European Medicines Agency

London, 21 June 2007
Doc. Ref. EMEA/287136/2008

QUESTIONS AND ANSWERS ON THE WITHDRAWAL OF THE MARKETING APPLICATION
for
VORAXAZE

International non-proprietary name (INN): ***glucarpidase***

On 21 May 2007, Protherics PLC officially notified the Committee for Medicinal Products for Human Use (CHMP) that they wish to withdraw their application for a marketing authorisation for Voraxaze, for the adjunctive treatment of patients experiencing or at risk of methotrexate toxicity.

What is Voraxaze?
Voraxaze is a powder to be made up into a solution for injection. It contains the active substance glucarpidase.

What was Voraxaze expected to be used for?
Voraxaze was to be used as an add-on treatment in patients already receiving a medicine, methotrexate, to prevent or treat the toxic effects of methotrexate.
Methotrexate is used to treat a number of diseases, including some types of cancer. Some cancer patients receive high doses, and, because of this, can experience toxic effects, such as damage to the kidneys, bone marrow suppression (leading to anaemia, an increased risk of infection and bleeding) and mucositis (an inflammation of the mucosa, the lining of organs such as the mouth, with soreness, redness and ulceration). These toxic effects can be life-threatening. Another medicine, folinic acid, is often given after the methotrexate to help control the toxicities ('rescue' treatment) but these may still develop despite the rescue treatment.
Voraxaze would have been used either as a treatment in patients who had developed such toxic effects, or as prevention in patients who were at risk of developing them, such as patients who have high levels of methotrexate in their blood, or those who have poorly functioning kidneys (when methotrexate may be eliminated more slowly).
Voraxaze was to be given to adults or children as a single injection if the level of methotrexate in the patient's blood was above a given 'threshold' at certain times after administration of methotrexate.

Because the number of patients with this condition is low, it is considered 'rare', and glucarpidase was designated an 'orphan medicine' (a medicine used in rare diseases) on 3 February 2003.

How is Voraxaze expected to work?
The active substance in Voraxaze, glucarpidase, is a copy of the naturally-occurring enzyme carboxypeptidase G2. Carboxypeptidase G2 was originally found in a *Pseudomonas* bacterium. It can break down methotrexate into substances that do not have any toxic effects. This helps the body eliminate excess methotrexate, and therefore reduces the potential for toxic effects.
The glucarpidase in Voraxaze is made by a method known as 'recombinant DNA technology': it is made by a bacterium that has received a gene (DNA) that makes it able to produce it. The recombinant enzyme acts in the same way as the natural carboxypeptidase G2.

What documentation did the company present to support its application to the CHMP?
The effects of Voraxaze were first tested in experimental models before being studied in humans.

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The studies in human involved a total of 222 patients in two main studies. Voraxaze was not compared to another treatment. All patients received the medicine as part of a compassionate use programme: the doctor requested Voraxaze from the manufacturer as soon as they encountered a patient with methotrexate toxicities who could possibly benefit from the medicine. The main measure of effectiveness was the reduction in blood levels of methotrexate.

How far into the evaluation was the application when it was withdrawn?
The application was at day 180 when the company withdrew. After the CHMP had assessed the responses from the company to a list of questions, there were still some unresolved issues outstanding.

The CHMP normally takes up to 210 days to evaluate a new application. Based on the review of the initial documentation, the CHMP prepares a list of questions at day 120, which is sent to the company. Once the company has supplied responses to the questions, the CHMP reviews them and may, before giving an opinion, ask any remaining questions at day 180. Following the CHMP's opinion, it usually takes around two months for the European Commission to grant a licence.

What was the recommendation of the CHMP at that time?
Based on the review of the data and the company's response to the CHMP list of questions at the time of the withdrawal, the CHMP had some concerns and was of the provisional opinion that Voraxaze could not have been approved for the adjunctive treatment of patients experiencing or at risk of methotrexate toxicity.

What were the main concerns of the CHMP?
The main concerns of the CHMP were related to the manufacture of Voraxaze. The production of the medicine had moved from the factory that made the medicine used in the studies, to another factory that was to make the commercial product. The Committee had concerns that this move was not yet fully organised, especially with regards to the way the production would be controlled (validation), and that the consequences of the move on the product's purity were not been fully understood. The Committee also had some concern regarding the use of Voraxaze with folinic acid. Folinic acid can also be broken down in the body by Voraxaze, and further studies should be carried out to look at the consequences of this when managing patients with methotrexate toxicities.

What were the reasons given by the company to withdraw the application?
The letter from the company notifying the EMEA of the withdrawal of the application is available here.

What are the consequences of the withdrawal for patients undergoing clinical trials / compassionate use programmes with Voraxaze?
The company informed the CHMP that there are no consequences for patients currently included in the clinical trials of Voraxaze. The company also plans to continue their compassionate use programme. 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.