EMA/COMP/318112/2005 Rev.4
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Mannitolum for the treatment of cystic fibrosis

First publication	9 February 2006
Rev.1: transfer of sponsorship	29 May 2007
Rev.2: sponsor's name change	29 July 2008
Rev.3: sponsor's change of address	14 June 2010
Rev.4: information about Marketing Authorisation	10 September 2013
Disclaimer Please note that revisions to the Public Summary of Opinion are purely administrative updates. Therefore, the scientific content of the document reflects the outcome of the Committee for Orphan Medicinal Products (COMP) at the time of designation and is not updated after first publication.	

On 7 November 2005, orphan designation (EU/3/05/325) was granted by the European Commission to Stricent AB, Sweden, for mannitolum for the treatment of cystic fibrosis.

The sponsorship was transferred to Pharmaxis UK Limited, United Kingdom, in October 2006. The sponsor subsequently changed name to Pharmaxis Pharmaceuticals Limited in May 2008.

What is cystic fibrosis?

Cystic fibrosis is a genetic disease. Genes located on structures (the so-called chromosomes) carry the genetic information that determines the characteristics of each individual. In humans, each cell has 23 pairs of chromosomes. For each pair one chromosome is inherited from the mother, and the other from the father. Cystic fibrosis is caused by abnormalities of a specific gene, called CFTR, carried by the seventh pair of chromosomes. Cystic fibrosis appears only when the CFTR gene is abnormal on both chromosomes of the seventh pair. The CFTR gene is responsible for the production of a protein that regulates the outflow of water and salts (like chloride) from cells that cover internal and external surfaces of the body, the so-called epithelial cells. The defective transport of water and salts, due to the lack of the regulatory protein, results in the thickening of the secretions (mucous) in several organs (e.g. lungs, pancreas). This leads to reduced functioning, chronic infection of the lungs and chronic inflammation (a body response to the injury caused to the tissue). In the long run, these events can induce damage to the lung tissue and the disease can become life threatening.

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

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

At the time of designation, cystic fibrosis affected approximately 1.3 in 10,000 people in the European Union (EU). This was equivalent to a total of around 61,000 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 the knowledge of the Committee for Orphan Medicinal Products (COMP).

What treatments are available?

At the time of submission of the application for the orphan drug designation lung infection and inflammation in cystic fibrosis were treated mainly with antibiotics. These can be taken in a number of ways such as through the mouth, through a vein or they can be inhaled as a fine mist of particles. Associated treatments included daily exercise and physical therapies and several other types of medications such as pancreatic enzymes and food supplements. Bronchodilators are medications that can enlarge the lumen of the airways. Mucolytics help to dissolve the secretions. Still other medications were used to fight the inflammation.

Mannitolum might be of potential significant benefit for the treatment of cystic fibrosis because it might improve the long-term outcome of patients. 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?

Mannitolum is a well known, naturally occurring sugar alcohol found in most vegetables. In this medicinal product mannitolum is prepared as a dry powder for inhalation. Mannitolum is an osmotic agent, which means that it can promote the flow of liquids across membranes. In cystic fibrosis patients, this medicinal product could have an effect on the physical properties of mucus and the volume (depth) of the airway surface fluid and thus facilitate the clearance of airway secretions.

What is the stage of development of this medicine?

The evaluation of the effects of inhaled mannitolum is ongoing in experimental models.

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

Mannitolum was not authorised anywhere worldwide for cystic fibrosis or designated as orphan medicinal product elsewhere for this condition, at the time of submission.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 9 September 2005 recommending the granting of this designation.

Update: Mannitolum (Bronchitol) has been authorised in the EU since 13 April 2012 for the treatment of cystic fibrosis (CF) in adults aged 18 years and above as an add-on therapy to best standard of care.

More information on Bronchitol can be found in the European public assessment report (EPAR) on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports

*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 25), Norway, Iceland and Liechtenstein.
At the time of designation, this represented a population of 466,600,000 (Eurostat 2005.

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 European Union) 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:

Pharmaxis Pharmaceuticals Limited
The Priory
Stomp Road
Burnham
Bucks SL1 7LW
United Kingdom
Telephone: +44 1628 902 121
Telefax: +44 1628 669 355
E-mail: info@pharmaxis.com.au

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	Mannitolum	Treatment of cystic fibrosis
Bulgarian	Манитол	Лечение на кистозна фиброза
Czech	Mannitol	Léčba cystické fibrózy
Danish	Mannitolum	Behandling af cystisk fibrose
Dutch	Mannitolum	Behandeling van cystische fibrose
Estonian	Mannitool	Tsüstilise fibroosi ravi
Finnish	Mannitolum	Kystisen fibroosin hoito
French	Mannitolum	Traitement de la mucoviscidose
German	Mannitol	Behandlung zystischer Fibrose
Greek	Mannitolum	Θεραπεία της κυστικής ίνωσης
Hungarian	Mannitol	Cisztikus fibrózis kezelése
Italian	Mannitolo	Trattamento della fibrosi cistica
Latvian	Mannitols	Cistiskās fibrozes ārstēšana
Lithuanian	Manitolis	Cistinės fibrozės gydymas
Maltese	Mannitol	Kura tal-fibrożi ċistiku
Polish	Mannitol	Leczenie zwłóknienia torbielowatego
Portuguese	Manitol	Tratamento da fibrose quística
Romanian	Manitol	Tratamentul fibrozei chistice
Slovak	Manitol	Terapia cystickej fibrózy
Slovenian	Manitol	Zdravljenje cistične fibroze
Spanish	Manitol	Tratamiento de la fibrosis quística
Swedish	Mannitol	Behandling av cystisk fibros
Norwegian	Mannitol	Behandling av cystisk fibrose
Icelandic	Mannitól	Meðferð við slímseigjusjúkdómi

[1] At the time of transfer of marketing authorisation