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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

2-{4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}-N-(methylsulfonyl)acetamide for the treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension

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Rev.2: sponsor's change of address	5 March 2015
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On 26 August 2005, orphan designation (EU/3/05/316) was granted by the European Commission to Nippon Shinyaku Co. Ltd, Germany, for 2-{4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}-N-(methylsulfonyl)acetamide for the treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension.

The sponsorship was transferred to Actelion Registration Limited, United Kingdom, in February 2009.

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 vessel that leads blood from the heart to the lungs) rises above normal levels. An increase of the number of smooth muscle cells in the walls of small 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 between 1 and 3 in 10,000 people in the European Union (EU). This was equivalent to a total of between 47,000 and 140,000 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?

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.

2-{4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}-N-(methylsulfonyl)acetamide might be of potential significant benefit for the treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension because it might improve the long-term outcome of the patients. The assumption 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?

In pulmonary arterial hypertension there appears to be an imbalance between vasoconstrictors (substances produced by certain cells that help to narrow the blood vessels) and vasodilators (substances produced by other cells that help to widen the blood vessels, such as prostacyclin). This imbalance seems to be caused, at least in part, by the lack or reduction of a certain enzyme, prostacyclin synthase, responsible to convert prostacyclin into his active form. Prostacyclin causes vasodilatation and has also a strong effect in blocking the platelets (blood cells responsible to make the blood clot) to make the clot. 2-{4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}-N-(methylsulfonyl)acetamide is a substance similar to prostacyclin and is expected to act in a similar way on the pulmonary arteries in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension.

What is the stage of development of this medicine?

The effects of 2-{4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}-N-(methylsulfonyl)acetamide were evaluated in experimental models.

At the time of submission of the application for orphan designation, no clinical trials in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension were initiated.

2-{4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}-N-(methylsulfonyl)acetamide 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.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 13 July 2005 recommending the granting of this designation.

*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 25), Norway, Iceland and Liechtenstein. At the time of designation, this represented a population of 466,600,000 (Eurostat 2005).

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 languages¹, Norwegian and Icelandic

Language	Active ingredient	Indication
English	2-{4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}-N-(methylsulfonyl)acetamide	Treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension
Bulgarian	2-{4-[(5,6-дифенилпиразин-2-ил)(изопропил)амино]бутокси}-N-(метилсулфонил)ацетамид	Лечение на пулмонална артериална хипертензия и хронична тромбоемболична пулмонална хипертензия
Czech	2-{4-[(5,6-difenylypyrazin-2-yl)(izopropyl)amino]butoxy}-N-(metylsulfonyl)acetamid	Léčba plicní arteriální hypertenze a chronické tromboembolické plicní hypertenze
Danish	2-{4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}-N-(methylsulfonyl)acetamid	Behandling af pulmonal arteriel hypertension og kronisk tromboembolisk pulmonal hypertension
Dutch	2-{4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}-N-(methylsulfonyl)acetamide	Behandeling van pulmonale arteriële hypertensie en chronische trombo-embolische pulmonale hypertensie
Estonian	2-{4-[5,6-difenüülpürasiin-2-üül](isopropüül)amino] butoksü}-N-(metüülsulfonüül) atsetamiid	Pulmonaalhüpertensiooni ja kroonilise tromboemboolse pulmonaalhüpertensiooni ravi
Finnish	2-{4-[(5,6-difenyylipyratsiini-2-yyli)(isopropyli)amino]butoksi}-N-(metyylisulfonyyli)asetamidi	Keuhkoverenkierron hypertension ja kroonisen tromboembolisen keuhkoverenpainetaudin hoito
French	2-{4-[(5,6-diphénylpyrazin-2-yl)(isopropyl)amino]butoxy}-N-(méthylsulfonyl)acétamide	Traitement de l'hypertension artérielle pulmonaire et de l'hypertension pulmonaire thromboembolique chronique
German	2-{4-[(5,6-Diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}-N-(methylsulfonyl)acetamid	Behandlung der pulmonalen arteriellen Hypertonie und der chronisch thromboembolischen pulmonalen Hypertonie
Greek	2-{4-[(5,6-διφαινυλοπυραζινο-2-υλ)(ισοπροπουλο)αμινο]βουτοξυ}-N-(μεθυλοσουλφονυλ)ακεταμίδιο	Θεραπεία της πνευμονικής αρτηριακής υπέρτασης και της χρόνιας πνευμονικής υπέρτασης θρομβοεμβολικής αιτιολογίας
Hungarian	2-{4-[(5,6-difenilpirazin-2-il)(izopropil)amino]butoxi}-N-(metilsulfonil)acetamid	Pulmonáris arteriális hipertónia és krónikus thromboemboliás pulmonáris kezelése
Italian	2-{4-[(5,6-difenil-pirazina-2-yl)(isopropil)ammino]butossi}-N-(metil sulfonil)acetamide	Trattamento dell'ipertensione arteriosa polmonare e dell'ipertensione polmonare cronica tromboembolica
Latvian	2-{4-[(5,6-difenilpirazīn-2-il)(izopropil)amino]butoksi}-N-(metilsulfonīl)acetamīds	Plaušu arteriālās hipertensijas un hroniskās tromboemboliskās plaušu hipertensijas ārstēšanai
Lithuanian	2-{4-[(5,6-difenilpirazin-2-il)(izopropil)amino]butoksi}-N-(metilsulfonil)acetamidas	Plaučių arterinės hipertenzijos ir lėtinės tromboembolinės plaučių hipertenzijos gydymas

