Post-Authorisation Safety study (PASS)
Study Report

Title	Additional risk minimization measures for Ruconest – European survey of educational materials for Ruconest
Protocol identifier	PHARM/EU/aRMM/01
EU PAS register nr	EU PAS 1000000680
Version of final report	1.0
Date	26 January 2026
Active substance	ATC code : B06AC04 Active substance : conestat alfa
Medicinal product	Ruconest 2100 U powder for solution for injection (vial only) Ruconest 2100 U powder and solvent for solution for injection (self-administration kit)
Product reference	EU/1/10/641/001 (vial only) EU/1/10/641/002 (self-administration kit)
Procedure number	EMEA/H/C/001223/MEA/019
Marketing authorisation holder	Pharming Group N.V
Joint PASS	No
Research question and objectives	The objective of this study was to evaluate the effectiveness of the risk minimisation materials for Ruconest distributed to treatment centres/prescribing physicians.
Countries of the Study	European union (EU) countries where Ruconest self-administration kit was launched Main participants planned: United Kingdom (UK), Bulgaria, Germany, Netherlands Participants (actual): UK
Author	[redacted]

Marketing authorisation holder

Marketing Authorisation Holder	Pharming Group N.V Darwinweg 24 2333 CR Leiden, The Netherlands
MAH Contact Person	[redacted]

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2 ABSTRACT

Title

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Keywords

Educational materials

Effectiveness

Rationale and background

The European Medicines Agency (EMA) requested Pharming Group N.V. to provide all Healthcare Professionals (HCPs) who were expected to prescribe Ruconest with an educational materials pack (patient and prescriber checklists, and patient diary); to study the effectiveness of these educational materials. As part of this effectiveness evaluation, the MAH conducted a survey of prescribing physicians' knowledge and understanding of specific risks associated with Ruconest, as described in the Product Information, and communicated to the HCPs via these educational materials.

Research question and objectives

The main objectives of this study were:

- 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 was 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 post-approval safety study (PASS) study C1 1412).

Study design

This was a cross-sectional survey among physicians who 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 had been available for at least one year.

Setting

An invitation to voluntarily participate in the survey was sent to the HCPs who received the educational materials. The invitation contained a link to access the questionnaire via a secure website. The survey was designed to take no more than 30 minutes. The response rates were monitored to keep track of the number of completed questionnaires. A reminder notice was sent if participants have not responded within 2 weeks after the first invitation, followed by a second reminder if required.

Due to the limited number of EU treatment centres and physicians treating hereditary angioedema (HAE) patients, the duration and extent of this study was intended to encompass a minimum of 20 completed questionnaires from at least 4 different countries. The distribution and collection of the questionnaires was planned to continue for at least one year after first start of data collection.

Subjects and study size, including dropouts

Population

All physicians who received educational materials in a country where the self-administration kit for Ruconest had been launched, were informed about the survey. One year after receipt of the educational materials, the physicians were asked to participate in an online survey. All physicians who prescribed Ruconest (vial-only and/or self-administration kit) to patients with HAE at least once during the 12 preceding months were eligible for participation.

Study size

At least 20 completed questionnaires from prescribing physicians from at least 4 countries were planned to be included.

Variables and data sources

Variables

Physician characteristics were collected (e.g. demographics, specialty, country, years in practice, number of HAE patients treated). The questionnaire evaluated the awareness, knowledge, and adherence to the educational materials. Summary tables were planned to include descriptive statistics; without formal hypothesis testing.

Data sources

- Completed questionnaires from an online survey among prescribing physicians.
- Adverse events from routine pharmacovigilance reporting and European registry study (post-authorisation safety study [PASS] study C1 1412).
- When the original website was no longer active, the questionnaire was adapted for manual entry in Word format and General Data Protection Regulation (GDPR) requirements, and sent via email to prescribing physicians.

Results

Initially, 22 HCPs were identified and invited and despite several reminders and reactivation of the survey in 2025, only 13 survey questionnaires were completed, all in the UK. The reactivation of the survey in 2025 included contacting directly (via email) potential current

Ruconest prescribers in EU countries with the reformatted questionnaire. Multiple alternative treatments currently exist in EU countries and Ruconest is no longer actively prescribed in EU. Still, 3 prescribers (2 in Bulgaria and 1 in the Netherlands) could be identified and contacted, however, without response after 3 reminders.

[redacted]

Results from the 13 survey responses obtained are presented as follows:

In total 13 HCPs completed the survey, all from the UK. Not all questions were answered by all participants; all questions were answered by not more than 8 participants. All 8 had their primary medical specialty in clinical immunology, with a various duration of experience but 4 participants had experience over 10 years. Five out of 8 participants were working in an academic teaching hospital. Out of 8 responders, 5 prescribed Ruconest both for administration by HCPs and for self-administration.

That Ruconest is contraindicated in case of an allergy to rabbits was known to all responders, also that the product is derived from milk from rabbits. All responders also knew they had to closely monitor the patient for symptoms of hypersensitivity after treatment with Ruconest. All responders were aware it is the responsibility of the prescribing physician to verify that the patient/caregiver is capable of safe and effective self-administration of Ruconest. The awareness for seeking immediate medical attention when using Ruconest for self-administration was not optimal.

All responders had read the SmPC, most read the immunological assessment guide and the checklist for the HCP, and half read the checklist for patients, the patient card and the patient diary. All responders provided patients with the patient diary, the majority provided the patient card and half of them provided the patient checklist. One responder did not see the added value of the patient card for patients.

When asked to describe their use of the educational materials when prescribing Ruconest for self-administration, half of the responders never used the patient card and also half frequently used the checklist for patients, other responses were given by 1 or 2 responders only.

All responders thought the educational materials were helpful to prepare the Ruconest solution, for administration of Ruconest either by HCP or for self-administration. Most also found them useful to address side effects and only half of responders considered them helpful to distinguish hypersensitivity reactions from those of an HAE attack in patients.

Most responders and their patients knew how to reconstitute and dose Ruconest.

All responders knew to check whether the patient understood each step and was cognitively and physically able to use Ruconest themselves.

Half of the responders received feedback from patients/caregivers on the educational materials, but when received, the feedback was that the educational materials were helpful.

The safety evaluation of the registry (PASS STUDY C1 1412) did not reveal any potential new safety signal or additional risks and confirmed the favorable safety profile of Ruconest, and data

are consistent with the results seen in several clinical studies with different subject populations. No hypersensitivity reactions were reported in the EU (C1 1412) registry study.

Cumulatively in Europe, 19 hypersensitivity related events were reported based on the MAH pharmacovigilance system, of which 18 events were reported up to and including 2020 and only 1 event as of 2021.

Discussion

In general, the educational materials were used and perceived as useful, and the main safety messages were understood.

The participating HCPs were aware of the need to take a careful history of rabbit allergy, the need to monitor for hypersensitivity reactions, and to verify whether the safety messages were understood by the patient and HCP, and what actions need to be taken when hypersensitivity reactions occur.

The patient/prescriber checklists and patient diary were used by the participants 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, however, the materials were not always provided to the patient.

Based on the low numbers of responders and of the available safety information, no conclusions can be drawn from the impact of the educational materials on the safety of using Ruconest in relation to hypersensitivity.

