13 April 2015
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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

(R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate for the treatment of myelofibrosis secondary to polycythaemia vera or essential thrombocythaemia

First publication	22 June 2009
Rev.1: sponsor's change of address	17 November 2010
Rev.2: transfer of sponsorship	3 March 2011
Rev.3: information about Marketing Authorisation	11 September 2013
Rev.4: sponsor's change of address	30 January 2015
Rev.5: withdrawal from the Community Register	13 April 2015
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.	

Please note that this product was withdrawn from the Community Register of designated Orphan Medicinal Products in February 2015 on request of the Sponsor.

On 3 April 2009, orphan designation (EU/3/09/620) was granted by the European Commission to Incyte Corporation Ltd, United Kingdom, for (R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate for the treatment of myelofibrosis secondary to polycythaemia vera or essential thrombocythaemia.

The sponsorship was transferred to Novartis Europharm Limited, United Kingdom, in September 2010.

What is myelofibrosis secondary to polycythaemia vera or essential thrombocythaemia?

Myelofibrosis is a disease in which the bone marrow (the spongy tissue inside the large bones in the body) becomes very dense and rigid, and produces abnormal and immature blood cells that replace the normal blood cells. It can develop as a reaction to polycythaemia vera (overproduction of red blood

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cells) or essential thrombocythaemia (overproduction of platelets, components that help the blood to clot). 'Essential' means that the thrombocythaemia is not caused by any known condition.

In myelofibrosis, 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 myelofibrosis can develop several symptoms, including pain in the bones, tiredness, weakness, infections and bleeding.

Myelofibrosis secondary to polycythaemia vera or essential thrombocythaemia is a debilitating disease that is long lasting and may be life threatening because it can lead to severe anaemia (low red blood cell counts) and infections, and can result in leukaemia (cancer of the white blood cells).

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

At the time of designation, myelofibrosis secondary to polycythaemia vera or essential thrombocythaemia affected approximately 0.01 in 10,000 people in the European Union (EU). This was equivalent to a total of around 500 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?

At the time of designation, although hydroxyurea was authorised in the EU for idiopathic myelofibrosis (myelofibrosis of unknown cause), it was not authorised for myelofibrosis secondary to polycythaemia vera or essential thrombocythaemia.

Treatments for this condition were aimed at relieving the symptoms of the disease, and included androgens (male hormones), glucocorticoids (a type of steroid) and erythropoietin (a hormone that stimulates the production of red blood cells) to treat anaemia, and surgery to remove the enlarged spleen. In some patients, bone marrow transplantation was used. This is a complex procedure where the bone marrow of the patient is destroyed and replaced with bone marrow from a matched donor.

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 overactivated. By blocking the 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 this medicine have been evaluated in experimental models.

At the time of submission of the application for orphan designation, clinical trials in patients with myelofibrosis secondary to polycythaemia vera or essential thrombocythaemia were ongoing.

At the time of submission, this medicine was not authorised anywhere in the EU for myelofibrosis secondary to polycythaemia vera or essential thrombocythaemia. Orphan designation of this medicine

[*]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 502,800,000 (Eurostat 2008).

had been granted in the EU for chronic idiopathic myelofibrosis and 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 9 February 2009 recommending the granting of this designation.

Update: (R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate (Jakavi) has been authorised in the EU since 23 August 2012 for treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis (also known as chronic idiopathic myelofibrosis), post-polycythaemia-vera myelofibrosis or post-essential-thrombocythaemia myelofibrosis.

