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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

N-(cyanomethyl)-4-(2-{[4-(morpholin-4-yl)phenyl]amino}pyrimidin-4-yl)benzamide, dihydrochloride salt for the treatment of primary myelofibrosis

First publication	15 August 2011
Rev.1: transfer of sponsorship	19 March 2012
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Disclaimer

Please note that revisions to the Public Summary of Opinion are purely administrative updates. Therefore, the scientific content of the document reflects the outcome of the Committee for Orphan Medicinal Products (COMP) at the time of designation and is not updated after first publication.

On 5 August 2011, orphan designation (EU/3/11/888) was granted by the European Commission to Cres Pharmaceuticals Limited, United Kingdom, for N-(cyanomethyl)-4-(2-{[4-(morpholin-4-yl)phenyl]amino}pyrimidin-4-yl)benzamide, dihydrochloride salt for the treatment of primary myelofibrosis.

The Sponsorship was transferred to YM BioSciences (UK) Limited, United Kingdom, in February 2012 and subsequently to Gilead Sciences International Ltd, United Kingdom, in May 2013.

What is primary myelofibrosis?

Primary myelofibrosis is a disease of unknown cause in which the bone marrow (the spongy tissue inside the large bones) becomes dense and fibrous, and starts producing abnormal immature blood cells that replace the normal blood cells.

In this disease, some immature blood cells migrate from the bone marrow to other organs, such as the spleen and liver, where they mature. This causes the organs to become enlarged. Patients with primary myelofibrosis can develop several symptoms, including bone pain, tiredness, weakness, infections and bleeding.

Primary myelofibrosis is a debilitating disease that is long lasting and life threatening because it results in severe anaemia (low red blood cell counts) and infections, and can lead to leukaemia (cancer of the white blood cells).

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

At the time of designation, primary myelofibrosis affected approximately 0.3 in 10,000 people in the European Union (EU). This is equivalent to a total of around 15,000 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).

What treatments are available?

At the time of designation, hydroxycarbamide and busulfan (which are also used to treat cancer) were authorised in the EU for primary myelofibrosis. In addition, medicines were authorised to treat the symptoms, including erythropoietin (a hormone that stimulates the production of red blood cells) to treat anaemia, and surgery to remove the enlarged spleen. In some patients, haematopoietic (blood) stem-cell transplantation was used to treat the disease. This is a complex procedure where the patient receives stem cells from a matched donor to help restore the bone marrow.

The sponsor has provided sufficient information to show that this medicine might be of significant benefit for patients with primary myelofibrosis because it works it works in a different way to existing treatments and may represent an alternative treatment for patients with this condition. This assumption will need to be confirmed at the time of marketing authorisation, in order to maintain the orphan status.

How is this medicine expected to work?

This medicine is thought to work by blocking some enzymes known as Janus kinases (JAKs). These enzymes can be found in some receptors on the surface of cells and are involved in the reproduction and growth of blood cells. In myelofibrosis, JAKs are more active than normal. By blocking these enzymes, this medicine is expected to slow down the abnormal growth of blood cells, reducing the symptoms of the disease.

What is the stage of development of this medicine?

The effects of N-(cyanomethyl)-4-(2-{[4-(morpholin-4-yl)phenyl]amino}pyrimidin-4-yl)benzamide, dihydrochloride salt have been evaluated in experimental models.

At the time of submission of the application for orphan designation, clinical trials with the medicine in patients with myelofibrosis were ongoing.

At the time of submission, this medicine was not authorised anywhere in the EU for primary myelofibrosis. Orphan designation of the medicine had been granted in the United States of America for myelofibrosis.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 5 May 2011 recommending the granting of this designation.

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*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.
At the time of designation, this represented a population of 507,700,000 (Eurostat 2011).

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:

