulative post-marketing data	Review of the post-marketing data up to 28 October 2018the DLP of 28 April 2024 using the SMQ Thrombo-embolic events revealed that a total of 101 cases with 118 thromboembolic events have been reported. Of these, 36 concerned port (re)placement, leaving 82 “real” TEEs, resulting in a reporting rate of 0.487 per 1,000 treatments. Of the 118 TEEs, 103 (85.5%) originated from [redacted], 14 from various non-sponsored studies from [redacted], and the last cases is a spontaneous case from [redacted] Risk factors observed in these patients included the presence of an indwelling venous catheter/access device, prior history of thrombosis, blood clot, hypertension, heart disease etc. A cumulative overview of thromboembolic events is presented in **Table SVII.2.2**in Annex 7.
Literature data	A PubMed search on Ruconest and thrombosis revealed 2 publications. Urwyler et al. described the use of Ruconest in the prevention of severe COVID-19 and reported 2 events of embolism (3.6%, n=56) and 1 event of pulmonary embolism in the intervention arm vs 0% in the control arm (n=27). None of the AEs or SAEs were judged as being related to the study drug Ruconest by the investigators (Urwyler et al, 2023). These cases have been entered into the safety database and are also included in Table SVII.8.1. Longhurst presented the evidence-based expert consensus for acute treatments for HAE. She reports that plasma-derived C1 inhibitors, but not recombinant C1 inhibitor, have been associated with venous and arterial thrombosis. A search in PubMed on HAE and thrombosis reveals more relevant publications: Gramstad et al. describe a baseline increased thrombo-inflammatory load in HAE as there is evidence for simultaneous hypercoagulation and low-grade inflammation and consider that HAE patients are in a subclinical attack state outside of clinically apparent oedema attacks (Gramstad et al, 2023). Grover et al. studied the risk of thrombosis in patient samples and mouse models. Patients with C1INH deficiency-associated HAE (C1INH-HAE) have increased circulating markers of activation of coagulation. Furthermore, we recently reported that patients with C1INH-HAE had a moderate but significant increased risk of venous thromboembolism. To further investigate the impact of C1INH deficiency on activation of coagulation and thrombosis, we conducted studies using patient samples and mouse models. Plasmas from patients with C1INH-HAE had significantly increased contact pathway-mediated thrombin generation. C1INH-deficient mice, which have been used as a model of C1INH-HAE, had significantly increased baseline circulating levels of prothrombin fragment 1+2 and thrombin-antithrombin complexes. In addition, whole blood from C1INH-deficient mice supported significantly increased contact pathway-mediated thrombin generation. Importantly, C1INH-deficient mice exhibited significantly enhanced venous, but not arterial, thrombus formation. Furthermore, purified human C1INH normalized contact pathway-mediated thrombin generation and venous thrombosis in C1INH-deficient mice. These findings highlight a key role for endogenous C1INH as a negative regulator of contact pathway-mediated coagulation in humans and mice. Further, this work identifies endogenous C1INH as an important negative regulator of venous thrombus formation in mice, complementing the phenotype associated with C1INH-HAE (Grover, 2023). Christiansen et al. describe the comorbidities found in HAE patients included in the US HAE Association Scientific Registry. In this registry, 485 patients with HAE-C1INH were included. The results for cardiovascular diseases were somewhat discordant. HAE-C1INH participants reported significantly less myocardial infarction, congestive heart failure, and stroke than the general population. Other forms of thrombo-embolic disease were not described (Christiansen, 2023).

Justification of reclassification	The MAH considers there is sufficient cumulative evidence to remove the important potential risks of thrombo-embolic complications from the safety specification, as accumulating scientific and clinical data retrieved in the almost 14 years since the IBD in Europe does not support the initial supposition. The number of events from clinical trials is very low. The post-marketing experience suggests a lower incidence in patients on Ruconest than in the general population and literature suggests that there is no association between TEEs and Ruconest and potentially a slightly increased TEE risk in HAE patients in general.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Important identified risk: Allergic reactions in patients with rabbit allergy

Name of the risk	Allergic reactions in patients with rabbit allergy
MedDRA search criteria	SMQ Hypersensitivity
Potential mechanism	Conestat alfa contains low amounts (<0.002%) of host-related impurities (HRI). Theoretically, these HRIs could trigger hypersensitivity reactions in subjects with cow's milk allergy or with rabbit allergy.
Evidence sources and strength of the evidence (scientific basis for suspecting the association)	This important identified risk was based on the data from clinical development of conestat alfa, literature on rabbit allergy, as well as post-marketing data (PSURs). 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 1 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, a history of allergic symptoms upon exposure to rabbits was disclosed after exposure to conestat alfa. During and following the event, blood samples for diagnostic immunology/allergy purposes were collected, and IgE measurements were strongly positive (3+ or 4+) for rabbit antigens. Skin testing to the study drug was positive.
Characterization of the risk	<u>Frequency</u> The frequency of allergic reactions in patients with rabbit allergy observed during clinical studies and post-marketing use is very low: *Cumulative clinical trial data* In the combined safety and efficacy studies performed with Ruconest, 301 subjects were exposed at least once to Ruconest. For all studies, allergy to rabbits was an exclusion criterion. One healthy volunteer in a Phase 1 study experienced an anaphylactic reaction upon administration of Ruconest as mentioned earlier. A post-hoc analysis of 130 subjects participating in the clinical trials revealed another 4 subjects who were positive for specific IgE to rabbit dander but did not display signs of allergic-type symptoms upon exposure to Ruconest. Study C1 1113 prospectively investigated the safety of conestat alfa in subjects diagnosed with an allergy to cow's milk or rabbits. In this study, which was designed to determine the negative predictive value of the skin test in a highly relevant population, 26 subjects with clinical cow's milk and/or rabbit allergy were included. Allergy was defined by a suggestive history of symptoms after exposure to cow's milk and/or rabbit dander, and sensitization. Conestat alfa was administered percutaneously in the skin prick test (SPT) procedure, intracutaneously in the intracutaneous skin test (ICT), and subcutaneously in the subcutaneous challenge (SC). Two subjects (both rabbit allergic, both with negative basophil activation test to conestat alfa), showed a positive ICT (erythema larger than positive control) to undiluted conestat alfa and did not undergo the drug challenge with conestat alfa

as per protocol. Two patients interrupted the study for personal reasons. None of the 22 subjects with negative SPT and ICT for conestat alfa had a Type I hypersensitivity reaction during the drug challenge with conestat alfa. Basophil activation tests performed with various allergens (cow's milk, rabbit dander, conestat alfa, and individual allergens from cow's and rabbit milk) did not show laboratory evidence of hypersensitivity; no cross-reactions between cow's milk-specific IgEs and rabbit milk proteins occurred.
Registry data
No hypersensitivity reactions were reported in the EU and US Registry studies.
Cumulative post-marketing data
Rabbit allergy is a contra-indication for the use of Ruconest, as indicated in the SmPC and Package Leaflet (PL). Up to the DLP of 28 April 2024, an estimated 30,410 treatments with Ruconest were administered 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 April 2024, 1,996 patients were exposed to Ruconest and had received an estimated 168,377 treatments. 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.
Cumulatively, the word "rabbit" was found in the narrative for 37 patients, including 5 patients with reported or documented rabbit allergy having reported hypersensitivity-type adverse events. A serious reaction was observed in the Phase I study patient described under cumulative clinical trial data. The 4 other hypersensitivity reactions were of a non-serious nature. All other cases with "rabbit" in the narrative reported non-serious hypersensitivity type adverse events or mentioned that patient had no or no known rabbit allergy.
Literature data
A PubMed search on "Ruconest rabbit allergy" revealed 5 publications. All 5 publications reported allergy to rabbits as a contra-indication (Urwyler, 2021; Valerieva, 2018; Cancian, 2018) or summarize the data on rabbit allergy and development of IgE antibodies from the Pharming-sponsored clinical trials with Ruconest (Davis & Bernstein, 2011; Varga & Farkas, 2011).

Absolute risk
Low.

Relative risk
Low.

Severity
Hypersensitivity reactions can be severe, as anaphylaxis can occur.
Type I hypersensitivity reactions may range from mild to severe (grade I to IV). Symptoms may develop for up to several hours post administration (see Table SVII.1).
The exact background prevalence of rabbit allergy is not known. It was demonstrated that for persons with occupational exposure to rabbits the prevalence of rabbit allergy was 4 to 22%. (Beeson et al. 1983, Bryant et al. 1995). For the whole population this is likely to be considerably lower.
In the combined safety and efficacy studies performed with Ruconest, 248 subjects were exposed at least once to Ruconest. For all studies, allergy to rabbits was an exclusion criterion. One healthy volunteer in a Phase 1 study experienced an anaphylactic reaction upon administration of Ruconest as mentioned earlier.

Table SVII-3 Type I hypersensitivity reactions (grade I to IV)

Grade	Symptoms			
	Dermal	**Abdominal**	**Respiratory**	**Cardiovascular**

	I	Pruritus Flush Urticaria Angioedema			
	II	Pruritus Flush Urticaria Angioedema (not mandatory)	Nausea Cramping	Rhinorrhoea Hoarseness Dyspnoea	Tachycardia Blood pressure change Arrhythmia
	III	Pruritus Flush Urticaria Angioedema (not mandatory)	Vomiting Defecation Diarrhoea	Laryngeal oedema Bronchospasm Cyanosis	Shock
	IV	Pruritus Flush Urticaria Angioedema (not mandatory)	Vomiting Defecation Diarrhoea	Respiratory arrest	Cardiac arrest

Reversibility
Hypersensitivity reactions are reversible when corrective treatment is timely administered.

Long-term outcomes
After adequate treatment of hypersensitivity reactions, no long-term sequelae are expected. All patients who had experienced a hypersensitivity reaction after Ruconest treatment have recovered.

Impact on quality of life
Limited to the impact at the very moment of the hypersensitivity reaction.

