20 December 2013
EMA/780804/2013
EMEA/H/C/000169/WS/355
EMEA/H/C/000255/WS/355

Questions and answers

Withdrawal of the application for a change to the marketing authorisation for Exelon and Prometax (rivastigmine)

On 21 November 2013, Novartis Europharm Ltd. officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wished to withdraw its application for a change to the marketing authorisations for the medicinal products Exelon and Prometax. The change concerned an extension of indication to allow the 13.3 mg/24h transdermal patch to be used to treat patients with severe Alzheimer's dementia.

What are Exelon and Prometax?

Exelon and Prometax are medicines that contain the active substance rivastigmine. They are available as capsules, oral solution and transdermal patches (patches that deliver the medicine through the skin) of various strengths.

Exelon and Prometax have been authorised in the European Union since May 1998. All forms of these medicines can be used for the treatment of patients with mild to moderately severe Alzheimer's dementia, a progressive brain disorder that gradually affects memory, intellectual ability and behaviour.

The capsules and oral solution can also be used to treat mild to moderately severe dementia in patients with Parkinson's disease.

What were Exelon and Prometax expected to be used for?

The 13.3 mg/24h transdermal patches of Exelon and Prometax were also expected to be used to treat patients with severe Alzheimer's dementia.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7129
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

How are Exelon and Prometax expected to work?

The transdermal patches of Exelon and Prometax are expected to work in patients with severe Alzheimer's dementia in the same way as they work in patients with mild to moderate Alzheimer's dementia.

In patients with Alzheimer's dementia, certain nerve cells die in the brain, resulting in low levels of the neurotransmitter acetylcholine (a substance that allows nerve cells to communicate with each other). The active substance in Exelon and Prometax, rivastigmine, works by blocking the enzymes that break down acetylcholine: acetylcholinesterase and butyrylcholinesterase. By blocking these enzymes, rivastigmine allows levels of acetylcholine to be increased in the brain, helping to reduce the symptoms of Alzheimer's dementia.

What did the company present to support its application?

The company presented the results of a 24-week main study involving 716 patients with moderately severe to severe Alzheimer's dementia, which compared the 13.3 mg/24h transdermal patch with a non-effective lower-dose, 4.6 mg/24h transdermal patch. The medicine was compared with a lower-dose patch rather than placebo (a dummy treatment) in this study because of previous experience of the company showing patients on placebo failing to complete their treatment. The main measures of effectiveness were changes in symptoms in two main areas: cognitive (the ability to think, learn and remember) and global (a combination of several areas including general function, cognitive symptoms, behaviour and the ability to carry out everyday activities).

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

The application was withdrawn after 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 response to the CHMP lists of questions, at the time of the withdrawal the CHMP had some concerns and was of the provisional opinion that the 13.3 mg/24h transdermal patch could not have been approved for the treatment of patients with severe Alzheimer's dementia. Although the 13.3 mg/24h transdermal patch had a greater effect on symptoms than the non-effective lower-dose patch, the CHMP was not convinced that this effect would translate into a clinically meaningful benefit, particularly for those patients with the most severe form of Alzheimer's dementia. In addition, even though the safety profile of the patch in patients with severe Alzheimer's dementia was similar to that in patients with mild to moderately severe Alzheimer's dementia, the CHMP was concerned that several side effects (including falls, vomiting and diarrhoea, dehydration, loss of appetite and psychiatric disorders) seemed to be more common and more severe in patients with severe Alzheimer's dementia. This could have more serious consequences in patients with severe disease, which is of concern in this more vulnerable population.

Therefore, at the time of the withdrawal, the CHMP was of the opinion that the benefits of Exelon/Prometax transdermal patch in the treatment of patients with severe Alzheimer's dementia did not outweigh its risks.

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

In its official letter, the company stated that its decision to withdraw the application was based on the CHMP's view that the data provided in support of the new indication are not sufficient to recommend approval.

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

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

The company informed the CHMP that there are no consequences for patients currently included in clinical trials with Exelon or Prometax.

If you are in a clinical trial and need more information about your treatment, contact the doctor who is giving it to you.

What is happening with Exelon and Prometax in their authorised indications?

There are no consequences for the use of Exelon and Prometax in their authorised indications.

The full European Public Assessment Report for Exelon can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European public assessment reports.

The full European Public Assessment Report for Prometax can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European public assessment reports.