RUCONEST®

IMMUNOLOGICAL ASSESSMENTS

NON-PROMOTIONAL EDUCATIONAL MATERIALS FOR PRESCRIBERS

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Summary

RUCONEST® (conestat alfa), a recombinant human C1 esterase inhibitor (rhC1-INH), is derived from milk of transgenic rabbits expressing the gene encoding for human C1-INH. As with any intravenously administered protein product, hypersensitivity reactions cannot be excluded and a few precautions are required prior to initiating treatment of RUCONEST® or when allergic reactions or lack of clinical response is seen following treatment with RUCONEST®.

These precautions are the following:

i. Prior to initiating treatment with RUCONEST® the medical history of all patients must include the assessment whether the patient may have developed signs and symptoms of a suspected rabbit allergy. It is possible that a patient may not be able to recall an allergy from an earlier period in their lives or are unaware that they have an allergy to rabbit fur. The physician should ensure appropriate probing questions are asked to discover whether the patient may have a possible allergy to rabbit fur. Questions to be asked could include:

   a. Have you been in contact with rabbits in the past?
   b. Upon contact with rabbits, did you get itching, rash, sneezing, itchy and runny nose, red and itchy eyes, coughing, shortness of breath or wheezing, or did you feel unwell in any way?

   In case of an affirmative response to the second question, alternative therapies of non-rabbit origin should be considered.

ii. It is important that careful information on the symptoms of hypersensitivity or allergy is given to the patient by the treating physician, and to make sure the patient knows the importance to immediately alert their physician if these symptoms develop.

iii. The instruction to immediately report any allergic reaction to rabbits should be periodically repeated.

iv. When the patient is prescribed with RUCONEST®, he or she should be given the Package Leaflet.

In case serious hypersensitivity/immunological adverse reactions upon administration of RUCONEST® develop, physicians are strongly encouraged to report these via the national reporting system.

Please report suspected adverse drug reactions (ADRs) to the HPRA via:
HPRA Pharmacovigilance
Website: **www.hpra.ie**

Side effects may also be reported to **safety.ie@pharming.com**.

Introduction

The active substance in RUCONEST® is recombinant human C1 inhibitor (rhC1-INH) (conestat alfa). The amino acid sequence of the recombinant form is identical to that of endogenous human C1-INH. RUCONEST® is expressed in the rabbit mammary gland cells and purified from milk of transgenic rabbits expressing the gene encoding for C1-INH. Although the purification process has been designed to eliminate to the maximum extent possible Host Related Impurities (HRI) originating from the rabbit milk, RUCONEST® contains traces of rabbit protein.

Recombinant protein products such as RUCONEST® may elicit antibodies against the recombinant protein and its endogenous counterpart, as well as against Host Related Impurities (HRI).

As with any intravenously administered protein product, hypersensitivity reactions cannot be excluded. Prior to initiation of treatment with RUCONEST®, patients should be queried for a known or suspected rabbit allergy. If such is the case, alternative therapies of non-rabbit origin should be considered. Patients must be closely monitored and carefully observed for any symptoms of hypersensitivity throughout and directly following the administration period. In case of anaphylactic reactions or shock, emergency medical treatment should be administered.

RUCONEST® therapy should be initiated under the guidance and supervision of a physician experienced in the diagnosis and treatment of hereditary angioedema, and it should be administered by a healthcare professional.

The potential immunological reactions associated with RUCONEST® are discussed in three chapters:

1. Type I hypersensitivity (immediate or anaphylactic reactions),
2. Neutralizing antibodies (resulting in reduced efficacy),
3. Type III hypersensitivity (immune complex hypersensitivity).

Each of these chapters addresses:

- Mechanisms involved in these reactions,
- Facts and findings supporting the risk,
- Medical history / Tests which can be used to prevent such reaction, or tests available to investigate events suspected of having an immunological basis,
- Treatment implications.

1. TYPE I HYPERSENSITIVITY (immediate or anaphylactic reactions)

Mechanism:

Type I hypersensitivity may present as urticaria, conjunctivitis, rhinitis, dyspnoea and / or shock and is mediated by IgE antibodies. Type I hypersensitivity may be difficult to distinguish from angioedema due to HAE. IgE antibodies are induced by previous exposure to the same or similar antigens as those triggering the reaction. For example:

- Patients allergic to rabbits can have pre-existing IgE antibodies that may react to the traces of rabbit protein impurities in RUCONEST®.
- Although cross-reactivity between cow milk and rabbit milk is considered unlikely, the possibility of such a cross-reactivity in a patient who has evidence of clinical allergy to cow milk cannot be excluded and the patient should be observed for signs and symptoms of hypersensitivity following RUCONEST® administration.

