STUDY INFORMATION

Title	Additional risk minimisation measures for Ruconest - European survey of educational materials for Ruconest
Protocol ID	PHARM/EU/aRMM/01
Version	Version 1.0
Date of last version of protocol	20 March 2018
EU PAS register number	-
Active substance	Conestat alfa (Pharmacotherapeutic group: Other haematological agents, drugs used in hereditary angioedema, ATC code: B06AC04)
Medicinal products	Ruconest 2100 U powder for solution for injection (vial only) Ruconest 2100 U powder and solvent for solution for injection (self-administration kit)
Product number (MA EU number)	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	Not applicable
Research question and objectives	The objective of this study is to evaluate the effectiveness of the risk minimisation materials for Ruconest distributed to treatment centres/prescribing physicians.
Country(-ies) of study	EU countries where Ruconest self-administration kit is launched
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APPROVALS	NAME	SIGNATURE	DATE
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LIST OF ABBREVIATIONS

AE	adverse event
aRMM	additional Risk Minimisation Measures
CRO	contract research organisation
EMA	European Medicines Agency
EC	European Commission
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERB	ethical review board
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
PL	Package Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PV	pharmacovigilance
QA	Quality Assurance
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
U	unit(s)

1. TITLE

Additional risk minimisation measures for Ruconest - European survey of educational materials for Ruconest

PHARM_EU_aRMM01, version 1.0, 20 March 2018 (PRAC approved 14 June 2018)

2. MARKETING AUTHORISATION HOLDER

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3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title
Additional risk minimisation measures for Ruconest - European survey of educational materials for Ruconest

Rationale and background
The European Medicines Agency (EMA) has requested Pharming Group N.V. to provide all Healthcare Professionals (HCPs) who are expected to prescribe Ruconest with an educational materials pack. The initial educational materials were updated following two regulatory procedures (II/0032: removal of routine IgE testing and X/0034: line extension of Ruconest self-administration) The MAH was requested to study the effectiveness of these educational materials. As part of this effectiveness evaluation, 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.

Research question and objectives
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 PAS study C1 1412).

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.

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 on 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 hereditary angioedema (HAE) at least once during the 12 preceding months will be eligible for participation.

Variables
Physician characteristics will be collected (e.g. demographics, specialty, country, years in practice, number of HAE patients treated). The questionnaire will evaluate the awareness, knowledge, and adherence to the educational materials. Summary tables will include descriptive statistics; no formal hypothesis testing will be conducted.

Data sources
Completed questionnaires from an online survey among prescribing physicians. Adverse events from routine pharmacovigilance reporting and European registry study (PAS study C1 1412).

Study size
At least 20 completed questionnaires from prescribing physicians from at least 4 countries will be included in the survey.

Data analysis
Data analyses will be descriptive and will entail tabular displays of mean values and the frequency distribution of item responses. Results will be analysed on an item-by-item or variable-by-variable basis. No formal hypothesis testing will be conducted.

Milestones
The following milestones are identified:
- Launch of the self-administration kit for Ruconest
- Start distribution questionnaires
- Start data collection
- End data collection
- Final study report

5. AMENDMENTS AND UPDATES

Not applicable.

6. MILESTONES

The milestones are related to the launch of the kit (Ruconest 2100 U powder and solvent for solution for injection). Countries planned to be included are Germany, France, United Kingdom, and the Netherlands (see Annex 1 for an overview on the current marketing authorisation status and planned launch dates for both market presentations).

To ensure that the study is representative of routine established practice, sufficient time is 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 questionnaires will be distributed to health care professionals one year after distribution of the educational materials (version including the kit) in countries where the kit has been launched. Distribution of the questionnaires is directly followed by start of data collection (see Table 1).

Table 1. Study milestones

Milestone(s)	Planned date	Actual date
Launch of the Ruconest self-administration kit	*July 2017**	July 2017
Start distribution of questionnaires	*July 2018**	-
Start of data collection	*July 2018**	-
End of data collection	*July 2020*	-
Final study report	*January 2021*	-

*Note: * (planned) date is for first country only; please refer to Annex 1 for additional countries.*

Study progress will be reported in Periodic Safety Update Reports (PSURs) and updates of the Risk Management Plan (RMP), if applicable. The end of data collection is planned for 2 years after launch in the first country. In case the number of completed surveys is less than 20, the protocol will be amended to extend the study or the methodology will be changed. The final study report will be available six months after the end of data collection.

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.

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 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[1] (self-administration kit) was completed in 2015. 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 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[2], both for the materials intended for the HCP as well as the materials for the patient (see also Annex 2). 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 is set-up in which HCPs are encouraged to enter patients (PAS study C1 1412[3]).

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 will also query prescribing physicians on feedback received from their patients (see Questions 25 and 26 in Annex 5). 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 will be made available to all identified potential new physicians at the treatment centres. All educational materials will be available for re-ordering directly via the MAH or its local representatives. In some countries the educational materials will be 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[4]. 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 are:

- 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 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 PAS study C1 1412).