Risk factors and risk groups	Patient factors Rabbit allergies are more prevalent in populations with occupational exposure (e.g. laboratory animal caretakers) or in households with pet rabbits. Dose Hypersensitivity reactions are not dose-dependent. At risk period In patients previously sensibilized to rabbits, the risk is highest at the first administration.
Preventability	Predictability Rabbit allergy is a contraindication for the use of Ruconest. Prospective patients should be queried for a possible rabbit allergy. Risk factors identified that can be minimized by routine or additional risk minimization activities If rabbit allergy has been established or is suspected, the patient should not receive Ruconest. Possibility of detection at an early stage which can mitigate seriousness If grade I hypersensitivity reactions develop, corrective treatment (such as antihistaminics, corticosteroids or other treatment required for anaphylactic reacitons) should be administered immediately and the patient should be monitored until disappearance of the symptoms.
Impact on the benefit-risk balance of the product	Mild hypersensitivity reactions cause discomfort (e.g., pruritus, urticaria). More severe hypersensitivity reactions may cause severe discomfort and may be life threatening, requiring hospitalization and/or emergency care. The most severe form of an allergic reaction is an anaphylactic reaction/shock. An anaphylactic reaction could be fatal if not treated, especially in conjunction with an HAE attack in the laryngeal region. If timely and

	appropriately treated, an anaphylactic reaction can be treated successfully with no sequelae. Based on the available data, patients without a rabbit allergy are unlikely to be affected. Even for the patients with a known clinical rabbit allergy, not all patients will have a reaction to conestat alfa, which was well demonstrated in Study C1 1113 where all the 17 rabbit allergic patients underwent a successful challenge with conestat alfa without any signs or symptoms of a type I allergic reaction after subcutaneous administration of conestat alfa. The available data from the conestat alfa clinical development program and subsequent post-marketing experience, as well as the fact that rabbit allergy has been included as a contraindication in EU SmPC and US prescribing information confirmed that this important identified risk has been minimized and therefore the impact on the risk-benefit balance of the product is considered low.
Public health impact	Absolute risk in relation to the size of the target population and consequential actual number of individuals affected Low, as a severe reaction has been reported in only one patient with a prior history of rabbit allergy. HAE is an orphan indication with a prevalence of approximately 1:50,000. Currently, there are approximately 5000 diagnosed patients in the EU. Overall outcome at population level Favorable. All patients with hypersensitivity reactions did recover.

Important identified risk: Lack of efficacy

Name of the risk	**Lack of efficacy**
MedDRA search criteria	SMQ Lack of Efficacy
Potential mechanism	Lack of efficacy is generally recognized as class effect associated with C1-INH products due to the presence of anti-C1-INH neutralizing antibodies when conestat alfa is administered to treat the approved indication, i.e., HAE due to C1-INH deficiency.
Evidence sources and strength of the evidence (scientific basis for suspecting the association)	This important identified risk is based on the data from clinical trials and post-marketing data on lack of efficacy (see PSUR). 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 hours. In a subsequent randomized controlled trial (Study C1 1310 RCT), 35/44 (80%) of patients 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 trial (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. The posology section in prescribing information in the EU and US stipulate a single dose of 50 U/kg body weight of Ruconest (up to a maximum dose of 4200 U at 84 kg or more) 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. Up to DLP of 28 October 2018, there have been 480 cases of lack of efficacy reported from post-marketing setting (cumulative patient exposure was estimated to be 2398), of which 370 were received during last PSUR (#11) reporting time interval. It is notable that in many cases, it was unspecified whether or not a second dose was administrated to the patient, consequently “real” lack of efficacy cannot be confirmed as the EU SmPC and US prescribing information indicate a second dose can be prescribed in case of no relief of the HAE symptoms. [redacted]

Characterization of the risk

Frequency

Cumulative clinical trial data

See Evidence source.

Registry data

Almost all attacks (4039/4045) in the EU Registry study were treated with a single dose of Ruconest. Six attacks were reported as treated with a second dose.

Cumulative post-marketing data

Cumulatively, 980 case reports mentioning 986 events of LoE have been received since the IBD.

Cumulative overview of LoE events

PT	Cumulatively	Comments
Drug ineffective	282	
Drug ineffective for unapproved indication	537	Includes Ruconestreports of HAE attack despite prophylactic treatment. Laryngeal attacks in the US are also coded as drug ineffective for unapproved indication.
Drug resistance	2	
Therapeutic product effect decreased	17	
Therapeutic product effect delayed	23	
Therapeutic product effect incomplete	118	
Therapeutic product ineffective for unapproved indication	1	Ruconest prophylaxis
Therapeutic response decreased	2	
Therapeutic response shortened	2	
Therapy non-responder	2	
Total	**986**	

Of note: sometimes multiple events of LoE have been reported for the same patient. This is for instance the case for some patients who use Ruconest prophylactically (unapproved indication), or for patients with severe HAE and frequent attacks who sometimes experienced slow resolving of attacks.

Other common circumstances associated with LoE: (respiratory) infection, which is a common trigger for HAE attack, which may recur when the infection is not yet over.

Treatment efficacy does not only depend on the intrinsic efficacy of the product, but also on the interval between the onset of symptoms and the administration of Ruconest. The shorter the interval, the shorter the time to resolution of the attack. In severe attacks, a single dose of Ruconest may not be sufficient and the prescribing information allows for a second dose to be administered.

Literature data

Longhurst (2017) has published the “Optimum use of acute treatments for HAE” and reported that acute treatment can reduce duration and severity of symptoms. Initial improvement may be delayed several hours, and full relief hours or days, after treatment. Nevertheless, most studies showed superiority over placebo in reducing time to improvement. Active treatment was also associated with a greater proportion of attacks with definitive response at 4 h. Onset of relief in attacks treated early occurred after a mean of 53.5 min compared with 114 min for attacks treated late. Hereditary angioedema is a lifelong condition and, for most, associated with multiple acute episodes. Therefore, it is important that treatments continue to be effective over the lifetime of the patient. Double-blind trials cannot feasibly address this question, which requires many years of observation.

However, limited observational studies have been reassuring, showing no loss of efficacy over several treatments (Longhurst, 2017).

Comparative table of time to onset and % responders of acute HAE treatments according to Longhurst

Product	Mean time to onset of response	Percentage responders after 4h
Ruconest	1.5h	90-100%
CINRYZE	2h	60%
BERINERT	0.5h	86%
Icatibant	1.5h	67%
Ecallantide	1.33h	69%

Some cases mention an ER visit for a laryngeal attack as description of LoE of Ruconest. This is not correct, as the latest treatment guidelines by WAO/EAACI [2021 revision and update; Maurer, 2021] state: "Laryngeal HAE attacks should be considered as medical emergencies. Rapid treatment with an effective HAE on-demand medication is essential in addition to preparing for emergency air-way management procedures if respiratory compromise develops. Intubation or surgical intervention, after the injection of on-demand medication, should be considered early in all progressive HAE at-tacks affecting the upper airway (Recommendation 8).". In the overview by Ferreira (2023) it is also stated that "patients who experience symptoms of laryngeal, tongue or throat swelling should seek emergency medical care as soon as possible, even after initial self-treatment" or "patients should seek emergency medical care in cases of upper airway impairment" and "seeking emergency care after upper airway swelling is essential to reduce the risk of asphyxia".
The US HAEA Medical Advisory Board 2020 Guidelines state: "There is a substantial risk of mortality associated with laryngeal attacks, and appropriate caution must be exercised in the management of these attacks. Patients who experience symptoms of laryngeal, tongue, or throat swelling should seek emergency medical care as soon as possible, even after initial self-treatment. Elective intubation should be considered for any patient with signs of respiratory distress who is not improving after treatment." [Busse, 2021].

Absolute risk
Low. The Registry data show that 99.85% of all attacks (4039/4045) in the EU Registry study were treated with a single dose of Ruconest.

Relative risk
Low.

Severity and reversibility
The severity of the consequences of lack of efficacy depends on the attack location. HAE attacks are very painful, but generally self-resolving within 2-5 days.
Laryngeal attacks are potentially life threatening and may require intubation to prevent asphyxiation. An attack will develop over several hours and early treatment of the (upcoming) attack may prevent symptoms to progress. Timely administration of Ruconest typically prevents risk of asphyxiation and therefore obviates the need of medical intervention. Consequently, lack of efficacy may still result in the need for medical intervention, including intubation. Although laryngeal attacks are the most serious manifestation of HAE, they are the least common also, estimated to represent approximately 1% of all attacks (Bork, 2006a). In case a patient experiences a laryngeal attack, the patient should immediately seek medical attention independent of an initial treatment with Ruconest.
Attacks are generally self-resolving in other locations. Lack of efficacy will extend the period to relief and hence prolong the duration of – generally severe – pain. Hence lack of efficacy may require pain treatment, occasionally in hospital.

Long-term outcomes

	In general, long-term outcomes of Lack of efficacy are good. No cases with fatal outcome have been received. Impact on quality of life Persistence of the HAE attack despite treatment with Ruconest can be painful and distressing.
Risk factors and risk groups	Patient factors Delay in treatment with Ruconest for a HAE attack is a risk factor for lack of efficacy. The longer the HAE attack is ongoing, the longer it takes to resolve. It is recommended to treat an attack from the moment of the first signs or symptoms. Dose Ruconest treatment is weight-based and it is important to administer the recommended dose based on the individual patient's weight. If needed, a second dose can be administered. At risk period Delayed treatment. Additive or synergistic risk factors Not identified.
Preventability	Possibility of detection at an early stage which can mitigate seriousness. The latest treatment guidelines by WAO/EAACI [2021 revision and update; Maurer, 2021] state: "Laryngeal HAE attacks should be considered as medical emergencies. Rapid treatment with an effective HAE on-demand medication is essential in addition to preparing for emergency air-way management procedures if respiratory compromise develops. Intubation or surgical intervention, after the injection of on-demand medication, should be considered early in all progressive HAE attacks affecting the upper airway (Recommendation 8).". Patients are recommended to seek medical attention for any laryngeal attack, even if the self-administered treatment seems effective.
Impact on the benefit-risk balance of the product	Given the low frequency of lack of effect, the impact is low.
Public health impact	Absolute risk in relation to the size of the target population and consequential actual number of individuals affected Low. HAE is an orphan indication with a prevalence of approximately 1:50,000. Currently, there are approximately 5000 diagnosed patients in the EU.

