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EMA/64185/2018

## Public summary of opinion on orphan designation

N-(tert-butylcarbamoyl)-5-cyano-2-((4'-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)oxy)benzenesulfonamide for the treatment of pulmonary arterial hypertension

On 22 February 2018, orphan designation (EU/3/18/1982) was granted by the European Commission to ATXA Therapeutics Limited, Ireland, for N-(tert-butylcarbamoyl)-5-cyano-2-((4'-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)oxy)benzenesulfonamide (also known as NTP42) for the treatment of pulmonary arterial hypertension.

### What is of 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 and less elastic, 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, selexipag, sildenafil, tadalafil and treprostinil. Lung transplantation or atrial septostomy

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\*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 517,400,000 (Eurostat 2018).

(where a small hole is created between the atria, the upper two chambers of the heart) were also used in some patients.

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with pulmonary arterial hypertension because laboratory studies showed that the medicine, given in combination with sildenafil, was more effective at reducing blood pressure than sildenafil alone. 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 blocks the action of a substance in the body called thromboxane. Thromboxane is involved in pulmonary hypertension by causing blood vessels to narrow. Patients with pulmonary arterial hypertension have too much thromboxane and by blocking the receptors to which thromboxane normally attaches, the medicine is expected to reduce 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 the 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 pulmonary arterial hypertension or designated as an orphan medicinal product elsewhere for this condition.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 18 January 2018 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<sup>1</sup>, Norwegian and Icelandic**

| Language  | Active ingredient                                                                                              | Indication                                         |
|-----------|----------------------------------------------------------------------------------------------------------------|----------------------------------------------------|
| English   | N-(tert-butylcarbamoyl)-5-cyano-2-((4'-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)oxy)benzenesulfonamide           | Treatment of pulmonary arterial hypertension       |
| Bulgarian | N-(терт-бутилкарбамоил)-5-циано-2-((4'-(дифлуорметокси)-[1,1'-бифенил]-3-ил)окси)бензенсулфонамид              | Лечение на белодробна артериална хипертония        |
| Croatian  | N-(tert-butylkarbamoyl)-5-cijano-2-((4'-(difluormetoksi)-[1,1'-bifenil]-3-il)oksi)benzensulfonamid             | Liječenje plućne arterijske hipertenzije           |
| Czech     | N-(terc-butylkarbamoyl)-5-kyano-2-((4'-(difluormethoxy)-[1,1'-bifenyl]-3-yl)oxy)benzensulfonamid               | Léčba plicní arteriální hypertenze                 |
| Danish    | N-(tert-butylcarbamoyl)-5-cyan-2-((4'-(difluormethoxy)-[1,1'-biphenyl]-3-yl)oxy)benzensulfonamid               | Behandling af pulmonal arteriel hypertension       |
| Dutch     | N-(tert-butylcarbamoyl)-5-cyaan-2-((4'-(difluormethoxy)-[1,1'-bifenyl]-3-yl)oxy)benzeensulfonamide             | Behandeling van pulmonale arteriële hypertensive   |
| Estonian  | N-(tert-butüülkarbamouül)-5-tsüano-2-((4'-(difluorometoksü)-[1,1'-bifenüül]-3-üül)oksü)benseensulfoonamiid     | Arteriaalse pulmonaalhüpertensiooni ravi           |
| Finnish   | N-(tert-butyylikarbamoyyli)-5-syaani-2-((4'-(difluorimetoksi)-[1,1'-bifenyyl]-3-yyli)oksi)bentseenisulfonamidi | Keuhkoverenkierron hypertension hoito              |
| French    | N-(tert-butylcarbamoyle)-5-cyano-2-((4'-(difluorométhoxy)-[1,1'-biphényle]-3-yl)oxy)benzènesulfonamide         | Traitement de l'hypertension artérielle pulmonaire |
| German    | N-(tert-Butylcarbamoyl)-5-Cyano-2-((4'-(Difluormethoxy)-[1,1'-Biphenyl]-3-yl)oxy)Benzolsulfonamid              | Behandlung der pulmonalen arteriellen Hypertonie   |
| Greek     | N-(τριτο-βουτυλοκαρβαμοϋλο)-5-κυανό-2-((4'-(διφθορομεθοξυ)-[1,1'-διφαινύλ]-3-υλ)οξυ)βενζολοσουλφοναμίδιο       | Θεραπεία της πνευμονικής αρτηριακής υπέρτασης      |
| Hungarian | N-(terc-butyl-karbamoil)-5-ciano-2-((4'-(difluormetoxi)-[1,1'-bifenil]-3-il)oxi)benzolszulfonamid              | Pulmonáris arteriális hipertónia kezelésé          |
| Italian   | N-(ter-butylcarbamoyl)-5-ciano-2-((4'-(difluorometossi)-[1,1'-bifenile]-3-ile)oxy)benzenesulfonamide           | Trattamento dell'ipertensione arteriosa polmonare  |
| Latvian   | N-(tert-butylkarbamoyl)-5-ciāno-2-((4'-(difluormetoksi)-[1,1'-bifenil]-3-il)oksi)benzēnsulfonamīds             | Plaušu arteriālās hipertensijas ārstēšana          |