The effectiveness measurement consists of process and outcome indicators[5]. The following process indicators are 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 are 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 administrating 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 are related to the hypersensitivity, reconstitution of the product and the immunological assessment document for HCPs and patient card, are applicable for both Ruconest presentations. Questions on how to instruct patients and usefulness of the checklists and the patient diary are specifically related to the self-administration kit.

Additionally, the respondents will be 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. The questionnaire is provided in Annex 5.

9. RESEARCH METHODS

9.1. Study design

The survey will be distributed in each EU market where Ruconest for self-administration is launched. After EMA approval of the line extension, the updated educational materials as listed in Annex 2 were submitted to the NCAs for review. Following national approval, the updated educational materials are/will be distributed. Twelve months later, all prescribing physicians who received these updated educational materials will be invited to participate in an online survey. If there will be an update of the educational materials while the survey is ongoing an additional question on which version is used of the educational materials will be added. For now, all countries will start with the same educational materials version at launch of the Ruconest self-administration kit.

The survey could already have started for the educational material's version as approved after the update in 2016 when the requirement to test for the presence of IgE antibodies against rabbit epithelium (dander) prior to initiation of Ruconest was deleted (see Annex 2). However, the MAH would like to receive combined responses to the full set of educational materials, including the additional materials for the self-administration kit, as the versions are not separate entities but intertwined. The MAH considers that distribution of a single survey covering both presentations would be most efficient and benefit the response rate, as this would reduce the burden and possibly also the willingness to participate for HCPs.

The comprehensibility, knowledge, usefulness and usage of the educational materials will be 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 (PAS study C1 1412) will be evaluated. Given the relative limited number of completed questionnaires to be expected and the low AE reporting rate for Ruconest, this evaluation will be executed in a qualitative fashion. If the AE reporting rate is increased, such that a quantitative evaluation of important safety findings can be performed, the study protocol will be amended prior to evaluation of the study results.

9.2. Setting

The CRO, PAINT-Consult, will send an invitation to participate in the survey to the HCPs who received the educational materials. The invitation will contain a link to access the questionnaire via a secure website. The survey has been designed to take no more than 30 minutes. The response rates will be monitored to keep track of the number of completed questionnaires. A reminder notice will be sent by the CRO if participants have not responded within 2 weeks after the first invitation, followed by a second reminder if required.

Participating HCPs will have the option of receiving compensation for their time and effort. The amount varies by country and is determined by national laws and reimbursement policies. NCAs as well other regulatory bodies will be notified, if required by national law.

A certain period is required for NCA approval of the educational materials and subsequent actual distribution of the self-administration kit upon approval. Similarly, it will take time for physicians to treat a sufficient number of patients and gain experience in prescribing patients with Ruconest for self-administration and receive feedback from patients. Therefore, the questionnaire will be distributed one year after launch of the self-administration kit.

Furthermore, the frequency of HAE attacks varies between patients (ranging from one attack per year, up to more than once-weekly attacks) and physicians are known to see the patients generally once or twice a year. In one survey, 5% of patients reported 1 attack per year, 43% between 2 and 6 attacks, and 52% 7 or more attacks per year[6].

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

9.3. Variables

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

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

Participating physicians first need to provide their consent to participate in the survey, in line with the General Data Protection Regulation (GDPR). If he/she does not agree, the survey will end. Following agreement, the questionnaire continues with a screening module to confirm eligibility (see Annex 5). Depending on the response, participation could either be terminated or continued. The following physician's characteristics will be collected: demographics, specialty, country, years in practice, number of HAE patients treated.

The key messages tested in the questionnaire apply to side effects (particularly hypersensitivity / allergic reactions), preparation of the Ruconest solution and self-administration of Ruconest. Additional questions explore 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 is the proportion of physicians that correctly respond to individual items of the questionnaire. The proportion responding correctly will be tabulated separately for each item. Physician's demographic information will be collected in order to further characterise the respondent population. This will include country, type of medical practice, and (range of) number of HAE patients treated.

The questionnaire will not collect adverse events. Any observed side effect can be addressed within the European registry for Ruconest (PAS study C1 1412) and should be reported via the national reporting system. Further effectiveness evaluation of the risk minimisation materials will be 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) cannot be considered in this study protocol.

9.4. Data sources

The primary data source will consist of the completed questionnaires that are filled in by the HCPs (online surveys). Other data sources include the company's ADR safety database and data from the European registry study (PAS study C1 1412) for the evaluation of adverse

events related to hypersensitivity reactions and other immunogenic/allergy related adverse events.

The MAH will provide the CRO with a list of all potential prescribers who have received the (updated) educational materials. The CRO will be responsible for survey distribution, data collection and data analysis. The survey will be an internet-based questionnaire that is accessible through a secure website. Each physician is requested to fill out only one questionnaire. The purpose of the study and the procedures are explained via a separate letter (see Annex 4). The MAH's medical affairs representatives will contact the site/HCP during the survey period to check whether there are any barriers to complete the survey. Only completed questionnaires from physicians who have prescribed Ruconest (either vial only or self-administration kit) at least once in the last 12 months will be evaluated.