Important potential risk: Allergic reaction due to the formation of IgE antibodies against rabbit allergens

Name of the risk	Allergic reaction due to the formation of IgE antibodies against rabbit allergens
MedDRA search criteria	SMQ Hypersensitivity
Potential mechanism	Host Related Impurities (HRI) of rabbit origin present in Ruconest might induce production of IgE. This could result in an allergic response upon re-exposure to Ruconest. This important potential risk was based on literature data on rabbit allergy, data from post-marketing exposure, and the IgE testing report.
Evidence sources and strength of the evidence (scientific basis for suspecting the association)	A post-hoc analysis of 137 subjects participating in the clinical trials revealed 2 subjects who had above threshold IgE 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 against rabbit meat. Only for this patient the induction of IgE to 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.
Characterization of the risk	Frequency *Cumulative clinical trial data* No cases have been reported from clinical trials. *Registry data* No hypersensitivity reactions were reported in the EU and US Registry studies. *Cumulative post-marketing data* Cumulatively, 2 patients with Immunoglobulin E (IgE) antibodies against rabbit allergens have reported adverse events (in 2017 and in 2019; see Table SVII.2.1 in Annex 7). The events (rash and pruritis in the first patient and itching on the face in the second patient) were assessed as non-serious. *Literature data* Cumulatively, only one publication based on Pharming data has been retrieved [Hack, 2013]. This publication concludes that the propensity of rhC1INH to induce IgE antibodies following repeated administration of rhC1INH is low. Subjects with substantially elevated anti-rabbit epithelium IgE antibodies and/or clinical allergy to rabbits may have an increased risk for an allergic reaction. No other risk factors for allergic reactions to rhC1INH have been identified. Absolute risk Low. Relative risk Low. Severity The reported cases were non-serious. However, Type I hypersensitivity reactions may range from mild to severe (grade I to IV). Symptoms may develop for up to several hours post-administration (see Table SVII.1). The most severe form of an allergic reaction is an anaphylactic reaction. An anaphylactic reaction could be fatal if not treated, especially in conjunction with an HAE attack in the laryngeal region. If timely and appropriately treated, an anaphylactic reaction can be treated successfully with no sequelae. Reversibility The reported cases showed full recovery. Long-term outcomes The reported cases showed full recovery. Impact on quality of life Low. The reported cases were non-serious and showed full recovery.
Risk factors and risk groups	Patient factors Risk groups or risk factors have not been identified. Dose Hypersensitivity reactions are not dose-dependent. At risk period In patients who develop Immunoglobulin E antibodies against rabbit allergens to rabbits, the risk will manifest after repeated administration, not at the first dose.
Preventability	From clinical perspective, developing assays to detect IgE antibodies to conestat alfa, rabbit milk and rabbit HRIs is not needed at present because 1) only one individual developed an allergic (anaphylactic) reaction following exposure to conestat alfa, but this would have been prevented if the individual had disclosed her past history of allergy and, 2) the development of assays to detect IgE antibodies to conestat alfa, rabbit milk and rabbit HRIs

	would require positive control samples from multiple individuals who have experienced an allergic reaction following exposure to conestat alfa; these are currently not available. A specific test against a specific antigen could be developed if a clinically relevant antigen had been identified. To date, with a single case of anaphylaxis, it is impossible to comment on the clinical relevance of potential antigens. From a risk management perspective, the educational materials for physicians and patients have been created and are being used to minimize this risk (see Section V.2).
Impact on the benefit-risk balance of the product	The actual impact on the risk-benefit balance for this important potential risk is considered low given the currently available data.
Public health impact	Absolute risk in relation to the size of the target population and consequential actual number of individuals affected Low. HAE is an orphan indication with a prevalence of approximately 1:50,000. Currently, there are approximately 5000 diagnosed patients in the EU.

Important potential risk: Allergic due to formation of other anti-Host Related Impurities (HRI) antibodies

Name of the risk	Allergic due to formation of other anti-Host Related Impurities (HRI) antibodies
MedDRA search criteria	SMQ Hypersensitivity
Potential mechanism	Host Related Impurities (HRI) of rabbit origin present in Ruconest might induce production of antibodies other than IgE (i.e. IgG, IgM, IgA).
Evidence sources and strength of the evidence (scientific basis for suspecting the association)	This important potential risk is based on the results from the immunogenicity testing report.
Characterization of the risk	Frequency *Cumulative clinical trial data* The formation of anti-HRI antibodies (IgG, IgM, IgA) was monitored in all adult subjects and HAE patients participating in the clinical development program for Ruconest. Occasionally, samples have been screened positive for anti-HRI antibodies using a displacement assay, but these were not associated with any clinical symptom. One of the theoretical risks associated with anti-HRI antibodies is the formation of immune complexes between the antigen (HRI) and the antibodies (anti-HRI). Although generally resulting antigen-antibody complexes are effectively removed, in certain circumstances immune complexes may induce pathological responses known as type III hypersensitivity reactions. Because Ruconest only contains traces (<20 parts per million) of HRI, precipitation of immune complexes is unlikely to occur. This important potential risk is based on the results from 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 addition, in Study C1 1209, 8 patients had positive antibodies to HRI, 2 of which were treatment emergent. There was no evidence of a temporal relationship between the presence of anti-HRI antibodies and adverse events. Immunogenicity testing was also conducted in Study C1 3201. During the study, 18 patients had positive anti-HRI antibodies confirmed by the displacement assay. Of these 18 patients, 9 had treatment-emergent anti-HRI antibodies and TEAEs. Among those 9

	patients, 5 had no TEAEs that were recorded at the time of or after the first confirmed positive anti-HRI antibody result. None of the patients who developed treatment-emergent antibodies in Study C1 3201 had TEAEs consistent with a hypersensitivity reaction. 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. One patient from a clinical study (C1 1310, [redacted]) with reported or documented other anti-Host Related Impurities (HRI) antibodies has reported adverse events. This patient received a first dose of Ruconest on [redacted] without any adverse events. He received a dose of placebo on [redacted] without adverse events. He received a second and a third dose of Ruconest on [redacted] without adverse events. Following the 4th dose of Ruconest on [redacted] he reported pruritus of both hands followed by a rash after 10 minutes (at 15:11) involving upper arms, face, parts of abdomen and back. On the same day after less than an hour (at 16:06), the symptoms started to improve. No corrective treatment was given to the patient for this event. The patient recovered completely on the same day at 18:06. The results indicate an increase in the anti-host related impurity (HRI) antibodies between the open-label (OL) administration on [redacted]. These antibodies were found to be confirmed positive with a displacement assay on the last visit, but not on the previous visits. All other antibodies, including IgE against rabbit dander, did not show any relevant change. Based on the emergence of anti-HRI antibodies and the clinical symptoms of pruritus and rash immediately following the administration of rhC1INH, a hypersensitivity reaction is suspected. *Registry data* No hypersensitivity reactions were reported in the EU and US Registry studies. *Cumulative post-marketing data* There are no post-marketing reports of allergic reactions due to the formation of other anti-HRI antibodies. *Literature data* Anti-HRI antibodies are only mentioned in the publication by Baker et al. who reports the pooled data from 2 Pharming-sponsored studies. No new information (Baker et al., 2017). <u>Absolute risk</u> Low. <u>Relative risk</u> Low. <u>Severity</u> The reported case was non-serious. <u>Reversibility</u> The reported case showed full recovery. <u>Long-term outcomes</u> The reported case showed full recovery. <u>Impact on quality of life</u> Low. The reported case showed non-serious symptoms of a duration of about 3h until by full recovery.
Risk factors and risk groups	Risk groups or risk factors have not been identified.
Preventability	Predictability Risk factors identified that can be minimized by routine or additional risk minimization activities

	Possibility of detection at an early stage which can mitigate seriousness
Impact on the benefit-risk balance of the product	Low.
Public health impact	Absolute risk in relation to the size of the target population and consequential actual number of individuals affected Low. HAE is an orphan indication with a prevalence of approximately 1:50,000. Currently, there are approximately 5000 diagnosed patients in the EU.

Important potential risk: Induction of acquired angioedema due to the formation of anti-C1-INH antibodies

Name of the risk	Induction of acquired angioedema due to the formation of anti-C1-INH antibodies
MedDRA search criteria	PT Acquired antioedema PT Anti-complement antibody
Potential mechanism	Although the vast majority of HAE patients is heterozygous for functional C1-INH and therefore have levels of endogenous C1-INH, conestat alfa may be recognized as foreign and may induce the formation of antibodies that in turn may cross-react with endogenous C1-INH.
Evidence sources and strength of the evidence (scientific basis for suspecting the association	This important potential risk was based on the results from 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 following single and repeat administrations, analyzed pharmacokinetics 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, there is no indication that neutralizing antibodies are being formed following treatment with Ruconest.
Characterization of the risk	Frequency *Cumulative clinical trial data* No cases of induction of AAE due to the formation of anti-C1-INH antibodies have been reported. *Registry data* In the EU Registry study (C1 1412), almost all attacks (4039/4045) were treated with a single dose of Ruconest. Six attacks were reported as treated with a second dose with 4200 U administered in total. Many patients received repeated doses: Patients were treated for up to 520 attacks and followed for a period of up to 11.3 years, and 98 patients received up to 100 treatments, 15 patients up to 200 treatments. 1 patient received 287 Ruconest treatments during 5 years and 1 patient received a total of 520 different treatments (318 Ruconest, 5 pdC1-INH and 197 Firazyr) during 10.8 years. However, no cases of induction of AAE due to the formation of anti-C1-INH antibodies have been reported. *Cumulative post-marketing data* There are no post-marketing reports of cases of induction of AAE due to the formation of anti-C1-INH antibodies. *Literature data* No publications were retrieved when searching for Ruconest and anti-C1-INH antibodies. A search for Ruconest and acquired angioedema only retrieved publications where Ruconest was used to treat acquired angioedema (Zubareva et al, 2021; Nowicki et al, 2020; Manson, 2014).

