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Public summary of opinion on orphan designation

(R)-2-(5-cyano-2-(6-(methoxycarbonyl)-7-methyl-3-oxo-8-(3-(trifluoromethyl)phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-5-yl)phenyl)-N,N,N-trimethylethanaminium methanesulfonate dehydrate for the treatment of cystic fibrosis

On 22 February 2018, orphan designation (EU/3/18/1988) was granted by the European Commission to Chiesi Farmaceutici S.p.A., Italy, for (R)-2-(5-cyano-2-(6-(methoxycarbonyl)-7-methyl-3-oxo-8-(3-(trifluoromethyl)phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-5-yl)phenyl)-N,N,N-trimethylethanaminium methanesulfonate dehydrate (also known as CHF6333) 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 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 517,400,000 (Eurostat 2018).

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What treatments are available?

At the time of designation, Kalydeco (ivacaftor) and Orkambi (ivacaftor and lumacaftor) 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 because laboratory studies show that it reduces inflammation in the airways and improves the effectiveness of antibiotics used for the condition. 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 effect of human neutrophil elastase (HNE), an enzyme produced by a type of white blood cells. HNE is involved in breaking down certain proteins and in encouraging inflammation. In patients with cystic fibrosis, the activity of HNE is increased, which can lead to lung damage and inflammation and encourage production of mucus. Using the medicine by inhalation is expected to reduce the effects of HNE and so reduce lung damage and airway infections.

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 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 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[1], Norwegian and Icelandic

Language	Active ingredient	Indication
English	(R)-2-(5-cyano-2-(6-(methoxycarbonyl)-7-methyl-3-oxo-8-(3-(trifluoromethyl)phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-5-yl)phenyl)-N,N,N-trimethylethanaminium methanesulfonate dehydrate	Treatment of cystic fibrosis
Bulgarian	(R)-2-(5-циано-2-(6-(метоксикарбонил)-7-метил-3-оксо-8-(3-(трифлуорометил)фенил)-2,3,5,8-тетрахидро-[1,2,4]триазоло[4,3-a]пиримидин-5-ил)фенил)-N,N,N-триметилетанаминиум метансулфонат дехидрат	Лечение на кистозна фиброза
Croatian	(R)-2-(5-cijano-2-(6-(metoksicarbonil)-7-metil-3-okso-8-(3-(trifluorometil)fenil)-2,3,5,8-tetrahidro-[1,2,4]triazolo[4,3-a]pirimidin-5-il)phenil)-N,N,N-trimetiletanaminium metansulfonat dehidrat	Liječenje cistične fibroze
Czech	(R)-2-(5-cyano-2-(6-(methoxycarbonyl)-7-methyl-3-oxo-8-(3-(trifluoromethyl)phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl)phenyl)-N,N,N-trimethylethanaminium methanesulfonat dehydrat	Léčba cystické fibrózy
Danish	(R)-2-(5-cyano-2-(6-(methoxycarbonyl)-7-methyl-3-oxo-8-(3-(trifluoromethyl)phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl)phenyl)-N,N,N-trimethylethanaminium methanesulfonate dehydrate	Behandling af cystisk fibrose
Dutch	(R)-2-(5-cyano-2-(6-(methoxycarbonyl)-7-methyl-3-oxo-8-(3-(trifluoromethyl)phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl)phenyl)-N,N,N-trimethylethanaminium methanesulfonate dehydrate	Behandeling van cystische fibrose
Estonian	(R)-2-(5-tsüano-2-(6-(metoksükarbonüüll)-7-metüül-3-okso-8-(3-(trifluorometüül)fenüül)-2,3,5,8-tetrahüdro-[1,2,4]triasolo[4,3-a]pürimidiin-5-üül)fenüül)-N,N,N-trimetüületanamiinium metaansulfonaat dehüdraat	Tsüstilise fibroosi ravi
Finnish	(R)-2-(5-syano-2-(6-(metoksikarbonyyli)-7-metyyli-3-okso-8-(3-(trifluorometyyli)fenyyli)-2,3,5,8-tetrahydro-[1,2,4]triatsolo[4,3-a]pyrimidiini-5-yl)fenyyli)-N,N,N-trimetyylietanaminium metanesulfonaatti dehydraatti	Kystisen fibroosin hoito
French	(R)-2-(5-cyano-2-(6-(methoxycarbonyl)-7-methyl-3-oxo-8-(3-(trifluoromethyl)phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl)phenyl)-N,N,N-trimethylethanaminium methanesulfonate dehydrate	Traitement de la mucoviscidose
German	(R)-2-(5-cyano-2-(6-(methoxycarbonyl)-7-methyl-3-oxo-8-(3-(trifluoromethyl)phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl)phenyl)-N,N,N-trimethylethanaminium methanesulfonat dehydrat	Behandlung zystischer Fibrose