9.5. Study size

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

As all (potential) prescribing physicians will 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. This is significantly higher than the response rate achieved in comparable studies, such as the 3.4 % in Agyemang et al.[5] and 3.6 % response rate found in the study of Ishihara et al.[7]

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 will be challenging. Efforts to maximise recruitment will be considered throughout the study by specifically contacting possible prescribers. Since all possible prescribers will have received the educational materials, this is not expected to bias the study outcome. If uptake into the survey is less than anticipated the protocol may be amended either by extending the study or changing the methodology.

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

9.6. Data management

The questionnaire will be completed online and data will be stored on a secure server. Every effort will be made to protect participant confidentiality.

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

The CRO will provide quarterly feedback to the MAH on the number of completed questionnaires. A status update will be provided within RMP and PSUR updates, as applicable. All data in the study updates and the final report will be provided to the MAH in such a way that the possibility of tracing the identity of the physician is impossible.

9.7. Data analysis

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

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

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

The results from the questionnaire will be 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 (PAS study C1 1412). Hypersensitivity reactions or other immunogenic/allergy related adverse events will be separately discussed and evaluated in the final report of this survey. This will include the evaluation of the concerned reported adverse reactions resulting from post-marketing reporting (pharmacovigilance data obtained from PSUR). If the numbers of events are sufficient, a further breakdown including their frequencies and occurrences per EU country will 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 (PAS study C1 1412) will be included in this evaluation. Adverse events will be 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 will be 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 is 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[1], subdivided in one anaphylactic reaction and seven (drug) hypersensitivity reactions, demonstrating effectiveness of educational material as measured by a further reduction of hypersensitivity cases seems challenging.

9.8. 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, have been assessed by the MAH during previous projects and are further assured via the research contract.

[1] Up to data lock point of 28 October 207, as included in the most recent PSUR.

9.9. Limitations of the research methods

One limitation is the limited number of physicians that can be included in this study. The target patient population is small (prevalence approximately 1:50,000) and within this small population Ruconest has a limited market share in most of the European countries. Moreover, Ruconest is prescribed exclusively by a very small, specialized group of experts operating in specialised medical care centres. The educational materials are distributed to all prescribing physicians that are working in the specialized care centres for patients with HAE. To increase the number of respondents, all treating physicians who received the educational materials will be sent a request to participate in the survey. The request for participation in the survey will be sent one year after the distribution of the educational materials (and launch of the kit). This increases the possibility that the HCP will prescribe Ruconest, and thereby making them more prone to participate in the survey.

Another factor that can influence the outcomes of the study is that physicians involved might not adequately complete the questionnaire and may 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 will be anonymised to Pharming Group N.V. and questions are 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 questionnaire.

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

The rationale for including only HCPs and not patients, is 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 expects patients to play an active role, by reading the patient materials (patient checklist and package leaflet as provided by the HCP), keeping their patient cards with them all the time, and filling in the patient diary. In case the HCP considers that the patient is not suitable for self-administration, or if a patient does 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 will be incorporated in the survey and thus be 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 will 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 will be 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 is not the main objective of the study.

The educational materials are 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 will differ. The items that will be questioned regarding safety information and instruction for the kit will be similar in each country.

10. PROTECTION OF HUMAN SUBJECTS

The legislation on data protection will be followed in accordance with Directive 95/46/EC of the European Parliament and of the Council for the Protection of Individuals with regard to the processing of personal data and on the free movement of such data.

This study will be conducted in accordance with applicable laws and regulations of the countries where the study is being conducted, as appropriate. After approval by the Pharmacovigilance Risk Assessment Committee (PRAC) the protocol will be submitted to ethical review boards (ERB) for approval whenever required by local law or to confirm that the study is considered non-interventional in that country. NCAs will be notified and approval sought as required by local laws and regulations. Progress reports will be submitted to ERBs and NCAs as required by local laws and regulations.

The MAH and CRO will ensure that all study information is handled and stored to allow for accurate reporting, interpretation and verification of that information, and that every effort will be made to protect the confidentiality of the participating physicians and any patient identifiers contained in returned information. Data collection will be performed by PAINT-Consult, on behalf of the MAH. PAINT-Consult will only include anonymised data in progress reports, study reports or any communication to the MAH or third parties. In the event the data returned contain an identifiable AE or product complaint, authorisation from the participating physician will be sought by PAINT-Consult prior to disclosing participant identifiers to the MAH.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The reporting of adverse events is not expected or requested during the survey. There are no free text fields into which the physician could enter AE information. Nevertheless, text will be included in the questionnaire and invitation to remind physicians to report any suspected AEs to the MAH and/or via the applicable national reporting systems. It is the physician's responsibility to report any serious adverse events related to Ruconest to the respective marketing authorization holder and/or to the regulatory authorities as per local regulatory requirements.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The CRO will provide quarterly status updates to the MAH about the number of completed questionnaires. Status updates will be included in routine PSURs and updates of the RMP. At the end of the study, the CRO will provide a study report that will be reviewed by the MAH. This report will contain a description of the objectives of the study, the methodology, the results and the conclusions of the study. The completed questionnaires and the study report must be treated as the confidential property of Pharming Group N.V. and may not be released to unauthorised people in any form (publications or presentations) without express written approval from the MAH. The final study report will be submitted to the EMA.

