European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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COMMITTEE FOR ORPHAN MEDICINAL PRODUCTS

PUBLIC SUMMARY OF POSITIVE OPINION FOR ORPHAN DESIGNATION OF forodesine hydrochloride for the treatment of acute lymphoblastic leukaemia

On 18 December 2006, orphan designation (EU/3/06/421) was granted by the European Commission to Napp Pharmaceuticals Research Limited, United Kingdom, for forodesine hydrochloride for the treatment of acute lymphoblastic leukaemia.
The name of the sponsor changed to Mundipharma Research Limited in 2007.

What is acute lymphoblastic leukaemia?

Acute lymphoblastic leukaemia 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 leukaemia develops, the bone marrow produces large numbers of abnormal blood cells. There are several types of leukaemias. Acute lymphoblastic leukaemia is a cancer of certain white blood cells called lymphocytes. There are two main types of lymphocytes: B-lymphocytes (B-cells) and T-lymphocytes (T-cells). In this disease either B- or T-lymphocytes multiply too quickly and live too long, so there are too many of them circulating in the blood. These leukaemic lymphocytes are not fully developed and do not work properly. Over a period of time these abnormal cells (also called malignant cells) replace the normal white cells, red cells and platelets in the bone marrow, thus leading to a decreased number of these normal cells in the blood. In turn, this facilitates bruising, haemorrhages and infections, and causes anaemia with its symptoms. Acute lymphoblastic leukaemia is the most common type of leukaemia in young children. This disease also affects adults, especially those aged 65 and older. People with acute leukaemia can be cured, particularly children. However, despite the available treatments, acute lymphoblastic leukaemia remains a serious and life threatening condition in a subgroup of patients, who are resistant to treatment or relapse after initial remission.

What are the methods of treatment available?

Treatment for leukaemia is complex and depends on a number of factors including the type of leukaemia, the extent of the disease and whether the leukaemia has been treated before. It also depends on the patient's age, symptoms, and general health. The primary treatment of acute lymphoblastic leukaemia is chemotherapy (using drugs to kill cancer cells) followed by, or combined with, radiotherapy (using high-energy x-rays or other types of high-energy rays to kill cancer cells). Bone marrow transplantation as a curative treatment option is also available.
Satisfactory argumentation has been submitted by the sponsor to justify the assumption that forodesine hydrochloride might be of potential significant benefit for the treatment of acute lymphoblastic leukaemia. This assumption will have to be confirmed at the time of marketing authorisation. This will be necessary to maintain orphan status.

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What is the estimated number of patients affected by the condition*[*]?
According to the information provided by the sponsor, acute lymphoblastic leukaemia was considered to affect about 28,000 persons in the European Union.

How is this medicinal product expected to act?
Forodesine hydrochloride is a substance acting specifically on an enzyme called purine nucleoside phosphorylase (PNP). Enzymes are proteins produced by the cells of the body; they speed up the conversion of certain substances into other substances. Forodesine is an inhibitor of PNP. Reducing the activity of this enzyme may cause the accumulation of a substance, called dGTP, which is toxic to these cells if present in high concentrations. Human lymphocytes, particularly malignant T- and B-cells may be susceptible to forodesine, because they have a relatively high activity of another enzyme, dCK, which actually generates dGTP, and a low activity of an opposing enzyme (5' nucleotidase), which instead would prevent dGTP accumulation. Since acute lymphoblastic leukaemia is caused by the uncontrolled growth of the malignant lymphocytes (B- or T- cells), forodesine might help in slowing down or stopping this uncontrolled cell growth.

What is the stage of development of this medicinal product?
The effects of the medicinal product were evaluated in experimental models.
At the time of submission of the application for orphan designation, two clinical trials in patients with acute lymphoblastic leukaemia were completed, and another trial was ongoing.
Forodesine hydrochloride was not marketed anywhere in the world for acute lymphoblastic leukaemia; it was designated as orphan medicinal product for this same condition in the United States on 13 August 2004.

According to Regulation (EC) No 141/2000 of 16 December 1999, the Committee for Orphan Medicinal Products (COMP) adopted on 9 November 2006 a positive opinion recommending the grant of the above-mentioned designation.

Opinions on orphan medicinal products designations are based on the following cumulative criteria: (i) the seriousness of the condition, (ii) the existence or not of alternative methods of diagnosis, prevention or treatment and (iii) either the rarity of the condition (considered to affect not more than five in ten thousand persons in the Community) or the insufficient return of development investments.

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

[*] Disclaimer: For the purpose of the designation, the number of patients affected by the condition is estimated and assessed based on data from the European Union (EU 25), Norway, Iceland and Lichtenstein. This represents a population of 459,700,000 (Eurostat 2004). This estimate is based on available information and calculations presented by the sponsor at the time of the application.

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Translations of the active ingredient and indication in all EU languages and Norwegian and Icelandic

Language	Active Ingredient	Indication
English	Forodesine hydrochloride	Treatment of acute lymphoblastic leukaemia
Czech	Forodesin hydrochlorid	Léčba akutní lymfoblastické leukémie
Danish	Forodesin hydroklorid	Behandling af akut lymfoblastær leukæmi
Dutch	Forodesinehydrochloride	Behandeling van acute lymfoblastaire leukemie
Estonian	Forodesiinihüdrokloriid	Ägeda lümfoblastilise leukeemia ravi
Finnish	Forodesiinihydrokloridi	Akuutin lymfoblastileukemian hoito
French	Chlorhydrate de forodesine	Traitement de la leucémie lymphoblastique aiguë
German	Forodesinhydrochlorid	Behandlung der akuten lymphatischen Leukämie
Greek	Υδροχλωρική Φοροδεσίνη	Θεραπεία της οξείας λεμφοβλαστικής λευχαιμίας
Hungarian	Forodezin -hidroklorid	Akut lymphoblastos leukaemia kezelése
Italian	Forodesina cloridrato	Trattamento della leucemia linfoblastica acuta
Latvian	Forodesīns hidrohlorīds	Akūtas limfoblastiskas leikozes ārstēšana
Lithuanian	Forodesino hidrochloridas	Ūmios limfoblastinės leukemijos gydymas
Polish	Forodezyny chlorowodorek	Leczenie ostrej białaczki limfoblastycznej
Portuguese	Cloridrato de forodesina	Tratamento da leucemia linfoblástica aguda
Slovak	Forodezíniumchlorid	Liečba akútnej lymfoblastickej leukémie
Slovenian	Forodesin hidroklorid	Zdravljenje akutne limfoblastne levkemije
Spanish	Forodesina clorhidrato	Tratamiento de la leucemia linfoblástica aguda
Swedish	Forodesinhydroklorid	Behandling av akut lymfatisk leukemi
Norwegian	Forodesinhydroklorid	Behandling av akutt lymfoblastisk leukemi
Icelandic	Fóródesín hýdróklóríð	Meðferð við bráðu eitlifrumuhvítblæði