ANNEX

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the member states

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The Member States must ensure that all conditions or restrictions with regard to the safe and effective use of the medicinal product described below are implemented in their national territory:

- Prior to launch of the product in the Member State, the national competent authority shall agree the content and format of the educational material with the Marketing Authorisation Holder.

- The Marketing Authorisation Holder (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 physician.

- Copies of the patient card to be given to patients before they receive Ruconest

<u>The educational material for the prescriber should include information on the following key elements:</u>

- That Ruconest should be initiated under the guidance and supervision of a physician experienced in the diagnosis and treatment of hereditary angioedema and should be administered by a health care professional.

- That patients treated with Ruconest should be monitored for clinical signs and symptoms of hypersensitivity during administration. Emergency medical treatment should be available immediately to be administered in case of anaphylactic reactions or shock.

- The fact that Ruconest is derived from milk of transgenic rabbits and contains trace of rabbit proteins (Host Related Impurities, HRI).

- That Ruconest is contra indicated in all patients with known or suspected rabbit allergy or with positive serum IgE antibodies against rabbit dander due to the risk of major allergic reactions, therefore:

    - Before initiating treatment with Ruconest all patients should be tested for the presence of IgE antibodies against rabbit epithelium (dander). Only patients who have been shown to have negative test results should be treated with Ruconest. The patients should receive a patient card that documents the negative result.

    - IgE testing should be repeated once a year or after 10 treatments, whichever occurs first. In addition, IgE testing should be repeated if symptoms of rabbit allergy develop.

    - Information about the appropriate methodology to be used for laboratory testing of serum IgE antibodies against rabbit epithelium (dander)

- That patients with clinical evidence of cow's milk allergy may have antibodies cross reacting with the rabbit milk impurities in Ruconest.

- A protocol for performing a skin prick test (SPT) with Ruconest and an intravenous test dosing schedule in patients with a negative skin prick test, including criteria for interpreting results, for patients with clinical features of cow's milk allergy.

- The need to inform patients about the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis, and that they should alert their physician if these symptoms occur.

- The potential risk of an immune complex-mediated type III hypersensitivity reaction due to the formation of antibodies directed against Host Related Impurities (HRI). Advice about the immunogenicity laboratory testing program for detecting these antibodies for following up suspected immune complex-mediated disease, and about the procedure to follow for the collection and shipment of a blood sample to the company's central laboratory. This testing should be provided free of charge.

- The risk of formation of anti-C1INH antibodies and therefore the potential risk of formation of neutralising antibodies. Advice about the immunogenicity laboratory testing program for these antibodies provided by the company for following up suspected emergence of neutralising antibodies and information about the procedure to follow for the collection and shipment of a blood sample to the company's central laboratory. This testing should be provided free of charge.

<u>The patient card should contain the following key elements:</u>

- That they are receiving Ruconest for treatment of acute attack of hereditary angioedema

- That Ruconest is derived from milk of transgenic rabbits and contains trace of rabbit proteins

- That they have been tested negative for IgE anti rabbit (dander) within the last year.

    - The patient card should include an area where patients can record the results of their last IgE anti Rabbit (dander) and the date of the test

    - a reminder that IgE anti rabbit (dander) testing should be repeated once a year or after 10 treatments, whichever occurs first. In addition, IgE testing should be repeated if symptoms of rabbit allergy develop.

    - The patient card should include an area where patients can record the date and dose of every treatment by Ruconest (highlighting every tenth treatment)

- The importance of monitoring for clinical signs and symptoms of hypersensitivity and that patients should alert their doctor if they develop such symptoms during or after receiving Ruconest.

- That patients treated with Ruconest should be monitored for clinical signs and symptoms of hypersensitivity during administration. Emergency medical treatment should be available immediately to be administered in case of anaphylactic reactions or shock.

- That they should be asked to carry the card and always show it to any health care professional treating them for acute attacks of hereditary angioedema.