More information on Jakavi 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

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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 European Union) 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	(R)-3-(4-(7H-pyrrolol[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate	Treatment of myelofibrosis secondary to polycythemia vera or essential thrombocythemia
Bulgarian	(R)-3-(4-(7H-пиролол[2,3-d]пиримидин-4-ил)-1H-пиразол-1-ил)-3-циклопентил пропаненитрил фосфат	Лечение на вторична миелофиброза при полицитемия вера или есенциална тромбоцитемия
Czech	(R)-3-(4-(7H-pyrrolol[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyklopentylpropanonitril fosfát	Léčba sekundární myelofibrózy na podkladě t-polycytémie vera či esenciální trombocytémie.
Danish	(R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropannitril fosfat	Behandling af myelofibrose sekundær til polycytæmia vera og essentiel trombocytæmi
Dutch	(R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidine-4-yl)-1H-pyrazool-1-yl)-3-cyclopentylpropaannitrielfosfaat	Behandeling van myelofibrose secondair aan polycythaemia vera ofwel secondair aan essentiële thrombocythaemia
Estonian	(R)-3-(4-(7H-pürrolool[2,3-d]pürimidiin-4-üül)-1H-pürasool-1-üül)-3-tsüklopentüülpropaannitriilfosfaat	Tõelisest polütsüteemiast või essentsiaalsest trombotsüteemiast tingitud müelofibroosi ravi
Finnish	(R)-3-(4-(7H-pyrroloili[2,3-d]pyrimidin-4-yyli)-1H-pyratsol-1-yyli)-3-syklopentyylipropaanitriilifosfaatti	Polysytemia verasta tai essentiaalisesta trombosytemiasta johtuvan myelofibroosin hoito
French	Phosphate de (R)-3-(4-(7H-pyrrolol[2,3-d]pyrimidine-4-yl)-1H-pyrazol-1-yl)-3-cyclopentyl-propanenitrile	Traitement de la myélofibrose due à la polyglobulie de Vaquez ou à la thrombocythémie essentielle
German	(R)-3-(4-(7H-Pyrrolol[2,3-d]pyrimidin-4-yl)-1H-Pyrazol-1-yl)-3-Cyclopentylpropannitrilphosphat	Behandlung von postpolyzythämischer und (essenzieller) postthrombozythämischer Myelofibrose
Greek	φωσφορικό (R)-3-(4-(7H-πυρολολ[2,3-d]πυριμιδιν-4-υλ)-1H-πυραζολ-1-υλ)-3-κυκλοπεντυλπροπανονιτρίλιο	θεραπεία των ασθενών με μυελοΐνωση δευτερογενούς αληθής πολυκυτταραιμίας ή ιδιοπαθούς θρομβοκυτταραιμίας
Hungarian	(R)-3-(4-(7H-pirrolol[2,3-d]pirimidin-4-il)-1H-pirazol-1-il)-3-ciklopentilpropánnitril-foszfát	Polycythaemia vera illetve esszenciális thrombocythaemia következtében fennálló myelofibrosis kezelése
Italian	(R)-3-(4-(7H-pirrolol[2,3-d]pirimidin-4-il)-1H-pirazol-1-il)-3-ciclopentil-propanonitrile fosfato	Trattamento della mielofibrosi secondaria a policitemia vera o trombocitemia essenziale

[1] At the time of designation

Language	Active ingredient	Indication
Latvian	(R)-3-(4-(7H-pirol[2,3-d]pirimidīn-4-il)-1H-pirazol-1-il)-3-ciklopentilpropānnitrila fosfāts	Sekundāras mielofibrozes ārstēšanai ko izraisījusi īstā policitēmija (*polycythaemia vera*) vai esenciālā trombocitēmija
Lithuanian	(R)-3-(4-(7H-pirolol[2,3-d]pirimidin-4-il)-1H-pirazol-1-il)-3-ciklopentil propano nitrilo fosfatas	Antrinės mielofibrozės gydymas, esant tikrąjai policitemijai ar pirminei trombocitopenijai
Maltese	(R)-3-(4-(7H-pyrrolol[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate	Kura tal-mjelofibrożi sekondarja għal poliċitemija vera jew trombożitemija essenzjali
Polish	fosforan (R)-3-(4-(7H-pirolol[2,3-d]pirymidyn-4-il)-1H-pirazol-1-il)-3-cyklopentylo-propanonitrylu	Leczenie mielofibrozy wtórnej, czerwienicy prawdziwej lub nadpłytkowości samoistnej
Portuguese	Fosfato de (R)-3-(4-(7H-pirrolol[2,3-d]pirimidina-4-il)-1H-pirazol-1-il)-3-ciclopentilpropanonitrilo	Tratamento da mielofibrose secundária a policitémia vera e a trombocitémia primária
Romanian	Fosfat de (R)-3-(4-(7H-pirolol[2,3-d]pirimidin-4-il)-1H-pirazol-1-il)-3-ciclopentil-propionitril	Tratamentul mielofibrozei secundare policitemiei vera sau trombocitemiei esenţiale
Slovak	(R)-3-(4-(7H-pyrolol[2,3-d]pyrimidín-4-yl)-1H-pyrazol-1-yl)-3-cyklopentylpropánnitril fosfát	Liečba myelofibrózy po polycytémii vera alebo esenciálnej trombocytémii
Slovenian	(R)-3-(4-(7H-pirolol[2,3-d]pirimidin-4-il)-1H-pirazol-1-il)-3-ciklopentil-propan-nitril fosfat	Zdravljenje mielofibroze zaradi prave policitemije ali esencialne trombocitopenije
Spanish	Fosfato de (R)-3-(4-(7H-pirrolol[2,3-d]pirimidina-4-il)-1H-pirazol-1-il)-3-ciclopentil propanonitrilo	Tratamiento la mielofibrosis secundaria a policitemia vera o a trombocitemia esencial
Swedish	(R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyklopentylpropan-nitrilfosfat	Behandling av myelofibros sekundär till polycytemia vera och essentiell trombocytemi
Norwegian	(R)-3-(4-(7H-pyrrolol[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-syklopentylpropannitrilfosfat	Behandling av myelofibrose sekundært til polycytemia vera eller essensiell trombocytemi
Icelandic	(R)-3-(4-(7H-pýrrolól (2,3-d]pýrimidín-4-ýl)-1H-pýrazól-1-ýl)-3-sýklópentýlprópannítríl fosfat	Lyfjameðferð sjúklinga með afleitt mergnetjuhersli í tengslum við rauðkornamergð og frumblóðflagnafjölgun (Thrombocythemia essentialis)