Marketing Authorisation Holder(s)

Pharming Group N.V.

Names and affiliations of principal investigators

Ruconest prescribers (anonymous)

3 LIST OF ABBREVIATIONS

Abbreviation	Full term
AE	Adverse Event
aRMM	Additional Risk minimization Measure
CRO	Clinical Research Organisation
EMA	European Medicine Agency
EU	European Union
GDPR	General Data Protection Regulation
IgE	Immunoglobulin E
HAE	Hereditary Angioedema
HCP	Healthcare Professional
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NCA	National Competent Authority
PAS	Post-approval study
PASS	Post-Authorisation Safety study
PL	Package Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SAE	Serious adverse events
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA query
U	Unit

4 INVESTIGATORS

Ruconest prescribers (anonymous):

Physicians who received the educational materials in a country where the self-administration kit for Ruconest had been launched, were informed on the study of the educational materials. One year after receipt of the educational materials, the physicians were asked to participate in an online survey. All physicians who prescribed Ruconest (vial-only and/or self-administration kit) to patients with HAE at least once during the 12 preceding months were eligible for participation.

5 OTHER RESPONSIBLE PARTIES

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6 MILESTONES

The milestones were related to the launch of the kit (Ruconest 2100 U powder and solvent for solution for injection). Countries planned to be included were Germany, France, United Kingdom, and the Netherlands.

To ensure that the study is representative of routine established practice, sufficient time was allowed following the launch and initial distribution of the educational materials in each country and start of the survey. After approval by the relevant authorities (if required by individual countries), the survey was distributed to health care professionals one year after distribution of the educational materials (version including the kit) in countries where the kit had been launched. Distribution of the survey was directly followed by start of data collection (see Table 1).

Table 1 Study milestones

Milestone(s)	Planned date	Actual date	Comments
Launch of the Ruconest self-administration kit	July 2017*	July 2017	
Start distribution of questionnaires	July 2018	December 2020	
Start of data collection	July 2018	January 2021	
End of data collection	July 2020	March 2021	This was last response received. In 2025 reactivation of the study occurred but without additional responses.
Registration in the EU PAS register	December 2020	July 2025	
Interim report	March 2021	March 2021	Quarterly interim reports (only one available since no further questionnaires were completed after Mar 2021)
Final report of study results	January 2021	December 2025	Due to late actual survey start (December 2020) and missing questionnaire to reach the target of 20 completed, the final report was subsequently delayed.

Study update information was provided in Periodic Safety Update Reports (PSURs). Since the number of completed surveys was less than 20, 2 years post launch in the first country, the study duration was extended in 2022 and reactivated in 2025. The extension and reactivation did not result in additional responses to the survey. Meanwhile, multiple alternative treatments now currently exist in EU countries [redacted]

7 RATIONALE AND BACKGROUND

The Marketing Authorisation for Ruconest (conestat alfa) was granted on 28 October 2010. The initial therapeutic indication was for the treatment of acute angioedema attacks in adults with hereditary angioedema (HAE) due to C1-esterase-inhibitor deficiency, which later was extended to adolescents in 2016 and to children aged ≥2 years in 2020.

Regulatory procedures

At the time of granting of the Marketing Authorisation, the educational materials consisted of an immunological assessment document for HCPs and a patient card. These were updated during the following regulatory procedures:

- Procedure II/0032 for the vial-only presentation: a type II variation where the routine immunoglobulin E (IgE) testing was removed. Instead, a request for a more detailed medical history (e.g. information on a known or suspected rabbit allergy) was included.
- Procedure X/0034: a line extension to add a new pharmaceutical form "powder and solvent for solution for injection"; a self-administration kit, including solvent and administration devices to facilitate administration by the patient or the caregiver in the home care setting.

Prior to approval of the line extension, a usability and readability focus test on the instructions for use of Ruconest 2100 U powder and solvent for solution for injection (self-administration kit) was completed in 2015 (Annex 1). The results showed that all 21 volunteers were able to independently prepare and administer the Ruconest solution for self-administration using the instructions for use, even without receiving the essential training beforehand. The few remaining difficulties were mainly related to the oversized label used for the powder vial, and volunteers occasionally skipping information in the instructions for use. Otherwise, the volunteers were able to easily locate and understand the provided information.

Based on the changes to sections 4.4 and 4.8 of the SmPC, corresponding changes to the educational materials, and the results of the usability test, the following aspects needed to be addressed in the additional Risk Minimisation Measures (aRMM):

a) risk of side effects, in particular hypersensitivity reactions or other immunological responses,

b) preparation of the Ruconest solution,

c) self-administration of Ruconest.

This resulted in an update of the educational pack for use with the self-administration kit, including a checklist for HCP, a checklist for patients and a patient diary.

Educational pack

The current, approved educational pack consists of six elements, as listed in Table 2. The high-level content of the educational materials is listed in Annex II D of the Product Information, both for the materials intended for the HCP as well as the materials for the patient (see protocol, Annex 1). After appropriate instruction and training and assessment of the suitability for Ruconest self-administration by the physician, patients and caregivers should be able to prepare and administer Ruconest correctly by following the instructions for use. In addition, a European

post-marketing registry was set-up in which HCPs are encouraged to enter patients (PASS study C1 1412).

Table 2 Educational pack for Ruconest

Educational pack elements	**Vial only** ***powder for solution for injection***	**Self-administration kit** ***powder and solvent for solution for injection***
Summary of Product Characteristics (SmPC) and Package Leaflet (PL)	✓	✓
Patient card	✓	✓
Immunological assessment document for HCP	✓	✓
HCP checklist		✓
Patient checklist		✓
Patient diary		✓

Distribution of educational materials

Prior to launch of the self-administration kit and after approval of the final content and format of the educational materials by the National Competent Authorities (NCAs), all HCPs who might prescribe Ruconest are provided with an (updated) educational pack (including patient materials). As the patient related materials (i.e., patient card, patient diary and checklist for patients) are distributed to patients through the HCP, the study also queried prescribing physicians on feedback received from their patients (see Annex 1).

The distribution process may vary per country, i.e. distribution may take place by means of a personal visit, by email, or by postal mail, as agreed with the NCA. In addition, the educational materials are available to all identified potential new physicians at the treatment centres. All educational materials are available for re-ordering directly via the MAH or its local representatives. In some countries the educational materials are available online, e.g. on the website of the NCA.

The number of HAE treatment centres is limited, generally with a small number of physicians treating HAE patients with Ruconest or other HAE medication. To ensure that the current knowledge about correct treatment with Ruconest is adequate, the MAH is in regular contact with the treating physicians. The distribution of the educational materials is tracked (including method and date of distribution, HCP name, name treatment centre, version of educational materials and person responsible for distribution). In case of any questions the HCP can contact the MAH or its local representatives.

Effectiveness evaluation of educational materials

In both regulatory procedures described above, the EMA requested a proposal to evaluate the effectiveness of the revised educational materials, including information on how they are used and who uses them in practice, whether the safety messages are understood and whether clinical knowledge / attitude / behaviour have changed as a result. The current survey has been set-up in line with GVP module XVI 2017. In addition, the EMA requested that the MAH should also

evaluate whether the incidence of adverse events (AEs) caused by hypersensitivity has changed using all sources of available data.