13. REFERENCES

1 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.

2 Ruconest: EPAR - Product Information. Current version available on http://www.ema.europa.eu.

3 C1 1412 - C1 inhibitor Treatment Registry to assess the Safety and Immunological Profile of Ruconest in the treatment of HAE Attacks - Ruconest registry (EU PAS Register Number: EUPAS7375).

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

5 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.

6 Riedl M., Gower R.G., Chrvala C.A. Current medical management of hereditary angioedema: results from a large survey of US physicians. Ann Allergy Asthma Immunol. 2011; 106(4):316-322.

7 Ishihara L., Lewis A., Kolli S., Brickel N. European survey of prescriber understanding of risk associated with retigabine. Drugs - Real World Outcomes. 2015; 2:345–353.

ANNEXES – List of stand-alone documents

Number	Document title
Annex 1	Marketing authorisation status
Annex 2	Overview of educational materials for Ruconest
Annex 3	ENCePP checklist for study protocols
Annex 4	Healthcare professional introduction to the Ruconest questionnaire
Annex 5	Questionnaire

ANNEX 1 – Marketing authorisation status

Pharming Group N.V. received the initial marketing authorisation for Ruconest 2100 U (EU/1/10/641/001) on 28 October 2010. This presentation (powder for solution for injection) is approved for administration by physicians and is launched in many EU countries (see table below). On 11 January 2017 the marketing authorization for the extension was approved for self-administration (Ruconest 2100 U powder and solvent for solution for injection, (EU/1/10/641/002). The first launch for this line extension was in July 2017.

The table below shows the actual and planned launch dates for both Ruconest presentations.

RUCONEST® (conestat alfa) marketing authorisation status in the European Union

Country	**Launch date** *powder for solution for injection* (EU/1/10/641/001)	**Launch date** *powder and solvent for solution for injection* (EU/1/10/641/002)
Austria	May 2011	Not planned
Belgium	Named patient basis only	Not planned
Bulgaria	May 2013	Not planned
Croatia	Nov 2014	Not planned
Cyprus	Not planned	Not planned
Czech Republic	Dec 2011	Not planned
Denmark	Dec 2010	Not planned
Estonia	Named patient basis only	Not planned
Finland	Dec 2012	Not planned
France	Apr 2012	Planned: 2018
Germany	Dec 2010	July 2017
Greece	Not planned	Not planned
Hungary	Jan 2014	Not planned
Iceland	Sep 2015	Not planned
Ireland	Not planned	Not planned
Italy	May 2012 (one region)	Not planned
Latvia	Named patient basis only	Not planned
Liechtenstein	Not planned	Not planned
Lithuania	Named patient basis only	Not planned
Luxembourg	Named patient basis only	Not planned
Malta	Not planned	Not planned
Netherlands	Aug 2011	Oct 2017
Norway	Jan 2011	Not planned
Poland	Apr 2013	Not planned
Portugal	Not planned	Not planned
Romania	Jul 2011	Not planned
Slovakia	Dec 2011	Not planned
Slovenia	Jun 2013	Not planned
Spain	Not planned	Not planned
Sweden	Oct 2011	Not planned

Country	**Launch date** *powder for solution for injection* (EU/1/10/641/001)	**Launch date** *powder and solvent for solution for injection* (EU/1/10/641/002)
United Kingdom	Dec 2010	Planned: 2018

Note: status of 15 March 2018.

ANNEX 2 – Overview of educational materials for Ruconest

Background

The European Commission (EC) granted a marketing authorisation valid throughout the European Union for Ruconest on 28 October 2010. After national approval of the first set of educational materials, consisting of an immunological assessment document and patient card, these were distributed in the countries where Ruconest (powder for solution for injection) was launched.

Following procedure II/32 the requirement for testing all new patients for IgE antibodies against rabbit epithelium (dander) prior to initiation of treatment and the requirement for repeat testing of IgE antibodies to rabbit dander were removed. The immunological assessment document and patient card were updated accordingly. A positive CHMP Opinion was received on 25 February 2016, followed by the EC decision on 31 March 2016.

On 11 January 2016 the MAH submitted a line extension application to the EMA. This covered a new presentation of Ruconest, powder and solvent for solution for injection, to enable administration of the drug at home (EMEA/H/C/001223/X/0034). The educational materials were extended specifically for the kit with checklists for the healthcare professional and patient, and a patient diary. A positive CHMP Opinion was received on 10 November 2016, followed by the EC decision on 11 January 2017.

