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Public summary of opinion on orphan designation

N-(trans-3-(5-((R)-1-hydroxyethyl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide for the treatment of cystic fibrosis

On 29 May 2019, orphan designation (EU/3/19/2163) was granted by the European Commission to Voisin Consulting S.A.R.L., France, for N-(trans-3-(5-((R)-1-hydroxyethyl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide (also known PTI-428) for the treatment of cystic fibrosis.

What is cystic fibrosis?

Cystic fibrosis is an inherited disease that affects the secretion of fluids from cells in the lungs and from the glands in the gut and pancreas. In cystic fibrosis, these fluids become thick, blocking the airways in the lungs and the flow of digestive juices in the gut and pancreas. This leads to inflammation and long-term infection of the lungs because of the build-up of thick mucus, and to poor growth and nutrition because of problems with the digestion and absorption of food.

Cystic fibrosis is caused by changes (mutations) in a gene that makes a protein called 'cystic-fibrosis transmembrane conductance regulator' (CFTR), which is involved in regulating the production of mucus and digestive juices.

Cystic fibrosis is a long-term debilitating and life-threatening disease because it severely damages the lung tissue, leading to problems with breathing and to recurrent chest infections.

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

At the time of designation, cystic fibrosis affected approximately 1 in 10,000 people in the European Union (EU). This was equivalent to a total of around 52,000 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).

*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 518,400,000 (Eurostat 2019).

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What treatments are available?

At the time of designation, Kalydeco (ivacaftor), Orkambi (ivacaftor and lumacaftor) and Symkevi (tezacaftor and ivacaftor) were authorised in the EU to treat patients with cystic fibrosis who have certain mutations in the gene for CFTR. Lung infection in cystic fibrosis was mainly treated with antibiotics. Other medicines used to treat the lung disease included anti-inflammatory medicines, bronchodilators (medicines that help to open up the airways in the lungs) and mucolytics (medicines that help break down mucus in the lungs). In addition, patients with cystic fibrosis were often given other types of medicines such as pancreatic enzymes (substances that help to digest and absorb food) and food supplements. They were also advised to exercise and to have physiotherapy.

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with cystic fibrosis. Early studies showed that adding the medicine to authorised treatments, including the medicine Orkambi, further improved lung function in patients with the most common mutation in the *CFTR* gene (called F508del). 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 mutations in the *CTFR* gene in patients with cystic fibrosis reduce the number of CFTR proteins on the cell surface or affect the way the protein works.

This medicine increases the number of CFTR proteins on the cell surface and is expected to make mucus and digestive juices less thick, thereby helping to relieve symptoms of the disease.

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, clinical trials with the medicine in patients with cystic fibrosis were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for the treatment of cystic fibrosis. Orphan designation of the medicine had been granted in the United States for this condition.

In accordance with Regulation (EC) No 141/2000, the COMP adopted a positive opinion on 17 April 2019, 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.