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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	N-(cyanomethyl)-4-(2-{[4-(morpholin-4-yl)phenyl]amino}pyrimidin-4-yl)benzamide, dihydrochloride salt	Treatment of primary myelofibrosis
Bulgarian	N-(цианометил)-4-(2-{[4-(морфолин-4-ил)фенил]амино}пиримидин-4-ил)бензамид дихидрохлорид сол	Лечение на първична миелофиброза
Czech	N-(kyanomethyl)-4-(2-{[4-(morfolin-4-yl)fenyl]amino}pyrimidin-4-yl)benzamid dihydrochlorid sůl	Léčba primární myelofibrózy
Danish	N-(cyanomethyl)-4-(2-{[4-(morpholin-4-yl)phenyl]amino}pyrimidin-4-yl)benzamid-dihydrochlorid-salt	Behandling af primær myelofibrose
Dutch	N-(cyanomethyl)-4-(2-{[4-(morfoline-4-yl)fenyl]amino}pyrimidine-4-yl)benzamidedihydrochloridezout	Behandeling van primaire myelofibrose
Estonian	N-(tsüanometüül)-4-(2-{[4-(morfoliin-4-üül)fenüül]amiino}pürimidiin-4-üül)bensamiid dihüdrokloriid sool	Esmase müelofibroosi ravi
Finnish	N-(syanometyyli)-4-(2-{[4-(morfoliini-4-yyli)fenyyli]amino}pyrimidiini-4-yyli)bentsamididihydrokloridisuola	Primaarisen myelofibroosin hoito
French	N-(cyanométhyle)-4-(2-{[4-(morpholine-4-yle)phényle]amino}pyrimidine-4-yle)benzamide dichlorhydrate	Traitement de la myélofibrose primitive
German	N-(Cyanomethyl)-4-(2-{[4-(Morpholin-4-yl)Phenyl]amino}pyrimidin-4-yl)Benzamid Dihydrochloridsalz	Behandlung der primären Myelofibrose
Greek	N-(κυανομέθυλ)-4(2-{[4-(μορφολινο-4-υλ)φαινυλ]αμινο}πυριμίδινο-4-υλ)βενζαμίδιο άλας διυδροχλωρικό	Θεραπεία της πρωτογενούς μυελοσκλήρυνσης
Hungarian	N-(cianometil)-4-(2-{[4-(morfolin-4-yl)fenil]amino}pirimidin-4-yl)benzamid dihidroklorid só	Primer mielofibrózis kezelésére
Italian	N-(cianometil)-4-(2-{[4-(morfolin-4-ile)fenil]ammino}pirimidin-4-ile)benzamide sale dicloridrato	Trattamento della mielofibrosi primitiva
Latvian	N-(ciānmetil)-4-(2-{[4-(morfolīn-4-il)fenil]amino}pirimidin-4-il)benzamīda dihidrohlorīda sāls	Primāras mielofibrozes ārstēšana
Lithuanian	N-(cianometil)-4-(2-{[4-(morfolin-4-il)fenil]amino}pirimidin-4-il)benzamidas dihidrochlorido druska	Pirminės mielofibrozės gydymas

[1] At the time of designation

Language	Active ingredient	Indication
Maltese	Melħ dihydrochloride ta' N-(cyanomethyl)-4-(2-{[4-(morpholin-4-yl)phenyl]amino}pyrimidin-4-yl)benzamide	Kura tal-mjelofibrożi primarja
Polish	N-(cyjanometylo)-4-(2-{[4-(morfolin-4-ylo)fenylo]amino}pirymidyn-4-ylo)benzamid dichlorowodorek	Leczenie mielofibrozy pierwotnej
Portuguese	N-(cianometil)-4-(2-{[4-(morfolina-4-il)fenil]amino}pirimidina-4-il)cloridrato de benzamida	Tratamento da mielofibrose primária
Romanian	Diclorhidrat de N-(cianometil)-4-(2-{[4-(morfolin-4-yl)fenil]amino}pirimidin-4-yl)benzamidă	Tratamentul mielofibrozei primitive
Slovak	N-(cyanometyl)-4-(2-{[4-(morfolín-4-yl)fenyl]amino}pyrimidín-4-yl)benzamid dihydrochlorid	Liečba primárnej myelofibrózy
Slovenian	N-(cianometil)-4-(2-{[4-(morfolin-4-il)fenil]amino}pirimidin-4-il)benzamid dihidroklorid soli	Zdravljenje primarne mielofibroze
Spanish	N-(cianometil)-4-(2-{[4-(morfolina-4-il)fenil]amino}pirimidina-4-il)benzamida sal de dihidrocloruro	Tratamiento de la mielofibrosis primaria
Swedish	N-(cyanometyl)-4-(2-{[4-(morfolin-4-yl)fenyl]amino}pyrimidin-4-yl)benzamid dihydrokloridsalt	Behandling av primär myelofibros
Norwegian	N-(cyanometyl)-4-(2-{[4-(morfolin-4-yl)fenyl]amino}pyrimidin-4-yl)benzamid dihydroklorid	Behandling av primær myelofibrose
Icelandic	N-(sýanómetýl)-4-(2-{[4-(morfoólín-4-ýl)fenýl]amínó}pýrimídín-4-ýl)benzamíð díhýdróklóríð salt	Meðferð á beinmergsnetjuhersli