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Withdrawal of the marketing authorisation application for Ambrisentan Zentiva (ambrisentan)

On 29 April 2019, Zentiva, k.s. officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a marketing authorisation for Ambrisentan Zentiva, for the treatment of pulmonary arterial hypertension (high blood pressure in the arteries of the lungs).

What is Ambrisentan Zentiva?

Ambrisentan Zentiva is a medicine that contains the active substance ambrisentan. It was to be available as tablets (5 and 10 mg).

Ambrisentan Zentiva was developed as a 'generic medicine'. This means that Ambrisentan Zentiva contained the same active substance and was intended to work in the same way as a 'reference medicine' already authorised in the European Union called Volibris. For more information on generic medicines, see the question-and-answer document here.

What was Ambrisentan Zentiva expected to be used for?

Ambrisentan Zentiva was expected to be used alone or combined with other medicines to treat adults with pulmonary arterial hypertension (high blood pressure in the arteries of the lungs). Ambrisentan Zentiva was to be used in patients with class II or III disease. The 'class' reflects the severity of the disease: 'class II' involves slight limitation of physical activity and 'class III' involves marked limitation of physical activity.

How does Ambrisentan Zentiva work?

The active substance in Ambrisentan Zentiva, ambrisentan, blocks the receptors (targets) for a hormone called endothelin, which causes blood vessels to narrow. By blocking the effect of endothelin, ambrisentan prevents the vessels becoming too narrow, helping to lower the blood pressure and improving symptoms.

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What did the company present to support its application?

Studies on the benefits and risks of the active substance in the approved use have already been carried out with the reference medicine, Volibris, and did not need to be repeated for Ambrisentan Zentiva.

As for every medicine, the company provided studies on the quality of Ambrisentan Zentiva. The company also carried out a study to investigate whether Ambrisentan Zentiva is 'bioequivalent' to the reference medicine. Two medicines are bioequivalent when they produce the same levels of the active substance in the body and are therefore expected to have the same effect.

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

The application was withdrawn after the CHMP had evaluated the documentation provided by the company and formulated lists 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's questions, at the time of the withdrawal, the CHMP had some concerns and was of the provisional opinion that Ambrisentan Zentiva could not have been approved for the treatment of pulmonary arterial hypertension.

The CHMP considered that the data on the manufacturing process were not complete and therefore had concerns about the way the medicine was to be produced. In addition, although the applicant had carried out a bioequivalence study with the higher strength (10 mg) which showed bioequivalence of this strength to the reference product, the data provided for the lower strength (5 mg) were insufficient to show bioequivalence with the reference medicine.

Therefore, at the time of the withdrawal, the CHMP was of the opinion that the company had not provided enough data to support the application for Ambrisentan Zentiva.

What were the reasons given by the company for withdrawing the application?

In its letter notifying the Agency of the withdrawal of the application, the company stated that the reason for the withdrawal was the additional investment in development activities needed to address the CHMP concerns.

The withdrawal letter is available here.

What consequences does this withdrawal have for patients in clinical trials?

The company informed the CHMP that there are no ongoing clinical trials with Ambrisentan Zentiva.