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Questions and answers

Positive opinion on the marketing authorisation for Defitelio (defibrotide)

Outcome of re-examination

On 25 July 2013, the Committee for Medicinal Products for Human Use (CHMP) recommended the granting of the marketing authorisation for the medicinal product Defitelio, intended for the treatment of severe hepatic veno-occlusive disease (VOD) in patients undergoing haematopoietic (blood) stem-cell transplantation. The company that applied for authorisation is Gentium S.p.A.

On 21 March 2013, the CHMP had originally adopted a negative opinion for both treatment and prevention of VOD in blood stem-cell transplantation therapy. At the request of the applicant, the CHMP started a re-examination of its opinion and following the re-examination, the CHMP adopted a final positive opinion recommending that the medicine be granted authorisation but only for the treatment of severe VOD in patients undergoing blood stem-cell transplantation.

What is Defitelio?

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

What is Defitelio to be used for?

Defitelio is to be used to treat severe veno-occlusive disease (VOD) in patients undergoing haematopoietic (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 VOD.

How does Defitelio work?

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

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bone marrow of cells before they receive healthy stem cells from a donor. The medicines used for this treatment can damage the lining of the blood vessels in the liver, leading to the formation of clots and obstruction of the vessels seen in VOD.

The active substance in Defitelio, defibrotide has an effect in increasing the breakdown of clots in the blood. In addition, there is experimental evidence that Defibrotide may protect the cells lining blood vessels.

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 initial negative opinion?

The CHMP concluded that the 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. 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 as a safety issue was identified in children who received high doses of Defitelio.

What happened during the re-examination?

The CHMP convened an expert group comprising specialists from across the EU. The group, which also included representatives from patients' organisations, evaluated a revised application from the company, which focused on treating severe VOD and preventing VOD only in patients at high risk.

The expert group sent their advice to the CHMP. While the CHMP was deciding on its final opinion, the applicant withdrew the prevention indication completely, leaving for consideration only the treatment indication for patients with severe VOD.

What were the conclusions of the CHMP following the re-examination?

As the CHMP had been concerned with the data on the benefits of Defitelio in the treatment of VOD, the applicant provided additional analysis from a US patient registry. The analysis showed that patients with severe VOD who received Defitelio plus standard care had better outcomes, including a higher

survival rate after 100 days following transplantation, than those given standard care alone. The CHMP considered the results from the registry along with other available data and concluded that the benefits of Defitelio outweigh its risks in the treatment of severe VOD in patients undergoing blood stem-cell transplantation.

A risk management plan will be put in place to minimize the risk associated with this medicine and the applicant will be required to provide further data on the medicine through a registry to be set up in the EU.

The CHMP recommended that Defitelio be authorised in the EU under 'exceptional circumstances'. This is because, due to the rarity of the disease, limited information was available at the time of the recommendation. The CHMP will review any new information that becomes available on a yearly basis.

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.

The summary of the positive opinion of the CHMP is published on the Agency's website: ema.europa.eu/Find medicine/Human medicines/Pending EC decisions.