European Medicines Agency

London, 24 January 2008
Doc. Ref. EMEA/37537/2008

QUESTIONS AND ANSWERS ON RECOMMENDATION FOR THE REFUSAL OF THE MARKETING AUTHORISATION
for
MYLOTARG

International non-proprietary name (INN): ***gemtuzumab ozogamicin***

On 20 September 2007, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Mylotarg 5 mg powder for solution for infusion, intended for the treatment of acute myeloid leukaemia. The company that applied for authorisation is Wyeth Europa Ltd.

The applicant requested a re-examination of the opinion. After having considered the grounds for this request, the CHMP re-examined the initial opinion, and confirmed the refusal of the marketing authorisation on 24 January 2008.

What is Mylotarg?
Mylotarg is a powder that is made up into a solution for infusion (drip into a vein). It contains the active substance gemtuzumab ozogamicin.

What was Mylotarg expected to be used for?
Mylotarg was expected to be used to treat acute myeloid leukaemia, a type of cancer of the white blood cells. Mylotarg was to be used to treat patients whose disease had come back after one previous course of treatment, and who were not suitable for other types of intensive chemotherapy such as high-dose cytarabine (another anticancer medicine). It was to be used in patients who were 'CD33-positive', meaning that their cancerous white blood cells had a protein called CD33 on their surface.
Mylotarg was designated as an orphan medicinal product on 18 October 2000 for acute myeloid leukaemia.

How is Mylotarg expected to work?
The active substance in Mylotarg, gemtuzumab ozogamicin, is a cytotoxic (cell-killing) substance that is linked to a monoclonal antibody. A monoclonal antibody is an antibody (a type of protein) that has been designed to recognise and bind to a specific structure (called an antigen) that is found on certain cells in the body.
The monoclonal antibody part of the active substance (gemtuzumab) has been designed to bind to CD33, an antigen which is found on the surface of acute myeloid leukaemia cells in about 80% of patients. When the antibody attaches to CD33, the cells absorb the antibody, as well as the cytotoxic substance that it is attached to. Inside the cells, the cytotoxic substance, which is called calicheamicin, is released. The calicheamicin then breaks up the leukaemia cells' DNA, eventually killing the cells.

What documentation did the company present to support its application to the CHMP?
The effects of Mylotarg were first tested in experimental models before being studied in humans.
The effects of Mylotarg were studied in three main studies involving a total of 277 patients with CD33-positive acute myeloid leukaemia, whose disease had come back after one previous course of treatment. In all three studies, the main measure of effectiveness was the proportion of patients who achieved 'complete remission' after a seven-month course of treatment. Complete remission is when the leukaemia cells can no longer be detected in the blood and are at very low levels in the bone marrow. Mylotarg was not compared to any other treatment in any of the studies.

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 16
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

What were the major concerns that led the CHMP to recommend the refusal of the marketing authorisation?

The CHMP was concerned that the studies of Mylotarg had not shown a benefit of the medicine, because of the way they were designed. A small proportion of the patients whose disease had come back after one previous course of treatment achieved complete remission. However, it was difficult to compare the effectiveness of Mylotarg and other treatments used for this disease, in terms of how long remission would last, how long it would take until the disease got worse, or what the medicines' effects would be on survival.

The Committee noted that there were side effects associated with Mylotarg. These included severe and long-lasting bone marrow suppression causing low levels of white blood cells and platelets, liver problems, and side effects related to the infusion, such as chills, fever and low blood pressure.

At that point in time, the CHMP was of the opinion that there was insufficient evidence to establish the effectiveness of Mylotarg in the treatment of acute myeloid leukaemia, and therefore that the medicine's benefits did not outweigh its risks. Hence, the CHMP recommended that Mylotarg be refused marketing authorisation. The CHMP refusal was confirmed after re-examination.

What are the consequences of the refusal for patients in clinical trials or compassionate use programmes using Mylotarg?

The company informed the CHMP that patients currently included in compassionate use programmes will continue to receive Mylotarg until they have finished their course of treatment. The company also stated that it will continue to supply Mylotarg for use in existing, ongoing clinical trials.

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.