



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Questions and answers

Refusal of the marketing authorisation for Balaxur (memantine hydrochloride / donepezil hydrochloride)

On 18 October 2012, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of the marketing authorisation for the medicinal product Balaxur, intended for the treatment of moderate to moderately severe Alzheimer's disease in patients who are already taking memantine and donepezil.

The company that applied for authorisation is Merz Pharmaceuticals GmbH, Germany.

What is Balaxur?

Balaxur is a medicine that contains two active substances, memantine hydrochloride and donepezil hydrochloride. It was expected to be available as tablets (20 mg/10 mg).

What was Balaxur expected to be used for?

Balaxur was expected to be used to treat moderate to moderately severe Alzheimer's disease, in patients who are already taking a daily dose of 20 mg memantine and 10 mg donepezil.

How is Balaxur expected to work?

Balaxur is a combination treatment containing two active substances which are already authorised in the EU to treat the symptoms of Alzheimer's disease. The causes of Alzheimer's disease are unknown, but the associated memory loss, disorientation and behavioural symptoms are believed to be due to a disturbance of neurotransmitters in the brain. Neurotransmitters are chemicals in the nervous system that allow nerve cells to communicate with one another.

Memantine works by blocking types of receptor called NMDA receptors, to which the neurotransmitter glutamate normally attaches. Changes in the way glutamate transmits signals within the brain have been linked to the memory loss seen in Alzheimer's disease, and over-activity of the NMDA receptors



can result in cell damage or death. By blocking NMDA receptors, memantine helps to reduce the symptoms of Alzheimer's disease. It is authorised to treat patients with moderate to severe forms of Alzheimer's disease.

Donepezil works by blocking the action of an enzyme which normally breaks down a neurotransmitter called acetylcholine. Acetylcholine levels are lower in people suffering from dementia in Alzheimer's disease. By slowing down the breakdown of acetylcholine, donepezil helps to reduce the symptoms of Alzheimer's disease. It is authorised to treat patients with mild to moderately severe forms of Alzheimer's disease.

What did the company present to support its application?

The effects of Balaxur were first tested in experimental models before being studied in humans.

The company did not carry out any new studies in patients with Alzheimer's disease. It presented the results of seven main studies, including patients (or a subset of patients) who received memantine and donepezil together. One main study involved 404 patients with moderate to severe Alzheimer's disease who were already taking donepezil. The effects of adding memantine to donepezil was compared with adding placebo for six months of treatment. The effectiveness of the combination treatment was assessed by comparing the patients' performance in cognitive tests and in carrying out daily living activities. In addition, the company pooled and analysed the results from the different studies together.

The company also presented information intended to show the use of memantine and donepezil in combination to treat Alzheimer's disease across the European Union, including the available guidelines for treating Alzheimer's disease in different European countries.

What were the CHMP's main concerns that led to the refusal?

The Committee was concerned that the studies presented by the company had negative results except for one main study, in which patients already taking donepezil performed better in cognitive tests and in daily living activities when memantine was added to donepezil treatment. However, due to the study design it did not demonstrate a clear benefit of the combination treatment, since it did not include a control arm for patients treated with memantine alone. The CHMP considered that the additional analyses provided by the company did not satisfy these concerns.

The Committee also noted that a published study did not show a significant improvement in patients taking the combination treatment when compared with memantine alone.

The combination of memantine and donepezil is used in some European countries to treat patients with moderate to moderately severe Alzheimer's disease. However, the CHMP considered that the treatment guidelines were not consistent across European countries and the company had not provided enough evidence to support the use of a combination tablet in these patients.

Therefore, the CHMP was of the opinion that the benefits of Balaxur did not outweigh its risks and recommended that it be refused marketing authorisation.

What consequences does this refusal have for patients in clinical trials?

The company informed the CHMP that there are no patients currently included in clinical trials with Balaxur in the European Union.