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Questions and answers

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

On 7 May 2015, Generics (UK) Limited 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 and as 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. For more information on generic medicines, see the question-and-answer document here.

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 with bipolar I disorder aged 13 years or over.

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 receptors on the surface of nerve cells in the brain. This action disrupts signals transmitted between brain cells by 'neurotransmitters', chemicals

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that allow nerve cells to communicate with each other. Aripiprazole is thought to act mainly by being a 'partial agonist' for 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 less strongly than the neurotransmitters. Since dopamine and 5-hydroxytryptamine are involved in schizophrenia and bipolar disorder, aripiprazole helps to normalise the activity of the brain, reducing psychotic and manic symptoms and preventing 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 tests to determine that Aripiprazole Mylan is bioequivalent to the reference medicine, Abilify. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

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 had concerns about the choice of one of the starting materials for the production of aripiprazole. The Committee also had some concerns about whether the tests to show bioequivalence had been carried out in accordance with the guidelines for Good Clinical Practice (GCP). Findings from a GCP inspection of the site involved in the studies raised serious questions about the reliability of the data submitted in support of the application.

Therefore, at the time of the withdrawal, the CHMP was of the opinion that the medicine could not have been approved based on the data presented by the company.

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 it was withdrawing its application because of the identification of GCP 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 no clinical trials or compassionate use programmes are currently ongoing or in place with Aripiprazole Mylan.