European Medicines Agency

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QUESTIONS AND ANSWERS ON THE MARKETING AUTHORISATION
for
CEPLENE

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

On 24 July 2008, the Committee for Medicinal Products for Human Use (CHMP) recommended the granting of a marketing authorisation for the medicinal product Ceplene 0.5 mg/0.5 ml solution for injection intended as maintenance therapy in acute myeloid leukaemia (AML).

On 19 March 2008, the CHMP had adopted a negative opinion for Ceplene. At the request of the applicant, the Committee started a re-examination of its opinion. Following the re-examination, the CHMP adopted a final positive opinion on 24 July 2008.

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

What is Ceplene to be used for?
Ceplene is to be used as maintenance treatment 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 is to be used during the patients' first 'remission' (a period without symptoms of the disease after the first course of treatment).
Ceplene was designated as an orphan medicinal product on 11 April 2005 for the treatment of AML.

How does Ceplene 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 improves the effectiveness of interleukin-2, a medicine that stimulates the immune system to attack cancerous cells. When Ceplene is given with interleukin-2, it increases 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 initially 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 combination with interleukin-2 did not outweigh its risks in the maintenance of remission in adults with AML. Hence, the CHMP recommended that Ceplene be refused marketing authorisation.

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What happened during the re-examination?
During the re-examination, the CHMP took advice from a group of experts specialising in the treatment of cancer, and looked at additional analyses of the main study's results that were supplied by the company.

What were the conclusions of the CHMP following re-examination?
The CHMP concluded that the results from the single main study, even if limited, are sufficient to demonstrate the effectiveness of the combination of Ceplene and interleukin-2, but that further data from new clinical studies are needed to confirm the effectiveness of the combination of Ceplene and interleukin-2 and to understand the role of Ceplene in the combination.
Therefore, the CHMP concluded that the benefits of Ceplene used in combination with interleukin-2 outweigh its risks as maintenance therapy in adults with AML and recommended that Ceplene be given a marketing authorisation. The Committee recommended authorisation under 'Exceptional Circumstances', because further information is awaited on the effectiveness of the combination of Ceplene and interleukin-2 and how the combination works. Every year, the CHMP will review any new data that may become available and the marketing authorisation will be updated as necessary.