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Questions and answers

Withdrawal of the marketing authorisation application for Aripiprazole Mylan (aripiprazole)

On 8 January 2016, Mylan S.A.S. officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a marketing authorisation for Aripiprazole Mylan, for the treatment of schizophrenia and the treatment and prevention of manic episodes in patients with bipolar I disorder.

What is Aripiprazole Mylan?

Aripiprazole Mylan is a medicine that contains the active substance aripiprazole. It was to be available as tablets (5, 10, 15 and 30 mg) and as 10 and 15 mg orodispersible tablets (tablets that dissolve in the mouth).

Aripiprazole Mylan was developed as a 'generic medicine'. This means that Aripiprazole Mylan is similar to a 'reference medicine' already authorised in the European Union (EU) called Abilify.

What was Aripiprazole Mylan expected to be used for?

Aripiprazole Mylan was expected to be used to treat schizophrenia in patients aged 15 years or over. It was also expected to be used to treat moderate to severe manic episodes and to prevent new manic episodes in adults with bipolar I disorder who have responded to the medicine in the past, and for up to 12 weeks to treat moderate to severe manic episodes in patients aged 13 years or over with bipolar I disorder.

How is Aripiprazole Mylan expected to work?

The active substance in Aripiprazole Mylan, aripiprazole, is an antipsychotic medicine. Its exact mechanism of action is unknown, but it attaches to several types of receptors on nerve cells in the brain. This action disrupts signals transmitted between brain cells by 'neurotransmitters', chemicals that nerve cells use to communicate with neighbouring cells. Aripiprazole is thought to be a 'partial

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agonist' on the receptors for the neurotransmitters dopamine and 5-hydroxytryptamine (also called serotonin). This means that aripiprazole acts like dopamine and 5-hydroxytryptamine by activating these receptors, but it has a weaker effect than the natural neurotransmitters. Aripiprazole's action alters dopamine and 5-hydroxytryptamine activity, which is abnormal in schizophrenia and bipolar disorder. This may help to reduce psychotic and manic symptoms and prevent them from returning.

What did the company present to support its application?

Because Aripiprazole Mylan is a generic medicine, the company had presented results of studies in volunteers to show that Aripiprazole Mylan 10-mg tablet and the 10-mg orodispersible tablet were bioequivalent to the corresponding tablets of the reference medicine, Abilify. Two medicines are bioequivalent when they produce the same levels of the active substance in the body. To support an application for a 'biowaiver', the company also presented laboratory tests to show that other strengths of Aripiprazole Mylan tablets dissolve in an identical way to the reference medicine. The biowaiver removes the need to repeat bioequivalence studies for all the other strengths of Aripiprazole Mylan tablets.

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

The application was withdrawn after the CHMP had evaluated the initial documentation provided by the company and formulated a list of questions. The company had not yet responded to the questions at the time of the withdrawal.

What was the recommendation of the CHMP at that time?

Based on the review of the data, at the time of the withdrawal, the CHMP was of the provisional opinion that Aripiprazole Mylan could not have been approved for the treatment of schizophrenia and for the treatment and prevention of manic episodes in patients with bipolar I disorder.

The CHMP considered that the tests to support a biowaiver were not acceptable. The CHMP considered that the dissolution tests required for the biowaiver had not been carried out according to existing recommendations and thus, bioequivalence for all the different strengths of tablets and orodispersible tablets had not been demonstrated.

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 Aripiprazole Mylan.

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

In its letter notifying the Agency of the withdrawal of application, the company stated that the reason for withdrawal was identification of manufacturing issues.

The withdrawal letter is available here.

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

The company informed the CHMP that there were no consequences for patients in clinical trials.