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Questions and answers on the withdrawal of the application for a change to the marketing authorisation for Abilify (aripiprazole)

On 17 November 2009, Otsuka Pharmaceutical Europe Ltd. officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a new indication for Abilify, in the treatment of resistant major depressive episodes.

What is Abilify?

Abilify is a medicine that contains the active substance aripiprazole. It is available as tablets, orodispersible tablets (tablets that dissolve in the mouth), an oral solution and a solution for injection.

Abilify has been authorised since June 2004. It is already used to treat schizophrenia, and to treat and prevent manic episodes (periods of extremely high mood) in patients with bipolar I disorder.

What was Abilify expected to be used for?

Abilify was also expected to be used, in addition to antidepressants, to treat major depressive episodes in patients who had not responded adequately to previous antidepressant treatment. Major depressive episodes are periods of depressed mood or loss of interest in everyday activities that last for at least two weeks in patients with major depression.

How is Abilify expected to work?

The active substance in Abilify, aripiprazole, is an antipsychotic medicine. Its exact mechanism of action is unknown, but it attaches to several different receptors on the surface of nerve cells in the brain. This disrupts signals transmitted between brain cells by 'neurotransmitters', chemicals 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 major depression, Abilify is expected to help to normalise the activity of the brain when it is added to antidepressants, reducing the symptoms of major depressive episodes.

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What documentation did the company present to support its application to the CHMP?

The company presented the results of three short-term and one long-term study to support its application.

The short-term studies involved patients with major depressive episodes that had not responded to up to three previous antidepressant treatments. At the start of the study, the patients were put on an eight-week course of an antidepressant (escitalopram, sertraline, venlafaxine, fluoxetine or paroxetine). Each patient received an antidepressant that they had not previously taken for the current depressive episode. The 1,090 patients who did not respond to this antidepressant then added either Abilify or placebo (a dummy treatment). The main measure of effectiveness was the change in symptoms over the six weeks of dual treatment. The short-term studies were 'double-blind', which means that neither the patients nor the investigators knew which patients were receiving Abilify and which were receiving placebo.

The long-term study looked at the maintenance of Abilify's effects when added to an antidepressant. The study lasted up to a year and involved 1,076 patients, some of whom had completed one of the three short-term studies. Abilify was not compared with any other treatments in this study and the patients knew which medicines they were taking.

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

The evaluation was withdrawn after 'day 90'. This means that 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 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 responses to the CHMP lists of questions, at the time of the withdrawal, the CHMP had some concerns and was of the provisional opinion that Abilify could not have been approved for the treatment of resistant major depressive episodes.

The CHMP was concerned over the patients included in the studies, as it was not clear whether they all had resistant depression, defined as failure to respond to at least two previous antidepressants. The Committee was also concerned that there was no long-term information from 'double-blind' studies looking at the maintenance of Abilify's effects and its ability to prevent depression coming back. Therefore, at the time of the withdrawal, the CHMP was of the opinion that the benefits of Abilify in the treatment of major depressive episodes did not outweigh its risks.

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

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

What are the consequences of the withdrawal for patients in clinical trials or compassionate use programmes using Abilify?

The company informed the CHMP that there are no consequences for patients currently in clinical trials or compassionate use programmes using Abilify. If you are in a clinical trial or compassionate use programme and need more information about your treatment, contact the doctor who is giving it to you.

What is happening with Abilify for the treatment of schizophrenia and the treatment and prevention of manic episodes in bipolar I disorder?

There are no consequences on the use of Abilify in its authorised indications, for which the balance of benefits and risks remains unchanged.

The full European Public Assessment Report for Abilify is available here.