In addition, the Product Information (SmPC and Annex II) and the RMP including the immunological assessment document within the educational materials were updated following the review of the PSUR from 2016 (EMEA/H/C/PSUSA/00000873/201610). A positive CHMP Opinion was received on 22 June 2017. This update to the immunological assessment document included the addition of one sentence. For most countries this is combined with the update of the educational pack following the line extension.

Product Information for Ruconest

The updated Annex II of the SmPC (Annex II D. Conditions or restrictions with regard to the safe and effective use of the medicinal product) contains the following condition:

- Additional Risk Minimization Measures

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

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

The educational pack should contain the following:

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

Overview of approved educational materials for Ruconest

Title	Version number	Date
Immunological assessments	V07.0	May 2017
Patient card	V03.0	February 2016
Healthcare professional educational material/checklist	V02.0	October 2016
Patient educational material/checklist	V03.0	November 2016
Patient diary	V01.0	March 2017

Note: based on RMP V18.0, dated 1 February 2018.

Each set of educational materials is translated into the local language and has been or will be submitted for approval by the National Competent Authority before launch of the self-administration kit.

Some countries only approved the initial version (version 1) and some countries only approved the IgE version (version 2). The national approval process for version 3, including the documents for the self-administration kit and changes after PSUSA/2016, is ongoing. The nationally approved educational materials will be distributed prior to launch of the self-administration kit (dependent on completion of the reimbursement process). An up-to-date list of launch and distribution status of the educational materials will be present in the study file. Progress and an overview of the countries included in the study will be reported in the PSUR and/or RMPs.

ANNEX 3 - ENCePP checklist for study protocols

Based on Revision 3 - Adopted by the ENCePP Steering Group on 01/07/2016

Study title:
Additional risk minimisation measures for Ruconest - European survey of educational materials for Ruconest

Study reference number:
PHARM/EU/aRMM/01

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[2]	☒	☐	☐	
1.1.2 End of data collection[3]	☒	☐	☐	
1.1.3 Study progress report(s)	☒	☐	☐	
1.1.4 Interim progress report(s)	☒	☐	☐	
1.1.5 Registration in the EU PAS register	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	

[2] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[3] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☐	☐	☒	
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☐	☐	☒	
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	
4.2.2 Age and sex?	☐	☐	☒	
4.2.3 Country of origin?	☒	☐	☐	
4.2.4 Disease/indication?	☒	☐	☐	
4.2.5 Duration of follow-up?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:	☐	☐	☒	
7.2.1. Selection biases (e.g. healthy user bias)	☐	☐	☒	
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☐	☐	☒	
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	
9.1.3 Covariates?	☐	☐	☒	
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	
10.2 Are descriptive analyses included?	☒	☐	☐	
10.3 Are stratified analyses included?	☐	☐	☒	
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.6 Is sample size and/or statistical power estimated?	☐	☒	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	
11.2 Are methods of quality assurance described?	☒	☐	☐	
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	☒	
12.1.2 Information bias?	☐	☐	☒	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	
15.2 Are plans described for disseminating study results externally, including publication?	☐	☐	☒	

Comments:

As this protocol is considered a non-imposed non-interventional study, the protocol will not be published in the EU PAS register.

Name of the main author of the protocol: Sanne van der Donk, PhD

Date: 20/Mar/2018

Signature: _____

ANNEX 4 – Healthcare professional introduction to the Ruconest questionnaire

Version 1.0 (English), March 2018

Introduction
Pharming Group N.V., the marketing authorisation holder of Ruconest (conestat alfa) is surveying healthcare professionals to assess awareness of safety issues and instructions for use for Ruconest reflected in recent label changes and updates of educational materials. This survey is part of an effort by the European Medicines Agency (EMA) and Pharming Group N.V. to evaluate the effectiveness of the revised educational materials, including information on how and who uses them in practice, whether the safety messages are understood by the patient and HCPs and whether clinical knowledge/attitudes/behaviour have changed as a result. The questionnaire will take about 30 minutes to complete.

Disclaimer
This research is sponsored by a pharmaceutical company, Pharming Group N.V. The aim of this research is to assess knowledge about the prescribing information for Ruconest. Taking part in this survey is voluntary. You may refuse to participate in the survey.

How we will use the information
The answers of the survey will be transferred from Pharming to the CRO. The CRO is responsible for the survey distribution and the collection and analysis of the data. Your answers to the questionnaire will be combined with those from other respondents. The results will include anonymized information only and will be transferred to Pharming and the EMA.

Honorarium
As appreciation for the time and effort you dedicated to complete the questionnaire you will be compensated with *[to be adapted to the specialty and country].* You may also choose not to accept the monetary compensation.

Privacy
The survey will be conducted in an anonymous way. The information collected will remain absolutely confidential and will only be used for the purposes of this survey. The results obtained will be presented in aggregated form to the MAH and regulatory agencies, mainly the EMA. No connections will be made between your identity and your answers to the survey.

