



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Public summary of opinion on orphan designation

1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl} cyclopropane-1-carboxamide and ivacaftor for the treatment of cystic fibrosis

On 27 February 2017, orphan designation (EU/3/17/1828) was granted by the European Commission to Vertex Pharmaceuticals (Europe) Limited, United Kingdom, for 1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl} cyclopropane-1-carboxamide (also known as tezacaftor) and ivacaftor for the treatment of cystic fibrosis.

What is cystic fibrosis?

Cystic fibrosis is a hereditary 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 less than 1 in 10,000 people in the European Union (EU). This was equivalent to a total of fewer than 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 515,700,000 (Eurostat 2017).



What treatments are available?

At the time of designation, Kalydeco (ivacaftor) and Orkambi (ivacaftor and lumacaftor) were authorised 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 this medicine might be of significant benefit for patients with cystic fibrosis. Early studies showed that this medicine improved lung function in patients with certain mutations in the CFTR gene that are currently not treated by the existing medicines. 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?

This medicine is made up of two substances, tezacaftor and ivacaftor, that work by improving activity of CFTR in the lungs, which is necessary to produce thin, normal mucus.

Ivacaftor is thought to restore the ability of CFTR channels to transport chloride ions into and out of cells (a key function of the protein), while tezacaftor is expected to increase the amount of and stabilise CFTR on the cell surface. The combination of the two substances is expected to thin the abnormal secretions, reduce symptoms of the disease and improve lung function.

What is the stage of development of this medicine?

The effects of the combination of tezacaftor and ivacaftor have been evaluated in experimental models.

At the time of submission of the application for orphan designation, clinical trials with this combination in patients with cystic fibrosis were ongoing.

At the time of submission, the combination was not authorised anywhere in the EU for cystic fibrosis 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 19 January 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	1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl} cyclopropane-1-carboxamide and ivacaftor	Treatment of cystic fibrosis
Bulgarian	1-(2,2-дифлуоро-2H-1,3-бензодиоксол-5-ил)-N-{1-[(2R)-2,3-дихидроксипропил]-6-флуоро-2-(1-хидрокси-2-метилпропан-2-ил)-1H-индол-5-ил} циклопропан-1-карбоксамид и ивакафтор	Лечение на кистозна фиброза
Croatian	1-(2,2-difluoro-2H-1,3-benzodioksol-5-il)-N-{1-[(2R)-2,3-dihidroksipropil]-6-fluoro-2-(1-hidroksi-2-metilpropan-2-il)-1H-indol-5-il} ciklopropan-1-karboksamid i ivakaftor	Liječenje cistične fibroze
Czech	1-(2,2-difluor-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluor-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl} cyklopropan-1-karboxamid a ivakaftor	Léčba cystické fibrózy
Danish	1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl} cyklopropan-carboxamid og ivacaftor	Behandling af cystisk fibrose
Dutch	1-(2,2-difluor-2H-1,3-benzodioxool-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluor-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indool-5-yl} cyclopropan-1-carboxamide en ivacaftor	Behandeling van cystische fibrose
Estonian	1-(2,2-difluoro-2H-1,3-bensodioksool-5-üül)-N-{1-[(2R)-2,3-dihüdroksüpropüül]-6-fluoro-2-(1-hüdroksü-2-metüülpropan-2-üül)-1H-indool-5-üül} tsüklopropan-1-karboksamiid ja ivakaftoor	Tsüstilise fibroosi ravi
Finnish	1-(2,2-difluoro-2H-1,3-bentsodioksol-5-yyli)-N-{1-[(2R)-2,3-dihidroksipropyli]-6-fluoro-2-(1-hydroksi-2-metyylipropan-2-yyli)-1H-indol-5-yyli} syklopropani-1-karboksamidi ja ivakaftori	Kystisen fibroosin hoito
French	1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-méthylpropane-2-yl)-1H-indol-5-yl} cyclopropane-1-carboxamide et ivacaftor	Traitement de la mucoviscidose
German	1-(2,2-Difluor-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluor-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl} cyclopropan-1-carboxamid und Ivacaftor	Behandlung zystischer Fibrose
Greek	1-(2,2-διφθορο-2H-1,3-βενζοδιοξολ-5-υλο)-N-{1-[(2R)-2,3-διυδροξυπροπουλο]-6-φθορο-2-(1-υδροξυ-2-μεθυλοπροπαν-2-υλο)-1H-ινδολ-5-υλο} κυκλοπροπανο-1-καρβοξαμίδιο και ivacaftor	Θεραπεία της κυστικής ίνωσης
Hungarian	1-(2,2-difluor-2H-1,3-benzodioxol-5-il)-N-{1-[(2R)-2,3-dihidroxiropil]-6-fluoro-2-(1-hidroxi-2-metilpropán-2-il)-1H-indol-5-il} ciklopropán-1-karboxamid és ivakaftor	Cisztikus fibrózis kezelése

