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Questions and answers

Positive opinion on the marketing authorisation for Bronchitol (mannitol)

Outcome of re-examination

On 18 October 2011, the Committee for Medicinal Products for Human Use (CHMP) recommended the granting of the marketing authorisation for the medicinal product Bronchitol for the treatment of cystic fibrosis as an add-on therapy to best standard of care. The company that applied for authorisation is Pharmaxis Pharmaceuticals Ltd.

On 23 June 2011 the CHMP had originally adopted a negative opinion for Bronchitol in adult patients with cystic fibrosis 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. At the request of the applicant, the CHMP started a re-examination of its opinion. Following the re-examination, the CHMP adopted a final positive opinion on 18 October 2011 recommending the granting of a marketing authorisation for Bronchitol for the treatment of cystic fibrosis in adults as an add-on therapy to best standard of care.

What is Bronchitol?

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

What is Bronchitol to be used for?

In the initial application, Bronchitol was intended for the treatment of cystic fibrosis in adult patients, either as add-on therapy to another treatment called rhDNase, or on its own in patients who cannot use or derive benefit from rhDNase. During the re-examination, the intended use of the medicine was changed to the treatment of cystic fibrosis in adult patients in addition to standard therapy.

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.

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
An agency of the European Union

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

How does Bronchitol 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 is to be inhaled by patients with cystic fibrosis, where it causes 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 initial negative opinion?

In June 2011 the CHMP was concerned 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 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 happened during the re-examination?

During the re-examination, the Committee looked again at the data from the main studies. The CHMP also took advice from a group of experts specialised in cystic fibrosis. A main focus of the re-examination was an investigation into whether the modest improvements in FEV_1 shown in the studies with Bronchitol outweighed its risks.

What were the conclusions of the CHMP following the re-examination?

Following advice from the experts and discussions within the Committee, the Committee took the view that the modest improvement in FEV_1 shown by the studies may be of benefit in patients with cystic fibrosis if Bronchitol is used in addition to the best standard care. However, the CHMP also decided that the use of Bronchitol should not depend on the whether or not patients can use or derive benefit from rhDNase as this was not addressed in the studies.

Regarding the safety of Bronchitol, the CHMP considered that sufficient measures have been proposed by the company to reduce the risk of narrowing of the airways in the lungs. Although the committee was still concerned about the risk of coughing up blood, it considered that the risk is manageable and should not preclude its use in patients who could benefit from it. The committee also considered the lack of suitable treatment alternatives for this disease. The CHMP therefore concluded that the benefits of Bronchitol in addition to standard therapy outweigh its risks for adult patients with cystic fibrosis and recommended that it be granted marketing authorisation. However, in order to obtain further information on effectiveness and safety of Bronchitol in children and adolescents with cystic fibrosis the committee requested the company to carry out a study in this patient group.

The summary of the positive opinion of the CHMP is published on the Agency's website ema.europa.eu/Find medicine/Human medicines/Pending EC decisions.