	Absolute risk Low to absent. Relative risk Low to absent. Severity Not assessable, as no cases have been reported so far. Reversibility Not assessable, as no cases have been reported so far. Long-term outcomes Not assessable, as no cases have been reported so far. Impact on quality of life Not assessable, as no cases have been reported so far.
Risk factors and risk groups	Risk groups or risk factors have not been identified.
Preventability	The company has made available anti-C1-INH antibody tests for any HAE patients meeting any of the following criteria: • In 2 consecutive acute angioedema attacks there is a need for a dose greater than 50 U/kg conestat alfa in any HAE patient that previously responded to treatment with 50 U/kg conestat alfa. • In 2 consecutive acute angioedema attacks a failure to respond to conestat alfa treatment within 4 hours despite adequate dosing of 50 U/kg in any HAE patient who previously responded to treatment with 50 U/kg conestat alfa. For HAE patients meeting at least one of these 2 criteria, the following immunogenicity testing panel will be recommended and made available: Measure functional C1-INH activity 15 minutes after infusion of adequate dose of Ruconest. If Cmax does not achieve at least 0.7 U/mL: Anti-conestat alfa antibody testing (IgG and IgM). If above cut-off values are observed in either anti-conestat alfa 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 plasma-derived C1-INH.
Impact on the benefit-risk balance of the product	Low, as no cases have been reported so far.
Public health impact	Absolute risk in relation to the size of the target population and consequential actual number of individuals affected Low. HAE is an orphan indication with a prevalence of approximately 1:50,000. Currently, there are approximately 5000 diagnosed patients in the EU.

Important potentials risk: Medication error

Name of the risk	Medication error
MedDRA search criteria	SMQ Medication error
Potential mechanism	Medication errors are unlikely to occur with this product when administered by a healthcare professional. In January 2017, the marketing authorization in the EU/EEA was extended following approval of Ruconest 2100 U powder and solvent for solution for injection. The Ruconest self-administration kit contains one vial of Ruconest, a vial of water for injections (solvent) and ancillaries for intravenous administration and enables the patient (or caregiver) to administer Ruconest. Although the patient or caregiver will be

	trained by an HCP, the patient or caregiver may not be as skilled as an HCP. This may result in an increased chance of medication error.
Evidence sours and strength of the evidence (scientific basis for suspecting the association	This important potential risk was based on post-marketing safety data. Up to DLP of 28 October 2018, 79 medication error cases including 86 relevant events have been observed in the post-marketing setting. The AEs reported alongside the medication errors were isolated events that were typically reported once or twice and not indicative of any issue in relation to the medication errors. A frequency cannot be determined.
Characterization of the risk	Frequency *Cumulative clinical trial data* No medication errors were reported from clinical studies. *Registry data* No medication errors were reported from the registry studies. *Cumulative post-marketing data* Up to DLP of 28 April 2024, 1310 events in the SMQ Medication errors cases have been observed in the post-marketing setting. The AEs reported alongside the medication errors were isolated events that were typically reported once or twice and not indicative of any issue in relation to the medication errors. A cumulative overview of medication errors is presented in Table SVII.2.3 in Annex 7. Of the 1310 events found by the SMQ, only a maximum of 159 are unintentional and therefore fulfil the criteria of medication error as "unintended failure in the drug treatment process" (Accidental overdose/underdose, Circumstance or information capable of leading to medication error, Contraindicated product prescribed, Drug delivery system issue, Expired product administered, Incorrect product administration duration, Injury associated with the device, Intercepted medication error/ product dispensing error/ product preparation error, Needle issue, Poor quality product administered, Product administration/dispensing /preparation/storage error, product preparation/prescribing issue, Product use complaint, Syringe issue, Underdose, wrong product administered, Wrong technique in device usage process, Wrong technique in product usage process). The real frequency of medication errors is therefore 159: 168,377 treatments or 0.94:1000 treatments. The number is stable over the years. Four medication errors with harm have been reported in only 3 patients, who experienced non-serious AEs: • Wrong technique in drug usage process (pushing Ruconest too fast) resulted in the patient getting sick. • Product prescribing error concerned a patient reported having been misdiagnosed with HAE. No alternative diagnosis provided. She reported dizziness, cognitive disorder and gait disturbances as ADR, but it is unclear whether these symptoms occurred in relation to Ruconest treatment. • Product storage error and Poor quality product administered concerned product stored in travel kit at high temperatures, same patient did not experience relief when administering the product. *Literature data* No literature data on medication errors with Ruconest were found. Absolute risk Low. Relative risk Low. Severity No cases associated with subsequent serious adverse events (harm) have been received. Reversibility The 3 non-serious cases with harm showed full reversibility of the symptoms.

	Long-term outcomes The 3 non-serious cases with harm showed full reversibility of the symptoms. Impact on quality of life Low.
Risk factors and risk groups	Lack of experience of the patient or caregiver could increase the risk of medication errors. Patients with difficult venous access will be at increased risk of injection errors.
Preventability	Ruconest is prescribed by a healthcare professional for patients experiencing HAE attacks. The prescription indicates the medication, strength, concentration and route of administration, and therefore the risk of medication errors is limited. As indicated in SmPC section 4.4, the prescribing physician will decide whether a patient is eligible for administration by a non-HCP (i.e. the patient or a non-HCP caregiver) and will provide training to ensure that the steps required for appropriate reconstitution, filling of the syringe(s) and administration, are understood by the patient or caregiver. Detailed instructions for use for the patient or caregiver are included in the PL. These instructions have been subjected to usability testing to ensure that they are clear and complete. Educational materials including checklists and information on self-administration for HCPs and patients are also implemented as additional risk minimization measures. In the Product Information for the self-administration kit for Ruconest, the healthcare professional is instructed to train the patient or a caregiver in administration of Ruconest. It will be at the discretion of the prescribing physician to decide whether a patient qualifies for self-administration of Ruconest in the home situation. Additionally, the educational material pack contains a checklist for both the HCP and patient (or caregiver) to ensure the patient/caregiver is competent to self-administer Ruconest.
Impact on the benefit-risk balance of the product	Low, the number of medication errors that fulfill the definition of "unintended failure in the drug treatment process" is low and none of these were associated with serious adverse reactions. The 3 reported cases of harm had non-serious reactions resulting in full recovery.
Public health impact	Absolute risk in relation to the size of the target population and consequential actual number of individuals affected: Low. HAE is an orphan indication with a prevalence of approximately 1:50,000. Currently, there are approximately 5000 diagnosed patients in the EU.

Important potential risk: Adverse events with self or home administration

Name of the risk	Adverse events with self or home administration
MedDRA search criteria	SMQ Embolic and thrombotic events SMQ Extravasation events (Broad), HLGT Administration site reactions HLT Non-site-specific procedural complications
Potential mechanism	The addition of the possibility for self-administration outside the hospital setting might increase the potential for medication errors and/or adverse events due to potential errors with the preparation, dosing or administration (see also the important potential risk 'medication error'). Ancillaries included in the self-administration kit (EU only) may break or may get contaminated.
Evidence sources and strength of the evidence (scientific basis for suspecting the association	Not available.
Characterization of the risk	Frequency *Cumulative clinical trial data* Not applicable. *Registry data*

	No events were reported associated with self- or home administration. *Cumulative post-marketing data* Post-marketing safety data review showed that up to DLP of 28 April 2024, a total of 18 procedure-related events were reported of which all were assessed as non-serious. All events concerned vascular access site complications. 11 events concerned administration by another person and 7 by the patient. 2 similar events have been reported by patients who received Ruconest from an HCP or for whom information on self- or home-administration is missing. It is not always possible to identify whether Ruconest was given in a hospital or at home by patients themselves based on the available information. Outcome was not reported in majority of the cases. Overall, no air embolism has been reported. Review of all the case reports associated with adverse events with self-administration did not suggest any new safety signal or concern. No changes in characteristics of this risk such as frequency and severity were detected and therefore this risk remains as an important potential risk. *Literature data* No data found. <u>Absolute risk</u> Low. <u>Relative risk</u> Low. <u>Severity</u> No cases of adverse events with self or home administration reporting serious adverse events have been received. <u>Reversibility</u> The non-serious cases concerned vascular access issues, for which reversibility is not an issue. <u>Long-term outcomes</u> All patients reporting AEs with self or home administration had a full recovery. <u>Impact on quality of life</u> Low.
Risk factors and risk groups	<u>Patient factors</u> Lack of experience of the patient or caregiver or patients with decreased venous access could increase the risk of inappropriate administration or dosage of Ruconest leading to adverse events. <u>Dose</u> Dose it not expected to influence the risk of adverse events with self or home administration. <u>At risk period</u> The risk is highest at the start of treatment, when patients or caregivers have limited experience with Ruconest administration. <u>Additive or synergistic risk factors</u> Not identified.
Preventability	In SmPC section 4.4 the healthcare professional is instructed to train the patient or a caregiver in administration of Ruconest. It will be at the discretion of the prescribing physician to decide whether a patient qualifies for self-administration of Ruconest in the home situation.

