European Medicines Agency

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Questions and answers on the withdrawal of the marketing application for Ellefore

International non-proprietary name (INN): ***desvenlafaxine***

On 13 October 2008, Wyeth Europa Ltd. officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a marketing authorisation for Ellefore, for the treatment of major depressive disorder.

What is Ellefore?
Ellefore is a medicine that contains the active substance desvenlafaxine. It was to be available as prolonged-release tablets (50, 100 and 200 mg). 'Prolonged release' means that the active substance is released from the tablets over a few hours.

What was Ellefore expected to be used for?
Ellefore was expected to be used to treat major depression in adults.

How is Ellefore expected to work?
The active substance in Ellefore, desvenlafaxine, is a 'serotonin-noradrenaline re-uptake inhibitor' (SNRI). It works by preventing the neurotransmitters 5-hydroxytryptamine (also called serotonin) and noradrenaline from being taken back up into nerve cells in the brain.
Neurotransmitters are chemicals that allow nerve cells to communicate with one another. By blocking their re-uptake, desvenlafaxine increases the amount of these neurotransmitters in the spaces between certain nerve cells, increasing the level of communication between the cells. Since these neurotransmitters are involved in the control of mood, blocking their re-uptake into nerve cells is expected to improve the symptoms of major depression.
Desvenlafaxine is derived from venlafaxine, an SNRI that has been used as an antidepressant since the 1990s. The substance has been slightly modified with the aim of reducing side effects in patients who have problems breaking venlafaxine down.

What documentation did the company present to support its application to the CHMP?
The effects of Ellefore were first tested in experimental models before being studied in humans.
Ellefore was compared with placebo (a dummy treatment) in nine main studies involving a total of over 3,000 adults with major depression.
Four of the studies involving 1,814 patients used a fixed dose of Ellefore, and another four involving 1,229 patients used doses of Ellefore that could be adjusted. In these short-term studies, the main measure of effectiveness was the change in depressive symptoms over the eight weeks of treatment. Two of the flexible-dose studies also included venlafaxine (however, the studies were not designed to compare the two medicines).
One long-term study looked at how long it took for symptoms to return in a total of 376 patients who had already shown a response to an initial 12 weeks of Ellefore treatment.
In all of the studies, the effectiveness of the medicine was measured using standard questionnaires for depression.

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 75 23 71 29
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

How far into the evaluation was the application when it was withdrawn?
The application was at day 166 when the company withdrew. The CHMP was assessing the responses given by the company to a list of questions.
The CHMP normally takes up to 210 days to evaluate a new application. Based on the review of the initial documentation, the CHMP prepares a list of questions at day 120, which is sent to the company. Once the company has supplied responses to the questions, the CHMP reviews them and may, before giving an opinion, ask any remaining questions at day 180. Following the CHMP's opinion, it usually takes around two months for the European Commission to grant a licence.

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 had some concerns and was of the provisional opinion that Ellefore could not have been approved for the treatment of major depressive disorder.

What were the main concerns of the CHMP?
The CHMP was concerned that, overall, the effectiveness of Ellefore had not been shown convincingly. In relation to its parent substance, venlafaxine, desvenlafaxine seemed to be less effective with no advantages in terms of safety and tolerability. Information on the short and long-term effectiveness of Ellefore was also considered to be insufficient, because too few patients in the studies took the doses of Ellefore that were intended for use and because the studies' results were inconsistent. Therefore, at the time of the withdrawal, the CHMP's view was that a benefit of Ellefore had not been sufficiently demonstrated and any benefits did not outweigh the identified risks.

What were the reasons given by the company to withdraw the application?
The letter from the company notifying the EMEA of the withdrawal of the application is available here.

What are the consequences of the withdrawal for patients undergoing clinical trials or compassionate use programmes with Ellefore?
The company informed the CHMP that there are no consequences for patients currently included in clinical trials with Ellefore and that there are no compassionate use programmes ongoing. If you are in a clinical trial and need more information about your treatment, contact the doctor who is giving it to you.