European Medicines Agency

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**QUESTIONS AND ANSWERS ON RECOMMENDATION FOR THE REFUSAL OF THE MARKETING AUTHORISATION**
**for**
**RHUCIN**

Common name: ***recombinant human C1 inhibitor***

On 13 December 2007, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Rhucin 150 U/ml powder for solution for injection, intended for the treatment of acute attacks of angioedema in patients with congenital C1 inhibitor activity deficiency. The company that applied for authorisation is Pharming Group N.V.

The applicant requested a re-examination of the opinion. After having considered the grounds for this request, the CHMP re-examined the initial opinion, and confirmed the refusal of the marketing authorisation on 19 March 2008.

**What is Rhucin?**
Rhucin is a powder to be made up into a solution for injection into a vein. It contains the active substance recombinant human C1 inhibitor.

**What was Rhucin expected to be used for?**
Rhucin was expected to be used to treat sudden attacks of angioedema (swelling of the blood vessels). It was to be used in patients who have low levels of a protein called 'C1 inhibitor' due to a congenital (inborn) deficiency.
Rhucin was designated as an orphan medicinal product on 11 May 2001 for treatment of angioedema caused by C1 inhibitor deficiency.

**How is Rhucin expected to work?**
The active substance in Rhucin, recombinant C1 inhibitor, is very similar to the natural blood protein 'C1 inhibitor'. C1 inhibitor is normally found in the blood, where it dampens down the activity of the 'complement system', which is part of the immune system (the body's natural defences). Patients with low levels of the active form of C1 inhibitor suffer from attacks of inflammation and swelling that affect various sites in the body. Rhucin was expected to be used as a replacement for the missing C1 inhibitor, correcting the deficiency and reducing the inflammation and swelling that cause angioedema.
The active substance in Rhucin is produced using 'recombinant DNA technology': it is extracted from the milk of rabbits that have had a gene (DNA) inserted, which makes them able to produce the human protein in their milk.

**What documentation did the company present to support its application to the CHMP?**
The effects of Rhucin were first tested in experimental models before being studied in humans. Rhucin was studied in two main studies involving a total of 48 adults with C1 inhibitor deficiency. In both studies, patients were given Rhucin if they had an attack of angioedema. In total, 17 attacks were treated in a total of 12 patients, but both studies were still ongoing at the time of the medicine's initial assessment. The main measure of effectiveness was how long it took for the patient's symptoms to improve. During the evaluation procedure, the company also supplied the initial results of a study

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comparing the effects of Rhucin with those of placebo (a dummy treatment). This included results from 25 patients.
The CHMP also took safety data into account from studies on healthy volunteers and from patients without symptoms who were treated with Rhucin.

**What were the major concerns that led the CHMP to recommend the refusal of the marketing authorisation?**
In December 2007, the CHMP was concerned that there was insufficient evidence to show the benefits and risks of Rhucin. In particular, the available studies were too small to show how effective Rhucin is in treating more severe forms of the disease, such as swelling in the larynx (voice box), or how safe and effective the medicine is when given to a patient more than once. There was also insufficient information over the likelihood of patients developing antibodies following repeated doses of Rhucin.
The Committee was also concerned over the possible presence of impurities in Rhucin, which could come from the rabbit milk from which the active substance is extracted and could affect the medicine's safety. The company had not demonstrated that the levels of the impurities or the antibodies could be measured in a reliable manner. In addition, there were concerns that the choice of the dose of Rhucin had not been sufficiently justified.
In March 2008, following the re-examination, the CHMP removed some of its major concerns, but remained concerned over the likelihood of the development of antibodies when Rhucin is given more than once, including its impact on safety and effectiveness. This included serious concerns over the risk of severe allergic reactions in patients receiving Rhucin.
Therefore, the CHMP was of the opinion that the benefits of Rhucin in the treatment of acute attacks of angioedema did not outweigh its risks. Hence, the CHMP recommended that Rhucin be refused marketing authorisation.

**What are the consequences of the refusal for patients in clinical trials or compassionate use programmes using Rhucin?**
The company informed the CHMP that there are no consequences for patients currently included in clinical trials or compassionate use programmes with Rhucin. If you are in a clinical trial or compassionate use programme and need more information about your treatment, contact the doctor who is giving it to you.