	Preparation and administration of Ruconest is a multi-step process. Detailed instructions for use for the patient are included in the patient leaflet. The instructions have been subjected to usability testing to ensure that they are clear and complete. Once the patient or caregiver has acquired a certain level of routine, the chance of errors will decrease.
Impact on the benefit-risk balance of the product	The impact on the individual patient is dependent on the type of the adverse event and could range from minimal impact to substantial. The actual impact of AEs with self-administration on the risk-benefit balance is considered low given the available post-marketing data.
Public health impact	It is not expected that this will impact the safety of patients in a significant way due to the limited impact observed thus far from case reports from the US market where self-administration was already allowed from the start. Although the incidence rate of AEs with self-administration is difficult to estimate due to the lack of accurate patient exposure data, the public health impact is considered limited given the rarity of the relevant events reported and the low incidence of the orphan disease HAE.

SVII.3.2 Presentation of the missing information

Missing Information: Data on pediatric patients aged 2 up to 5 years

Table SVII.3: Missing information: Data on pediatric patients aged 2 up to 5 years

Name of the missing information	**Data on pediatric patients aged 2 up to 5 years**
MedDRA search criteria	Patients aged 2-5 years of age
Evidence sources and strength of the evidence (scientific basis for suspecting the association)	*Clinical studies in pediatric patients* *[Submitted for the pediatric indication Procedure No. EMEA/H/C/001223/II/0053/G, 2019, approved 2020]* Study C1 1209 was an open-label, Phase 2, non-comparative, multinational, multicenter clinical study in pediatric patients in the age range from 2 to 13 years, with a confirmed diagnosis of HAE. This study has included 20 pediatric patients, of whom 6 patients were below the age of 6 at the time of the administration of the first dose in this study. [redacted]. Patients were eligible for treatment with conestat alfa at a dose of 50 U/kg body weight up to a maximum of 4200 U if they presented to the clinic within 5 hours of onset with an acute attack. The primary objective was to assess the clinical safety, immunogenicity and tolerability of conestat alfa in this pediatric subset of patients with HAE. Secondary, pharmacokinetic and pharmacodynamic parameters and efficacy of conestat alfa were assessed. A total of 73 attacks were treated in 9 female and 11 male patients, with a mean age of 8.2 years at Presentation of Attack 1 (range 5-14 years). Overall, in the Safety Analysis Set, 11 patients experienced at least one treatment-emergent adverse event (TEAEs). Two patients (10%) reported TEAEs of severe intensity after study treatment (Abdominal pain and Vomiting), and for 2 patients (10%) TEAEs were reported that were considered possibly related to study treatment by the Investigator (Abnormal lymphocyte morphology, 4 events reported). In the absence of a temporal association in 3 of these events and a negative rechallenge, these events were considered unlikely related to conestat alfa by the Sponsor. Clinically, the most suitable explanation given was the presence of a sub-clinical infection, which is common in this population. The other TEAEs were of mild or moderate intensity, and unrelated to study treatment. Three patients experienced 9 treatment-emergent serious adverse events that occurred after study treatment for Attacks 1, 2, or 4; of which the most common were for the SOCs Infections and infestations and included Bronchitis, Pneumonia, Tonsillitis, and Viral infection. The most common TEAEs across all attacks were in the SOCs of Infections and infestations (7/20 patients [35%]), Gastrointestinal disorders (4/20

patients [20%]), and Investigations (3/20 patients [15%]), and included Nasopharyngitis, Vomiting, Viral infection, and Abnormal lymphocyte morphology. There was no evidence of an increase in the TEAE frequency across attacks, although a higher proportion of patients experienced TEAEs after study treatment for Attack 1 (8/20 patients [40%]) and Attack 4 (3/7 patients [43%]) compared to after treatment for the remaining attacks. There were no deaths or discontinuations due to TEAEs during the study.
Treatment with conestat alfa did not result in any significant trends in routine clinical laboratory safety parameter data across attacks. Two patients reported clinically significant abnormalities during the study; a high value for erythrocyte sedimentation rate and a high value for monocytes and low value for white blood cell count were reported. There were no clinically meaningful changes in any of the vital signs' parameters during the study. As patient age increased with increasing number of attacks, mean weight at Presentation generally increased across attacks. Most abnormal physical examination findings reported during the study were related to HAE. Most patients had normal or abnormal, but not clinically significant, ECG results at Presentation of attack and post-infusion. Sporadic, transient immune responses to conestat alfa and HRI were observed, but with no associated clinical findings. Furthermore, none of the patients developed neutralizing antibodies to C1-INH and no impact of immunogenicity on clinical efficacy or safety was observed.
The results from this study are consistent with the findings in previous clinical studies with conestat alfa in adult and adolescent patients with HAE and support the efficacy of conestat alfa at a dose of 50 U/kg for the repeat treatment of acute HAE attacks in pediatric patients.

Population PK results
Pharmacokinetics
For all patients who received a single iv administration of rhC1INH for the first attack, concentrations of functional C1INH were maximal for the majority of patients at 5 minutes post-dose with individual values ranging from 62% to 168% of normal. At 2 to 4 hours post-dose, functional C1INH concentrations were lower than 5 minutes post-dose values but above Baseline (Presentation) values for the majority of patients (range 28% to 81% of normal, based upon 18/20 patients). As per study inclusion criteria, all 20 patients had concentrations of functional C1INH that were < 50% of normal at Baseline (Presentation). A total of 18/20 patients had concentrations of functional C1INH that were > 70% of normal (the lower limit of the normal range) at the 5 minutes and/or 2 to 4 hours post-dose time points.
Functional C1INH pharmacokinetic concentrations were expressed as a percentage of normal, based upon a pool of plasma from healthy subjects (Siemens – Standard Human Plasma sourced in Germany), which was originally set at 100%. Due to an inadequate number of sampling time points; the only PK parameters calculated in this study were AUC0-3 and Cmax. Upon administration of a single iv dose of rhC1INH 50 U/kg for the first attack, arithmetic mean functional C1INH Cmax was 123.2% of normal (range 62% to 168%), and AUC0-3 was 170.87% of normal (range 95.20% to 243.58%).
At 2 to 4 hours post-dose, functional C1INH concentrations were lower than 5 minutes post-dose values but above baseline values for the majority of patients (range 28% to 81% of normal, based on 18/20 patients. A total of 18/20 patients had concentrations of functional C1INH > 70% of normal (the lower limit of the normal range) at the 5 minutes and/or 2 to 4 hours post-dose time points.

Table SVII.4: Functional C1 Esterase Inhibitor (C1INH) (% of Normal) Over Time for First Attack Only (PK/PD Concentration Set)

	Presentation n=20	5 Minutes Post-dose n=19	2-4 Hours Post-dose n=20
N>LLQ	1	19	19
Arithmetic mean	13.2	123.2	43.5
SD	5.14	28.32	16.15

CV (%)	39.1	23.0	37.1
Median	12.0	122.0	41.0
Min, Max	12, 35	62, 168	12, 81
Geometric mean	12.7	119.8	40.5
Geometric CV (%)	24.3	25.5	42.4

Source: Table 14.2.2.1.1 (study C1 1209)
C1INH = C1 esterase inhibitor, CV = coefficient of variation, LLQ = lower limit of quantification, n = number of patients with observation, PD = pharmacodynamic(s), PK = pharmacokinetic(s), SD = standard deviation. N>LLQ refers to the number of patients with C1INH concentrations above the LLQ.

Pharmacodynamics

For all patients who received a single iv administration of rhC1INH for the first attack, arithmetic mean and individual patient C4 concentrations generally decreased from Baseline (Presentation) values at 5 minutes post-dose before increasing above Baseline (Presentation) values at 2 to 4 hours post-dose, although individual patient data were variable.

Mean C4 concentrations at Presentation were comparable across attacks, with the exception of an increased mean C4 concentration at Attack 5, which was however highly variable (73 µg/mL; 7.25 - 187.00 µg/mL) and was measured only for 6 patients.

Table 4: C4 Concentrations (µg/mL) Over Time for First Attack Only (PK/PD Concentration Set)

	Presentation n=20	**5 Minutes Post-dose n=19**	**2-4 Hours Post-dose n=20**
N>LLQ	16	14	18
Arithmetic mean	38.160	26.376	55.815
SD	36.4307	18.4498	51.5839
CV (%)	94.468	69.948	92.419
Median	24.700	21.400	37.650
Min, Max	7.25, 137.00	7.25, 71.00	7.25, 227.00
Geometric mean	26.293	20.495	39.218
Geometric CV (%)	109.231	88.457	109.291

Source: Table 14.2.2.2 (study C1 1209)
C1INH = C1 esterase inhibitor, CV = coefficient of variation, LLQ = lower limit of quantification, n = number of patients with observation, PD = pharmacodynamic(s), PK = pharmacokinetic(s), SD = standard deviation. N>LLQ refers to the number of patients with C1INH concentrations above the LLQ.

Discussion on clinical pharmacology

Blood samples for the assessment of PK and PD were collected prior to administration, directly following infusion (5 minutes post-infusion) and one sample between 2 and 4 hours post-infusion. For each sample for PK C1INH activity and for PD C4 were measured. C4 data was additionally collected at presentation of each subsequent acute HAE attack. For PK, only for the first attack, Cmax and AUC0-3 were calculated.

Pharmacokinetics

For the assessment of PK the functional C1INH activity was reported as percentage of normal based on a pool of plasma from healthy patients which was originally set at 100%. The MAH clarified during the P46 procedure that a commercial standardized product was used (Siemens – Standard Human Plasma sourced in Germany) and not a pool of samples from studies in healthy volunteers. The same standard was used for the analysis of PK samples in the adult studies.

The collected data showed an increase to 123% (62-168%) 5 minutes post dose and values approaching baseline at 2-4 h post dose (Table 11-8). These findings are

consistent with the results for adult and adolescent patients, where the 50 U/kg dose also restored the C1INH level to normal for about 2 hours.

