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Questions and answers

Withdrawal of the marketing authorisation application for Tyvaso (treprostinil sodium)

On 17 February 2010, United Therapeutics Europe Ltd officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a marketing authorisation for Tyvaso, intended to be used as an 'add on' treatment for patients with pulmonary arterial hypertension.

What is Tyvaso?

Tyvaso is a medicine that contains the active substance treprostinil sodium. It was to be available as a nebuliser solution.

What was Tyvaso expected to be used for?

Tyvaso was expected to be used to treat patients with pulmonary arterial hypertension (PAH) to improve exercise capacity (the ability to carry out physical activity). PAH is abnormally high blood pressure in the arteries of the lungs.

Tyvaso was to be used in patients with PAH classified as 'New York Heart Association functional class III' who were also being treated with either an 'endothelin receptor antagonist' or a 'phosphodiesterase-5 inhibitor' (other medicines for PAH). The class reflects the seriousness of the PAH: class III involves marked limitation of physical activity. Tyvaso was expected to be given by inhalation, with the patient breathing the medicine directly into the lungs.

Tyvaso was designated an 'orphan medicine' (a medicine to be used in rare diseases) on 14 April 2004 for pulmonary arterial hypertension.

How is Tyvaso expected to work?

PAH is a debilitating disease where there is severe narrowing of the blood vessels of the lungs. It causes high blood pressure in the vessels taking blood from the heart to the lungs. This pressure reduces the amount of oxygen that can get into the blood, making physical activity more difficult.

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The active substance in Tyvaso, treprostinil sodium, is an analogue of prostacyclin, a naturally occurring molecule that causes blood vessels to expand. When it is inhaled, treprostinil sodium is expected to cause the blood vessels in the lungs to expand, which could relieve the abnormally high blood pressure in the arteries of the lungs.

What did the company present to support its application?

Because medicines containing treprostinil have been available in Europe since 2005, the company use some of these data to support its application for Tyvaso. The company presented results of one main study involving 235 patients with PAH who were also receiving either an endothelin receptor antagonist or a phosphodiesterase-5 inhibitor. The patients were given as an add-on to their existing treatment either Tyvaso or placebo (a dummy medicine). The main measure of effectiveness was the change in the distance patients could walk in six minutes after 12 weeks of treatment.

How far into the evaluation was the application when it was withdrawn?

The application was withdrawn after 'day 181'. This means that the CHMP had evaluated the documentation provided by the company and formulated a list of questions. After the CHMP had assessed the company's responses to the last round of questions, there were still some unresolved issues.

What was the recommendation of the CHMP at that time?

Based on the review of the data and the company's response to the CHMP list*s* of questions, at the time of the withdrawal, the CHMP had concerns. The main concern was that inspections of two sites where the single main study was carried out showed that the study had not been conducted in compliance with 'good clinical practice' (GCP). As a consequence, the results of the study were not considered to be reliable and the CHMP concluded that the medicine could not have been approved based on the data presented by the company.

What were the reasons given by the company to withdraw the application?

The letter from the company notifying the Agency of the withdrawal of the application is available here.

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

The company informed the CHMP that at the time of the withdrawal there was one on going clinical study in Europe and that Tyvaso was also being supplied on a compassionate use basis at one specialist centre in Germany. Treatment of these patients will continue until alternative treatments are obtained.

The summary of the opinion of the Committee for Orphan Medicinal Products for Tyvaso is available here.