8 November 2011
EMA/COMP/272429/2008 Rev.1
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

N-(2,4-Di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide for the treatment of cystic fibrosis

On 8 July 2008, orphan designation (EU/3/08/556) was granted by the European Commission to Voisin Consulting S.A.R.L., France, for N-(2,4-Di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide for the treatment of cystic fibrosis.

The sponsorship was transferred to Vertex Pharmaceuticals (U.K.) Limited, United Kingdom, in August 2011.

What is cystic fibrosis?

Cystic fibrosis is a hereditary (genetic) disease that affects the production of secretions (such as mucus) from the glands in the body. It affects the lungs and the digestive system (gut) in particular. Cystic fibrosis is caused by abnormalities in a gene called 'cystic fibrosis transmembrane conductance regulator' (CFTR). The *CFTR* gene is responsible for the production of CFTR, a protein that regulates the production of mucus and digestive juices by acting as a chloride ion channel to allow proper movement of salt and water in and out of certain cells in the lungs and other tissues. In patients with cystic fibrosis, there is an overproduction of mucus in the lungs and a reduced production of digestive juices from the pancreas (an organ near the stomach). This leads to long-term infection and inflammation of the lungs and problems with the digestion and absorption of food resulting in poor growth.

Cystic fibrosis is a long lasting and life-threatening disease.

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

At the time of designation cystic fibrosis affected approximately 1.2 in 10,000 people in the European Union (EU)[*]. This is equivalent to a total of around 60,000 people, and is below the threshold for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor and 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 27), Norway, Iceland and Liechtenstein. This represents a population of 502,282,135 (Eurostat 2008).

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7040
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

What treatments are available?

At the time of submission of the application for orphan drug designation, lung infection and inflammation in cystic fibrosis were mainly treated with physiotherapy and antibiotics. Other medicines used to treat the lung disease included bronchodilators (medicines that help to open up the airways in the lungs) and mucolytics (medicines that help dissolve the mucus in the lungs). In addition, patients are often given other types of medicine such as pancreatic enzymes (substances that help to digest and absorb food) and food supplements. They are also advised to exercise and to undergo physiotherapy.

N-(2,4-Di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide might be of potential significant benefit for the treatment of cystic fibrosis because it is expected to bring relief of the symptoms of the disease by acting in a different way to existing treatments. This assumption will have to be confirmed at the time of marketing authorisation. This will be necessary to maintain the orphan status.

How is this medicine expected to work?

N-(2,4-Di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide is thought to restore the ability of CFTR channels to transport chloride ions into and out of cells. This is intended to help maintain the proper level of salt and water on airway surfaces, reducing the formation and accumulation of mucus in the lung, and thus improving the symptoms of the disease.

What is the stage of development of this medicine?

The effects of N-(2,4-Di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide have been evaluated in experimental models.

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

At the time of submission, N-(2,4-Di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide was not authorised anywhere in the world for the treatment of cystic fibrosis. Orphan designation of N-(2,4-Di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide had been granted in the United States for cystic fibrosis.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 14 May 2008 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:

Vertex Pharmaceuticals (U.K.) Limited
88 Milton Park
Abingdon
Oxfordshire OX14 4RY
United Kingdom
Telephone: +44 1235 438 804
Telefax: +44 1235 835 880

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-(2,4-Di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide	Treatment of cystic fibrosis
Bulgarian	N-(2,4-Ди-терт-бутил-5-хидроксифенил)-1,4-дихидро-4-оксохинолин-3-карбоксамид	Лечение на кистозна фиброза
Czech	N-(2,4-Di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinolin-3-karboxamid	Léčba cystické fibrózy
Danish	N-(2,4-di-tert-butyl-5-hydroxyfenyl)-1,4-dihydro-4-oxoquinolin-3-karboxamid	Behandling af cystisk fibrose
Dutch	N-(2,4-di-tert-butyl-5-hydroxyfenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide	Behandeling van cystische fibrose
Estonian	N-(2,4-di-tert-butüül-5-hüdroksüfenüül-)-1,4-dihüdro-4-oksokinoliin-3-karboksamiid	Tsüstilise fibroosi ravi
Finnish	N-(2,4-Di-tert-butyyli-5-hydroksifenyyli)-1,4-dihydro-4-oksokinoliini-3-karboksamiidi	Kystisen fibroosin hoito
French	N-(2,4-di-tert-butyl-5-hydroxyphényl)-1,4-dihydro-4-oxoquinoline-3-carboxamide	Traitement de la mucoviscidose
German	N-(2,4-Di-tert-Butyl-5-Hydroxyphenyl)-1,4-Dihydro-4-oxoquinolin-3-carboxamid	Behandlung zystischer Fibrose
Greek	N-(2,4-δι-τερτ-βουτυλ-5-υδροξυφαινύλ)-1,4-διυδρο-4-οξοκινολίνη-3-καρβοξαμίδιο	Θεραπεία της κυστικής ίνωσης
Hungarian	N-(2,4-di-terc-butil-5-hidroxifenil)-1,4-dihidro-4-oxokinolin-3-karboxamid	Cisztikus fibrózis kezelése
Italian	N-(2,4-di-tert-butil-5-idrossifenil)-1,4-diidro-4-ossochinolina-3-carbossamide	Trattamento della fibrosi cistica
Latvian	N-(2,4-Di-tert-butil-5-hidroksifenil)-1,4-dihidro-4-oksohinolīn-3-karboksamīds	Cistiskās fibrozes ārstēšana
Lithuanian	N-(2,4-ditertbutil-5-hidroksifenil)-1,4-dihidro-4-oksochinolino-3-karboksamidas	Cistinės fibrozės gydymas
Maltese	N-(2,4-Di-tert-butil-5-idroxifenil)-1,4-di-idro-4-oxokinolin-3-carboxamide	Kura tal-fibrożi ċistiku
Polish	N-(2,4-Di-tert-butylo-5-hydroksyfenyl)-1,4-dihydro-4- oksochinolino-3-karboksamid	Leczenie zwłóknienia torbielowatego
Portuguese	N-(2,4-Di-tert-butil-5-hidroxifenil)-1,4-diidro-4-oxoquinolina-3-carboxamida	Tratamento da fibrose quística
Romanian	N-(2,4- Di-terţ-butil-5-hidroxifenil)-1,4-dihidro-4-oxichinolină-3-carboxiamidă	Tratamentul fibrozei chistice
Slovak	N-(2,4-diterc-butyl-5-hydroxyfenyl)-1,4-dihydro-4-oxochinolín-3-karboxamid	Terapia cystickej fibrózy

[1] At the time of designation

Language	Active Ingredient	Indication
Slovenian	N-(2,4-Di-terc-butil-5-hidroksifenil)-1,4-dihidro-4-oksikvinolin-3-karboksamid	Zdravljenje cistične fibroze
Spanish	N-(2,4-Di-terc-butil-5-hidroxifenil)-1,4-dihidro-4-oxoquinolin-3-carboxamida	Tratamiento de la fibrosis quística
Swedish	N-(2,4-Di-tert-butyl-5-hydroxifenyl)-1,4-dihydro-4-oxokinolin-3-karboxamid	Behandling av cystisk fibros
Norwegian	N-(2,4-Di-tert-butyl-5-hydroksyfenyl)-1,4-dihydro-4-oksokinolin-3-karboksamid	Behandling av cystisk fibrose
Icelandic	N-(2,4-Tví-tert-bútýl-5-hýdroxýfenýl)-1,4 tvíhýdró-4-óxóquínólín-3-karboxamíð	Meðferð við slímseigjusjúkdómi