European Medicines Agency

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

International non-proprietary name (INN): ***histamine dihydrochloride***

On 19 March 2008, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Ceplene 1 mg/ml solution for injection, intended for the maintenance of remission in acute myeloid leukaemia (AML). The company that applied for authorisation is EpiCept GmbH. It may request a re-examination of the opinion within 15 days of receipt of notification of this negative opinion.

What is Ceplene?
Ceplene is a solution for injection that contains the active substance histamine dihydrochloride.

What was Ceplene expected to be used for?
Ceplene was expected to be used in combination with interleukin-2 (an anticancer medicine) in adults with acute myeloid leukaemia (AML), a type of cancer affecting the white blood cells. It was to be used during the patients' first 'remission' (a period without symptoms of the disease after the first course of treatment) to increase the length of time until the leukaemia comes back.
Ceplene was designated as an orphan medicinal product on 11 April 2005 for the treatment of AML.

How is Ceplene expected to work?
The active substance in Ceplene, histamine dihydrochloride, is an immune modulator, meaning that it alters the activity of the immune system (the body's natural defences). It is a form of histamine, a naturally-occurring substance in the body that is involved in many processes. In the treatment of AML, it is thought to work by protecting immune system cells from damage. This may improve the effectiveness of interleukin-2, a medicine that stimulates the immune system to attack cancerous cells. When Ceplene is given with interleukin-2, it is expected to increase the length of time until AML comes back.

What documentation did the company present to support its application to the CHMP?
The effects of Ceplene were first tested in experimental models before being studied in humans.
The effectiveness of Ceplene was studied in one main study involving 320 adults with AML who were in remission following leukaemia treatment. Ceplene was given in combination with interleukin-2 and compared with no treatment. The main measure of effectiveness was the length of time until the disease came back or the patient died.

What were the major concerns that led the CHMP to recommend the refusal of the marketing authorisation?
The CHMP was concerned that the single main study did not provide sufficient evidence to allow the approval of Ceplene, because the study's results were not considered to be compelling enough. In addition, the Committee noted that the evidence presented in support of the application was limited, especially with regards to how the combination of Ceplene and interleukin-2 works.
Therefore, at that point in time, the CHMP was of the opinion that the benefits of Ceplene in the maintenance of remission in adults with AML did not outweigh its risks. Hence, the CHMP recommended that Ceplene be refused marketing authorisation.

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What are the consequences of the refusal for patients in clinical trials or compassionate use programmes using Ceplene?
The company informed the CHMP that there are currently no patients with AML in clinical trials or compassionate use programmes for Ceplene in Europe.