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SCIENCE MEDICINES HEALTH

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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Methyl 4, 6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo [3, 4-b]pyridine-3-yl]-5-pyrimidinyl(methyl)carbamate for the treatment of pulmonary arterial hypertension including chronic thromboembolic pulmonary hypertension

First publication	10 July 2008
Rev.1: transfer of sponsorship	2 September 2009
Rev.2: transfer of sponsorship	17 November 2011
Rev.3: information about Marketing Authorisation	24 April 2014
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 20 December 2007, orphan designation (EU/3/07/518) was granted by the European Commission to Bayer HealthCare AG, Germany, for Methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4 b]pyridine-3-yl]-5-pyrimidinyl(methyl)carbamate for the treatment of pulmonary arterial hypertension including chronic thromboembolic pulmonary hypertension.

The sponsorship was transferred to Bayer Schering Pharma AG, Germany, in April 2009. Bayer Shering Pharma AG changed its name to Bayer Pharma AG in October 2011.

What is pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension?

Pulmonary arterial hypertension is a rare blood vessel disorder of the lung in which the pressure in the pulmonary artery (the blood vessel that leads from the heart to the lungs) rises above normal levels. An increase of the number of smooth muscle cells in the walls of small lung arteries (a phenomenon called proliferation) that are remodelling the vessels, may lead to obstructions in the microcirculation, which will then lead to an increase in the blood pressure.

Chronic thromboembolic pulmonary hypertension is a complication representing less than 1% of all cases of acute pulmonary embolism (the sudden blocking of a lung artery by a clot or foreign material which has been brought to its site by the blood current), which directly leads to pulmonary



hypertension. Pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension are chronically debilitating and life-threatening.

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

At the time of designation, pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension affected less than 2 in 10,000 people in the European Union (EU). This was equivalent to a total of fewer than 100,000 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?

Several medicinal products were authorised for the treatment of pulmonary arterial hypertension in the Community at the time of submission of the application for orphan drug designation. Methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-pyrimidinyl(methyl)carbamate might be of potential significant benefit for the treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension, in particular with regards to improved efficacy based on the new mechanism of action. This benefit will have to be confirmed at the time of marketing authorisation and will be necessary to maintain the orphan status.

How is this medicine expected to work?

One of the mechanisms that contributes to pulmonary arterial hypertension is the body's ability to increase the thickness of the pulmonary vessels. In pulmonary arterial hypertension this ability is not well regulated and the vessels become more narrow. As the inner space of the vessels becomes smaller, it is increasingly difficult for blood to go through the vessels and the disease worsens.

Methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-pyrimidinyl(methyl)carbamate is expected to stimulate a protein called soluble guanylate cyclase (sGC) that is present in vascular cells and platelets. Since activation of the sGC protein may lead to dilatation of blood vessels, inhibition of cell proliferation and cell migration, a favourable effect on the condition is expected.

What is the stage of development of this medicine?

At the time of submission, the effects of methyl 4, 6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo [3, 4-b] pyridine-3-yl]-5-pyrimidinyl (methyl) carbamate were evaluated in experimental models.

At the time of submission of the application for orphan designation, clinical trials in patients with pulmonary arterial hypertension including chronic thromboembolic pulmonary hypertension were completed.

Methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-pyrimidinyl(methyl)carbamate was not authorised anywhere worldwide for pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension or designated as orphan medicinal product elsewhere for this condition, at the time of submission.

*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 500,300,000 (Eurostat 2007).

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 8 November 2007 recommending the granting of this designation.

Update: Methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-pyrimidinyl(methyl)carbamate (Adempas) has been authorised in the EU since 27 March 2014 for the following therapeutic indications:

Chronic thromboembolic pulmonary hypertension (CTEPH)

Adempas is indicated for the treatment of adult patients with WHO Functional Class (FC) II to III with

- inoperable CTEPH,
- persistent or recurrent CTEPH after surgical treatment,

to improve exercise capacity.

Pulmonary arterial hypertension (PAH)

Adempas, as monotherapy or in combination with endothelin receptor antagonists, is indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO Functional Class (FC) II to III to improve exercise capacity.

Efficacy has been shown in a PAH population including aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease.

More information on Adempas 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:

Bayer Pharma AG
D-13342 Berlin
Germany
Telephone: +49 214 305 1348
Telefax: +49 214 305 1603
E-mail: medical-information@bayerhealthcare.com

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 languages¹, Norwegian and Icelandic