Additional information
If you have experience any problems with the questionnaire, please contact *[to be completed after online survey has been created]*. For questions related to the content or background of the survey, please contact PAINT-Consult at info@paint-consult.com. In case you wish to contact Pharming Group N.V. directly, please do so at medicalinformation@pharming.com.

Reporting of adverse reactions
To allow continued monitoring of the benefit/risk balance of Ruconest, you are asked to report any suspected adverse reaction via the national reporting system or to Pharming Group N.V. directly via safety@pharming.com.

ANNEX 5 - Questionnaire

Version 1.0 (English), March 2018
The questionnaire will be made available in the local language upon approval by PRAC/EMA.

European survey of educational materials for Ruconest - Questionnaire

Dear Physician,

The European Medicines Agency (EMA) requested Pharming Group N.V. (Darwinweg 24, 2333 CR Leiden, the Netherlands), the Marketing Authorisation Holder (MAH) of Ruconest (conestat alfa), to evaluate prescriber's awareness and understanding of the additional risk minimisation measures (educational materials) for Ruconest in the European Union. This survey is being sent to all physicians treating patients with hereditary angioedema (HAE) across countries within the European Union, who have received the (updated) educational materials for Ruconest. Since you have received the educational materials for Ruconest, you have been identified as a potential participant in this survey. The information will be processed and reported anonymously and will only be used for the purposes of this survey. The results obtained will be presented to the MAH and regulatory agencies in an aggregated form. We kindly ask you to fill in the questionnaire regarding your experience and understanding of the educational materials for Ruconest. The survey will take approximately 30 minutes to complete for which you will be offered financial compensation (please refer to the introduction letter for more information).

<< START SURVEY >>
<< POP-UP SCREEN >> *This screen will contain text in line with the General Data Protection Regulation (GDPR) that will be valid as from 25 May 2018. This will include the collection of the consent of the physician involving the collection, storage, use and processing of personal data of the physician and information on data protection rights.*

The first questions are intended to assess your eligibility for participation.

<< BEGIN ELIGIBILITY QUESTIONS >>

a. Please indicate the country where you practice medicine within the European Union

<< DROP-DOWN BOX WITH EU COUNTRIES WHERE KIT HAS BEEN LAUNCHED >>

b. Have you prescribed Ruconest at least once within the last 12 months?
☐yes
☐no << TERMINATE >>
☐I don't remember << TERMINATE >>

Terminate message:
'Thank you for your interest in participating in this survey. As this survey is targeted at physicians who have recent experience with Ruconest, unfortunately you cannot proceed with the survey.
Kind regards,
Pharming Group N.V. and PAINT-Consult'

c. Are you liaised to Pharming Group N.V. or a regulatory body (e.g. the European Medicines Agency or a national regulatory agency)?
☐yes << TERMINATE >>
☐no

Terminate message:
'Thank you for your interest in participating in this survey, unfortunately you cannot proceed with the survey due to possible conflicts of interest.

Kind regards,
Pharming Group N.V. and PAINT-Consult'

d. Do you agree to take part in this survey on Ruconest?
☐yes
☐no << TERMINATE >>
Terminate message:
'Thank you for your time.
Kind regards,
Pharming Group N.V. and PAINT-Consult'

<< END ELIGIBILITY QUESTIONS >>

Introduction
Thank you for agreeing to participate in this study.
As appreciation for the time and effort you will dedicate to completion of the questionnaire you will be compensated with *[to be adapted to the specialty and country]*. Please provide your account details at the end of the survey. You may also choose not to accept the monetary compensation.

☐Please tick this box if you do not want to be paid.

We ask you to complete this survey in one session. Please note that you will not be able to go back to previous questions once you have provided a response. *<< To be confirmed with IT expert if practically feasible. If not feasible, this should be removed from the protocol. >>*

If you experience any problems with the questionnaire, please contact *[to be completed after online survey has been created]*. For questions related to the content or background of the survey, please contact PAINT-Consult at info@paint-consult.com. In case you wish to contact Pharming Group N.V. directly, please do so at medicalinformation@pharming.com.

[Note: Correct responses are highlighted in green]

Main questions
The next set of questions are related to Ruconest prescription and administration and the educational materials for Ruconest. Please tick one box, unless otherwise indicated.

1. Which form of Ruconest did you prescribe in the last 12 months?
☐Ruconest *(to be administered by a healthcare professional)*
☐Ruconest for home use *(kit for self-administration)*
☐both the above Ruconest products

2. When was the last time you prescribed Ruconest?
- Ruconest **to be administered by a healthcare professional**

☐I did not yet prescribe this Ruconest presentation
☐less than 1 month ago
☐between 1 month and less than 3 months ago
☐between 3 months and less than 6 months ago

☐more than 6 months ago

Tick the total number of individual patients you prescribed Ruconest *(to be administered by a healthcare professional):*

☐1-2, ☐3-5, ☐6-10, ☐11-20, ☐over 20

- Ruconest **kit for self-administration at home**

☐I did not yet prescribe this Ruconest presentation

☐less than 1 month ago

☐between 1 month and less than 3 months ago

☐between 3 months and less than 6 months ago

☐6 months ago or more

Tick the total number of individual patients you prescribed Ruconest *(kit for self-administration)*:

