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Questions and answers

Positive opinion on the marketing authorisation for Deltyba[1] (delamanid)

Outcome of re-examination

On 21 November 2013, the Committee for Medicinal Products for Human Use (CHMP) recommended the granting of a conditional marketing authorisation for the medicinal product Deltyba for the treatment of lung infections due to multidrug-resistant tuberculosis when alternative treatments cannot be used due to resistance or intolerance. The company that applied for authorisation is Otsuka Novel Products GmbH.

On 25 July 2013, the CHMP had originally adopted a negative opinion for Delamanid in multidrug-resistant tuberculosis. 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 21 November 2013 recommending the granting of a conditional marketing authorisation for Deltyba, but restricting its use to treatment of tuberculosis affecting the lungs and to situations where alternative treatments cannot be used due to resistance or intolerance.

What is Deltyba?

Deltyba is a medicine that contains the active substance delamanid. It is to be available as tablets.

What is Deltyba to be used for?

Deltyba is to be used to treat tuberculosis, an infection caused by the bacterium *Mycobacterium tuberculosis* (*M. tuberculosis*). It is to be used in patients with tuberculosis that is affecting the lung and that is multidrug resistant (resistant to at least isoniazid and rifampicin, two standard anti-tuberculosis medicines). It is used together with other standard medicines and only when alternative medicines cannot be used in its place.

Deltyba was designated an 'orphan medicine' (a medicine to be used in rare diseases) on 1 February 2008 for the treatment of tuberculosis.

[1] Previously known as Delamanid

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How does Deltyba work?

The active substance in Deltyba, delamanid, is an antibiotic active against *M. tuberculosis*. Although the precise mode of action is unclear, Deltyba is known to block the production of essential components (called methoxy-mycolic and keto-mycolic acid) of the cell walls of *M. tuberculosis,* which will cause the bacteria to die.

What did the company present to support its application?

The effects of Deltyba were first tested in experimental models before being studied in humans.

The company presented results of one main study involving 481 patients with tuberculosis resistant to standard treatments. Patients in the study were given Deltyba or placebo (a dummy treatment) for two months in addition to their other treatments, and the main measure of effectiveness was the proportion of patients who no longer had the bacteria in their sputum (phlegm).

After the main study had finished, patients had the option to receive treatment with Deltyba for six months in an extension study. In addition, a majority of patients who entered the main study were followed up in a registry study for up to 24 months after entering the main study.

What were the CHMP's main concerns that led to the initial negative opinion?

At the time of the initial opinion, the CHMP was not convinced that the benefits of Deltyba in the treatment of multidrug resistant tuberculosis had been sufficiently shown. The CHMP considered that the duration of treatment in the main study (two months) was too short to establish the effectiveness of delamanid in treating tuberculosis when added to other anti-tuberculosis medicines. As Deltyba was to be used for at least six months, the data from two months' treatment could not be used to predict the effectiveness of delamanid when given for six months. In addition, the results of the extension and follow-up studies could not be used to support the longer term use of Deltyba as the studies included only those patients who had agreed to take part and who might therefore not be representative of all patients. Finally, the CHMP was of the view that it was not possible to determine from the data submitted the most appropriate dosing for Deltyba.

Therefore, at that point in time, the CHMP was of the opinion that the benefits of Deltyba did not outweigh its risks and recommended that it be refused marketing authorisation.

What happened during the re-examination?

During the re-examination, the company restricted the intended use of the medicine to the treatment of tuberculosis affecting the lungs.

The CHMP then looked again at the data from the main studies. The Committee also took advice from a group of experts specialising in infectious diseases. A main focus of the re-examination was an investigation into whether the data from two months could be used to predict the effectiveness of delamanid when given for six months.

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

Following a re-analysis of the data in the light of the most recent international standards and studies from the literature, and following advice from the experts and discussions within the Committee, the CHMP took the view that although it cannot be assumed that the study results showing effectiveness at two months automatically predict effectiveness at six months, this was considered likely. In addition,

an on-going clinical study will examine responses at six months and should provide confirmation of the long-term effectiveness. The CHMP recommended that an additional study should be carried out to confirm that the current recommended dose is the most appropriate dose.

Regarding the safety of Deltyba, the safety profile was considered manageable and several measures were introduced to minimise the risks, including a study to confirm the long-term safety. Furthermore the Committee highlighted the medical need for new agents to treat multidrug-resistant tuberculosis.

Taking the above into consideration, the Committee concluded that the benefits of Deltyba outweigh its risks in treating lung infections due to multidrug resistant tuberculosis when alternative treatments cannot be used provided that further studies are carried out on the long-term effectiveness of Deltyba. The CHMP therefore recommended that Deltyba be granted a conditional marketing authorisation requiring the company to carry out the additional studies to find out more about the medicine's benefits and safety in the long term.

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.

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