European Medicines Agency

London, 19 July 2007
Doc. Ref. EMA/318692/2007

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

Active substance: ***adenovirus-mediated* Herpes simplex *virus-thymidine kinase gene***

On 13 July 2007, Ark Therapeutics officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a marketing authorisation for Cerepro, for the treatment of patients with operable high-grade glioma. Cerepro was designated an orphan medicinal product on 6 February 2002.

What is Cerepro?

Cerepro is a medicine containing a gene (a *Herpes simplex* virus thymidine kinase gene) carried by an adenovirus. It is made up into a solution that is injected directly into the brain during surgery.

What was Cerepro expected to be used for?

Cerepro was to be used in combination with ganciclovir sodium to treat high-grade glioma in patients who are eligible for surgery. Glioma is a type of brain tumour that begins in 'glial' cells (the cells that surround and support nerve cells).
Cerepro was intended for use during an operation. After removing as much of the brain tumour as possible, the surgeon would have made up to 70 small injections of Cerepro into the area from where the tumour was removed. Cerepro injection was to be followed by a two-week course of treatment with ganciclovir sodium, starting five days after the operation. Cerepro would only have worked in combination with ganciclovir.

How is Cerepro expected to work?

Cerepro contains the gene for the enzyme 'thymidine kinase' from the herpes virus. The gene is carried within a 'vector', a type of virus that has been altered genetically so that it can carry a gene (DNA) into the cells of the body. The virus in Cerepro is an 'adenovirus' that has been engineered so that it cannot make copies of itself and therefore does not cause infections in humans.
When Cerepro is injected into the brain, the modified virus is taken up by the cells near the injection sites. The cells then start to produce the thymidine kinase enzyme. This enzyme helps to convert ganciclovir into a form which can kill cells that are dividing, including any cancerous cells that were not removed during the operation.

What documentation did the company present to support its application to the CHMP?

The effects of Cerepro were first tested in experimental models before being studied in humans. Cerepro has also been studied in 36 patients with high-grade glioma. The study compared the effects of adding Cerepro and ganciclovir sodium to standard treatment with the effects of standard treatment alone. The main measure of effectiveness was how long the patients survived after the first operation.

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

The evaluation had finished and the CHMP had given a negative opinion. The company had requested a re-examination of the negative opinion, but this had not yet finished when the company withdrew.

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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 given a negative opinion and did not recommend a marketing authorisation for Cerepro for the treatment of patients with operable high-grade glioma.

What were the main concerns of the CHMP?
The CHMP had concerns that a benefit of Cerepro had not yet been shown. It was concerned over the low number of patients included in the main study of Cerepro, which prevented a benefit of the medicine being demonstrated. The Committee also had concerns over the ways in which the study had been carried out, which made it difficult to interpret the results. In addition, the CHMP considered there to be insufficient information on the safety of Cerepro, and, since the benefits of the medicine had not been demonstrated, that its risks, when used in combination with ganciclovir, could be of concern.
Therefore, at the time of the withdrawal, the CHMP's view was that a benefit of Cerepro had not been sufficiently demonstrated and any benefits did not outweigh the identified risks.

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 in clinical trials with Cerepro?
The company informed the CHMP that there are no consequences for patients currently included in clinical trials with Cerepro. If you are in a clinical trial and need more information about your treatment, contact the doctor who is giving it to you.

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