¹ At the time of designation

Language	Active ingredient	Indication
Italian	1-(2,2-difluoro-2H-1,3-benzodiossol-5-il)-N-{1-[(2R)-2,3-diidrossipropil]-6-fluoro-2-(1-idrossi-2-metilpropan-2-il)-1H-indol-5-il}ciklopropan-1-carbossamide e ivacaftor	Trattamento della fibrosi cistica
Latvian	1-(2,2-difluor-2H-1,3-benzodioksol-5-il)-N-{1-[(2R)-2,3-dihidroksipropil]-6-fluor-2-(1-hidroksi-2-metilpropān-2-il)-1H-indol-5-il}ciklopropān-1-karboksamīds un ivakaftors	Cistiskās fibrozes ārstēšana
Lithuanian	1-(2,2-difluoro-2H-1,3-benzodioksol-5-il)-N-{1-[(2R)-2,3-dihidroksipropil]-6-fluoro-2-(1-hidroksi-2-metilpropan-2-il)-1H-indol-5-il}ciklopropan-1-karboksamidas ir ivakaftoras	Cistinės fibrozės gydymas
Maltese	1-(2,2-difluoro-2H-1,3-benzodioksol-5-yl)-N-{1-[(2R)-2,3-diidroksipropil]-6-fluoro-2-(1-idroksi-2-metilpropan-2-yl)-1H-indol-5-il}ciklopropan-1-karboksamida u ivakaftor	Kura tal-fibroži ċistiku
Polish	1-(2,2-difluoro-2H-1,3-benzodioksol-5-yl)-N-{1-[(2R)-2,3-dihydroksypropylo]-6-fluoro-2-(1-hydroksy-2-metylopropan-2-yl)-1H-indolo-5-yl}cyklopropano-1-karboksyamid oraz iwakaftor	Leczenie zwłóknienia torbielowatego
Portuguese	1-(2,2-difluoro-2H-1,3-benzodioxol-5-il)-N-{1-[(2R)-2,3-dihidroxiopropil]-6-fluoro-2-(1-hidroxi-2-metilpropan-2-il)-1H-indol-5-il}ciklopropano-1-carboxamida e ivacaftor	Tratamento da fibrose quística
Romanian	1-(2,2-difluoro-2H-1,3-benzodioxol-5-il)-N-{1-[(2R)-2,3-dihidroxiopropil]-6-fluoro-2-(1-hidroxi-2-metilpropan-2-il)-1H-indol-5-il}ciklopropan-1-carboxamidă și ivacaftor	Tratamentul fibrozei chistice
Slovak	1-(2,2-difluór-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluór-2-(1-hydroxy-2-metylpropán-2-yl)-1H-indol-5-yl}cyklopropán-1-karboxamid a ivakaftor	Terapia cystickej fibrózy
Slovenian	1-(2,2-difluoro-2H-1,3-benzodioksol-5-il)-N-{1-[(2R)-2,3-dihidroksipropil]-6-fluoro-2-(1-hidroksi-2-metilpropan-2-il)-1H-indol-5-il}ciklopropan-1-karboksamid in ivakaftor	Zdravljenje cistične fibroze
Spanish	1-(2,2-difluoro-2H-1,3-benzodioxol-5-il)-N-{1-[(2R)-2,3-dihidroxiopropil]-6-fluoro-2-(1-hidroxi-2-metilpropano-2-il)-1H-indol-5-il}ciklopropano-1-carboxamida e ivacaftor	Tratamiento de la fibrosis quística
Swedish	1-(2,2-difluoro-2H-1,3-bensodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxipropyl]-6-fluoro-2-(1-hydroxi-2-metylpropan-2-yl)-1H-indol-5-yl}cyklopropan-1-karboxamid och ivacaftor	Behandling av cystisk fibros
Norwegian	1-(2,2-difluor-2H-1,3-benzodioksol-5-yl)-N-{1-[(2R)-2,3-dihydroksypropyl]-6-fluor-2-(1-hydroksy-2-metylpropan-2-yl)-1H-indol-5-yl}syklopropan-1-karboksamid og ivakaftor	Behandling av cystisk fibrose
Icelandic	1-(2,2-díflúor-2H-1,3-bensódíoxól-5-ýl)-N-{1-[(2R)-2,3-dihýdroxýprópýl]-6-flúor-2-(1-hýdroxý-2-metylprópan-2-ýl)-1H-indól-5-ýl}sýklóprópan-1-karboxamíð og ívacaftor	Meðferð við slímseigjuskjúkdómi