Pharmacodynamics

The data for a single dose indicate that the C4 concentrations decrease from baseline towards 5 minutes post-dose and then increase above baseline at 2-4 hours post-dose. The measurements are, however, very variable. Nevertheless, the results are comparable to the previously presented data for adult and adolescent patients.

Conclusions on clinical pharmacology

Overall, the results presented for the paediatric population are in accordance with the results obtained for the adult and adolescent patient population.

Efficacy data

The MAH intended to recruit children between 2 and 13 years of age. The 20 recruited and treated patients were however between 5 and 14 years old (mean 8.20) at presentation of attack 1. In the screening dataset patients' age ranged from 2-13 years. The MAH discussed why no children between 2 and 4 years were treated. 20 children were enrolled in this age range, but none were treated for events during the study. Only two presented in a study centre with untreated attacks at the age of 4 but did not meet the treatment criteria for this attack. No information is given on how many children between 2 and 4 years had events or their severity and if and how they were treated otherwise. The MAH explained that some parents had home treatment available and argued that this was preferable over a long drive to the centre. However, it is not clear how often this occurred, or which alternative treatments have been used. Therefore, no treatment data is available for 2- to 4-year-old patients.

However, the need for treatment of acute HAE attacks is also present for 2- to 4-year-old patients. This is also reflected by the PIP requirement to conduct a study in paediatric patients from 2 years of age and above. It is acknowledged that feasibility of a study in this age group is limited. The availability of patients is limited in this orphan setting, other approved products for the treatment of HAE attacks in patients from 2 years of age are available and complying with all requirements in clinical trials might be an additional burden for the parents/caregivers. This might be especially true for very young children, as indeed observed in study C1 1209 (screened patients in this age group but no treatment data available).

The MAH was requested to address the lack of data in children 2 to 4 years of age and discuss the lower age limit of 2 years in the intended indication. A respective discussion has been presented by the MAH upon request including an additional literature review and popPK model with respective simulations:

Although the documentation of the literature search is missing, the review seems to be comprehensive and includes relevant data for this application and supports the difficulties to recruit patients in the age range of 2 to 4 years of age. Although episodes occur already at this age, attack frequency increase between 3 and 6 years of age and again later. Further, abdominal attacks in this age group may be more difficult to diagnose as the symptoms are often similar to other common paediatric diseases. It has also been seen in study C1 1209 that it is difficult to include this young patient population also due to existing treatment alternatives.

The popPK model predicted overall similar concentrations of Ruconest for adults, adolescents and children after administration of the recommended dose of 50 U/kg. Although a slight decrease in children < 5 years of age was predicted, this would still translate into 90% of children reaching maximum concentration of 0.7 U/mL. The MAH argued that in case this would lead to an insufficient clinical response, therefore an additional dose could still be administered. This argumentation is agreed and the second dose is also implemented in the SmPC.

Given the mode of action of Ruconest as enzyme replacement and assuming similar concentrations are achieved (as claimed by the popPK model and seen in children of 5-13 years), it is considered reasonable that the efficacy data derived from children (≥5 years), adolescents and adult patients can be extrapolated to younger children. Further,

the registry study was also modified to include respective patients in order to gather data in the post marketing.

Efficacy in children from the age of 5 years old have been demonstrated based on the clinical data. There was no data provided for children between 2 to 4 years of age. Extrapolation of the efficacy in children from the age of 2 years is accepted based on the mechanism of action, the provided population PK model and the available clinical data from the age of 5 years. The simulation results based on the population PK model were further considered acceptable to support the dose recommendation in young patients (2-4 years).

Adverse events
Overall, in the Safety Analysis Set, 11 patients (55.0%) experienced at least one treatment-emergent adverse event (TEAE) after treatment with rhC1INH. The majority of TEAEs were of mild or moderate intensity, and not related to study treatment. Two patients (10.0%) reported TEAEs of severe intensity after study treatment for Attack 1 (abdominal pain [one patient] and vomiting [one patient]), and two patients (10.0%) reported TEAEs considered possibly related to study treatment (abnormal lymphocyte morphology events after study treatment for Attacks 1 and 2 [one patient] and Attack 4 [one patient]).
The only possibly related TEAE was “abnormal lymphocyte morphology events“, and was reported four time for two patients after three attacks on a total of four occasions (attack 1,2 and 4 (twice)). The MAH clarified upon request during the preceding P46 procedure that all events occurred not immediately after treatment but a couple of days after (earliest 10 days) and that three of the four events occurred more than 30 days after treatment (31, 38, 55 days).
There was no evidence of an increase in the TEAE frequency across attacks, although a higher proportion of patients experienced TEAEs after study treatment for Attack 1 (8/20 patients [40.0%]) and Attack 4 (3/7 patients [42.9%]) compared to following treatment for the remaining attacks.
Eight patients (40%) experienced a subsequent attack that required treatment before completing the follow-up visits. The number of subsequent attacks ranges from 1 up to 9.
A total of 10/20 patients (50.0%) experienced TEAEs within 24 hours of completion of rhC1INH infusion and 8/20 patients (40.0%) experienced TEAEs within 28 days of completion of rhC1INH infusion. The most common TEAEs across all attacks were in the SOCs of infections and infestations (7/20 patients [35.0%]), gastrointestinal disorders (4/20 patients [20.0%]), and investigations (3/20 patients [15.0%]), and included nasopharyngitis, vomiting, viral infection, and abnormal lymphocyte morphology.

Overall, in the Safety Analysis Set, three patients experienced nine treatment-emergent SAEs (TESAEs) that occurred after study treatment for Attacks 1, 2, or 4. The most common TESAEs were grouped as SOC infections and infestations and included bronchitis, pneumonia, tonsillitis, and viral infection. Six patients were below the age of 6 at the time of the administration of the first dose in this study. [redacted] None of these patients experienced any AEs assessed as related to Ruconest. Most AEs were unrelated, incidental viral infections. One SAE was reported 4h after administration of Ruconest. This event of tonsillitis was also assessed as not related by investigator and MAH.

No AEs of special interest were reported during this study (such as type I hypersensitivity reactions against IgE, type III hypersensitivity reactions against rhC1INH, induction of acquired angioedema, or thromboembolic complications).

	Hypersensitivity to host related impurities (HRI) is an identified risk for Ruconest, also included in the SmPC. Therefore, patients were excluded if a history of allergy to rabbits or rabbit-derived products was known. An additional assessment of immunogenicity reaction was also performed in study C1 1209. The assessment of immunogenicity reactions was performed based on the blood samples collected also for the PK and PD analysis. The samples were tested for anti- C1INH and anti-HRI antibodies (Abs). Sporadic, transient immune responses to rhC1INH and HRI were observed, but with no associated clinical findings. Two patients had confirmed Abs against C1INH at screening or presentation of attack. Eight patients experienced confirmed anti-HRI Abs. None of the patients developed neutralizing Abs to C1INH and no impact of immunogenicity on clinical efficacy or safety was observed. No AEs concerning anaphylactic reactions were observed by any patient in this study. **Conclusions** The overall B/R of Ruconest is positive in children from the age of 2 years and above. *Registry data* No patients aged 2-4 years were included in the Registry after opening of the Registry to this patient group in 2020. The youngest patient included was 5 years old, but no treatment was reported for this participant. *Post-marketing experience* Cumulatively up to 28 April 2024, 11 cases from [redacted] reporting 20 events in 10 pediatric patients aged 2 to 5 years. All reported events can be classified as either off label use/product use issue (not further specified) without adverse events, HAE (which is the indication rather than the event) or concurrent illnesses/conditions that are frequent in this age group (e.g. viral infection, anger). No events were suspect of a causal relation with Ruconest. All cases were non-serious except for one case of swelling (i.e. underlying disease), which was categorized as serious due to an ER visit (PHAUS2018000331). Table SVII.2.5 provides a cumulative overview of post-marketing AEs in patients ages 2-5 years.
Population in need for further characterization	Apart from routine pharmacovigilance, Pharming had changed the protocol for the EU registry for Ruconest (Study C1 1412) to include this younger age group.However, .no patients aged 2-4 years have been included. The youngest patient included was 5 years old, but no treatment was reported for this participant. Furthermore, additional text is proposed in SmPC sections 4.2 and 4.4, to emphasize that there are no clinical data available for the use of conestat alfa in children aged less than 5 years. Due to the absence of clinical data in children aged 2 up to 5 years, monitoring for any symptoms of hypersensitivity during and after administration is recommended in this age group. Treatment should be based on the physician's benefit/risk assessment for each individual patient.
Anticipated risk/consequence of the missing information	There is no evidence for an increased risk associated with use of Ruconest for HAE in pediatric patients aged 2-5 years, but the number of patients exposed to Ruconest for this orphan disease, with the onset of symptoms usually starting between the ages of 5 and 11 years of age (de Albuquerque Campos, 2021) is unavoidably low. Use of Ruconest for HAE in pediatric patients aged 2-5 years will be continued to be monitored as missing information.
Text in Section 4.2	*Paediatric population* Ruconest may be used in paediatric patients (2 years and older) at the same dose as in adults (50 U/kg body weight). The safety and efficacy of Ruconest in children less than 2 years old have not been established. No clinical data are available.

