European Medicines Agency

London, 24 April 2008
Doc. Ref. EMEA/138069/2008

# QUESTIONS AND ANSWERS ON THE WITHDRAWAL OF A CHANGE TO THE MARKETING AUTHORISATION for EVOLTRA

International non-proprietary name (INN): ***clofarabine***

On 18 March 2008, Bioenvision Ltd, a wholly owned subsidiary of Genzyme Corporation, officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a change to the marketing authorisation for Evoltra. The change concerned an extension of indication to add the treatment of acute myeloid leukaemia in elderly patients. Evoltra was designated as an orphan medicine for this condition on 8 May 2003.

**What is Evoltra?**
Evoltra is a concentrate that is made up into a solution for infusion (drip into a vein). It contains the active substance clofarabine.
Evoltra is already used to treat children with acute lymphoblastic leukaemia (ALL, cancer of the lymphocytes, a type of white blood cell). It is used when the disease has not responded to, or has come back (relapsed), after at least two other treatments, and when no other treatment is expected to work.

**What was Evoltra expected to be used for?**
In the new indication, Evoltra was also expected to be used to treat patients aged over 65 years who have acute myeloid leukaemia (AML, cancer of the myeloid cells, a type of immature white blood cell). It was to be used in patients who are not suitable for intensive chemotherapy, because they have certain genetic abnormalities in their myeloid cells, 'secondary' AML (AML following a previous blood disorder) or another disease in addition to AML, or because they are 70 years of age or older.

**How is Evoltra expected to work?**
The active substance in Evoltra, clofarabine, is a cytotoxic (a medicine that kills cells that are dividing, such as cancer cells). It belongs to the group of anti-cancer medicines called 'antimetabolites'. Clofarabine is an analogue of adenine, which is part of the DNA, the fundamental genetic material of cells. In the body, clofarabine takes the place of adenine, and interferes with the enzymes involved in making genetic material. This stops the cells making new DNA and slows down the growth of tumour cells.

**What documentation did the company present to support its application to the CHMP?**
The company presented results from one main study involving 66 patients aged 65 years or older with AML, who had not been treated before and were considered to be unsuitable for intensive chemotherapy. The study did not compare Evoltra with any other treatment. The main measure of effectiveness was the number of patients who went into 'remission' (clearance of leukaemia from the bone marrow and complete or partial recovery of blood cell counts to normal levels).

**How far into the evaluation was the application when it was withdrawn?**
The application was at day 90 when the company withdrew. After the CHMP had assessed the responses from the company to a list of questions, there were still some unresolved issues outstanding.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

**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 some concerns and was of the provisional opinion that Evoltra could not have been approved for the treatment of the treatment of AML in elderly patients.

**What were the main concerns of the CHMP?**
The CHMP was concerned that the main study was not sufficient to establish the benefit of Evoltra in the treatment of AML in elderly patients who were unsuitable for intensive chemotherapy, and that the results of a study comparing Evoltra with standard treatment would be necessary to determine the medicine's effectiveness. The Committee was concerned that the main study included a number of patients who could have been suitable for intensive chemotherapy and this could have made the effectiveness of Evoltra look more promising. There were also some concerns over the medicine's side effects affecting the kidneys.
Therefore, at the time of the withdrawal, the CHMP's view was that a benefit of Evoltra 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 or compassionate use programmes using Evoltra?**
The company informed the CHMP that this withdrawal has no consequences for patients enrolled in clinical trials or compassionate use programmes with Evoltra. If you are in a clinical trial or compassionate use programme and need more information about your treatment, contact the doctor who is giving it to you.

**What is happening for Evoltra for treatment of ALL in children?**
There are no consequences on the use of Evoltra in the authorised indication, for which the balance of benefits and risks remains unchanged.