



Committee for Orphan Medicinal Products

Public summary of positive opinion for orphan designation of **4-ethoxy-2-(piperazin-1-yl)-7-(pyridin-4-yl)-5H-pyrimido[5,4-b]indol** for the treatment of chronic lymphocytic leukaemia

On 14 November 2007, orphan designation (EU/3/07/487) was granted by the European Commission to Curacyte Discovery GmbH, Germany, for 4-ethoxy-2-(piperazin-1-yl)-7-(pyridin-4-yl)-5H-pyrimido[5,4-b]indol for the treatment of chronic lymphocytic leukaemia.

The sponsorship was transferred to BlackSwan Pharma GmbH, Germany, in September 2009.

What is chronic lymphocytic leukaemia?

Chronic lymphocytic 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, in the bone marrow, cells, called “blasts”, divide and mature into several different types of blood cells with 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 support blood clotting. When leukaemia develops, the bone marrow produces large numbers of abnormal blood cells. Over a period of time these abnormal cells replace the normal white cells, red cells and platelets in the bone marrow, which reduces the number of normal cells in the blood and leads to anaemia, coagulation problems (bruising, haemorrhages) and repeated infections. There are several types of leukaemias; chronic lymphocytic leukaemia is a cancer of a type of white blood cells called B-lymphocytes. The lymphocytes multiply and live too long, so there are too many of them circulating in the blood. These leukaemic lymphocytes seem normal, but they are not fully developed and do not work properly. Chronic lymphocytic leukaemia is the most common type of leukaemia; it mainly affects older people, being rare in people under the age of 40. Chronic lymphocytic leukaemia is chronically debilitating and life-threatening, due to the severe consequences and the poor long-term survival for high-risk patients.

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

At the time of designation, chronic lymphocytic leukaemia affected approximately 3.5 in 10,000 people in the European Union (EU)*. This is equivalent to a total of around 175,000 people, and is below the threshold for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor and knowledge of the Committee for Orphan Medicinal Products (COMP).

What treatments are 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 age, symptoms, and the general health of the patient. Some people with B-cell chronic

*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 27), Norway, Iceland and Liechtenstein. This represents a population of 498,000,000 (Eurostat 2006).

lymphocytic leukaemia never have treatment, if their illness is not causing any symptoms and is progressing slowly. Treatment is often started only if and when the symptoms become troublesome. Current main treatment of chronic lymphocytic leukaemia 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.

Satisfactory argumentation has been submitted by the sponsor to justify the assumption that 4-ethoxy-2-(piperazin-1-yl)-7-(pyridin-4-yl)-5H-pyrimido[5,4-b]indol might be of potential significant benefit for the treatment of chronic lymphocytic leukaemia, because of its new mechanism of action and that it may provide a major contribution to patient care. These assumptions 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?

4-ethoxy-2-(piperazin-1-yl)-7-(pyridin-4-yl)-5H-pyrimido[5,4-b]indol is a compound that binds to and inhibits (blocks) the action of an enzyme (a protein that triggers chemical reactions in the body) called phosphodiesterase E4, that degrades a molecule called cyclic adenosine monophosphate (cAMP), inside cells. Cancer cells in chronic lymphocytic leukaemia are known to express this enzyme. The sponsor has suggested that when cAMP is not degraded properly and starts accumulating due to the inhibition of this enzyme, a chain reaction leading to the destruction and consequent death of the cancer cells is initiated.

What is the stage of development of this medicine?

The evaluation of the effects of 4-ethoxy-2-(piperazin-1-yl)-7-(pyridin-4-yl)-5H-pyrimido[5,4-b]indol in experimental models is ongoing.

At the time of submission of the application for orphan designation, no clinical trials in patients with chronic lymphocytic leukaemia were initiated.

The medicinal product was not authorised anywhere worldwide for the treatment of chronic lymphocytic leukaemia or designated as orphan medicinal product elsewhere for this condition, at the time of submission.

According to Regulation (EC) No 141/2000 of 16 December 1999, the Committee for Orphan Medicinal Products (COMP) adopted on 12 September 2007 a positive opinion recommending the grant of the above-mentioned designation.

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 Community) 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.