Facts:

In the RUCONEST® clinical trial programme for HAE one healthy volunteer developed a type I hypersensitivity reaction following a first exposure to RUCONEST®. The subject had an undisclosed pre-existing allergy to rabbits. In the meantime more than 1500 doses have been administered to 268 subjects in clinical trials with RUCONEST® without any further reports of serious hypersensitivity/anaphylactic reactions.

Medical history:

Due to the risk of possible allergic reactions, RUCONEST® is contra-indicated in patients with a **known or suspected rabbit allergy**, therefore:

- Before initiating treatment with RUCONEST® the past medical and current medical history of all patients should be carefully assessed for a known or suspected rabbit allergy.

Treatment:

Patients treated with RUCONEST® should be monitored for clinical signs and symptoms of hypersensitivity during and directly following administration.

Emergency medical treatment should be available to be administered immediately in case of anaphylactic reactions or shock.

It is important to inform patients about the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis, and to instruct them that they should immediately alert their physician if any of these symptoms occur.

Patients should also be periodically instructed to report any allergic reaction to rabbits (e.g. annually).

It is also important to inform the patient about the difference between a hereditary angioedema attack and a hypersensitivity reaction.

In case a Type I hypersensitivity to RUCONEST® is suspected or if symptoms of allergy develop, the patient should stop treatments with RUCONEST®. Other treatment options of non-rabbit origin should be considered.

2. NEUTRALIZING ANTIBODIES (resulting in reduced efficacy)

Mechanism:

Formation of neutralizing antibodies against C1-INH could reduce the levels of functional C1-INH and result in reduced clinical response (see below for criteria which may trigger immunological testing). If antibodies were to bind to endogenous C1-INH, the clinical condition would be comparable to that of Acquired Angioedema (AAE), a rare condition typically caused by the presence of neutralizing antibodies to endogenous C1-INH, produced by a lymphoma or associated with an autoimmune disease.

Facts:

During the clinical trial programme, pre- and post-exposure plasma samples were collected. The presence of antibodies against C1-INH in the plasma samples was screened using 6 different Enzyme Linked Immuno Sorbent Assays (ELISAs), which detect IgM, IgG and IgA antibodies against pdC1-INH and against rhC1-INH (IgG results shown in figure below).

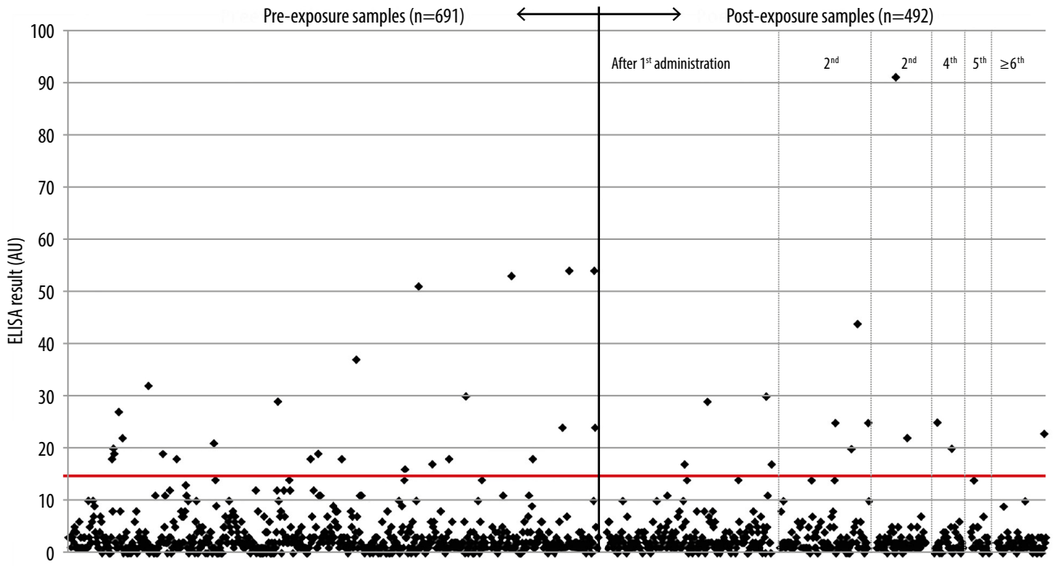


Figure shows IgG-specific anti-rhC1-INH antibody measurements in HAE patients before 1st rhC1-INH treatment and after rhC1-INH treatment. The horizontal red line represents the cut-off level of the ELISA. The last column is a compilation of all post-exposure samples from the subjects receiving a 6th administration up to 26th administrations.

