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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

4,6,4'-Trimethylangelicin for the treatment of cystic fibrosis

On 19 June 2013, orphan designation (EU/3/13/1137) was granted by the European Commission to Rare Partners srl Impresa Sociale, Italy, for 4,6,4'-trimethylangelicin for the treatment of cystic fibrosis.

What is cystic fibrosis?

Cystic fibrosis is a hereditary disease that affects the cells in the lungs and the glands in the gut and pancreas that secrete fluids such as mucus and digestive juices. In cystic fibrosis, these fluids become thick and viscous, blocking the airways and the flow of digestive juices. This leads to problems with the digestion and absorption of food, resulting in poor growth, and to long-term infection and inflammation of the lungs because of excess mucus not being cleared away.

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

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

At the time of designation, cystic fibrosis affected approximately 0.8 in 10,000 people in the European Union (EU). This was equivalent to a total of around 41,000 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?

At the time of designation, lung infection in cystic fibrosis was mainly treated with antibiotics. Kalydeco (ivacaftor) was authorised in a subgroup of patients with cystic fibrosis (with the G551D mutation). Other medicines used to treat the lung disease included anti-inflammatory agents, 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 with cystic fibrosis were often given other types of

*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 509,000,000 (Eurostat 2013).

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medicines such as pancreatic enzymes (substances that help to digest and absorb food) and food supplements. They were also advised to exercise and to undergo physiotherapy.

The sponsor has provided sufficient information to show that 4,6,4'-trimethylangelicin might be of significant benefit for patients with cystic fibrosis because early studies in experimental models show that it works in a different way to existing treatments and might improve the outcome of patients with this 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?

Cystic fibrosis is caused by a mutation in the *CFTR* gene. The mutation causes problems with CFTR channels on the surface of cells involved in the production of mucus and digestive juices. These channels are used for the transport of ions (charged atoms and molecules) in and out of the mucus-secreting cells. When the channels are defective, mucus and digestive juices can become abnormally thick.

4,6,4'-Trimethylangelicin is expected to restore and increase the ability of CFTR channels to transport ions into and out of cells. This is expected to make the secretions less thick and so relieve symptoms of the disease.

4,6,4'-Trimethylangelicin is also expected to work by reducing the production of an inflammatory substance called interleukin 8 (IL-8). By reducing the production of IL-8, this medicine is expected to reduce the inflammatory complications in cystic fibrosis.

What is the stage of development of this medicine?

At the time of submission of the application for orphan designation, the evaluation of the effects of 4,6,4'-trimethylangelicin in experimental models was ongoing.

At the time of submission, no clinical trials with 4,6,4'-trimethylangelicin in patients with cystic fibrosis had been started.

At the time of submission, 4,6,4'-trimethylangelicin 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 15 May 2013 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:

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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	4,6,4'–trimethylangelicin	Treatment of cystic fibrosis
Bulgarian	4,6,4'–триметилангелицин	Лечение на кистозна фиброза
Czech	4,6,4'–trimethylangelicin	Léčba cystické fibrózy
Danish	4,6,4'–trimethylangelicin	Behandling af cystisk fibrose
Dutch	4,6,4'–trimethylangelicine	Behandeling van cystische fibrose
Estonian	4,6,4'–trimetüülangelitsiin	Tsüstilise fibroosi ravi
Finnish	4,6,4'-trimetyyliangelisiini	Kystisen fibroosin hoito
French	4,6,4'–trimethylangelicine	Traitement de la mucoviscidose
German	4,6,4'–trimethylangelicin	Behandlung zystischer Fibrose
Greek	4,5,4 – τριμεθυλαγγελισίνη	Θεραπεία της κυστικής ίνωσης
Hungarian	4,6,4'–trimetilangelicin	Cisztikus fibrózis kezelése
Italian	4,6,4'–trimetilangelicina	Trattamento della fibrosi cistica
Latvian	4,6,4'-trimetilangelicīns	Cistiskās fibrozes ārstēšana
Lithuanian	4,6,4'–trimetilangelicinas	Cistinės fibrozės gydymas
Maltese	4,6,4'–trimethylangelizin	Kura tal-fibrożi ċistiku
Polish	4,6,4'τριμεθυλαγγελισίνη	Leczenie zwłóknienia torbielowatego
Portuguese	4,6,4'–trimetilangelicina	Tratamento da fibrose quística
Romanian	4,6,4'–trimetilangelicin	Tratamentul fibrozei chistice
Slovak	4,6,4'–trimetylangelicín	Terapia cystickej fibrózy
Slovenian	4,6,4'–trimetilangelicin	Zdravljenje cistične fibroze
Spanish	4,6,4'-trimetilangelicina	Tratamiento de la fibrosis quística
Swedish	4,6,4'–trimetylangelicin	Behandling av cystisk fibros
Norwegian	4,6,4'-trimetylangelicin	Behandling av cystisk fibrose
Icelandic	4,6,4'–trímethýlangelícín	Meðferð við slímseigjusjúkdómi

[1] At the time of designation