[1] At the time of designation

Language	Active ingredient	Indication
Greek	(R)-2-(5-κυανο-2-(6-(μεθοξυκαρβονυλ)-7-μεθυλ-3-οξο-8-(3-(τριφθορομεθυλ)φαινυλ)-2,3,5,8-τετραϋδρο-[1,2,4]τριαζολο[4,3-α]πυριμιδιν-5-υλ)φαινυλ)-N,N,N-τριμεθυλαιθαναμμώνιο μεθανοσουλφονικό ανυδρο	Θεραπεία της κυστικής ίνωσης
Hungarian	(R)-2-(5-cyano-2-(6-(methoxycarbonyl)-7-methyl-3-oxo-8-(3-(trifluoromethyl)phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl)phenyl)-N,N,N-trimethylethanaminium methanesulfonat dehydrat	Cisztikus fibrózis kezelése
Italian	(R)-2-(5-ciano-2-(6-(metossicarbonil)-7-metil-3-oxo-8-(3-(trifluorometil)fenil)-2,3,5,8-tetraidro-[1,2,4]triazolo[4,3-a]pirimidin-5-yl)fenil)-N,N,N-trimetiletanamminium metanosulfonato deidrato	Trattamento della fibrosi cistica
Latvian	(R)-2-(5-ciano-2-(6-(metoksikarbonil)-7-metil-3-okso-8-(3-(trifluorometil)fenil)-2,3,5,8-tetrahidro-[1,2,4]triazolo[4,3-a]pirimidīn-5-il)fenil)-N,N,N-trimetiletānamīnija metānsulfonāta dehidrāts	Cistiskās fibrozes ārstēšana
Lithuanian	(R)-2-(5-ciano-2-(6-(metoksikarbonil)-7-metil-3-okso-8-(3-(trifluorometil)fenil)-2,3,5,8-tetrahidro-[1,2,4]triazolo[4,3-a]pirimidin-5-il)fenil)-N,N,N-trimetiletanamino metanesulfonato dehidratas	Cistinės fibrozės gydymas
Maltese	(R)-2-(5-ċjano-2-(6-(metossikarbonil)-7-metil-3-osso-8-(3-(trifluworometil)fenil)-2,3,5,8-tetraidro-[1,2,4]triażolo[4,3-a]pirimidina-5-il)fenil)-N,N,N-trimetilletanaminju metansulfonat deidrat	Kura tal-fibrożi ċistiku
Polish	Odwodniony metanosulfonian (R)-2-(5-cyjano-2-(6-(metoksycarbonyl)-7-metyl-3-oxo-8-(3-(trifluorometyl)fenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl)fenyl)-N,N,N-trimetyletanaminium	Leczenie zwłóknienia torbielowatego
Portuguese	Metanossulfonato desidratado de (R)-2-(5-ciano-2-(6-(metoxicarbonil)-7-metil-3-oxo-8-(3-(trifluorometil)fenill)-2,3,5,8-tetra-hidro-[1,2,4]triazol[4,3-a]pirimidin-5-il)fenil)-N,N,N-trimetiletanaminio	Tratamento da fibrose quística
Romanian	Metansulfonat dehidrat de (R)-2-(5-ciano-2-(6-(meoxicarbonil)-7-metil-3-oxo-8-(3-(trifluorometil)fenil)-2,3,5,8-tetrahidro-[1,2,4]triazolo[4,3-a]pirimidin-5-il)fenil)-N,N,N-trimetiletanaminiu	Tratamentul fibrozei chistice
Slovak	(R)-2-(5-cyano-2-(6-(metoxykarbonyl)-7-metyl-3-oxo-8-(3-(trifluorometyl)fenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidín-5-yl)fenyl)-N,N,N-trimetyletánamínium metánesulfonát dehydrát	Terapia cystickej fibrózy
Slovenian	(R)-2-(5-ciano-2-(6-(metoksikarbonil)-7-metil-3-okso-8-(3-(trifluorometil)fenil)-2,3,5,8-tetrahidro-[1,2,4]triazolo[4,3-a]pirimidin-5-il)fenil)-N,N,N-trimetiletanaminium metansulfonatdehidrat	Zdravljenje cistične fibroze

Language	Active ingredient	Indication
Spanish	(R)-2-(5-ciano-2-(6-(metoxicarbonil)-7-metil-3-oxo-8-(3-(trifluorometil)fenil)-2,3,5,8-tetrahidro-[1,2,4]triazolo[4,3-a]pirimidin-5-il)fenil)-N,N,N-trimetiletanaminium metanesulfonate dehidrato	Tratamiento de la fibrosis quística
Swedish	(R)-2-(5-cyano-2-(6-(metoxykarbonyl)-7-metyl-3-oxo-8-(3-(trifluorometyl)fenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl)fenyl)-N,N,N-trimetyletanaminium metansulfonat dehydrat	Behandling av cystisk fibros
Norwegian	(R)-2-(5-cyano-2-(6-(methoksycarbonyl)-7-metyl-3-okso-8-(3-(trifluorometyl)fenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl)fenyl)-N,N,N-trimetyletanaminiummetansulfonatdehydrat	Behandling av cystisk fibrose
Icelandic	(R)-2-(5-cýanó-2-(6-(methoxýcarbónýl)-7-metýl-3-oxó-8-(3-(tríflúórómetýl)phenýl)-2,3,5,8-tetrahýdró-[1,2,4]tríazóló[4,3-a]pýrimídín-5-ýl)phenýl)-N,N,N-trímetýlethanamíníum methansúlfónat dehýdrat	Meðferð við slímseigjusjúkdómi