Language	Active Ingredient	Indication
English	Methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-pyrimidinyl(methyl)carbamate	Treatment of pulmonary arterial hypertension including treatment of chronic thromboembolic pulmonary hypertension
Bulgarian	Метил 4,6-диамино-2-[1-(2-флуоробензил)-1H-пиразоло[3,4-б]пиридин-3-ил]-5-пиримидинил(метил)карбамат	Лечение на белодробна артериална хипертония, включително лечение на хронична тромбоемболична белодробна хипертония
Czech	Methyl- 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-pyrimidinyl(methyl)karbamát	Léčba plicní arteriální hypertenze včetně chronické tromboembolické plicní hypertenze
Danish	Methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-pyrimidinyl(methyl)karbamát	Behandling af pulmonal arteriel hypertension inklusive behandling af kronisk tromboembolisk pulmonal hypertension
Dutch	Methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-pyrimidinyl(methyl)carbamaat	Behandeling van pulmonale arteriële hypertensie met inbegrip van behandeling van chronische trombo-embolische pulmonale hypertensie
Estonian	Metüül 4,6-diamino-2-[1-(2-fluorobensüül)-1H-pürasolo[3,4-b]püridiin-3-üül]-5-pürimidinüül(metüül)karbamaat	Pulmonaalhüpertensiooni kaasa arvatud kroonilise tromboemboolse pulmonaalhüpertensiooni ravi
Finnish	Metyyli-4,6-diamino-2-[1-(2-fluoribentsyyli)-1H-pyratsolo[3,4-b]pyridin-3-yyli]-5-pyrimidinyyli(metyyli)karbamaatti	Keuhkoverenkierron hypertension, krooninen tromboembolinen keuhkoverenpainetauti mukaanlukien, hoito
French	Méthyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-pyrimidinyl carbamate de méthyle	Traitement de l'hypertension artérielle pulmonaire y compris l'hypertension pulmonaire thromboembolique chronique
German	Methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-pyrimidinyl(methyl)carbamát	Behandlung der pulmonalen arteriellen Hypertonie, einschließlich der chronisch thromboembolischen pulmonalen Hypertonie
Greek	Πυριμιδινυλομεθυλοκαρβαμιδικός μεθύλο 4,6-διαμίνo-2[1-2(φθοροβένζυλο)-1 ^H -πυραζολο [3,4-b]πυριδινό-3]-5-υλ-εστέρας	Θεραπεία της πνευμονικής αρτηριακής υπέρτασης περιλαμβανομένης της θεραπείας της χρόνιας πνευμονικής υπέρτασης θρομβοεμβολικής αιτιολογίας

¹ At the time of designation

Language	Active Ingredient	Indication
Hungarian	Metil 4,6-diamino-2-[1-(2-fluorobenzil)-1H-pirazolo[3,4-b]piridin-3-il]-5-pirimidinil(metil)karbamát	Pulmonáris arteriális hipertónia kezelése beleértve a krónikus thromboemboliás pulmonáris hipertóniát
Italian	Metil 4,6-diammino-2-[1-(2-fluorobenzil)-1H-pirazolo[3,4-b]piridin-3-yl]-5-pirimidinil(metil)carbammato	Trattamento dell'ipertensione arteriosa polmonare, compresa il trattamento dell'ipertensione polmonare cronica tromboembolica
Latvian	Metil-4,6-diamino-2-[1-(2-fluorobenzil)-1H-pirazolo [3,4-b]piridīn-3-il]-5-pirimidinil(metil)karbamāts	Plaušu arteriālās hipertensijas un hroniskās tromboemboliskās plaušu hipertensijas ārstēšana
Lithuanian	Metil 4,6-diamino-2-[1-(2-fluorobenzil)-1H-pirazolo[3,4-b]piridino-3-il]-5-pirimidinil (metil) karbamatas	Plaučių arterinės hipertenzijos gydymas, įskaitant lėtinės tromboembolinės plaučių hipertenzijos gydymą
Maltese	Methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-pyrimidinyl(methyl)carbamate	Kura ta' pressjoni arterjali pulmonari għolja li tinkludi l-kura tal-pressjoni pulmonari trombo-embolika għolja kronika
Polish	Metylo 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pirazolo[3,4-b]piridino-3-yl]-5-pirimidinylo(metylu)karbaminian	Leczenie tętniczego oraz przewlekłego zakrzepowo-zatorowego nadciśnienia płucnego
Portuguese	Metil 4,6-diamino-2-[1-(2-fluorobenzil)-1H-pirazol[3,4-b]piridina-3-ilo]-5-pirimidinil(metil) carbamato	Tratamento da hipertensão arterial pulmonar incluindo a hipertensão pulmonar tromboembólica crónica
Romanian	Metil 4,6-diamino-2-[1-(2-fluorobenzil)-1H-pirazolo[3,4-b]piridin-3-il]-5-pirimidinil(metil) carbamat	Tratamentul hipertensiunii arteriale pulmonare incluzând tratamentul hipertensiunii pulmonare tromboembolice cronice
Slovak	Metyl-4,6-diamino-2-[1-(2-fluórbenzyl)-1H-pyrazolo[3,4-b]pyridín-3-yl]-5-pyrimidín-1-yl(metyl)karbamát	Liečba pľúcnej arteriálnej hypertenzie vrátane liečby chronickej tromboembolickej pľúcnej hypertenzie
Slovenian	Metil 4,6-diamino-2-[1-(2-fluorobenzil)-1H-pirazolo[3,4-b]piridin-3-il]-5-pirimidinil(metil)karbamát	Zdravljenje pljučne arterijske hipertenzije vključno s kronično tromboembolično pljučno hipertenzijo
Spanish	Metil 4,6-diamino-2-[1-(2-fluorobencil)-1H-pirazolo[3,4-b]piridin-3-il]-5-pirimidinil(metil) carbamato	Tratamiento de la hipertensión arterial pulmonar, incluyendo el tratamiento de la hipertensión pulmonar tromboembólica crónica

Language	Active Ingredient	Indication
Swedish	Metyl 4,6-diamin-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-pyrimidinyl(metyl)karbamat	Behandling av pulmonell arteriell hypertension inclusive behandling av kronisk tromboembolisk pulmonell hypertension
Norwegian	Metyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridin-3-yl]-5-pyrimidinyl(metyl)karbamat	Behandling av pulmonal arteriell hypertensjon inkludert behandling av kronisk tromboembolisk pulmonal hypertensjon
Icelandic	Metthýl 4,6-dtvíamínó-2-[1-(2-fluóróbensýl)-1H-pýrazoló[3,4-b]pýridín-3-il]-5-pýrimídínýl(methýll)karbamat	Meðferð við háþrýstingi í lungnablóðrás þar með talin meðferð við langvinnum háþrýstingi í lungnablóðrás í kjölfar segareks