8 RESEARCH QUESTION AND OBJECTIVES

The main objectives of this study were:

- to evaluate the HCPs' awareness of the need to take a careful history of rabbit allergy, the need to monitor for hypersensitivity reactions, and to verify whether the safety messages are understood by the patient and HCP, and what actions need to be taken when hypersensitivity reactions occur.
- to evaluate whether the patient/prescriber checklists and patient diary are 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.

A secondary study objective of this study was 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 PASS study C1 1412).

The effectiveness measurement consisted of process and outcome indicators (Agyemang 2017). The following process indicators were defined to gather evidence that the implementing steps of additional risk minimisation measures have been successful:

- records of distribution of educational materials to treatment centres/prescribing physicians (via tracking tool)
- confirmation of the distribution of the educational materials to the patient by the physician (via questionnaire)

The following outcome indicators were defined to address the objectives, by means of a questionnaire:

- distribution of educational materials to HCPs
- physician's prescription history of Ruconest
- physician's awareness and use of existing educational materials
- physician's understanding of possible risks and key safety information, including required actions, as provided in the educational materials
- physicians' opinion on the quality and clarity of the educational materials
- query whether the physician assesses that patients are capable of preparing and administering Ruconest themselves, recognising hypersensitivity reactions, how to distinguish them from HAE attack, and know what to do and whom to contact
- query for feedback from patients regarding quality and clarity of the information presented in the patient card, diary and checklist as received from the physician

Questions that were related to the hypersensitivity, reconstitution of the product and the immunological assessment document for HCPs and patient card, were applicable for both Ruconest presentations. Questions on how to instruct patients and usefulness of the checklists and the patient diary were specifically related to the self-administration kit.

Additionally, the respondents were asked several questions to obtain information on their medical specialty, country in which they practice, further demographics, and prescribing history

regarding Ruconest, as specifically requested by EMA/PRAC (Pharmacovigilance Risk Assessment Committee). The questionnaire is provided in Annex 1.

9 AMENDMENTS AND UPDATES

When the original website for the survey was no longer active, the survey was adapted for manual entry in Word format and GDPR requirements, and sent via email to prescribing physicians. Both versions are provided in Annex 1.

10 RESEARCH METHODS

Full details of the research methods are presented in the protocol in Annex 1.

10.1 Study design

The survey was planned to be distributed in each EU market where Ruconest for self-administration was launched. After EMA approval of the line extension, the updated educational materials as listed in the protocol were submitted to the NCAs for review. Following national approval, the updated educational materials were distributed. Twelve months later, all prescribing physicians who received these updated educational materials were invited to participate in an online survey.

The comprehensibility, knowledge, usefulness and usage of the educational materials were primarily assessed, including the awareness of possible risks. At the start and end of the data collection period for the questionnaire, relevant data obtained from routine pharmacovigilance reporting (post-marketing data) as per the most recent PSUR and data from the European registry study for Ruconest (PASS study C1 1412) were evaluated. Given the relatively limited number of completed questionnaires to be expected and the low AE reporting rate for Ruconest, this evaluation was planned to be executed in a qualitative fashion.

10.2 Setting

The CRO, PAINT-Consult, sent an invitation to participate in the survey to the HCPs who received the educational materials. The invitation contained a link to access the questionnaire via a secure website. The survey had been designed to take no more than 30 minutes. Reminder notices were sent.

Participating HCPs had the option of receiving compensation for their time and effort as allowed by national laws and reimbursement policies.

The questionnaire was distributed one year after launch of the self-administration kit.

Due to the limited number of EU treatment centres and physicians treating HAE patients, the duration and extent of this study was intended to encompass a minimum of 20 completed questionnaires from at least 4 different countries. The distribution and collection of the questionnaires was planned to continue for at least one year after first start of data collection.

During the reactivation of the study, the questionnaires were sent to the HCPs by Pharming.

10.3 Subjects

The population for analysis comprised all physicians who met the eligibility criteria and completed the online questionnaire.

10.4 Variables

Physicians' understanding of specific risks for Ruconest and procedures specifically related to the self-administration kit was assessed using a questionnaire. Knowledge and awareness of, and adherence to the educational materials was evaluated and results were expressed as proportions. Summary tables include descriptive statistics. No formal hypothesis testing was conducted.

The questionnaire was composed of multiple choice and close-end questions. Response options presented in a list were randomised. All items in the questionnaire must be answered to complete the survey.

Participating physicians first needed to provide their consent to participate in the survey, in line with the GDPR. If he/she did not agree, the survey ended. Following agreement, the questionnaire continued with a screening module to confirm eligibility. Depending on the response, participation could either be terminated or continued.

The key messages tested in the survey applied to side effects (particularly hypersensitivity / allergic reactions), preparation of the Ruconest solution and self-administration of Ruconest. Additional questions explored the usage and helpfulness of the educational materials, based on the physician's practical experience as well as patient's feedback on Ruconest.

The outcome of the survey was the proportion of physicians that correctly responded to individual items of the questionnaire. The proportion responding correctly was tabulated separately for each item. Physician's demographic information was collected in order to further characterise the respondent population. This included country, type of medical practice, years in practice, and (range of) number of HAE patients treated.

The questionnaire did not collect adverse events. Any observed side effects were to be addressed within the European registry for Ruconest (PASS study C1 1412) and reported via the national reporting system. Further effectiveness evaluation of the risk minimisation materials was measured using process indicators on distributed materials in reaching the target population.

Due to the limited number of physicians expected to participate in this study, a validity calculation of outcome measurements (e.g. precision, accuracy, sensitivity, specificity) could not be considered in this study protocol.

10.5 Data sources and measurement

The primary data source was the completed questionnaires filled in by the HCPs. Other data sources included the company's safety database and data from the European registry study (PASS study C1 1412) for the evaluation of adverse events related to hypersensitivity reactions and other immunogenic/allergy related adverse events.

The MAH provided the CRO with a list of all potential prescribers who had received the (updated) educational materials. The CRO was responsible for survey distribution, data collection and data analysis. The survey was initially an internet-based questionnaire that was accessible through a secure website, and later the survey was sent via email. Each physician was requested to fill out only one questionnaire. The purpose of the study and the procedures were explained via a separate letter (see protocol, Annex 1). The MAH's medical affairs representatives contacted the site/HCP during the survey period to check whether there were any barriers to complete the survey. Only completed questionnaires from physicians who had prescribed Ruconest (either vial only or self-administration kit) at least once in the last 12 months were evaluated.

10.6 Bias

One limitation of the study was the limited number of physicians that could be included in this study. The target patient population was small (prevalence approximately 1:50,000) and within

this small population Ruconest had a limited market share in most of the European countries. Moreover, Ruconest was prescribed exclusively by a very small, specialized group of experts operating in specialised medical care centres. The educational materials were distributed to all prescribing physicians that were working in the specialized care centres for patients with HAE. To increase the number of respondents, all treating physicians who received the educational materials were sent a request to participate in the survey. The request for participation in the survey was sent one year after the distribution of the educational materials (and launch of the kit). This increased the possibility that the HCP would prescribe Ruconest, and thereby making them more prone to participate in the survey.