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	N-(trans-3-(5-((R)-1-hydroxyethyl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide	Treatment of cystic fibrosis
Bulgarian	N-(транс-3-(5-((R)-1-хидроксиетил)-1,3,4-оксадиазол-2-ил)циклобутил)-3-карбоксамид	Лечение на кистозна фиброза
Croatian	N-(trans-3-(5-((R)-1-hidroksietil)-1,3,4-oksadiazol-2-il)ciklobutil)-3-fenilisoksazol-5-karboksamid	Liječenje cistične fibroze
Czech	N-(trans-3-(5-((R)-1-hydroxyethyl)-1,3,4-oxadiazol-2-yl)cyklobutyl)-3-fenylisoxazol-5-karboxamid	Léčba cystické fibrózy
Danish	N-(trans-3-(5-((R)-1-hydroxyethyl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-3-phenylisoxazol-5-carboxamid	Behandling af cystisk fibrose
Dutch	N-(trans-3-(5-((R)-1-hydroxyethyl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamide	Behandeling van cystische fibrose
Estonian	N-(trans-3-(5-((R)-1-hüdroksüetüül)-1,3,4-oksadiasool-2-üül)tsüklobutüül)-3-fenüülisoksasool-5-karboksamiid	Tsüstilise fibroosi ravi
Finnish	N-(trans-3-(5-((R)-1-hydroksietyyli)-1,3,4-oksadiatsol-2-yyli)syklobutyyli)-3-fenyyli-isoksatsoli-5-karboksamidi	Kystisen fibroosin hoito
French	N-(trans-3-(5-((R)-1-hydroxyéthyl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-3-phénylisoxazole-5-carboxamide	Traitement de la mucoviscidose
German	N-(trans-3-(5-((R)-1-hydroxyethyl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-3-phenylisoxazole-5-carboxamid	Behandlung zystischer Fibrose
Greek	N-(τρανς-3-(5-((R)-1-υδροξυαιθυλ)-1,3,4-οξαδιαζολ-2-υλ)κυκλοβουτυλ)-3-φαινυλισοξαζολο-5-καρβοξαμίδη	Θεραπεία της κυστικής ίνωσης
Hungarian	N-(transz-3-(5-((R)-1-hidroxietil)-1,3,4-oxadiazol-2-il)ciklobutil)-3-fenilizoxazol-5-karboxamid	Cisztikus fibrózis kezelése
Italian	N-(trans-3-(5-((R)-1- idrossietil)-1,3,4-oxadiazol-2-il)ciclobutil)-3-fenillisoxazolo-5-carbossamide	Trattamento della fibrosi cistica

[1] At the time of designation

Language	Active ingredient	Indication
Latvian	N-(trans-3-(5-((R)-1-hidroksietil)-1,3,4-oksadiazol-2-il)ciklobutil)-3-fenilizoksazola-5-karboksamīds	Cistiskās fibrozes ārstēšana
Lithuanian	N-(trans-3-(5-((R)-1-hidroksietil)-1,3,4-oksadiazol-2-il)ciklobutil)-3-fenilisoksazolio-5-karboksamidas	Cistinės fibrozės gydymas
Maltese	N-(trans-3-(5-((R)-1-idrossietili)-1,3,4-ossadiazol-2-il)ċiklobutil)-3-fenilisossazol-5-karbossamid	Kura tal-fibrożi ċistiku
Polish	N-(trans-3-(5-((R)-1-hydroksyetylo)-1,3,4-oksadiazolo-2-ylo)cyklobutylo)-3-fenylizoksazol-5-karboksyamid	Leczenie zwłóknienia torbielowatego
Portuguese	N-(trans-3-(5-((R)-1-hidroxietil)-1,3,4-oxadiazol-2-il)ciclobutil)-3-fenilisoxazol-5-carboxamida	Tratamento da fibrose quística
Romanian	N-(trans-3-(5-((R)-1-hidroxietil)-1,3,4-oxadiazol-2-il)ciclobutil)-3-fenilizoxazol-5-carboxamidă	Tratamentul fibrozei chistice
Slovak	N-(trans-3-(5-((R)-1-hydroxyetyl)-1,3,4-oxadiazol-2-yl)cyklobutyl)-3-fenylisoxazol-5-karboxamid	Terapia cystickej fibrózy
Slovenian	N-(trans-3-(5-((R)-1-hidroksietil)-1,3,4-oksadiazol-2-il)ciklobutil)-3-fenilizoksazol-5-karboksamid	Zdravljenje cistične fibroze
Spanish	N-(trans-3-(5-((R)-1-hidroxietil)-1,3,4-oxadiazol-2-il)ciclobutil)-3-fenilisoxazol-5-carboxamida	Tratamiento de la fibrosis quística
Swedish	N-(trans-3-(5-((R)-1-hydroxyetyl)-1,3,4-oxadiazol-2-yl)cyclobutyl)-3-fenylisoxazole-5-karboxamide	Behandling av cystisk fibros
Norwegian	N-(trans-3-(5-((R)-1-hydroksyetyl)-1,3,4-oksadiazol-2-yl)syklobutyl)-3-fenylisoksazol-5-karboksamid	Behandling av cystisk fibrose
Icelandic	N-(trans-3-(5-((R)-1-hýdroxýetýl)-1,3,4-oxadíazól-2-ýl)cyclobútýl)-3-fenýlísoxazól-5-karboxamíð	Meðferð við slímseigjusjúkdómi