<sup>1</sup> At the time of designation

| Language   | Active ingredient                                                                                         | Indication                                       |
|------------|-----------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| Lithuanian | N-(tert-butylkarbamoil)-5-ciano-2-((4'-(difluormetoksi)-[1,1'-bifenil]-3-il)oksi)benzensulfonamidas       | Plaučių arterinės hipertenzijos gydymas          |
| Maltese    | N-(tert-butylkarbamojl)-5-ċjano-2-((4'-(difluworometossi)-[1,1'-bifenil]-3-il)ossi)benžensulfonamid       | Kura ta' pressjoni arterjali pulmonari għolja    |
| Polish     | N-(tert-butylkarbamoil)-5-cyano-2-((4'-(difluorometoksy)-[1,1'-bifenyl]-3-yl)oksi)benzenosulfonamid       | Leczenie tętniczego nadciśnienia płucnego        |
| Portuguese | N-(terc-butylkarbamoil)-5-ciano-2-((4'-(difluorometoxi)-[1,1'-bifenil]-3-il)oxi)benzenossulfonamida       | Tratamento da hipertensão arterial pulmonar      |
| Romanian   | N-(tert-butylkarbamoil)-5-ciano-2-((4'-(difluormetoxi)-[1,1'-bifenil]-3-il)oxi)benzensulfonamidă          | Tratamentul hipertensiunii arteriale pulmonare   |
| Slovak     | N-(terc-butylkarbamoyl)-5-kyano-2-((4'-(difluormetoxi)-[1,1'-bifenyl]-3-yl)oxy)benzénsulfonamid           | Liečba pľúcnej artériovej hypertenzie            |
| Slovenian  | N-(terc-butylkarbamoil)-5-ciano-2-((4'-(difluorometoksi)-[1,1'-bifenil]-3-il)oksi)benzensulfonamid        | Zdravljenje pljučne arterijske hipertenzije      |
| Spanish    | N-(terc-butylkarbamóilo)-5-ciano-2-((4'-(difluorometoxi)-[1,1'-bifenilo]-3-ilo)oxígeno)benzenosulfonamida | Tratamiento de la hipertensión arterial pulmonar |
| Swedish    | N-(tert-butylkarbamoyl)-5-cyano-2-((4'-(difluormetoxi)-[1,1'-bifenyl]-3-yl)oxi)bensensulfonamid           | Behandling av pulmonell arteriell hypertension   |
| Norwegian  | N-(tert-butylkarbamoyl)-5-cyano-2-((4'-(difluormetoksy)-[1,1'-bifenyl]-3-yl)oksi)benzensulfonamid         | Behandling av pulmonal arteriell hypertensjon    |
| Icelandic  | N-(tert-bútýlkarbamóýl)-5-cýanó-2-((4'-(díflúormetoxý)-[1,1'-bífenýl]-3-ýl)oxý)bensensúlfónamíð           | Meðferð við háþrýstingi í lungnablóðrás          |