Another factor that could influence the outcomes of the study was that physicians involved might not adequately complete the survey and respond positively rather than truthfully. As is the case with questionnaires in general, socially desirable behavioural responses must be mentioned. To reduce the probability of this happening, the questionnaire was anonymised to the MAH and questions were not leading but designed to elicit a truthful response. It is not possible to detect whether or not physicians use risk minimisation materials whilst answering the questions in the survey.

These limiting influences were actively countered by the medical affairs department, which carefully conveyed the usefulness of the study to the participating physicians and took all appropriate measures to ensure data quality. In case the response rate was low, possible alternative methods of contact were looked into, such as sending letters and contacting physicians by telephone. In addition, the length of survey was such that it did not overtax physicians participating in this study.

The rationale for including only HCPs and not patients, was that (1) educational materials are provided to the HCP and distribution to patients occurs through the prescribing physician, (2) anonymised distribution of surveys to patients, follow-up on no response, and processing are challenging, (3) the scope of the patient educational materials is limited in comparison to those for the HCPs. In addition, the MAH expected patients to play an active role, by reading the patient materials (patient checklist and package leaflet (PL) as provided by the HCP), keeping their patient cards with them all the time, and filling in the patient diary. In case the HCP considered that the patient was not suitable for self-administration, or if a patient did not feel confident to administer Ruconest him or herself at home, Ruconest for self-administration should not be prescribed. Nevertheless, some of these more patient-specific items were incorporated in the survey and thus indirectly covered via the HCPs.

Regarding the evaluation of a change in incidence of adverse events related to hypersensitivity, it is difficult to determine this with routine pharmacovigilance, as it would be difficult to differentiate between a change in reporting rate and a true change in the frequency of hypersensitivity reactions. A change in reporting rates could be due either to a) newly implemented encouragement of HCPs and patients to report serious hypersensitivity-related adverse events, b) an increase in the incidence of allergic reactions due to removal of the need for IgE pre-testing, or c) a decrease in the incidence of allergic reactions because of the additional information within the educational materials on the need for a careful initial and periodic assessment of the patient with respect to any allergy to rabbits. Due to the rarity of HAE disease and the low frequency of hypersensitivity related AEs, there was a limited chance of obtaining a meaningful outcome for this endpoint. However, quantification of risk reduction for

hypersensitivity events as a measure of effectiveness of the educational materials was not the main objective of the study.

The educational materials were submitted for review and approval by the NCAs, resulting in different approval dates and possible minor differences in content of the country-specific versions of the educational materials. The inclusion times per country differed. The items that were questioned regarding safety information and instruction for the kit was similar in each country.

10.7 Study size

A minimal number of questionnaires needed to be completed, regardless of the prescription of the vial only, self-administration kit, or both. This number was based on the total numbers of invited physicians, considering an envisaged response rate based on literature data.

As all (potential) prescribing physicians were planned to be contacted to participate, no additional sample size calculation is used in the study protocol. Based on the expected number of treatment centres and physicians, a response rate of about 25% would be needed to reach this number.

Given the rarity of the disease and the limited number of EU treatment centres and physicians treating HAE patients in general, a minimum of 20 completed questionnaires was challenging. Efforts to maximise recruitment were considered throughout the study by specifically contacting possible prescribers. Since all possible prescribers had received the educational materials, this was not expected to bias the study outcome.

The population for analysis was to comprise all physicians who met the eligibility criteria and completed the online questionnaire.

10.8 Data transformation

The survey was completed online and data were stored on a secure server. Every effort was made to protect participant confidentiality.

Analyses were conducted with anonymised data using a SPSS statistics program file (PASW Statistics, version 18.0). Only anonymised data were made available to Pharming Group N.V. in accordance with privacy protection rules.

The CRO provided quarterly feedback to the MAH on the number of completed surveys as long as new surveys were received. A status update was provided within the risk management plan (RMP) and PSUR updates, as applicable. All data in the study updates and the final report were provided to the MAH in such a way that the possibility of tracing the identity of the physician is impossible.

10.9 Statistical methods

Data analysis was descriptive. Awareness, knowledge, and adherence were evaluated and results expressed as percentages and means by question and HCP, as applicable. No formal hypothesis testing was conducted.

The following items were reported, as appropriate:

- number of HCPs receiving the (updated) educational materials pack

- number of questionnaires sent out to HCPs
- number and percentage of HCPs eligible and ineligible for participation
- number and percentage of HCPs who completed the questionnaire
- frequency distribution of responses to each question

The outcomes were summarised for all countries combined, and per country if possible. Additional analyses may be performed as needed.

Physicians' general medical practice and demographic data were intended to explore possible differences between physician's subsets in understanding, knowledge and use of the educational materials.

The results from the questionnaire were compared in a descriptive manner with other data obtained since approval of Ruconest; such as reported adverse events related to hypersensitivity based on post-marketing data from the most recent PSUR and data from the European registry study (PASS study C1 1412). Hypersensitivity reactions or other immunogenic/allergy related adverse events are separately discussed and evaluated in the final report of this survey. This includes the evaluation of the concerned reported adverse reactions resulting from post-marketing reporting (pharmacovigilance data obtained from PSUR). If the numbers of events were sufficient, a further breakdown including their frequencies and occurrences per EU country would be considered, taking into account the sales volume a) once before launch of the self-administration kit, b) after launch of the self-administration kit, and c) for non-EU countries. Also data from the European registry study (PASS study C1 1412) will be included in this evaluation. Adverse events were reported using the preferred terms taken from the Medical Dictionary for Regulatory Activities (MedDRA).

It should be noted that routine pharmacovigilance cannot determine whether the 'incidence' of adverse events related to hypersensitivity has changed, as it is difficult to differentiate between a change in reporting rate and a true change in the frequency of these adverse events. Thus, a change in reporting rate of hypersensitivity cases could result from:

a. An increase in the incidence of adverse events, which was theoretically conceivable due to the removal of the requirement to test for IgE anti-rabbit dander. This questionnaire was specifically created to mitigate this concern.
b. A decrease in the incidence of adverse events related to hypersensitivity because of the additional information in the educational materials on the need for a careful initial and periodic screening of the patient for allergy to rabbits.

Due to the fact that clinical studies (2) and post-approval marketing experience (6) have shown only eight cases of immune disorders, subdivided in one anaphylactic reaction and seven (drug) hypersensitivity reactions, demonstrating effectiveness of educational material as measured by a further reduction of hypersensitivity cases seemed challenging.

10.10 Quality control

Concerning storage of records and archiving, the CRO will store the data from the questionnaires for a minimum of 10 years, including backups of the entire data set.

The qualifications of the CRO had been assessed by the MAH during previous projects and were further assured via the research contract.

11 RESULTS

All data from the survey are listed in Annex 1. The survey was one list with several starting questions, followed by 32 questions, and several closing questions. In the results output in Annex 1, question 2 was divided over 3 questions; the final results show 33 questions.

The questions in the surveys were grouped following the outcome indicators as described in Section 8 in the protocol. Most question results have been grouped in tables; some questions are described in text. See Table 3 for the reference to where the results are presented in this report, per outcome indicator as described in the protocol.

