



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

(S)-8-{2-amino-6-[1-(5-chloro-biphenyl-2-yl)-(R)-2,2,2-trifluoro-ethoxy]-pyrimidin-4-yl}-2,8-diaza-spiro[4.5]decane-3-carboxylic acid ethyl ester for the treatment of pulmonary arterial hypertension

On 20 April 2017, orphan designation (EU/3/17/1861) was granted by the European Commission to Biological Consulting Europe Ltd, United Kingdom, for (S)-8-{2-amino-6-[1-(5-chloro-biphenyl-2-yl)-(R)-2,2,2-trifluoro-ethoxy]-pyrimidin-4-yl}-2,8-diaza-spiro[4.5]decane-3-carboxylic acid ethyl ester (also known as KAR5585) for the treatment of pulmonary arterial hypertension.

What is pulmonary arterial hypertension?

Pulmonary arterial hypertension is a condition in which patients have abnormally high blood pressure in the arteries that supply the lungs. In pulmonary arterial hypertension, the muscles in the walls of the arteries in the lungs become thicker and the arteries become narrower, making it harder for blood to flow to the lungs.

Pulmonary arterial hypertension is a long-term debilitating and life-threatening condition that shortens patients' life expectancy because it may lead to difficulty breathing and heart failure.

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

At the time of designation, pulmonary arterial hypertension affected less than 2 in 10,000 people in the European Union (EU). This was equivalent to a total of fewer than 103,000 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 medicines were authorised for the treatment of pulmonary arterial hypertension in the EU at the time of designation. They included ambrisentan, bosentan, epoprostenol, iloprost, macitentan, riociguat, sildenafil, tadalafil and treprostinil. Surgery was also used in some patients to carry out a

*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 28), Norway, Iceland and Liechtenstein. This represents a population of 515,700,000 (Eurostat 2017).



lung transplant or atrial septostomy (where a small hole is created between the upper two chambers of the heart, the atria).

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with pulmonary arterial hypertension because early laboratory studies show that combining it with another available treatment (ambrisentan) produced greater reduction in blood pressure and thickness of the arteries than either medicine alone, or than the combination of ambrisentan with tadalafil. 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?

The medicine is a 'pro-drug' which is converted in the body into its active substance. This active substance blocks an enzyme called tryptophan hydroxylase 1, which controls an important step in the production of serotonin. Patients with pulmonary arterial hypertension produce too much serotonin in their blood vessels, and this is thought to play a role in the development of the condition. Blocking serotonin production with the medicine is therefore expected to relieve symptoms of pulmonary arterial hypertension.

What is the stage of development of this medicine?

The effects of the medicine have been evaluated in experimental models.

At the time of submission of the application for orphan designation, no clinical trials with this medicine in patients with pulmonary arterial hypertension had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for the condition. Orphan designation of the medicine had been granted in the United States for pulmonary arterial hypertension.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 15 March 2017 recommending the granting of this 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 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:

Contact details of the current sponsor for this orphan designation can be found on EMA website, on the medicine's [rare disease designations page](#).

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 | (S)-8-{2-amino-6-[1-(5-chloro-biphenyl-2-yl)-(R)-2,2,2-trifluoro-ethoxy]-pyrimidin-4-yl}-2,8-diazaspiro[4.5]decane-3-carboxylic acid ethyl ester | Treatment of pulmonary arterial hypertension |
| Bulgarian | (S)-8-{2-амино-6-[1-(5-хлоро-бифенил-2-ил)-(R)-2,2,2-трифлуоро-етокси]-пиримидин-4-ил}-2,8-диаза-спиро[4.5]декан-3-карбоксилно-киселинен етил естер | Лечение на белодробна артериална хипертония |
| Croatian | Etilni ester (S)-8-{2-amino-6-[1-(5-klorbifenil-2-il)-(R)-2,2,2-trifluoroetoksi]-pirimidin-4-il}-2,8-diazaspiro[4.5]dekan-3-karboksilne kiseline | Liječenje plućne arterijske hipertenzije |
| Czech | Ethylester kyseliny (S)-8-{2-amino-6-[1-(5-chlorbifenyl-2-yl)-(R)-2,2,2-trifluorethoxy]pyrimidin-4-yl}-2,8-diazaspiro[4.5]dekan-3-karboxylové | Léčba plicní arteriální hypertenze |
| Danish | (S)-8-{2-amino-6-[1-(5-chlorobiphenyl-2-yl)-(R)-2,2,2-trifluoroethoxy]-pyrimidin-4-yl}-2,8-diazaspiro[4.5]decan-3-carboxylsyreethylester | Behandling af pulmonal arteriel hypertension |
| Dutch | (S)-8-{2-amino-6-[1-(5-chloorbifenyl-2-yl)-(R)-2,2,2-trifluorethoxy]-pyrimidine-4-yl}-2,8-diazaspiro[4,5]decaan-3-carbonzuurethylester | Behandeling van pulmonale arteriële hypertensie |
| Estonian | (S)-8-{2-amino-6-[1-(5-kloro-bifenüül-2-üül)-(R)-2,2,2-trifluoro-etoksü]-pürimidiin-4-üül}-2,8-diasaspiro[4,5]dekaan-3-karboksüülhappe etüülester | Arteriaalse pulmonaalhüpertensiooni ravi |
| Finnish | (S)-8-{2-amino-6-[1-(5-klooribifenyyl-2-yyli)-(R)-2,2,2-trifluoroetoksi]-pyrimidin-4-yyli}-2,8-diatsaspiro[4.5]dekaani-3-karboksylihappoetyyliesteri | Keuhkoverenkierron hypertension hoito |
| French | (S)-8-{2-amino-6-[1-(5-chloro-biphényl-2-yl)-(R)-2,2,2-trifluoro-éthoxy]-pyrimidine-4-yl}-2,8-diazaspiro[4.5]décane-3-carboxylate d'éthyle | Traitement de l'hypertension artérielle pulmonaire |
| German | (S)-8-{2-Amino-6-[1-(5-chlor-biphenyl-2-yl)-(R)-2,2,2-trifluorethoxy]-pyrimidin-4-yl}-2,8-diazaspiro[4.5]decan-3-carbonsäureethylester | Behandlung der pulmonalen arteriellen Hypertonie |
| Greek | (S)-8-{2-αμινο-6-[1-(5-χλωρο-διφαινυλ-2-υλ)-(R)-2,2,2-τριφθορο-αιθοξυ]-πυριμιδιν-4-υλ}-2,8-διαζασπειρο[4.5]δεκανο-3-καρβοξυλικός αιθυλεστέρας | Θεραπεία της πνευμονικής αρτηριακής υπέρτασης |
| Hungarian | (S)-8-{2-amino-6-[1-(5-klór-bifenil-2-il)-(R)-2,2,2-trifluór-etoxi]-pirimidin-4-il}-2,8-diazaspiro[4.5]dekán-3-karboxilsav-etilészter | Pulmonáris arteriális hipertónia kezelése |
| Italian | Estere etilico dell'acido (S)-8-{2-amino-6-[1-(5-cloro-difenil-2-il)-(R)-2,2,2-trifluoro-etossi]-pirimidin-4-il}-2,8-diaza-spiro[4.5]decano-3-carbossilico | Trattamento dell'ipertensione arteriosa polmonare |
| Latvian | (S)-8-{2-amino-6-[1-(5-hlor-bifenil-2-il)-(R)-2,2,2-trifluor-etoksi]-pirimidīn-4-il}-2,8-diaza- | Plaušu arteriālās hipertensijas ārstēšana |

