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Questions and answers

Refusal of the marketing authorisation for Bronchitol

mannitol

On 23 June 2011 the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Bronchitol, intended for the treatment of cystic fibrosis.

The company that applied for authorisation is Pharmaxis Pharmaceuticals UK Ltd. It may request a re-examination of the opinion within 15 days of receipt of notification of this negative opinion.

What is Bronchitol?

Bronchitol is a medicine that contains the active substance mannitol. It was to be available as capsules containing a powder for inhalation.

What was Bronchitol expected to be used for?

Bronchitol was expected to be used for the treatment of cystic fibrosis in adult patients. It was to be used either as add-on therapy to rhDNase (another treatment for cystic fibrosis) or on its own in patients who do not benefit from or cannot use rhDNase.

Cystic fibrosis is an inherited 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 and causing chest infections, poor growth and other health problems.

Bronchitol was designated an 'orphan medicine' (a medicine to be used in rare diseases) on 7 November 2005 for cystic fibrosis.

How is Bronchitol expected to work?

The active substance in Bronchitol, mannitol, is a naturally occurring polyol (a sugar alcohol) that is widely used as an osmotic agent. This means that it can promote osmosis (the flow of liquid across a membrane). Bronchitol was to be inhaled by patients with cystic fibrosis, where it is expected to cause

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8668
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

the inflow of fluid into the airway secretions in the lungs, making them less viscous and therefore easier to be cleared away.

What did the company present to support its application?

The applicant presented data on experimental models from the scientific literature supplemented with tests in experimental models.

The company presented the results of two main studies in 642 patients over six years old with mild or moderate cystic fibrosis. The patients received either 400 mg of inhaled mannitol twice daily or 50 mg of inhaled mannitol twice daily (which was considered ineffective and hence intended as a 'dummy' treatment). Some patients also received additional treatment with rhDNase. The main measure of effectiveness was the improvement in patients' forced expiratory volume in one second (FEV_1), measured over 26 weeks in both studies. FEV_1 is the maximum volume of air a person can breathe out in one second.

What were the CHMP's main concerns that led to the refusal?

The major concern of the CHMP was that the effectiveness and benefit of Bronchitol had not been established. Patients treated with Bronchitol had only a small improvement in FEV_1 and it was not clear if this would really be sufficient to improve the patients' condition. Moreover, the actual extent of this small improvement was difficult to ascertain since the results of the studies were not consistent across the different age groups.

Therefore, at that point in time, the CHMP was of the opinion that the benefits of Bronchitol had not been shown to outweigh its risks (particularly narrowing of the airways in the lungs, and coughing of blood) and recommended that it be refused marketing authorisation.

What consequences does this refusal have for patients in clinical trials or compassionate use programmes?

The company informed the CHMP that there are no consequences on patients currently included in clinical trials with Bronchitol. However, although there are no immediate consequences on patients currently included in compassionate use programmes with Bronchitol, supply by this route is likely to be stopped by March 2012.

If you are in a clinical trial or compassionate use programme and need more information about your treatment, contact the doctor who is giving it to you.

The summary of the opinion of the Committee for Orphan Medicinal Products for Bronchitol can be found on the Agency's website ema.europa.eu/Find medicine/Human medicines/Rare disease designation.