EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Questions and answers

Refusal of the marketing authorisation for Heparesc (human heterologous liver cells)

Outcome of re-examination

On 25 June 2015, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Heparesc, intended for the treatment of urea cycle disorders. The company that applied for authorisation is Cytonet GmbH & Ci KG.

The applicant had requested a re-examination of the opinion. After considering the grounds for this request, the CHMP re-examined the initial opinion and confirmed the refusal of the marketing authorisation on 22 October 2015.

What is Heparesc?

Heparesc is a medicine that contains living cells from the liver of a healthy donor which have been manipulated and then frozen for long-term storage. The medicine was to be given by slow injection through a tube inserted by a surgical procedure into the portal vein (a vein leading directly to the patient's liver).

Heparesc was developed as a type of advanced therapy medicine called a 'somatic cell therapy product'. This is a type of medicine containing cells or tissues that have been manipulated so that they can be used to cure, diagnose or prevent a disease.

What was Heparesc expected to be used for?

Heparesc was to be used for the treatment of children from birth up to 3 years of age with specific urea cycle disorders. These are rare inborn conditions in which the liver does not produce particular enzymes involved in removing nitrogen from the body via a substance called urea. As a result, toxic waste products build up in the blood in the form of ammonia which can lead to brain damage, convulsions (fits), coma and death.

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The specific urea cycle disorders for which Heparesc was intended to be used are called carbamoylphosphate synthetase 1 deficiency, ornithine transcarbamylase deficiency, argininosuccinate synthetase deficiency (citrullinaemia type 1), argininosuccinate lyase deficiency (argininosuccinic aciduria) and arginase deficiency (hyperargininaemia). Heparesc was intended to help temporary management of these conditions in children until they are big enough to be given a liver transplant to cure them.

Heparesc was designated an 'orphan medicine' (a medicine to be used in rare diseases) on 14 September 2007 for ornithine transcarbamylase deficiency, and 17 December 2010 for the other above conditions. The summaries of the opinion of the Committee for Orphan Medicinal Products for Heparesc can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/Rare disease designation.

How is Heparesc expected to work?

Heparesc is made of liver cells from an organ donor who can produce the enzyme that is missing in patients with urea cycle disorders. When the medicine is injected into the portal vein leading to the liver, some of the liver cells it contains are expected to settle in the recipient's liver and start producing the missing liver enzyme, thus helping to reduce the symptoms of the disease.

What did the company present to support its application?

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

The company presented the results of two main studies involving a total of 20 children with urea cycle disorders in which the effects of Heparesc were compared with historical results in children who had not received Heparesc treatment. The main measures of effectiveness were the change in the levels of ^{13}C-labelled urea production (a test intended to show the ability to produce urea) after treatment as compared to before, and the number, length and severity of any episodes of high ammonia in the blood during the studies.

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

Because Heparesc is an advanced therapy medicine, it was assessed by the Committee for Advanced Therapies (CAT). Taking into account the assessments performed by the CAT, the CHMP concluded that Heparesc could not be approved for the treatment of children with urea cycle disorders.

The CHMP had concerns about the design and conduct of the studies, which cast doubt on their results and whether these could have occurred by chance. In addition, the CHMP had concerns about the clinical relevance of the results of the tests that measured the ability to produce urea.

The Committee thus considered that the benefits of treatment had not been sufficiently demonstrated. Therefore, at the time of the initial evaluation, the CHMP was of the opinion that the benefits of Heparesc did not outweigh its risks and recommended that it be refused marketing authorisation.

During the re-examination the CAT and CHMP looked again at the data from the company, and also consulted experts in the treatment of urea cycle disorders. Both Committees confirmed their opinion that the effectiveness of Heparesc in the treatment of these disorders had not been sufficiently demonstrated. Although taking into account the challenges of developing the medicine, including the difficulty of enrolling patients due to the rarity of the disease, the CHMP therefore concluded that the benefits of Heparesc did not outweigh its risks and maintained the previous recommendation that the medicine 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 the refusal had no consequences for patients in clinical trials or compassionate use programmes.