20 February 2013
EMA/COMP/86675/2005 Rev.3
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Histamine dihydrochloride for the treatment of acute myeloid leukemia

On 11 April 2005, orphan designation (EU/3/05/272) was granted by the European Commission to Maxim Pharmaceuticals Europe Ltd, United Kingdom, for histamine dihydrochloride for the treatment of acute myeloid leukaemia.

The sponsorship was transferred to EpiCept GmbH, Germany, in August 2006 and subsequently to Meda AB, Sweden, in October 2012.

What is acute myeloid leukemia?

Acute myeloid leukemia is a disease in which cancer cells are found in the blood and the bone marrow. The bone marrow is the spongy tissue inside the large bones in the body. Normally, the bone marrow makes cells called “blasts” that mature into several different types of blood cells that have specific functions in the body. These include red cells, white cells and platelets. Red blood cells carry oxygen and other materials to all tissues of the body. White blood cells fight infection. Platelets make the blood clot. When leukemia develops, the bone marrow produces large numbers of abnormal blood cells. There are several types of leukemias. In myeloid leukemia blasts that are developing into white blood cells called granulocytes are affected. The blasts do not mature and become too many. These blast cells are then found in the blood and also accumulate in the bone marrow. Leukemia can be acute (when it develops quickly with many blasts). Acute myeloid leukemia is life-threatening.

What is the estimated number of patients affected by the condition?

At the time of designation, acute myeloid leukemia affected approximately 0.7 in 10,000 people in the European Union (EU). This was equivalent to a total of around 33,000 people*, and is below the ceiling for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor and the knowledge of the Committee for Orphan Medicinal Products (COMP).

*Disclaimer: For the purpose of the designation, the number of patients affected by the condition is estimated and assessed on the basis of data from the European Union (EU 25), Norway, Iceland and Liechtenstein.
At the time of designation, this represented a population of 466,600,000 (Eurostat 2005).

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

What treatments are available?

Treatment for leukemia is complex and depends on a number of factors including the type of leukemia, the extent of the disease and whether the leukemia has been treated before. It also depends on the age, the symptoms, and the general health of the patient. The primary treatment of acute myeloid leukemia is chemotherapy (using drugs to kill cancer cells) Several products were authorised for the condition in the Community at the time of submission of the application for orphan drug designation. Histamine dihydrochloride in combination with existing treatment could be of potential significant benefit for the treatment of acute myeloid leukemia because it might improve the long-term outcome of the patients.. The assumption will have to be confirmed at the time of marketing authorisation. This will be necessary to maintain the orphan status.

How is this medicine expected to work?

It is not completely understood how histamine dihydrochloride works. It is suggested by the sponsor that it only acts together with another medicinal product (interleukin 2). Together they cause the destruction of the tumour cells through specific cells of the human defence system (the so-called “natural killer” cells).

What is the stage of development of this medicine?

The effects of histamine dihydrochloride were evaluated in experimental models.

At the time of submission of the application for orphan designation, clinical trials in patients with acute myeloid leukemia were ongoing.

Histamine dihydrochloride was not marketed anywhere worldwide for acute myeloid leukemia, at the time of submission. Orphan designation of histamine dihydrochloride was granted in the United States for the use as an adjunct to cytokine therapy in the treatment of acute myeloid leukemia.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 3 March 2005 recommending the granting of this designation.

Update: Histamine dihydrochloride (Ceplene) has been authorised in the EU since 7 October 2008. Ceplene maintenance therapy is indicated for adult patients with acute myeloid leukaemia in first remission concomitantly treated with interleukin-2 (IL-2). The efficacy of Ceplene has not been fully demonstrated in patients older than age 60.

More information on Ceplene can be found in the European public assessment report (EPAR) on the Agency’s website: ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports

_____

Opinions on orphan medicinal product designations are based on the following three criteria:

- the seriousness of the condition;
- the existence of alternative methods of diagnosis, prevention or treatment;
- either the rarity of the condition (affecting not more than 5 in 10,000 people in the EU) or insufficient returns on investment.

Designated orphan medicinal products are products that are still under investigation and are considered for orphan designation on the basis of potential activity. An orphan designation is not a marketing authorisation. As a consequence, demonstration of quality, safety and efficacy is necessary before a product can be granted a marketing authorisation.

For more information

Sponsor's contact details:

Meda AB
Pipers väg 2A
SE-170 73 Solna
Sweden
Telephone: +46 8 630 19 00
Telefax: +46 8 630 19 50
http://www.meda.se/contact-us

For contact details of patients' organisations whose activities are targeted at rare diseases see:

- Orphanet, a database containing information on rare diseases which includes a directory of patients' organisations registered in Europe.
- European Organisation for Rare Diseases (EURORDIS), a non-governmental alliance of patient organisations and individuals active in the field of rare diseases.

Translations of the active ingredient and indication in all official EU languages[1], Norwegian and Icelandic

Language	Active Ingredient	Indication
English	Histamine dihydrochloride	Treatment of acute myeloid leukaemia
Bulgarian	Хистаминов дихидрохлорид	Лечение на остра миелоидна левкемия
Czech	Histamin dihydrochlorid	Léčení akutní myeloidní leukémie
Danish	Histamin dihydroklorid	Behandling af akut myeloid leukæmi
Dutch	Histamine dihydrochloride	Behandeling van acute myeloïde leukemie
Estonian	Histamiin-dihüdrokloriid	Ägeda müeloidse leukeemia ravi
Finnish	Histamiinidihydrokloridi	Akuutin myelooisen leukemian hoito
French	Dichlorhydrate d'histamine	Traitement de la leucémie aiguë myéloïde
German	Histamindihydrochlorid	Behandlung der akuten myeloischen Leukämie
Greek	Διυδροχλωριδιακή ισταμίνη	Θεραπεία οξείας μυελώδους λευχαιμίας
Hungarian	Hisztamin-dihidroklorid	Akut myeloid leukaemia kezelése
Italian	Istamina dicloridrato	Trattamento della leucemia mieloide acuta
Latvian	Histamīna dihidrohlorīds	Akūtas mieloīdās leikēmijas ārstēšana
Lithuanian	Histamino dihidrochloridas	Ūmios mieloleukemijos gydymas
Maltese	Histamine dihydrochloride	Kura ta' lewkimja majelojda akuta
Polish	Histaminy dichlorowodorek	Leczenie ostrej białaczki szpikowej
Portuguese	Dicloridrato de histamina	Tratamento da leucemia mielóide aguda
Romanian	Diclorhidrat de histamină	Tratamentul leucemiei mieloide acute
Slovak	Histamín dihydrochlorid	Liečba akútnej myeloidnej leukémie
Slovenian	Histaminijev-dihidroklorid	Zdravljenje akutne mieloične levkemije
Spanish	Dihidrocloruro de histamina	Tratamiento de la leucemia mieloide aguda
Swedish	Histamindihydroklorid	Behandling av akut myeloid leukemi
Norwegian	Histamin-dihydroklorid	Behandling av akutt myelogen levkemi
Icelandic	Histamín díhýdróklóríð	Meðferð við bráða kyrningahvítblæði

[1] At the time of transfer of sponsorship