European Medicines Agency

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Questions and answers on the withdrawal of the application for a change to the marketing authorisation for Stalevo

International non-proprietary name (INN): ***levodopa, carbidopa and entacapone***

On 6 March 2009, Orion Corporation officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a new indication for Stalevo, to add the treatment of early Parkinson's disease in adults who are starting levodopa treatment.

What is Stalevo?
Stalevo is a medicine that contains three active substances: levodopa, carbidopa and entacapone. It is available as tablets.
Stalevo is already used to treat adults with Parkinson's disease (a progressive brain disorder that causes shaking, slow movement and muscle stiffness) who are already being treated with a combination of levodopa and an inhibitor of dopa decarboxylase (the standard treatment for Parkinson's disease) but are having 'fluctuations' towards the end of the period between two doses of their medication. Fluctuations happen when the effects of the medication wear off and symptoms re-emerge. They are linked with a reduction in the effect of levodopa, when the patient experiences sudden switches between being 'on' and able to move, and being 'off' and having difficulty moving about. Stalevo is used when these fluctuations cannot be treated with the standard combination alone.

What was Stalevo expected to be used for?
Stalevo was also expected to be used to treat adults with early Parkinson's disease who are starting levodopa treatment.

How is Stalevo expected to work?
In early Parkinson's disease, Stalevo is expected to work in the same way as it does in its existing indication.
In patients with Parkinson's disease, the cells in the brain that produce the neurotransmitter dopamine begin to die and the amount of dopamine in the brain decreases. The patients then lose their ability to control their movements reliably. All of the active substances in Stalevo work to restore the levels of dopamine in the parts of the brain that control movement and co-ordination. Levodopa is converted into dopamine in the brain, and both carbidopa and entacapone block some of the enzymes that are involved in the breakdown of levodopa in the body. As a result, levodopa remains active for longer, helping to improve the symptoms of Parkinson's disease.

What documentation did the company present to support its application to the CHMP?
The company presented the results of one study involving 423 adults with Parkinson's disease who needed to start treatment with levodopa. The study compared Stalevo with a combination of levodopa and carbidopa (but without entacapone, the extra enzyme blocker included in Stalevo). The patients were not told which treatment they were taking. The main measure of effectiveness was the change in symptoms after 39 weeks of treatment.

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

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How far into the evaluation was the application when it was withdrawn?
The application was at day 193 when the company withdrew. After the CHMP had assessed the responses from the company to a list of questions, there were still some unresolved issues outstanding. The CHMP normally takes up to 90 days to adopt an opinion after it has received an application for a change to a marketing authorisation. Following the CHMP's opinion, it usually takes around six weeks for the European Commission to update the licence.

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 list of questions, at the time of the withdrawal, the CHMP had some concerns and was of the provisional opinion that Stalevo could not have been approved for the treatment of early Parkinson's disease.

What were the main concerns of the CHMP?
The CHMP was concerned that the benefits of Stalevo over the combination of levodopa and carbidopa without entacapone were too small to be relevant for patients starting levodopa treatment. In addition, the benefits of Stalevo over levodopa and carbidopa were mainly seen in patients taking Stalevo who had discoloration of the urine, which is a known side effect of entacapone, the extra component in Stalevo. There was no explanation for the improvement in this group of patients, which was more marked than in patients taking Stalevo who did not have urine discoloration. This could mean that some patients were able to guess which treatment they were taking, making the results of the study less convincing. Stalevo was also linked to side effects affecting the stomach and gut, such as diarrhoea and weight loss.
Therefore, at the time of the withdrawal, the CHMP's view was that a benefit of Stalevo in the treatment of adults with Parkinson's disease who are starting levodopa treatment 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 with Stalevo?
The company informed the CHMP that this withdrawal has no impact on patients in clinical trials with Stalevo. 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 Stalevo used for the treatment of fluctuations in patients with Parkinson's disease who are already being treated with levodopa and a dopa decarboxylase inhibitor?
There are no consequences on the use of Stalevo in its authorised indication, for which the balance of benefits and risks remains unchanged.

The full European Public Assessment Report (EPAR) for Stalevo is available here.