Table 3 Locations of the results of the survey in this report, by outcome indicator

Outcome indicators as in protocol Section 8	Section	Table/text	Question numbers[a]
Distribution of educational materials to HCPs - participants	11.1	Table 4	a,b,c,d
Demographics – descriptive data	11.2	Table 5	28, 29, 30, 31, 32, 33
Physician's prescription history of Ruconest	11.4.1	Table 6	1, 2, 3,
Physician's awareness and use of existing educational materials	11.4.2	Text: 13, 20 Table 7	4, 6, 7, 8, 9, 10, 11, 13, 14, 19, 20
Physician's understanding of possible risks and key safety information, including required actions, as provided in the educational materials	11.4.3	Table 8	5, 12, 15, 16, 17
Physicians' opinion on the quality and clarity of the educational materials	11.4.4	Text: 24,25 Table 9	21, 22, 23, 24, 25
Query whether the physician assesses that patients are capable of preparing and administrating Ruconest themselves, recognising hypersensitivity reactions, how to distinguish them from HAE attack, and know what to do and whom to contact	11.4.5	Text: 18	18
Query for feedback from patients regarding quality and clarity of the information presented in the patient card, diary and checklist as received from the physician	11.4.6	Text: 27 Table 10	26, 27

a Based on the results as in Appendix.

11.1 Participants Survey

Pharming has ceased marketing Ruconest in Europe and is planning to withdraw the EU marketing authorisation in 2026 for commercial reasons.

Initially, 22 participants were identified and invited to the survey and despite several reminders , only 13 survey questionnaires were completed. A reactivation of the survey in 2025 included contacting directly (via email) potential current Ruconest prescribers in EU countries with the reformatted questionnaire. Multiple alternative treatments currently exist in EU countries and Ruconest is no longer actively prescribed in EU. Still, 3 prescribers (2 in Bulgaria and 1 in the Netherlands) could be identified and contacted, however, without response after 3 reminders.

[redacted]

[redacted]

Of the 25 invited HCPs, 13 HCPs completed the survey, all using the website. Not all questions were answered by all participants; all questions were answered by not more than 8 participants. Eligibility results are presented in Table 4.

Table 4 Participants of the survey

		Response	
		Percentage (%)	**Total (n)**
a. Country of practicing medicine (N=13)	United Kingdom	100.00	13
b. Prescribed Ruconest in last 12 months (N=13)	Yes	84.62	11
	No	15.38	2
c. Liaised to Pharming or a regulatory body? (N=11)	Yes	27.27	3
	No	72.73	8
	Not answered	NA	2
d. Agree to participate in survey (N=8)	Yes	100.00	8
	No	0	0
	Not answered	NA	5

NA=not applicable.

11.2 Descriptive data Survey

Demographics of the participants are presented in Table 5; all these questions were answered by 8 participants. Four were male, 3 female and 1 preferred not to answer this question. Half of them, 4 participants, were between 30-39 years old. Also 4 participants had more than 15 years in medical practice. All 8 participants had their primary medical specialty in clinical immunology, with a various duration of experience, but 4 over 10 years in this specific field of medicine. Five out of 8 participants were working in an academic teaching hospital.

Table 5 Demographics of the participants of the survey

Question		**Response**	
		Percentage (%)	**Total (n)**
28. What is your gender? (N=8)	Male	50.00	4
	Female	37.50	3
	I prefer not to answer	12.50	1
	Not answered	NA	5
29. What is your age category? (N=8)	<30 years old	0	0
	30-39 years old	50.00	4
	40-49 years old	25.00	2
	50-59 years old	12.50	1
	≥60 years old	12.50	1
	Not answered	NA	5

Table 5 Demographics of the participants of the survey

Question		Response	
		Percentage (%)	Total (n)
30. For how many years have you been in medical practice? (N=8)	Less than 3 years	0	0
	3 to 5 years	0	0
	6 to 10 years	25.00	2
	11 to 15 years	25.00	2
	More than 15 years	50.00	4
	Not answered	NA	5
31. How would you classify your primary medical specialty? (N=8)	Dermatology	0	0
	Ear, nose & throat (ENT)	0	0
	Paediatrics	0	0
	Allergology	0	0
	Internal medicine	0	0
	Clinical immunology	100.00	8
	Other (please specify)	0	0
	Not answered	NA	5
32. For how many years have you been working in this field of medicine? (N=8)	Less than 3 years	12.50	1
	3 to 5 years	25.00	2
	6 to 10 years	12.50	1
	11 to 15 years	25.00	2
	More than 15 years	25.00	2
	Not answered	NA	5
33. In which setting do you spend most of your time when practicing? (N=8)	Specialised medical centre	25.00	2
	Academic teaching hospital	62.50	5
	General community hospital	0	0
	Private practice	12.50	1
	Not answered	NA	5

NA=not applicable.

11.3 Outcome data Survey

Not applicable

11.4 Main results Survey

11.4.1 Physician's prescription history of Ruconest

Not all questions were answered by all participants. Out of 8 responders, 5 prescribed Ruconest both for HCPs and for self-administration (Table 6). Out of 7 responders, 4 prescribed Ruconest to be administered by HCPs to 1-2 patients, and 1 each to 3-5, 6-10, and 11-20 patients. For Ruconest self-administration, 2 HCPs prescribed this to 1-2 patients, 3 to 3-5 patients, and 1 to 6-10 patients.

Table 6 Survey results for prescribing history

Question		Response	
		Percentage (%)	Total (n)
1. Which form of Ruconest did you prescribe last 12 months? (N=8)	Ruconest (to be administered by a healthcare professional)	25.00	2
	Ruconest kit for self-administration	12.50	1
	Both the above Ruconest products	62.50	5
	Not answered	NA	5
2a. When was the last time you prescribed Ruconest to be administered by an HCP (N=7)	Less than 1 month ago	28.57	2
	Between 1 month and less than 3 months ago	57.14	4
	Between 3 months and less than 6 months ago	0	0
	More than 6 months ago	14.29	1
	Not answered	NA	6
2b. Number of individual patients you prescribed Ruconest to be administered by an HCP (N=7)	1-2	57.14	4
	3-5	14.29	1
	6-10	14.29	1
	11-20	14.29	1
	Over 20	0	0
	Not answered	NA	6
3a. When was the last time you prescribed Ruconest kit for self-administration (N=6)	Less than 1 month ago	33.33	2
	Between 1 month and less than 3 months ago	66.67	4
	Between 3 months and less than 6 months ago	0	0
	More than 6 months ago	0	0
	Not answered	NA	7
3b. Number of individual patients you prescribed Ruconest kit for self-administration (N=6)	1-2	33.33	2
	3-5	50.00	3
	6-10	16.67	1
	11-20	0	0
	Over 20	0	0
	Not answered	NA	7

HCP=healthcare professional, NA=not applicable.

11.4.2 Physician's awareness and use of existing educational materials

Table 7 presents the results for questions related to physician's awareness and use of educational materials. Only 3 out of 8 responders knew that Ruconest is to be stored not above 25°C. Seven out of 8 knew the color and clarity of Ruconest, and that foam should be minimized was known to 6 out of 8 responders. That each vial of Ruconest (2100 U) should be reconstituted with 14 ml water for injections was known by 7 out of 8 responders. Most responders knew why you shouldn't shake when dissolving the powder during preparation (7 out of 8), that 2 powder vials

are required for a patient weighing 70 kg (6 out of 8) and that 21 ml is the appropriate volume for a patient weighing 63 kg (6 out of 8).

