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Public summary of opinion on orphan designation

Tacrolimus for the treatment of pulmonary arterial hypertension

On 23 August 2017, orphan designation (EU/3/17/1912) was granted by the European Commission to Vivus B.V., the Netherlands, for tacrolimus 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 in 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 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 data show that it may improve

*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).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

the outcome of patients whose disease did not respond to previous treatment. 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?

In pulmonary arterial hypertension, tacrolimus is expected to work by restoring 'the BMP signalling pathway'. This mechanism affects cells that make up lung arteries. In pulmonary arterial hypertension, the pathway does not work normally, which leads to excessive cells in the lung arteries, causing the arteries to narrow and so raise the blood pressure in the lungs. Tacrolimus is expected to attach to the proteins FKBP12 and calcineurin which are normally involved in the BMP signalling pathway. By attaching to these proteins, tacrolimus is expected to restore the signalling pathway, thus reducing the blood pressure in the lungs.

Tacrolimus has been authorised in the EU for several years to prevent organ rejection following a transplant.

What is the stage of development of this medicine?

The effects of tacrolimus have been evaluated in experimental models.

At the time of submission of the application for orphan designation, clinical trials with tacrolimus in patients with pulmonary arterial hypertension were ongoing.

At the time of submission, tacrolimus was not authorised anywhere in the EU for pulmonary arterial hypertension. Orphan designation of tacrolimus 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 13 July 2017 recommending the granting of this designation.

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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 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 languages[1], Norwegian and Icelandic

Language	Active ingredient	Indication
English	Tacrolimus	Treatment of pulmonary arterial hypertension
Bulgarian	Такролимус	Лечение на белодробна артериална хипертония
Croatian	Takrolimus	Liječenje plućne arterijske hipertenzije
Czech	Tacrolimusum	Léčba plicní arteriální hypertenze
Danish	Tacrolimus	Behandling af pulmonal arteriel hypertension
Dutch	Tacrolimus	Behandeling van pulmonale arteriële hypertensive
Estonian	Takroliimus	Arteriaalse pulmonaalhüpertensiooni ravi
Finnish	Takrolimuusi	Keuhkoverenkierron hypertension hoito
French	Tacrolimus	Traitement de l'hypertension artérielle pulmonaire
German	Tacrolimus	Behandlung der pulmonalen arteriellen Hypertonie
Greek	Τακρόλιμους	Θεραπεία της πνευμονικής αρτηριακής υπέρτασης
Hungarian	Takrolimusz	Pulmonáris arteriális hipertónia kezelése
Italian	Tacrolimus	Trattamento dell'ipertensione arteriosa polmonare
Latvian	Takrolimus	Plaušu arteriālās hipertensijas ārstēšana
Lithuanian	Takrolimuzas	Plaučių arterinės hipertenzijos gydymas
Maltese	Takrolimus	Kura ta' pressjoni arterjali pulmonari għolja
Polish	Takrolimus	Leczenie tętniczego nadciśnienia płucnego
Portuguese	Tacrolímus	Tratamento da hipertensão arterial pulmonar
Romanian	Tacrolimus	Tratamentul hipertensiunii arteriale polmonare
Slovak	Takrolimus	Liečba pľúcnej artériovej hypertenzie
Slovenian	Takrolimus	Zdravljenje pljučne arterijske hipertenzije
Spanish	Tacrolimus	Tratamiento de la hipertensión arterial pulmonar
Swedish	Tacrolimus	Behandling av pulmonell arteriell hypertension
Norwegian	Takrolimus	Behandling av pulmonal arteriell hypertensjon
Icelandic	Takrólímus	Meðferð við háþrýstingi í lungnablóðrás

[1] At the time of designation