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Questions and answers

Refusal of the marketing authorisation for Defitelio (defibrotide)

On 21 March 2013, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Defitelio, intended for the treatment and prevention of hepatic veno-occlusive disease in blood stem cell transplantation therapy.

The company that applied for authorisation is Gentium S.p.A. It may request a re-examination of the opinion within 15 days of receipt of notification of this negative opinion.

What is Defitelio?

Defitelio is a medicine that contains the active substance defibrotide. It was to be available as a concentrate for solution for infusion (drip into a vein).

What was Defitelio expected to be used for?

Defitelio was expected to be used to treat and prevent hepatic veno-occlusive disease (VOD) in patients undergoing blood stem cell transplantation. VOD is a condition in which the veins in the liver become blocked, leading to liver dysfunction.

Defitelio was designated an 'orphan medicine' (a medicine to be used in rare diseases) on 29 July 2004 for the treatment and prevention of hepatic veno-occlusive disease.

How was Defitelio expected to work?

VOD is usually a complication resulting from treatment given to patients before their blood stem cell transplantation. This treatment, known as 'myeloablative chemotherapy', is given to patients to clear

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their bone marrow of cells before they receive healthy stem cells from a donor. The medicines used in this treatment can cause injury to the liver, leading to clots in the blood vessels seen in VOD.

The active substance in Defitelio, defibrotide, is expected to work in VOD by dissolving and reducing the formation of clots in the blood vessels of the liver, and thereby preventing or reversing the damage caused by the myeloablative chemotherapy. Another way it was expected to work was by protecting the cells of the blood vessels in the liver from the harmful effect of the chemotherapy.

What did the company present to support its application?

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

The applicant presented results of one main study on the prevention of VOD. This study involved 356 children and adolescents who were to undergo blood stem cell transplantation and who were at high risk of VOD. Around half of the patients were given Defitelio before the transplantation while the other half were not given the medicine. The study compared the number of patients in the two groups who had VOD 30 days after transplantation.

Another main study evaluated the effectiveness of Defitelio in treating VOD following blood stem cell transplantation. In this study, 102 patients with severe VOD were treated with Defitelio and the number who had completely recovered 100 days after transplantation was compared with results from a historical control group. The historical control group consisted of records of 32 patients who had VOD in the past and were not treated with Defitelio.

What were the CHMP's main concerns that led to the refusal?

The CHMP concluded that results from the prevention study did not provide sufficiently convincing evidence of the medicine's benefit and there were problems with the way the study was conducted, including problems with documentation and the reporting of data.

In the treatment study, the number of patients in the historical control group was considered to be too low and the Committee was concerned about the fact that some patients who were originally chosen to be in the historical control group were excluded from the study. It was therefore not possible to conclude on the medicine's benefit as a treatment.

In addition, there was a lack of data on the way the medicine is eliminated by the kidneys in children and patients with reduced kidney function. This concerned the Committee since a safety concern was identified in children who received high doses of Defitelio.

Therefore the CHMP concluded that the benefits of Defitelio did not outweigh its risks and recommended that it be refused marketing authorisation.

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

The company informed the CHMP that there are no consequences for patients currently in clinical trials and expanded access programmes. EU patients will continue to have access to defibrotide under a named patient program (NPP) where available.

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