Plasma samples with above cut-off level values were tested for neutralizing antibodies against C1-INH. The results are summarized as follows:

- No persistent antibody responses to pdC1-INH or rhC1-INH were observed.
- No neutralizing antibodies to C1-INH were found.

Tests:

Clinical suspicion of neutralizing antibodies can be triggered by reduced clinical response:

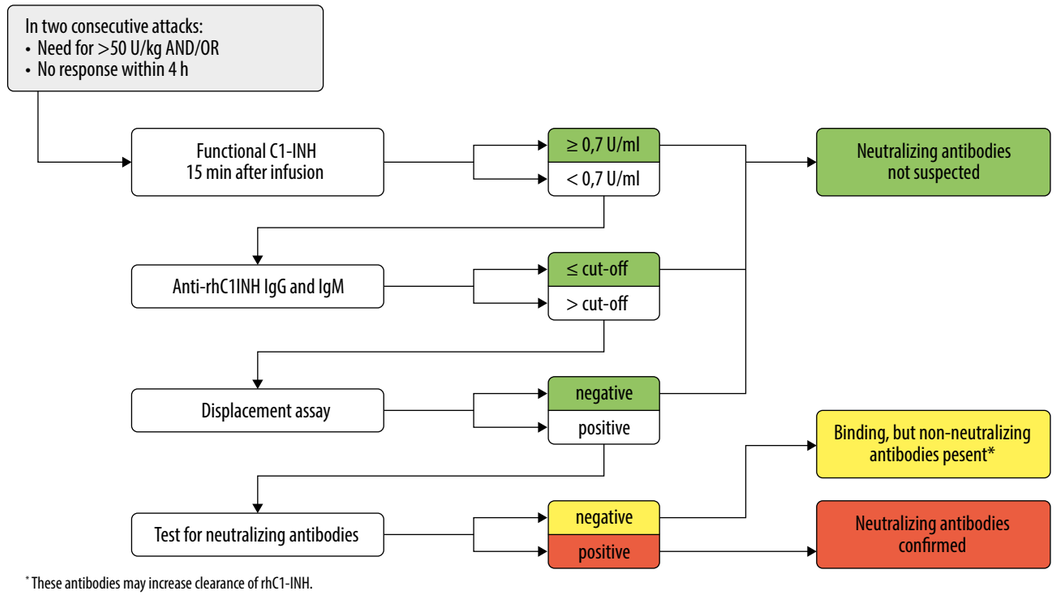
(a) In two consecutive acute angioedema attacks in any HAE patient who previously responded to treatment with 50 U/kg RUCONEST®, the requirement for two doses of RUCONEST® to treat the attack.

AND / OR

(b) In two consecutive acute angioedema attacks in an HAE patient who previously responded to treatment with 50 U/kg RUCONEST®, the failure to respond to RUCONEST® treatment within 4 hours despite adequate dosing of 50 U/kg.

As a first diagnostic step it is recommended to measure functional C1-INH activity 15 minutes after infusion of 50 U/kg dose of RUCONEST®. Concentrations of >0.7 U/ml exclude the presence of clinically significant neutralizing antibodies.

Pharming Technologies B.V. provides access to an immunological laboratory testing program for follow-up of the suspected emergence of neutralizing antibodies. The testing program should be considered for HAE patients who meet criteria (a) or (b) above, and who do not achieve functional C1-INH >0.7 U/ml 15 minutes after infusion of a 50 U/kg dose of RUCONEST® (see above):



* These antibodies may increase clearance of rhC1-INH.

A testing kit can be requested by e-mail to **medinfo.ie@pharming.com**.

Plasma sample collection and shipping procedures are detailed in APPENDIX A.

Samples will be tested according to the following algorithm:

- ELISA tests detect IgG and IgM antibodies against rhC1-INH. These tests are based on the binding of such antibodies to immobilized rhC1-INH.
- If either anti-rhC1-INH antibody test results in above cut-off level values, a confirmatory displacement test is performed to discriminate between specific and non-specific responses.
- If specific antibodies are confirmed, the ability of these antibodies to neutralize functional pdC1-INH is tested with a neutralizing antibody assay.

The complete testing strategy for suspected neutralizing antibodies is summarized in the schedule below.