☐1-2, ☐3-5, ☐6-10, ☐11-20, ☐over 20

3. At which temperature should powder vials of Ruconest be stored?

☐below minus 18 °C

☐between 2 and 8 °C

☐not above 25 °C

☐at room temperature

4. In which case is Ruconest contraindicated?

☐allergy to rats

☐allergy to cow's milk

☐allergy to grass pollen

☐allergy to rabbits

5. Which colour and clarity should the prepared Ruconest solution have before use?

☐white and milky/cloudy

☐colourless and clear

☐colourless to slightly blue and clear

☐yellow, but clear

6. During preparation of Ruconest solution, what is correct relating to foam?

☐shake the prepared solution as much as possible until sufficient foam is visible

☐try to transfer sufficient foam into the syringe

☐foam in the prepared solution shows that the product is overlay

☐whilst foaming does not impact the quality and safety of the product, avoid foam being transferred into the syringe

7. How many millilitres of water for injection should be drawn up in the syringe to prepare the solution of one vial?

☐10 ml

☐14 ml

☐21 ml

☐28 ml

8. Why shouldn't you shake when dissolving the powder during preparation of the solution?

☐to minimise foaming

☐to avoid particles entering the solution
☐to minimise discolouration
☐to avoid the solution becoming too viscous

9. How many powder vials are required for a patient weighing 70 kg?
☐1 vial
☐2 vials
☐3 vials
☐4 vials

10. What is the appropriate volume of prepared Ruconest solution for a patient weighing 63 kg?
☐11 ml
☐14 ml
☐19 ml
☐21 ml
☐25 ml

11. After treatment with conestat alfa (Ruconest), patients must be closely monitored and carefully observed for any symptoms of … ?
Please select the correct answer.
☐arrhythmia
☐hallucination
☐hypersensitivity
☐heart failure

12. Based on your own experience for prescribing Ruconest, and/or feedback received from patients, please tick the options that best matches your experience.

Statement	**Physician's experience**		**Patient's feedback**	
	yes	**no**	**yes**	**no**
I understand the dosing scheme.	☐	☐	☐	☐
If the body weight is more than 42 kg I need to use 2 vials.	☐	☐	☐	☐
I know that I need to dose a certain volume (ml) depending on my body weight.	☐	☐	☐	☐
I know I can administer a second dose within 24 hours if the first dose shows no effect.	☐	☐	☐	☐

13. Patients need to be instructed to mark the following items on the patient diary when using Ruconest for self-administration:
Please tick all items that apply. More than one correct answer may have to be selected!
☐colour of the prepared solution
☐batch number
☐any persons close to the patient during administration
☐expiry date of Ruconest
☐date and time of treatment

14. Ruconest is a recombinant form of human C1 inhibitor. It is derived from the milk from:

Please select the correct answer.

☐cows

☐rabbits

☐goats

☐humans

15. It is the responsibility of the <…..> to verify that the patient/caregiver is capable of safe and effective self-administration of Ruconest at home.

Please select the single best answer for this statement.

☐patient/caregiver

☐prescribing physician

16. When using Ruconest for self-administration immediate medical attention should be sought in case of:

Please tick all items that apply.

☐an acute laryngeal HAE attack

☐lack of efficacy

☐failure to gain arterial access

☐a facial HAE attack

☐hypersensitivity after administration of Ruconest

17. Please mark all steps a patient/caregiver must be able to do before they can self-administer Ruconest?

Please complete each item.

Step to be taken	Correct	Incorrect	I don't know
Prior to prescribing Ruconest ask the patient the following questions:			
- Have you been in contact with rabbits in the past?	☐	☐	☐
- Have you been in contact with cats in the past?	☐	☐	☐
- Upon contact with rabbits, did you get allergic symptoms such as itching, rash or breathing difficulties?	☐	☐	☐
- Upon contact with cats, did you get allergic symptoms such as itching, rash or breathing difficulties?	☐	☐	☐
- Are you allergic for cow's milk?	☐	☐	☐
- Upon contact with rabbits, did you get allergic symptoms such as itching, rash or breathing difficulties?	☐	☐	☐
- Do you have any relatives with an allergy to rabbits?	☐	☐	☐
Prior to prescribing Ruconest kit for self-administration, check if the patient/caregiver:			
- has experience with subcutaneous injection.	☐	☐	☐
- has an emergency kit at home if serious side effects occur.	☐	☐	☐
- understands each step in the instructions for use.	☐	☐	☐
- is cognitively and physically able to use Ruconest themselves.	☐	☐	☐