¹ At the time of designation

| Language | Active ingredient | Indication |
|------------|---|--|
| | spiro[4.5]dekān-3-karbonskābes etilesteris | |
| Lithuanian | (S)-8-{2-amino-6-[1-(5-chloro-bifenil-2-il)-(R)-2,2,2-trifluoro-etoksi]-pirimidin-4-il}-2,8-diaza-spiro[4,5]dekano-3-karboksirūgšties etilo esteris | Plaučių arterinės hipertenzijos gydymas |
| Maltese | (S)-8-{2-ammino-6-[1-(5-kloro-bifenil-2-il)-(R)-2,2,2-trifluoro-etossi]-pirimidin-4-il}-2,8-dijaža-spiro[4.5]dekan-3-etil ester acidu karbossiliku | Kura ta' pressjoni arterjali pulmonari għolja |
| Polish | Ester etylowy kwasu (S)-8-{2-amino-6-[1-(5-chloro-bifenylo-2-ylo)-(R)-2,2,2-trifluoro-etoksy]-pirimidyno-4-ylo}-2,8-diaza-spiro[4.5]dekano-3-karboksylowego | Leczenie tętniczego nadciśnienia płucnego |
| Portuguese | Éster etílico de ácido (S)-8-{2-amino-6-[1-(5-cloro-bifenil-2-il)-(R)-2,2,2-trifluoro-etoxi]-pirimidin-4-il}-2,8-diaza-spiro[4.5]decano-3-carboxílico | Tratamento da hipertensão arterial pulmonar |
| Romanian | Etil ester al acidului (S)-8-{2-amino-6-[1-(5-cloro-bifenil-2-il)-(R)-2,2,2-trifluoro-etoxi]-pirimidin-4-il}-2,8-diaza-spiro[4.5]decan-3-carboxilic | Tratamentul hipertensiunii arteriale pulmonare |
| Slovak | Etyl ester kyseliny (S)-8-{2-amino-6-[1-(5-chlór-bifenylo-2-yl)-(R)-2,2,2-trifluóretoxy]pyrimidín-4-yl}-2,8-diazaspiro[4.5]dekán-3-karboxylovej | Liečba pľúcnej artériovej hypertenzie |
| Slovenian | Etilni ester (S)-8-{2-amino-6-[1-(5-kloro-bifenil-2-il)-(R)-2,2,2-trifluoro-etoksi]-pirimidin-4-il}-2,8-diaza-spiro[4.5]dekan-3-karboksilne kisline | Zdravljenje pljučne arterijske hipertenzije vključno |
| Spanish | Éster etílico de ácido (S)-8-{2-amino-6-[1-(5-cloro-bifenil-2-il)-(R)-2,2,2-trifluoro-etoxi]-pirimidina-4-il}-2,8-diaza-espiro[4.5]-decano-3-carboxílico | Tratamiento de la hipertensión arterial pulmonar |
| Swedish | (S)-8-{2-amino-6-[1-(5-klorbifenyl-2-yl)-(R)-2,2,2-trifluoretoksi]-pyrimidin-4-yl}-2,8-diazaspiro[4.5]dekan-3-karboxylsyraetyl ester | Behandling av pulmonell arteriell hypertension |
| Norwegian | (S)-8-{2-Amino-6-[1-(5-klorbifenyl-2-yl)-(R)-2,2,2-trifluoretoksy]-pyrimidin-4-yl}-2,8-diaza-spiro[4.5]dekan-3-karboxylsyreetyl ester | Behandling av pulmonal arteriell hypertensjon |
| Icelandic | (S)-8-{2-aminó-6-[1-(5-klórbífenýl-2-ýl)-(R)-2,2,2-tríflúretoxy]-pýrimídín-4-ýl}-2,8-díasaspíró[4,5]dekan-3-karboxýlsýruetyl ester | Meðferð við háþrýstingi í lungnablóðrás |