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

Document Date: London, 29 November 2005
Doc.Ref.: EMEA/COMP/1071/02 Rev. 2

Please note that this product was withdrawn from the Community Register of designated Orphan Medicinal Products in November 2004 on request from the sponsor.

COMMITTEE FOR ORPHAN MEDICINAL PRODUCTS

PUBLIC SUMMARY OF POSITIVE OPINION FOR ORPHAN DESIGNATION OF carbamic acid, [[4-[[3-[[4-[1-(4-hydroxyphenyl)-1-methyl-ethyl]phenoxy]methyl]phenyl]methoxy]-phenyl]iminomethyl]-,ethyl ester (amelubant) for treatment of cystic fibrosis

On 26 June 2002, orphan designation (EU/3/02/105) was granted by the European Commission to Boehringer Ingelheim International GmbH, Germany, for amelubant for the treatment of cystic fibrosis.

What is cystic fibrosis?
Cystic fibrosis is a genetic disease caused by mutations 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 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 are the methods of treatment available?
The lung infection and inflammation in cystic fibrosis is treated mostly with antibiotics. These can be taken in a number 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 can enlarge the lumen of the airways. Mucolytics help to dissolve the secretions. Still other medications are used to fight the inflammation. Although this is still an assumption at this stage, amelubant might be of potential significant benefit for the treatment of cystic fibrosis, because it has a new mechanism of action.

What is the estimated number of patients affected by the condition*?
According to the information provided by the sponsor, cystic fibrosis was considered to affect about 49,000 persons in the European Union.

How is this medicinal product expected to act?
White blood cells are part of the immune system, the system that defends the body against diseases. Certain white blood cells produce substances that mediate inflammation. One of these is called leukotriene B_4 (LTB_4). This substance increases passage across blood vessels and attracts additional white blood cells to the site. In this way the inflammation process is maintained and increased. In

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 70 40
E-mail: orphandrugs@emea.eu.int www.emea.eu.int

order to cause this response, LTB_4 has to bind to a receptor on other cells. Amelubant interferes with this binding and tends to nullify the action of LTB_4.

What is the stage of development of this medicinal product?
The effects of amelubant 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 (phase 1). In the United States orphan drug status was granted on 15 January 2002 for management of cystic fibrosis. Amelubant had not been marketed anywhere worldwide for cystic fibrosis, 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 22 May 2002 a positive opinion recommending the grant of the above-mentioned designation.

_____

Opinions on orphan medicinal products designations are based on the following cumulative criteria: (i) the seriousness of the condition, (ii) the existence or not of alternative methods of diagnosis, prevention or treatment and (iii) either the rarity of the condition (considered to affect not more than five in ten thousand persons in the Community) or the insufficient return of development investments.

Designated orphan medicinal products are still investigational products which have been considered for designation on the basis of potential activity. An orphan designation is not a marketing authorisation. As a consequence, demonstration of the quality, safety and efficacy will be necessary before this product can be granted a marketing authorisation.

For more information:
Sponsor's contact details:
Boehringer Ingelheim International GmbH
Binger Straße 173
D-55216 Ingelheim am Rhein
Germany
Telephone: +49 61 32 770
Telefax: + 49 61 32 720

*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 377,000,000 (Eurostat 2001) 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.