Missing Information: Data on pregnant and breastfeeding women

Table SVII.5: Missing information: Data on pregnant and breastfeeding women

Name of the missing information	**Data on pregnant and breastfeeding women**
MedDRA search criteria	SMQ Pregnancy and neonatal topics
Evidence sources and strength of the evidence (scientific basis for suspecting the association)	Pregnant or breastfeeding women have been excluded from the clinical development program (see Section SIV.3). *Cumulative clinical study data* No pregnancies or breastfeeding were reported during the Ruconest development program. *Registry data* Three pregnancies were reported in study C1 1412. 1 patient received 41 doses of Ruconest and had a live delivery at full term. 1 patient received 9 doses of Ruconest and had a live delivery with no complications and the third patient received 8 doses of Ruconest and delivered at full term through a cesarian section. These 3 pregnancies are discussed in the total of 193 post-marketing pregnancies. There were no reports of breastfeeding during use of Ruconest from the Registry. *Cumulative post-marketing data pregnancy* The safety database contains 193 cases reporting use of Ruconest during pregnancy. Of these, 24 (13.4%) were reported from Bosnia and Herzegovina, Bulgaria, Czech Republic, Croatia, Germany, France, UK, Israel, Italy, Macedonia, Poland, Portugal and Romania and 169 originated from the US (87.6%). A cumulative overview of the pregnancy cases is provided in Table SVII.2.4 in Annex 7. The high percentage of US cases may be explained by the distribution of Ruconest by only 4 Specialty Pharmacies. Their cases show the use of a standard question during refill calls asking “are you currently pregnant or nursing or planning to become pregnant?". The number of reported pregnancies per year is low. The first report dates from 2008. The number of cases varied from 1-36 per year, with a rather stable number of pregnancies reported between 23 and 36 in the period 2018-2024. There were 8 cases reporting spontaneous abortion, of which two occurred in the same patient. This patient reported having fertility problems. There were 17 associated baby cases. Three reported congenital abnormalities: born with 2 mandibular teeth, cryptorchism (and developmental delay at 15 months) and tongue tie. These abnormalities are frequent within the general population. Since the information was received from the patients during refill calls, no causality was assessed by the reporter. Premature birth was reported in 5 pregnancies: on premature birth at 23 WG had a fatal outcome, one birth considered twins born at 30 WG ([redacted] no complications reported), one mother with pre-eclampsia delivered at 35 WG ([redacted] newborn with transient tachypnea), one newborn was born at 36+5 WG ([redacted] no complications), one newborn at 36 WG (healthy baby) and one newborn at 31 WG after C-section (admitted to the NICU, no details provided). Postnatal complications in the infants were transient and concerned transitory tachypnea of the newborn, low oxygen levels at birth, neonatal jaundice (2x, once in Rh incompatibility, no complications), respiratory distress of the newborn, fever (after meconium in amniotic fluid and bradycardia during delivery) and bruising on the head and difficult temperature control. All outcomes were favorable and expected in a population of 193 pregnancies. Two baby reports were remarkable: [redacted]: The week after Ruconest administration, patient experienced low amniotic fluids and fetus had lost one pound in weight. [redacted]: Limb and lip swelling in the fetus after facial HAE attack in mother while she started having cervical dilatation. Vaginal delivery 2 h after Ruconest administration. Facial edema of infant had resolved. Healthy male infant, Apgar 8-9.

	Literature case, Grivcheva-Panovska (2020), first report of an HAE attack in utero. Genetic testing later confirmed the infant had HAE type I. Cumulative post-marketing data Breastfeeding Cumulatively, the database contains 39 reports of Maternal exposure during breast feeding. Most of these cases are from the US, where the Specialty Pharmacy routinely asks, “are you currently pregnant or nursing or planning to become pregnant?". In none of these cases, any adverse events in the breast-fed baby were reported. The longest lactation duration reported was 14 months. Literature data Literature on Ruconest in pregnancy is limited. The global safety database contains pregnancy cases from abstracts published by Caires, Moldovan and Staubach-Renz who reported a total of 20 pregnancy cases in patients on Ruconest (Caires, 2019; Moldovan, 2019; Staubach-Renz, 2021). Moldovan published 14 pregnancy cases on Ruconest that had been spontaneously reported to Pharming or concerned a clinical study case. These cases were not counted double. Literature on lactation in patients using Ruconest is limited. We found the publication by Moldovan, who reported 15 cases of pregnancy, of whom 1 has breast fed her baby and the publication by Staubach-Renz who reported one woman who became pregnant and breast fed the baby. These cases are included in the database. No other relevant literature was retrieved.
Population in need for further characterization	Although the number of 193 pregnancy reports is impressive for an orphan drug with an estimated incidence of 1: 50,000 inhabitants, the cases originate from spontaneous reporting and details on the pregnancy and the pregnancy outcome are often missing.
Anticipated risk/consequence of the missing information	Given the cumulative evidence available to date, there is no indication that Ruconest would induce birth defects, negatively affects the pregnancy or delivery, induces premature birth or induces postnatal complications in newborns. On the other side, Ruconest is effective during pregnancy and effective treatment of HAE attacks can protect the fetus. The MAH will continue to monitor pregnancy cases.
Text in Section 4.6	Pregnancy and breast-feeding There is no experience with the use of Ruconest in pregnant and breast-feeding women. In one animal study reproductive toxicity was observed (see section 5.3). Ruconest is not recommended for use during pregnancy or breast-feeding, unless the treating physician judges the benefits to outweigh the possible risks. Fertility There are no data on the effects of Ruconest on male or female fertility.

PART II: MODULE SVIII – SUMMARY OF THE SAFETY CONCERNS AFTER RECLASSIFICATION OF THE RISKS BASED ON CUMULATIVE DATA

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Allergic reactions in patients with rabbit allergy • 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 • Medication error • Adverse events with self or home administration
Missing information	• Data on pediatric patients aged 2 up to 5 years • Data on pregnant and breastfeeding women

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaire for allergic or hypersensitivity reactions:

In case of a suspected serious hypersensitivity/immunogenicity reaction, a questionnaire will be sent to the reporter to facilitate collection of all relevant information (see Annex 4).

Other forms of routine pharmacovigilance activities for pregnancy notification and outcome:

In case pregnancy is reported during treatment with Ruconest, further information is gathered regarding the pregnancy and the outcome (see Annex 4).

III.2 Additional pharmacovigilance activities

Ruconest EU registry

Study short name and title: Ruconest registry. C1 inhibitor treatment registry to assess the safety and immunological profile of Ruconest in the treatment of HAE Attacks (Study C1 1412).

Rationale and study objectives: 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.

Study design: Non-interventional treatment registry of HAE patients treated with plasma-derived C1-INH or Ruconest. The aim is to recruit 300 patients treated with Ruconest. Additionally, the study will continue until 100 patients have been exposed to Ruconest for at least 3 attacks. Enrolment into the plasma-derived C1-INH arm will be unrestricted.

Study population: Patients are recruited in countries both inside and outside Europe.

Milestones: Study progress was reported periodically in the DSUR and PSUR and in updates to the RMP.

The registry is now considered completed with the inclusion of 92 patients (37 male/55 female, ages 17-81 years), who were treated with rhC1-INH in the registry for 4045 attacks in 9 European countries. Patients were treated for up to 520 attacks and followed for a period of up to 11.3 years. 98 patients received up to 100 treatments, 15 patients up to 200 treatments.

Efficacy results: Patients reported relief within 4 hours in 98,0% (3966/4045) of the Ruconest treated attacks, 90,5% (180/199) of the pdC1-INH treated attacks and 97% (577/595) of the Firazyr/Icatibant treatments.

Almost all attacks (4039/4045) were treated with a single dose of Ruconest. Six attacks were reported as treated with a second dose with 4200 U administered in total.

Safety results: 57 events were reported in 42 case reports. Among those 57 events, 12 were serious, but not related to Ruconest treatment. No hypersensitivity or thrombotic/thromboembolic events were

reported for any of the treatments. Overview of the pregnancy cases: 1 patient received 41 doses of Ruconest and had a live delivery at full term. 1 patient received 9 doses of Ruconest and had a live delivery with no complications and the third patient received 8 doses of Ruconest and delivered at full term through a caesarian section.

Conclusion: no efficacy or safety concerns did arise from the real-world experience as captured in the Ruconest registry.

Progress update: the Registry is being closed and the final CSR will be submitted in March 2025.

Survey of the aRMM for Ruconest

Study short name and title: Additional risk minimization measures (aRMM) for Ruconest – European survey of educational materials for Ruconest (PHARM/EU/aRMM/01).

Rationale and study objectives: 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 that 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 EU registry).

Study design: This is a cross-sectional survey among physicians who have received the updated educational materials for Ruconest for self-administration, prescribe Ruconest, and practice in one of the countries where Ruconest for self-administration was formally launched and has been available for at least one year.

Study population: All physicians who have received the educational materials in a country where the self-administration kit for Ruconest has been launched, will be informed of the study by an appropriate Pharming representative. One year after receipt of the educational materials, the physicians will be asked to participate in an online survey. All physicians who have prescribed Ruconest (vial-only and/or self-administration kit) to patients with HAE at least once during the 12 preceding months will be eligible for participation.

Milestones: The following milestones are identified: 1) launch of the self-administration kit for

Ruconest; 2) start distribution questionnaires, 3) start data collection, 4) end data collection, and 5) final study report. Study progress will be reported periodically in the PSUR and in updates to the RMP.

Progress update: the survey is still ongoing.

