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Questions and answers

Withdrawal of the marketing authorisation application for Kalbitor (ecallantide)

On 11 November 2011, Dyax s.a. officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a marketing authorisation for Kalbitor, intended for the treatment of symptoms of acute attacks of hereditary angioedema.

What is Kalbitor?

Kalbitor is a medicine that contains the active substance ecallantide. It was to be available as a solution for injection.

What was Kalbitor expected to be used for?

Kalbitor was expected to be used to treat symptoms of attacks of hereditary angioedema. Patients with hereditary angioedema have attacks of swelling that can occur anywhere in the body, such as in the face, limbs, gut and throat, causing discomfort and pain and sometimes in the case of throat attacks difficulty in breathing.

Kalbitor was designated an 'orphan medicine' (a medicine to be used in rare diseases) on 18 December 2002 for the treatment of angioedema.

How is Kalbitor expected to work?

The active substance in Kalbitor, ecallantide, blocks an enzyme in the blood called 'kallikrein'.

Kallikrein is part of a complex network of proteins (known as the kallikrein-kinin system) that has several effects in the body, one of which results in increased levels of a protein called bradykinin that causes the blood vessels to widen and leak fluid into the surrounding tissue. This leakage of fluids

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causes the swelling attacks seen in angioedema. By blocking the actions of kallikrein, Kalbitor is expected to help reduce the swelling and related symptoms of angioedema.

The ecallantide in Kalbitor is produced by a method known as 'recombinant DNA technology'. This means that it is made by a cell that has received a gene (DNA), which makes the cell able to produce it.

What did the company present to support its application?

The effects of Kalbitor were first tested in experimental models before being studied in humans.

The company presented the results of two main studies in patients aged 10 years and above who had hereditary angioedema. There were 72 patients in one study and 96 in the other. The patients were treated with either Kalbitor or placebo (a dummy treatment) within 8 hours of having an attack. Those judged to be at risk of blockage of the airway were given additional treatments if required.

The main measure of effectiveness was based on the improvement in patients' symptoms after four hours. Other measures included the time that it took for the attack to resolve.

How far into the evaluation was the application when it was withdrawn?

The application was withdrawn after 'day 181'. This means that the CHMP had evaluated the documentation provided by the company and formulated lists of questions. After the CHMP had assessed the company's responses to the last round of questions in an oral explanation, there were still some unresolved issues.

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 lists of questions, at the time of the withdrawal, the CHMP had some concerns and was of the provisional opinion that Kalbitor could not have been approved.

The CHMP had concerns about hypersensitivity reactions, which were seen at a higher rate in patients treated with Kalbitor. Hypersensitivity reactions occur when the body's immune system reacts against a medicine, and include reactions commonly known as allergic reactions. The CHMP also had concerns related to the effectiveness of the proposed doses in heavier patients.

Therefore, at the time of the withdrawal, the CHMP was of the opinion that the benefits of Kalbitor did not outweigh its risks.

What were the reasons given by the company for withdrawing the application?

The letter from the company notifying the Agency of the withdrawal of the application is available.

What consequences does this withdrawal have for patients in clinical trials or compassionate use programmes?

The company has informed the CHMP that the withdrawal will not have any consequences for patients enrolled in any trials.

The summary of the opinion of the Committee for Orphan Medicinal Products for Kalbitor can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/Rare disease designation.