18. Prior to today, were you aware of the educational materials for Ruconest?

☐yes

☐no << GO TO QUESTION 28 >>

19. To which extent did you read the educational materials for Ruconest?
Please complete each item.

Item	**Read**			
	All of it	Some of it	None	I don't remember
Immunological assessment guide	☐	☐	☐	☐
Checklist for healthcare professional	☐	☐	☐	☐
Checklist for patients	☐	☐	☐	☐
Patient card	☐	☐	☐	☐
Patient diary	☐	☐	☐	☐
Summary of Product Characteristics	☐	☐	☐	☐

20. Do you provide your patients with the patient card when prescribing Ruconest / Ruconest kit for self-administration?
☐yes, to all patients, and I strongly recommend using it
☐yes, to all patients, but I leave it up to the patient whether or not to use it.
☐yes, to some of the patients
☐yes
☐no
☐no, I don't see the added value of the patient card for patients

21. Do you provide your patients with the patient checklist when prescribing Ruconest, kit for self-administration?
☐yes, all patients
☐yes, some of the patients
☐no
☐no, because when I prescribe Ruconest to patients, no further checking is required

22. Do you provide your patients with the patient diary when prescribing Ruconest?
☐yes, only when prescribing Ruconest *(to be administered by a healthcare professional)*
☐yes, only when prescribing Ruconest *(kit for self-administration)*
☐no

23. What best describes your use of the educational materials, provided to physicians when prescribing Ruconest/ Ruconest for self-administration?
Please complete each item.

Educational material / tool	I use these materials			
	never	sometimes	frequently	always
Immunological assessments	☐	☐	☐	☐
Patient card	☐	☐	☐	☐
Healthcare professional educational material/checklist	☐	☐	☐	☐

Patient educational material/checklist	☐	☐	☐	☐
Patient diary	☐	☐	☐	☐
Summary of Product Characteristics	☐	☐	☐	☐

24. Were the educational materials for Ruconest helpful for the following aspects?
Please complete each item.

Aspect	**The educational material is effective/helpful in preventing or recognising safety events or taking the right steps**				
	yes	mostly yes	neither yes/no	mostly no	not at all
To address side effects; particularly hypersensitivity or other immunological reactions	☐	☐	☐	☐	☐
To distinguish hypersensitivity reactions from those of an HAE attack in patients	☐	☐	☐	☐	☐
To prepare the Ruconest solution	☐	☐	☐	☐	☐
For administration of Ruconest by a healthcare professional	☐	☐	☐	☐	☐
For self-administration of Ruconest by patient or caregiver at home	☐	☐	☐	☐	☐

25. Did you receive any feedback from patients on the educational materials for patients?
☐yes
☐no << GO TO QUESTION 28 >>

26. 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 for self-administration.
Please complete each item.

Educational material	**The educational material is effective/helpful**				
	yes	mostly yes	neither yes/no	mostly no	not at all
Ruconest patient card	☐	☐	☐	☐	☐
Patient checklist	☐	☐	☐	☐	☐
Patient diary	☐	☐	☐	☐	☐

Demographics and practice information

Finally, the European Medicines Agency requested Pharming to collect information about all HAE-treating physicians regarding demography, background, and medical practice. Answers to these questions will help

Pharming to improve educational materials and incorporate elements that are relevant for specific subsets of physicians (age, region, etc.) The information provided below will only be made available to the MAH in an anonymized and aggregated form.

Please tick the appropriate boxes.

27. What is your gender?
    ☐female
    ☐male
    ☐I prefer not to answer

28. What is your age category?
    ☐< 30 years old
    ☐30-39 years old
    ☐40-49 years old
    ☐50-59 years old
    ☐> 60 years old

29. For how many years have you been in medical practice?
    ☐less than 3 years
    ☐3 to 5 years
    ☐6 to 10 years
    ☐11 to 15 years
    ☐more than 15 years

30. How would you classify your primary medical specialty?
    ☐dermatology
    ☐ear, nose & throat (ENT)
    ☐paediatrics
    ☐allergology
    ☐internal medicine
    ☐clinical immunology
    ☐other - *Please specify* :.....

31. For how many years have you been working in this specific field of medicine?
    ☐less than 3 years
    ☐3 to 5 years
    ☐6 to 10 years
    ☐11 to 15 years
    ☐more than 15 years

32. In which setting do you spend most of your time when practising?
    ☐specialised centre
    ☐academic teaching hospital
    ☐general community hospital
    ☐private practice
    ☐other - *Please specify* :.....

This was the final question.
Thank you for your time and support!

The questionnaires will be evaluated by PAINT-Consult. PAINT-Consult will treat the content of the questionnaires as confidential and the results of the study will be reported in an anonymised manner.

Reporting of adverse reactions
To allow continued monitoring of the benefit/risk balance of Ruconest, you are asked to report any suspected adverse reactions via the national reporting system or to Pharming Group N.V.

Compensation
To provide you with a payment for your time and effort in completing this survey, please provide us with the following information.

Your account details:

Name: .....

Bank details:

IBAN number: .....

<<END>>

Concluding message:
'Thank you for your participation in this survey. We greatly appreciate your time and effort.
Kind regards,
Pharming Group N.V. and PAINT-Consult'