All physicians (n=8) correctly assessed that patients need to be instructed to mark the batch number on the patient diary, and most (87.5%) also for the expiry date and the date and time of treatment. However, also 87.5% assessed, incorrectly, that patients need to be instructed to mark the expiry date on the patient diary.

The results of questions 13 and 20 are not presented in Table 7 but in text:

Based on the responder's own experience for prescribing Ruconest, all (n=8) responded they understood the dosing scheme, that 2 vials are needed if body weight is more than 42 kg, that for dosing a certain volume is needed depending on the patient's body weight, and a second dose can be administered within 24 hours if the first dose had no effect (question 13a). Based on the feedback the responders received from patients on the patients' experience, all (n=7) responded they understood the dosing scheme, that 2 vials are needed if body weight is more than 42 kg, that for dosing a certain volume is needed depending on the patient's body weight, and a second dose can be administered within 24 hours if the first dose had no effect (question 13b).

To the question (question 20) 'to which extent you read the educational materials', all (n=6) read the SmPC, most (4 of 6) read the immunological assessment guide and the checklist for the HCP, and half (3 of 6) read the checklist for patients, the patient card and the patient diary.

Table 7 Survey results related to awareness and use of existing educational materials

Question		Response	
		Percentage (%)	Total (n)
4. At which temperature should Ruconest powder vials be stored? (N=8)	Below minus 18°C	0	0
	Between 2 and 8°C	37.50	3
	Not above 25°C	37.50	3
	At room temperature	25.00	2
	Not answered	NA	5
6. Which colour and clarity should the prepared Ruconest solution have before use? (N=8)	White and milky/cloudy	0	0
	Colourless and clear	87.50	7
	Colourless to slightly blue and clear	0	0
	Yellow, but clear	12.50	1
	Not answered	NA	5

Table 7 Survey results related to awareness and use of existing educational materials

Question		Response	
		Percentage (%)	Total (n)
7. During the preparation of the Ruconest solution, which statement is correct relating to foam? (N=8)	Shake the prepared solution as much as possible until sufficient foam is visible	0	0
	Try to transfer sufficient foam into the syringe	12.50	1
	Foam in the prepared solution shows that the product is overlay	12.50	1
	Whilst foaming does not impact the quality and safety of the product, avoid foam being transferred into the syringe	75.00	6
	Not answered	NA	5
8. How many milliliters of water for injection should be drawn up in the syringe to prepare the solution of one vial? (N=8)	10 ml	0	0
	14 ml	87.50	7
	21 ml	12.50	1
	28 ml	0	0
	Not answered	NA	5
9. Why shouldn't you shake when dissolving the powder during preparation of the solution? (N=8)	To minimise foaming	87.50	7
	To avoid particles entering the solution	0	0
	To minimise discolouration	12.50	1
	To avoid the solution becoming too viscous	0	0
	Not answered	NA	5
10. How many powder vials are required for a patient weighing 70 kg? (N=8)	1 vial	12.50	1
	2 vials	75.00	6
	3 vials	0	0
	4 vials	12.50	1
	Not answered	NA	5
11. What is the appropriate volume of prepared Ruconest solution for a patient weighing 63 kg? (N=8)	11 ml	0	0
	14 ml	12.50	1
	19 ml	0	0
	21 ml	75.00	6
	25 ml	12.50	1
	Not answered	NA	5

Table 7 Survey results related to awareness and use of existing educational materials

Question		Response	
		Percentage (%)	Total (n)
14. Patients need to be instructed to mark the following items on the patient diary when using Ruconest kit for self-administration: Please tick all items that apply. More than one correct answer may have to be selected!. (N=8)	Colour of the prepared solution	25.00	2
	Batch number	100.00	8
	Any person close to the patient during administration	0	0
	Expiry date of Ruconest	87.50	7
	Date and time of treatment	87.50	7
	Not answered	NA	5
19. Prior to today, were you aware of the educational materials for Ruconest? (N=8)	Yes	75.00	6
	No	25.00	2
	Not answered	NA	5

HCP=healthcare professional, NA=not applicable.
The results of questions 13 and 20 are not presented in this table but in text in this section.

11.4.3 Physician's understanding of possible risks and key safety information, including required actions, as provided in the educational materials

That Ruconest is contraindicated in case of an allergy to rabbits was known to all responders (n=8), also that it is derived from milk from rabbits (Table 8). All responders (n=8) also knew they had to closely monitor the patient for symptoms of hypersensitivity after treatment with Ruconest. Finally, all responders (n=8) were aware it is the responsibility of the prescribing physician to verify that the patient/caregiver is capable of safe and effective self-administration of Ruconest. The awareness for seeking immediate medical attention when using Ruconest for self-administration was not optimal in the 8 responders to this question.

Table 8 Survey results related to understanding of possible risks and key safety information

Question		Response	
		Percentage (%)	Total (n)
5. In which case is Ruconest contraindicated? (N=8)	Allergy to rats	0	0
	Allergy to cow's milk	0	0
	Allergy to grass pollen	0	0
	Allergy to rabbits	100.00	8
	Not answered	NA	5
12 After treatment with Ruconest, patients must be closely monitored and carefully observed for any symptoms of … ? (N=8)	Arrhythmia	0	0
	Hallucination	0	0
	Hypersensitivity	100.00	0
	Heart failure	0	0
	Not answered	NA	5

Table 8 Survey results related to understanding of possible risks and key safety information

Question		Response	
		Percentage (%)	Total (n)
15. Ruconest is a recombinant form of human C1 esterase inhibitor. It is derived from the milk from:	Cows	0	0
	Rabbits	100.00	8
	Goats	0	0
	Humans	0	0
	Not answered	NA	5
16. It is the responsibility of the ..... to verify that the patient/caregiver is capable of safe and effective self-administration of Ruconest. (N=8)	Patient / caregiver	0	0
	Prescribing physician	100.00	8
	Not answered	NA	5
17. When using Ruconest for self-administration immediate medical attention should be sought in case of: Please tick all items that apply (N=8)	An acute laryngeal HAE attack	62.50	5
	Lack of efficacy	25.00	2
	Failure to gain arterial access	25.00	2
	A facial HAE attack	25.00	2
	Hypersensitivity after administration of Ruconest	87.50	7
	Not answered	NA	5

HAE=hereditary angioedema, NA=not applicable.

11.4.4 Physicians' opinion on the quality and clarity of the educational materials

All responders (n=6) provided patients with the patient diary, the majority provided the patient card and half of them provided the patient checklist (Table 9). One responder did not see the added value of the patient card for patients.

The results of questions 24 and 25 are not presented in Table 9 but in text:

When asked to describe their use of the educational materials when prescribing Ruconest for self-administration, the responses (n=6) were diverse (Question 24). Half of the responders never used the patient card and also half frequently used the checklist for patients, other responses were given by 1 or 2 responders only.

All (n=6) responders thought the educational materials helpful to prepare the Ruconest solution, for administration of Ruconest by both HCP or for self-administration (Question 25). Most (66.7%) also found them useful to address side effects and only 50.0% considered them helpful to distinguish hypersensitivity reactions from those of an HAE attack in patients.