Treatment:

The clinical picture and treatment options for patients with neutralizing antibodies would be similar to those in patients with Acquired Angioedema (AAE). Acute attacks of AAE generally require higher doses of C1-INH than attacks of HAE. C1-INH administration has been the treatment of choice in case of a life-threatening AAE attack. In addition to supportive therapy such as intubation in case of life-threatening attacks, treatment with icatibant can also be considered.

3. TYPE III HYPERSENSITIVITY (IMMUNE COMPLEX HYPERSENSITIVITY)

Mechanism:

Formation of antibodies against C1-INH or against Host Related Impurities (HRI) could result in type III hypersensitivity. The reaction mediated by immune complexes can be generalized or may involve individual organs (symptoms of "transfusion reaction" or "serum sickness").

Facts:

During the clinical trial programme, pre- and post-exposure plasma samples were collected. In addition to the screening for anti-C1-INH antibodies described above, an Enzyme Linked Immuno Sorbent Assay (ELISA) was used to detect the presence of IgM, IgG as well as IgA antibodies against HRIs (results shown in figure below).

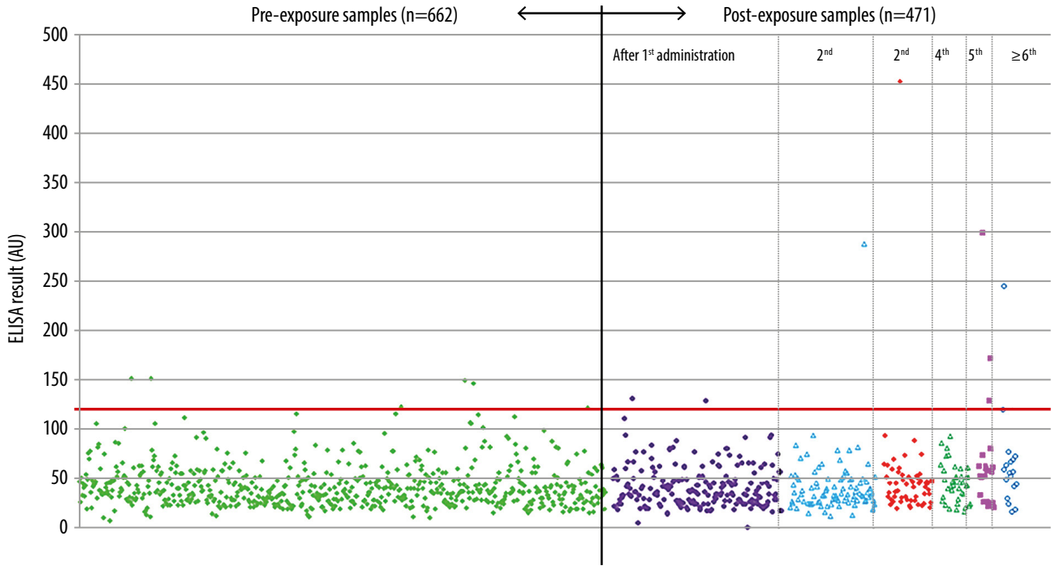


Figure shows the anti-HRI antibody assessment in symptomatic HAE patients after repeat treatment with rhC1-INH. The red line represents the cut-off level for the ELISA. The last column is a compilation of all post-exposure samples from the subjects receiving a 6th administration up to 26 administrations.

Plasma samples which tested positive on the screening ELISA were tested in a confirmatory displacement assay. The results are summarized as follows:

- No persistent antibody responses to C1-INH were observed.
- Anti-HRI antibodies above cut-off level were found in some patients but were not associated with clinical symptoms of an immunological reaction.

Tests:

Pharming Technologies B.V. provides access to an immunological laboratory testing program for the follow-up of suspected hypersensitivity reactions. The testing program should be considered for HAE patients who meet criteria (c) and/or (d) below

(c) Type III hypersensitivity reaction (skin, joints, or kidney symptoms) in the days or weeks following a RUCONEST® administration which after investigation of other causes cannot be fully explained by exposure and reaction to other antigens.

(d) Type III hypersensitivity reactions on two consecutive occasions in the days or weeks following administration of RUCONEST®.