III.3 Summary table of additional pharmacovigilance activities

Table III.1: Additional pharmacovigilance activities

Study ***Status***	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not Applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not Applicable				
Category 3 – Required additional pharmacovigilance activities (by the competent authority)				
Data collection from participation in the Ruconest registry (C1 1412) *Data Completed*	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.	- to expand the safety database for Ruconest - serious allergic reactions or anaphylaxis	Regular updates	Data will be reviewed on an ongoing basis as part of signal detection and reported within the PSUR and RMP updates.
			Final report	31Mar2025
Effectiveness evaluation of educational materials for Ruconest (PHARM/EU/ aRMM/01) *Planned*	To evaluate the usefulness and HCPs awareness of the educational materials for Ruconest and whether key safety messages are understood by the prescriber and communicated to their patients. To evaluate whether the reporting rate of adverse events related to hypersensitivity reactions after administration of Ruconest has changed.	- to measure the effectiveness of the educational materials	Regular updates	Study progress will be reported in the PSUR and RMP updates.
			Final report	31/01/2026

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

[redacted]

PART V:RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1 Routine risk minimization measures

Table V.1: Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Allergic reactions in patients with rabbit allergy	Routine risk communication: *SmPC section 4.2, 4.3 and 4.4* *PL section 2* Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation for starting treatment with Ruconest is included in SmPC section 4.2. • A known or suspected rabbit allergy is listed as a contraindication in SmPC section 4.3. • SmPC section 4.4 describes that patients need to be queried about prior exposure to rabbits and signs and symptoms suggestive of an allergic reaction and what to do if they would occur. • PL section 2 states not to use Ruconest in case of allergy to rabbits.
Lack of efficacy	Routine risk communication: **SmPC section 4.2** **PL section 3** Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation for additional dose (50 U/kg up to 4200 U) in case of insufficient clinical response is included in SmPC section 4.2. • PL section 3 states that in case of insufficient clinical effect a second dose may be used, with a maximum of 2 doses within 24 hours.
Allergic reaction due to the formation of IgE antibodies against rabbit allergens	Routine risk communication: *SmPC section 4.4* *PL section 4* Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC section 4.4 describes how to detect symptoms of hypersensitivity reactions and that patients need to be queried about prior exposure to rabbits. • PL section 4 describes symptoms of a possible allergy that may indicate that the patient has developed an allergy to Ruconest.
Allergic reaction due to formation of other anti-Host Related Impurities (HRI) antibodies	Routine risk communication: *SmPC section 4.4* *PL section 4* Routine risk minimization activities recommending specific clinical measures to address the risk: • How to detect symptoms of hypersensitivity reactions is included in SmPC section 4.4. • PL section 4 describes symptoms of a possible allergy that may indicate that the patient has developed an allergy to Ruconest.
Induction of acquired angioedema due to the formation of anti-C1-INH antibodies	Routine risk communication: Not applicable
Medication error	Routine risk communication: Not applicable

Safety concern	Routine risk minimization activities
Adverse events with self or home administration	Routine risk communication: *SmPC section 4.4* *PL section 3* Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC section 4.4 states that potential risks associated with home-treatment are related to the administration itself. • PL section 3 describes the instructions for use for Ruconest for self-administration.
Data on pediatric patients aged 2 up to 5 years	Routine risk communication: *SmPC section 5.2* *PL section 2* Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC section 4.2 states that no clinical data are available for the use of Ruconest in this age group. • SmPC section 4.4 states that due to the absence of clinical data in children aged 2 up to 5 years, monitoring for any symptoms of hypersensitivity during and after administration is recommended in this age group. • PL section 2 described that Ruconest has not been studied in children younger than 5 years of age.
Data on pregnant and breastfeeding women	Routine risk communication: *SmPC section 4.6* *PL section 2* Routine risk minimization activities recommending specific clinical measures to address the risk: • SmPC section 4.6 states that there is no experience with the use of Ruconest in pregnant and breast-feeding women. Ruconest is not recommended for use during pregnancy or breast-feeding, unless the treating physician judges the benefits to outweigh the possible risks. • PL section 2 describes that it is not recommended to use Ruconest during pregnancy or breast-feeding. If the patient plans to become pregnant, she should discuss this with her doctor before starting to use Ruconest.

V.2 Additional risk minimization measures

Educational materials

The use of Educational materials for the introduction of Ruconest treatment to patients may be responsible for the low rates of events related to the risks as described in the summary of safety concerns. Use of these materials will be continued.

Objectives:

The educational materials have been introduced and implemented to manage certain risks and improve the risk-benefit balance of Ruconest. Those risks as well as the relevant objectives are presented in Table V.2:.

Table V.2: Objective of additional risk minimization measure for each risk

Risks	Objective
Important identified risks	
Allergic reactions in patients with rabbit allergy	To reduce the risk of hypersensitivity reactions; known or

	suspected rabbit allergy is a contraindication.
Lack of efficacy	To provide guidance on what to do in case of insufficient clinical response.
Important potential risks	
Allergic reaction due to the formation of IgE antibodies against rabbit allergens	To create awareness on the importance of checking for prior exposure to rabbits and signs and symptoms suggestive of an allergic reaction and provide guidance on what needs to be done in case these occur.
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	To create awareness of formation of neutralizing antibodies which could result in reduced efficacy.
Medication error	To provide sufficient and clear guidance to the treating physician and the patient (and their caregiver) on how to use the Ruconest self-administration kit
Adverse events with self or home administration	

Rationale for the additional risk minimization activity:

The educational materials consist of the following documents:

- Immunological Assessments (non-promotional educational materials for prescribers)
- Patient card
- Checklist for healthcare professionals
- Checklist for patients
- Patient diary

For both Ruconest presentations (powder for solution for injection, and powder and solvent for solution for injection), the healthcare professional is informed of possible hypersensitivity or other immune reactions to Ruconest, testing regimens to identify such reactions and actions to be taken when such an event occurs. The patient card also contains information on possible hypersensitivity reactions after administration of Ruconest and actions to be taken when such a reaction occurs. The patient is instructed to always carry the patient card with them.

Additionally, for Ruconest powder and solvent for solution for injection, the healthcare professional is provided with a checklist to assist in training of the patient or caregiver for the use of Ruconest. For the patient or caregiver, a checklist is provided to ensure that all necessary training has been received to enable safe and effective use of Ruconest. A patient diary is to be given to patients before they receive Ruconest.

In addition, some immunogenicity tests were developed to further evaluate certain risks, e.g., anti-HRI antibody testing were made available for patients who experienced a type III hypersensitivity reaction (skin, joints or kidney symptoms) in the days or weeks following a Ruconest administration which after investigation of other causes cannot be fully explained by exposure and reaction to other antigens.

Target audience and (planned) distribution path:

Target audience: treating physicians and patients (and/or patients' caregivers).

Distribution path: Healthcare Professionals who are expected to prescribe Ruconest and patients who plan to use Ruconest for self-administration are provided with an educational pack. The educational materials contain the key messages as defined in Annex IID of the Product Information

for Ruconest (see Annex 6). Both the content and distribution plan are agreed with each national competent authority. The educational pack includes the educational materials and the SmPC and PL for Ruconest.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Treating physicians will be queried for clarity, completeness and effectiveness of the educational materials (see Study PHARM/EU/aRMM/01).

V.3 Summary of risk minimization measures

Table V.3: Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Allergic reactions in patients with rabbit allergy	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*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Hypersensitivity questionnaire for suspected cases of hypersensitivity* Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)*
Lack of efficacy	Routine risk minimization measures: *SmPC section 4.2* *PL section 3* Additional risk minimization measures: *Educational materials for physicians and patients*	Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)*
Allergic reaction due to the formation of IgE antibodies against rabbit allergens	Routine risk minimization measures: *SmPC section 4.4* *PL section 4* Additional risk minimization measures: *Educational materials for physicians and patients*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Hypersensitivity questionnaire for suspected cases of hypersensitivity* Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)*
Allergic reaction due to formation of other anti-Host Related Impurities (HRI) antibodies	Routine risk minimization measures: *SmPC section 4.4* *PL section 4* Additional risk minimization measures: *Educational materials for physicians and patients*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Hypersensitivity questionnaire for suspected cases of hypersensitivity* Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)*
Induction of acquired angioedema due to the formation of anti-C1-INH antibodies	Routine risk minimization measures: *Not applicable* Additional risk minimization measures: *Educational materials for physicians and patients*	Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)*
Medication error	Routine risk minimization measures: *Not applicable* Additional risk minimization measures: *Educational materials for physicians and patients*	Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)*

Safety concern	Risk minimization measures	Pharmacovigilance activities
Adverse events with self or home administration	Routine risk minimization measures: *SmPC section 4.4* *PL section 3* Additional risk minimization measures: *Educational materials for physicians and patients*	Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)*
Data on pediatric patients aged 2 up to 5 years	Routine risk minimization measures: *SmPC section 4.2 and 4.4* *PL section 2* Additional risk minimization measures: *None*	Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)*
Data on pregnant and breastfeeding women	Routine risk minimization measures: *SmPC section 4.6* *PL section 2* Additional risk minimization measures: *Educational materials for physicians and patients*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Pregnancy notification form* *Pregnancy outcome form* Additional pharmacovigilance activities: *Ruconest registry (Study C1 1412)*

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, adolescents, and children (aged 2 years and above) 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).

List of important risks and missing information	
Important identified risks	Allergic reactions in patients with rabbit allergy
	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
	Medication error
	Adverse events 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 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: 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.
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, 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: 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 events 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 5.2* *PL section 2*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None* 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*

Missing information – Data on pregnant and breastfeeding women	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *None* 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

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).

PART VII: ANNEXES

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Annex 4 Specific adverse drug reaction follow-up forms

- Pregnancy notification form
- Pregnancy outcome form
- Hypersensitivity questionnaire

Note: these forms are not Ruconest-specific, but are forms routinely used for collection of additional data in pregnancy and hypersensitivity cases

Annex 6 Details of proposed continued risk minimization activities

Approved key messages of the continued risk minimization measures

Physician educational material:

- Summary of Product Characteristics (SmPC)
- Guide for healthcare professionals (Immunological Assessments/non-promotional educational materials for prescribers)
- Prescriber checklist (HCP checklist)
- Patient card

Educational material for the patient:

- Package Leaflet (PL)
- Patient checklist
- Patient diary
- Patient card

Physician educational material:

The educational materials for the Healthcare Professional (Immunological Assessments/non-promotional educational materials for prescribers and HCP checklist) include information on the following key elements (see also SmPC Annex IID):

- 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.
- The need to inform patients about the early signs of hypersensitivity reactions including hives, generalized 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-C1-INH antibodies and therefore the potential risk of formation of neutralizing antibodies. Advice about the immunogenicity laboratory testing program for these antibodies provided by the company for following up suspected emergence of neutralizing 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 patient information pack:

The educational materials for patients/non-Healthcare Professionals should include information on the following key elements (see also SmPC Annex IID):

- **Patient checklist**

  - 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

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

- **Patient card**
  - 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.

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