Table 9 Survey results related to physician's opinion on the quality and clarity of the educational materials

Question		Response	
		Percentage (%)	Total (n)
21. Do you provide your patients with the patient card when prescribing Ruconest / Ruconest kit for self-administration? (N=6)	Yes, to all patients, and I strongly recommend using it	50.00	3
	Yes, to all patients, but I leave it up to the patient whether or not to use it	16.67	1
	Yes, to some of the patients	0	0
	Yes	0	0
	No	16.67	1
	No, I don't see the added value of the patient card for patients	16.67	1
	Not answered	NA	7
22. Do you provide your patients with the patient checklist when prescribing Ruconest kit for self-administration? (N=6)	I have not yet prescribed Ruconest kit for self-administration	33.33	2
	Yes, to all patients	33.33	2
	Yes, to some of the patients	16.67	1
	No	16.67	1
	No, because when I prescribe Ruconest to patients, no further checking is required	0	0
	Not answered	NA	7
23. Do you provide your patients with the patient diary when prescribing Ruconest? (N=6)	Yes, only when prescribing Ruconest (to be administered by an HCP)	50.00	3
	Yes, only when prescribing Ruconest kit for self-administration	0	0
	Yes, when prescribing both the above Ruconest products	50.00	3
	No	0	0
	Not answered	NA	7

HCP=healthcare professional, NA=not applicable.
The results of questions 24 and 25 are not presented in this table but in text in this section.

11.4.5 Query whether the physician assesses that patients are capable of preparing and administrating Ruconest themselves, recognising hypersensitivity reactions, how to distinguish them from HAE attack, and know what to do and whom to contact

The responders to Question 18 all (n=8, 100.0%) knew to ask the patient/caregiver the following question before prescribing Ruconest: "Upon contact with rabbits, did you get allergic symptoms such as itching, rash or breathing difficulties?" Most responders (87.5%) knew this for "Have you been in contact with rabbits in the past?" Also most responders (87.5%) knew that these questions did not have to be asked for cats. That they are supposed to ask whether the patient/caregiver has relatives with an allergy to rabbits was only known by 37.5% of responders.

Of the 8 responders, 6 (75.0%) knew that they did not have to ask patients/caregiver whether they are allergic for cow's milk.

The second part of Question 18 was related to what needs to be checked with the patient/caregiver prior to prescribing Ruconest for self-administration; all (n=8) knew to check whether the patient understood each step and was cognitively and physically able to use Ruconest themselves. Most responders (62.5%) incorrectly checked whether the patient /caregiver had experience with subcutaneous infections.

11.4.6 Query for feedback from patients regarding quality and clarity of the information presented in the patient card, diary and checklist as received from the physician

Half of the responders received feedback from patients/caregivers on the educational materials (Table 10). All (n=3) responders received feedback from their patients that the educational materials were helpful.

Table 10 Survey results related to whether the physician assesses that patients are capable and well informed to use the product

Question			Response	
			Percentage (%)	Total (n)
26. Did you receive any feedback from patients on the educational materials for patients?	Yes		50.00	3
	No		50.00	3
	Not answered		NA	7
27. Based on feedback you have received from patients, please indicate below how helpful the following materials are for your patients, in general, when prescribing Ruconest kit for self-administration. Please complete each item.	Patient card	Yes	100.0	3
	Checklist for patients	Yes	100.0	3
	Patient diary	yes	100.0	3
	Not answered		NA	10

NA=not applicable.

11.5 Other analyses

Not applicable.

11.6 Adverse events/adverse reactions from other sources

A secondary study objective of this study was 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 PASS study C1 1412).

The questionnaire did not collect adverse events. Any observed side effect was to be addressed within the European registry for Ruconest (PASS study C1 1412), Section 11.6.1, and reported via the national reporting system, Section 11.6.2.

11.6.1 PASS study C1 1412

The aim of the Ruconest Registry reported as PASS Study C1 1412 was to assess the safety and the immunological profile of Ruconest or pdC1INH in the treatment of acute attacks of HAE, in an observational setting. Treatment with C1 inhibitor products (either Ruconest or pdC1INH [e.g., Berinert and Cinryze]) or other approved treatment (e.g. Firazyr]) was to be performed in accordance with medical practice at the full discretion of the treating physician and in accordance with the prescribing information for the registered products. The objectives were:

- To observe the adverse event (AE) profile and insufficient efficacy, following single and repeated treatment with Ruconest or pdC1INH of acute angioedema attacks.
- To assess the immunological profile of Ruconest, in particular in relation to:
  - type I hypersensitivity
  - type III hypersensitivity
  - development of neutralizing antibodies against C1 inhibitor

A total of 70 patients received Ruconest only with a mean (standard deviation [SD]) duration in the study of 947.8 (743.3) days, and 27 patients received mixed treatments with a mean (SD) duration in the study of 1846.0 (1268.8) days. In addition, 8 patients received pdC1INH only and 10 patients received Firazyr only. These results are not discussed here.

In total, 17 patients treated with Ruconest only, reported insufficient efficacy after at least one treatment administration. Two adolescent patients (1 who received Ruconest only and 1 who received mixed treatments) reported insufficient efficacy after at least one treatment administration.

Treatment response was defined post-hoc if a patient reported improvement within 4 hours after treatment. In the subset of the adult patients who administered Ruconest at least once, the response rate was high (>95%) for all treatment locations. Response rate was consistent across different attack locations, with continued efficacy of repeated treatments with Ruconest for subsequent acute angioedema attacks. The 2 adolescent patients also mainly showed treatment response (>77%).

Fourteen patients treated with Ruconest only reported 32 AEs and 7 patients treated with mixed treatments reported 14 AEs.

In the adults safety analysis set, 2 patients who received Ruconest only treatment died during the Registry (PTs; Death [caused by SARS-CoV-2 infection] and Laryngeal oedema). A total of 7 non-fatal serious AEs (SAEs) (Breast cancer [2 SAEs in 1 patient], Hospitalisation: [3 SAEs in 2 patients], Pyelonephritis acute, and Vestibular disorder) occurred in 5 patients (3 Ruconest and 2 on mixed treatment). None of the deaths or SAEs were considered as related to the treatment.

No AEs of special interest including hypersensitivity reactions and thrombotic/thrombo-embolic events, or AEs related to self-administration of Ruconest, were reported during the Registry study. None of the patients that self-administered Ruconest reported any medication errors or AEs related to the self-administration.

Three patients that participated in the Registry study were exposed to Ruconest during pregnancy. The outcomes of all three pregnancies were full-term live births (two vaginal deliveries, and one cesarian section). There were no reported complications before, during or after any of the deliveries.

Overall, the safety evaluation of this registry did not reveal any potential new safety signal or additional risks and confirmed the favorable safety profile of Ruconest, and data are consistent with the results seen in several clinical studies with different subject populations.

11.6.2 Adverse events from periodic safety update report

A secondary study objective of this study was to evaluate whether the reporting rate of hypersensitivity events after administration of Ruconest would change (based on data from routine pharmacovigilance reporting).

The cumulative line listings of AEs pertaining to hypersensitivity with Ruconest (post-marketing and clinical trials), with a data lock point of the latest PSUR#23 (28-Oct-2025), showed that cumulatively 734 cases were reported containing 841 events pertaining to the standardised MedDRA query (SMQ) Hypersensitivity. Based on the total of 10919 events reported for Ruconest (until data lock point of 28-Oct-2025), the cumulative reporting rate for Hypersensitivity AEs was 7.7%.