¹ At the time of transfer of sponsorship

Language	Active ingredient	Indication
Maltese	2-{4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy}-N-(methylsulfonyl)acetamide	Kura ta' pressjoni arterjali pulmonari għolja u ta' pressjoni pulmonari trombo-embolika għolja kronika
Polish	2-{4-[(5,6-difenylopyrazin-2-ylo)(izopropyl)amino]butoksy}-N-(metylosulfonylo)acetamid	Leczenie tętniczego nadciśnienia płucnego oraz przewlekłego zakrzepowo-zatorowego nadciśnienia płucnego
Portuguese	2-{4-[(5,6-difenilpirazin-2-il)(isopropil)amino]butoxi}-N-(metilsulfonil)acetamida	Tratamento da hipertensão arterial pulmonar e da hipertensão pulmonar tromboembólica crónica
Romanian	2-{4-[(5,6-difenilpirazin-2-il)(izopropil)amino]butoxi}-N-(metilsulfonil)acetamidă	Tratamentul hipertensiunii arteriale pulmonare și al hipertensiunii pulmonare cronice tromboembolice
Slovak	2-{4-[(5,6-difenylopyrazín-2-yl)(izopropyl)amino]butoxy}-N-(metylsulfonyl)acetamid	Liečba pľúcnej arteriálnej hypertenzie a chronickej tromboembolickej pľúcnej hypertenzie
Slovenian	2-{4-[(5,6-difenilpirazin-2-il)(izopropil)amino]butoksi}-N-(metilsulfonil)acetamid	Zdravljenje pljučne arterijske hipertenzije in kronične tromboembolične pljučne hipertenzije
Spanish	2-{4-[(5,6-difenilpiracina-2-il)(isopropil)amino]butoxi}-N-(metilsulfonil)acetamida	Tratamiento de la hipertensión arterial pulmonar y de la hipertensión pulmonar tromboembólica crónica
Swedish	2-{4-[(5,6-difenylopyrazin-2-yl)(isopropyl)amino]butoxi}-N-(metylsulfonyl)acetamid	Behandling av pulmonell arteriell hypertension samt kronisk tromboembolisk pulmonell hypertension
Norwegian	2-{4-[(5,6-difenylopyrazin-2-yl)(isopropyl)amino] butoksy}-N-(metylsulfonyl)acetamid	Behandling av pulmonal arteriell hypertensjon og kronisk tromboembolisk pulmonal hypertensjon
Icelandic	2-{4-[(5,6-tvífenýlpýrazín-2-ýl)(ísóprópýl)amínó]bútoxý}-N-(metýlsúlfónýl)acetamíð	Meðferð við háþrýstingi í lungnablóðrás og langvinnum háþrýstingi í lungnablóðrás í kjölfar segareks