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

Language	Active Ingredient	Indication
English	4-ethoxy-2-(piperazin-1-yl)-7-(pyridin-4-yl)-5H-pyrimido[5,4-b]indole	Treatment of chronic lymphocytic leukaemia
Bulgarian	4-етокси-2-(пиперазин-1-ил)-7-(пиридин-4-ил)-5H-пиримидо[5,4-b]индол	лечение на хронична лимфоцитна левкемия
Czech	4-ethoxy-2-(piperazín-1-yl)-7-(pyridín-4-yl)-5H-pyrimido[5,4-b]indol	Léčba chronické lymfatické leukémie
Danish	4-ethoxy-2-(piperazin-1-yl)-7-(pyridin-4-yl)-5H-pyrimido[5,4-b]indol	Behandling af kronisk lymfocytær leukæmi
Dutch	4-ethoxy-2-(piperazin-1-yl)-7-(pyridin-4-yl)-5H-pyrimido[5,4-b]indol	Behandeling van chronische lymfocyttaire leukemie
Estonian	4-etoksü-2-(piperasiin-1-üül)-7-(püridiin-4-üül)-5H-pürimido[5,4-b]indool	Kroonilise lümfoidleukeemia ravi
Finnish	4-etoksi-2-(piperatsiini-1-yyli)-7-(pyridiini-4-yyli)-5H-pyrimido[5,4-b]indoli	Kroonisen lymfosyyttileukemian hoito
French	4-éthoxy-2-(pipérazine-1-yl)-7-(pyridine-4-yl)-5H-pyrimido[5,4-b]indole	Traitement de la leucémie lymphoïde chronique
German	4-Ethoxy-2-(piperazin-1-yl)-7-(pyridin-4-yl)-5H-pyrimido[5,4-b]indol	Behandlung der chronisch-lymphatischen Leukämie
Greek	4-αιθοξύ-2-(πιπεραζιν-1-υλο)-7-(πυριδιν-4-υλο)-5H-πυριμιδο[5,4-b]ινδόλη	Θεραπεία της χρόνιας λεμφοκυτταρικής λευχαιμίας
Hungarian	4-etoxi-2-(piperazin-1-il)-7-(piridin-4-il)-5H-pirimido[5,4-b]indol	Krónikus lymphoid leukémia kezelése
Italian	4-etossi-2-(piperazin-1-il)-7-(piridin-4-il)-5H-pirimido[5,4-b]indolo	Trattamento della leucemia linfocitica cronica
Latvian	4-etoksi-2-(piperazin-1-yl)-7-(piridīn-4-yl)-5H-pirimido[5,4-b]indols	Hroniskas limfocitiskās leikēmijas ārstēšana
Lithuanian	4-etoksi-2-(piperazin-1-il)-7-(piridin-4-il)-5H-pirimido[5,4-b]indolas	Lėtinės limfocitinės leukemijos gydymas
Maltese	4-ethoxy-2-(piperazin-1-yl)-7-(pyridin-4-yl)-5H-pyrimido[5,4-b]indole	Kura tal-lewkimja limfoċitika kronika
Polish	4-etoksy-2-(piperazyn-1-ylo)-7-(pirydyn-4-ylo)-5H-piryrido[5,4-b]indol	Leczenie przewlekłej białaczki limfatycznej
Portuguese	4-etoxi-2-(piperazin-1-il)-7-(piridina-4-il)-5H-pirimido[5,4-b]indole	Tratamento da leucemia linfocítica crónica
Romanian	4-etoxi-2-(piperazin-1-il)-7-(piridin-4-il)-5H-pirimido[5,4-b]indol	Tratamentul leucemiei limfoide cronice
Slovak	4-etoxy-2-(piperazín-1-yl)-7-(pyridín-4-yl)-5H-pyrimido[5,4-b]indol	Liečba chronickej lymfocytovej leukémie
Slovenian	4-etoksi-2-(piperazin-1-il)-7-(piridin-4-il)-5H-pirimido[5,4-b]indol	Zdravljenje kronične limfatske levkemije
Spanish	4-etoxi-2-(piperazín-1-il)-7-(piridín-4-il)-5H-pirimido[5,4-b]indol	Tratamiento de la leucemia linfocítica crónica
Swedish	4-ethoxy-2-(piperazin-1-yl)-7-(pyridin-4-yl)-5H-pyrimido[5,4-b]indol	Behandling av kronisk lymfatisk leukemi

Norwegian	4-etoksy-2-(piperazin-1-yl)-7-(pyridin-4-yl)-5H-pyrimido[5,4-b]indol	Behandling av kronisk lymfatisk leukemi
Icelandic	4-etoxý-2-(píperazín-1-ýl)-7-(pýridín-4-ýl)-5H-pýrímídó[5,4-b]indól	Meðferð á langvinnu eitilfrumuhvítblæði