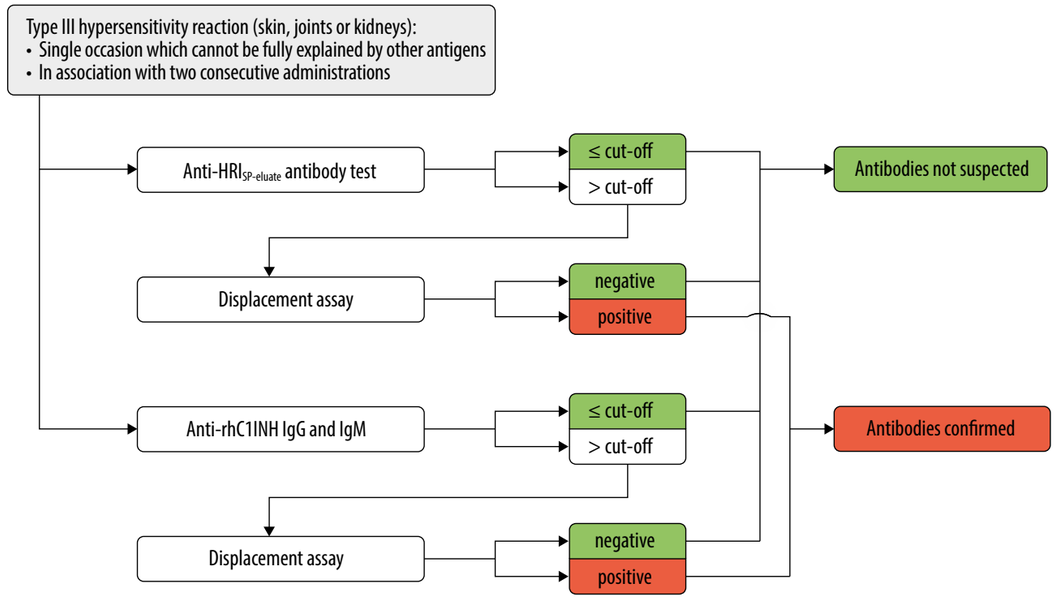
A testing kit can be requested by e-mail to **medinfo.ie@pharming.com**.

Plasma sample collection and shipping procedures are detailed in APPENDIX A.

Samples will be tested according to the following algorithm:

- ELISA tests detect IgG and IgM antibodies against rhC1-INH. These tests are based on the binding of such antibodies to immobilized rhC1-INH.
- If either of the anti-rhC1-INH antibody tests results in above cut-off level values, a confirmatory displacement test is performed to discriminate between specific and non-specific responses.
- Another ELISA detects the presence of total Ig against Host Related Impurities (HRI). This anti-HRISP-eluate ELISA measures the binding of antibodies to antigens obtained from the first purification step in the manufacturing process (SP-eluate). This assay is therefore highly specific and sensitive for HRIs in RUCONEST®.
- If above cut-off values are observed in the anti-HRISP-eluate test, a confirmatory displacement test is performed on the sample to discriminate between specific and non-specific responses.

The complete testing strategy for suspected type III hypersensitivity to RUCONEST® is summarized in the schedule below.



Treatment:

Positive results from the antibody testing should preclude further treatment with RUCONEST®. Acute symptomatic treatment of type III hypersensitivity includes anti-inflammatory agents.

APPENDIX A

EXAMPLE PLASMA SAMPLE COLLECTION AND SHIPPING PROCEDURES.

Upon request, for patients suspected to have developed neutralizing antibodies or type III hypersensitivity to RUCONEST® and meeting the criteria specified in the educational materials, a RUCONEST® Immunology assessment testing kit will be sent with following content:

- 8 labels
- 2 citrate tubes
- 4 cryovials
- Plasma sampling instructions (see below)
- Sample collection notification fax

PLASMA SAMPLE COLLECTION INSTRUCTIONS:

Prior to the blood sampling, please fill in the patient's details and date as requested on the label.

- Draw 4.5 mL of blood into a citrate tube using standard venipuncture techniques.
- Label the citrate tube with the patient's identification label in a horizontal way, not length wise.
- Centrifuge the sample to isolate the plasma from the red blood cells at 1000 x g (approximately 2000 rpm) for 10 – 15 minutes at room temperature.
- Label the cryovials with the patient's identification label in a horizontal way.
- Draw off the plasma (supernatant) and transfer 2 x 0.75 mL of the plasma to the labelled cryovials.
- Freeze and store the plasma samples (2 cryovials x 0.75 mL) upright at or below -70°C as soon as possible.
- Discard the remaining plasma according to standard local procedures.

SHIPPING PLASMA SAMPLES:

Please send the sample collection notification fax, and the courier will contact you to arrange pick-up of the samples.

NOTES