More specifically, the post-marketing events for European countries (including the UK, for data up to and including 2020):

- Cumulatively in Europe, 422 adverse events were reported for Ruconest, of which 267 events were reported up to and including 2020 and 155 events as of 2021.
- Cumulatively in Europe, 19 events pertaining to the Hypersensitivity (SMQ) were reported, of which 18 events were reported up to and including 2020 and only 1 event as of 2021.
- This results in a hypersensitivity reporting rate of 18/267=6.7% up to and including 2020 and a hypersensitivity reporting rate of 1/155=0.6% as of 2021.

However, these data cannot result in a conclusion since:

- The cumulative number of reported hypersensitivity events in Europe is very low.
- In Europe, the sales of Ruconest decreased in the consecutive years, which could have impacted the number of reported adverse events (including hypersensitivity events).
- It is unclear if the decrease in reporting rate of hypersensitivity events was influenced by the RMMs.

12 DISCUSSION

12.1 Key results

In total 13 HCPs completed the survey, all from the UK. Not all questions were answered by all participants; all questions were answered by not more than 8 participants. All 8 had their primary medical specialty in clinical immunology, with a various duration of experience but 4 participants had over 10 years of experience. Five out of 8 participants were working in an academic teaching hospital. Out of 8 responders, 5 prescribed Ruconest both to be administered by an HCP and for self-administration. Out of 7 responders, 4 prescribed Ruconest to be administered by HCPs to 1-2 patients, and 1 each to 3-5, 6-10, and 11-20 patients. For Ruconest self-administration, 2 HCPs prescribed this to 1-2 patients, 3 to 3-5 patients, and 1 to 6-10 patients.

That Ruconest is contraindicated in case of an allergy to rabbits was known to all responders, also that it is derived from milk from rabbits. All responders also knew they had to closely monitor the patient for symptoms of hypersensitivity after treatment with Ruconest. All responders were aware it is the responsibility of the prescribing physician to verify that the patient/caregiver is capable of safe and effective self-administration of Ruconest. The awareness for seeking immediate medical attention when using Ruconest for self-administration was not optimal.

All responders had read the SmPC, most read the immunological assessment guide and the checklist for the HCP, and half read the checklist for patients, the patient card and the patient diary. All responders provided patients with the patient diary, the majority provided the patient card and half of them provided the patient checklist. One responder did not see the added value of the patient card for patients.

When asked to describe their use of the educational materials when prescribing Ruconest for self-administration, half of the responders never used the patient card and also half frequently used the checklist for patients, other responses were given by 1 or 2 responders only.

All responders thought the educational materials were helpful to prepare the Ruconest solution, for administration of Ruconest by either HCP or for self-administration. Most also found them useful to address side effects and only half of responders considered them helpful to distinguish hypersensitivity reactions from those of an HAE attack in patients.

Most responders and their patients knew how to reconstitute and dose of Ruconest.

All responders knew to check whether the patient understood each step and was cognitively and physically able to use Ruconest themselves.

Half of the responders received feedback from patients/caregivers on the educational materials, but when received, the feedback was that the educational materials were helpful.

The safety evaluation of the registry (PASS STUDY C1 1412) did not reveal any potential new safety signal or additional risks and confirmed the favorable safety profile of Ruconest, and data are consistent with the results seen in several clinical studies with different subject populations. No hypersensitivity reactions were reported in the EU (C1 1412) registry study.

Cumulatively in Europe, 19 hypersensitivity events were reported based on the MAH pharmacovigilance system, of which 18 events were reported up to and including 2020 and only 1 event as of 2021.

12.2 Limitations

A limited number of physicians responded, 13 in total, and all from 1 country; no questions were answered by more than 8 physicians. There was no obvious grouping of questions related to the objectives.

This survey did not collect safety data, safety data is available from registry report and MAH pharmacovigilance system, which makes it difficult to compare these sources of data.

The data from the MAH pharmacovigilance system should be interpreted with care because the numbers are very low. Due to the fact that clinical studies (2) and post-approval marketing experience (6) have shown only eight cases of immune disorders, subdivided in one anaphylactic reaction and seven (drug) hypersensitivity reactions, demonstrating effectiveness of educational material as measured by a further reduction of hypersensitivity cases seemed challenging.

12.3 Interpretation

The small number of participating HCPs were generally aware of the need to take a careful history of rabbit allergy, the need to monitor for hypersensitivity reactions, and to verify whether the safety messages were understood by the patient and HCP, and what actions need to be taken when hypersensitivity reactions occur.

The patient/prescriber checklists and patient diary were used by the participants 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, but not always provided to the patient.

Overall, the educational materials were generally well used and perceived as useful, and the main safety messages were understood.

Based on the low numbers of responders and of the available safety information, no conclusions can be drawn from the impact of the educational materials on the safety of using Ruconest in relation to hypersensitivity.

12.4 Generalisability

The small number of responders were all from one country, and had the same medical specialty, but with various duration of experience, working in various settings, and with various experience with prescribing Ruconest to be administered by an HCP or for self-administration.

13 OTHER INFORMATION

Not applicable.

14 CONCLUSION

In general, the educational materials were used and perceived as useful, and the main safety messages were understood.

The small number of participating HCPs were generally aware of the need to take a careful history of rabbit allergy, the need to monitor for hypersensitivity reactions, and to verify whether the safety messages were understood by the patient and HCP, and what actions need to be taken when hypersensitivity reactions occur.

The patient/prescriber checklists and patient diary were used by the participants 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, but not always provided to the patient.

Based on the low numbers of responders and of the available safety information, no conclusions can be drawn from the impact of the educational materials on the safety of using Ruconest in relation to hypersensitivity.

15 REFERENCES

Agyemang E, Bailey L, Talbot J. Additional risk minimisation measures for medicinal products in the European Union: a review of the implementation and effectiveness of measures in the United Kingdom by one marketing authorisation holder. Pharm Med. 2017;31:101-112. doi 10.1007/s40290-017-0184-8

Guideline on good pharmacovigilance practices (GVP). Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2). 31 March 2017.

APPENDICES

Annex 1 List of stand-alone documents

Number	Document reference number	Date	Title
1	PHARMEUaRMM01	20 Mar 2018	Protocol PHARMEUaRMM01 v1.0 20180320
2	PHARMEUaRMM01-Q1	 03 Jul 2018 03 Jul 2025	Questionnaires PHARMEUaRMM01 v1.0 20180703 PHARMEUaRMM01 v2.0 adapted_03Jul2025
3	PHARMEUaRMM01-Results	11 Feb 2025	2025.2.11 download of Results Summary
4	C1 1412	24 Mar 2025	Ruconest Registry Report. C1 inhibitor Treatment Registry to assess the Safety and Immunological Profile of Ruconest in the treatment of HAE Attacks.
5	Study Report - Usability test and readability focus test of the Instructions for use of Ruconest 2100 U powder and and solvent for solution for injection, self-administration kit	4 Dec 2015	Report of usability test and readability focus test of the instructions for use of Ruconest 2100 U powder and solvent for solution for injection, self-administration kit, version 1.1 and dated 4 December 2015.

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