European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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Please note that this product was withdrawn from the Community Register of designated Orphan Medicinal Products in July 2008 on request of the Sponsor.

Committee for Orphan Medicinal Products

Public summary of positive opinion for orphan designation of engineered protein inhibitor of human neutrophil elastase for the treatment of cystic fibrosis

On 9 July 2003, orphan designation (EU3/03/152) was granted by the European Commission to Debioclinic SA, France, for engineered protein inhibitor of human neutrophil elastase for the treatment of cystic fibrosis.

What is cystic fibrosis?
Cystic fibrosis is a genetic disease caused by a permanent transmissible change (so called mutation) in a gene on chromosome 7. Each individual has a pair of these chromosomes, each derived from one parent. The disease appears only when the gene is mutated on both chromosomes. This type of genetic disease is called "autosomal recessive". Normally, the gene is used to make a protein, called cystic fibrosis transmembrane conductance regulator (CFTR) that regulates transport of water and salts in certain cells. These are the cells that cover internal and external surfaces of the body, the so-called epithelial cells. In cystic fibrosis the protein is defective due to the mutations. This results in defective water and salt transport and thick secretions in several organs (e.g. lungs, pancreas). For example, secretions in the airways show a decrease in water content. This leads to chronic infection of the lungs and chronic inflammation (a response to the injury caused to the tissue). This is a major burden for cystic fibrosis patients. In the long run, these events damage the lung and the disease can become life-threatening.

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 is equivalent to a total of around 50,000 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).

What treatments are available?
Several medicinal products were authorised for the treatment of cystic fibrosis within the Community at the time of submission of the application for orphan drug designation. The lung infection and inflammation in cystic fibrosis is treated mostly with antibiotics. These can be taken in a number of ways such as through the mouth, through a vein or as a fine mist of particles that can be inhaled. Associated treatments include daily exercise and physical therapies and several other types of medications such as pancreatic enzymes and food supplements. Bronchodilators are medications that

[*]Disclaimer: The number of patients affected by the condition is estimated and assessed for the purpose of the designation, for a European Community population of 385,000,000 (Eurostat 2002) and may differ from the true number of patients affected by the condition. This estimate is based on available information and calculations presented by the sponsor at the time of the application.

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can enlarge the opening of the airways and thereby facilitate the breathing. Mucolytics are medications that help to dissolve the secretions, which make breathing difficult for the patients.
Engineered protein inhibitor of human neutrophil elastase might be of potential significant benefit for the treatment of cystic fibrosis. This is because it may act differently from other medicinal products. 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?
Elastase is an enzyme secreted by neutrophils (white blood cells that help kill bacteria) in the lung. Elastase has many important functions in a healthy person. In patients with cystic fibrosis however, the concentration can be too high and the elastase starts to have negative effects instead e.g. damaging the architecture of the lung and airways. It also leads to production of abnormal secretions leading to mucous build-up, which makes breathing harder. Engineered protein inhibitor of human neutrophil elastase is similar to a naturally occurring human protein that helps to protect the surface of the lung against the elastase activity. The hypothesis is that engineered protein inhibitor of human neutrophil elastase will restore the elastase balance and therefore enhance the capacity of the neutrophils to kill bacteria. There is also a chance that mucus secretion will decrease, and this may help antibiotics to kill bacteria more effectively.

What is the stage of development of this medicine?
The evaluation of the effects of engineered protein inhibitor of human neutrophil elastase in experimental models is ongoing. At the time of submission of the application for orphan designation, two clinical trials in patients with cystic fibrosis were completed.

Engineered protein inhibitor of human neutrophil elastase was not marketed anywhere worldwide for cystic fibrosis or designated as orphan medicinal product elsewhere for this condition, at the time of submission.

According to Regulation (EC) No 141/2000 of 16 December 1999, the Committee for Orphan Medicinal Products (COMP) adopted on 13 June 2003 a positive opinion recommending the grant of the above-mentioned 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 Community) 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.

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Translations of the active ingredient and indication in all EU languages

Language	Active Ingredient	Indication
English	Engineered protein inhibitor of human neutrophil elastase	Treatment of cystic fibrosis
Danish	Teknisk fremstillet proteinhæmmer af human neutrofil elastase	Behandling af cystisk fibrose
Dutch	Recombinant proteine remmer van humane neutrofiel-elastase	Behandeling van cystische fibrose
Finnish	Rekombinantti humaanin neutrofiilielastaasin estäjäproteiini	Kystisen fibroosin hoito
French	Inhibiteur protéique recombinant de l'élastase leucocytaire humaine	Traitement de la mucoviscidose
German	Recombinater Proteininhibitor der humanen neutrophilen Elastase	Behandlung der zystischen Fibrose
Greek	πρωτεϊνικός Αναστολέας της ανθρώπινης Ουδετεροφιλικής Ελαστάσης, προϊόν γενετικής μηχανικής	Θεραπεία της κυστικής ίνωσης
Italian	Inibitore proteico dell'elastasi umana dei neutrofili derivato da ingegneria genetica	Trattamento della fibrosi cistica
Portuguese	Inibidor proteico recombinante da elastase do neutrófilo humano	Tratamento da fibrose quística
Spanish	Proteina recombinante inhibidora de la elastasa de neutrófilos humanos	Tratamiento de la fibrosis quística
Swedish	Rekombinant inhibitorprotein av humant neutrofilelastas	Behandling av cystisk fibros