



**Questions and answers on recommendation for the refusal of a change to the marketing authorisation
for
Cymbalta/Xeristar**

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

On 23 October 2008, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of a change to the marketing authorisation for the medicinal product Cymbalta/Xeristar 30 mg and 60 mg gastroresistant capsules. The change concerned an extension of indication to add the treatment of fibromyalgia. The companies that applied for authorisation are Eli Lilly Nederland B.V. (for Cymbalta) and Boehringer Ingelheim International GmbH (for Xeristar). They may request a re-examination of the opinion within 15 days of receipt of notification of this negative opinion.

What is Cymbalta/Xeristar?

Cymbalta/Xeristar is a medicine containing the active substance duloxetine. It is available as gastroresistant capsules. 'Gastroresistant' means that the capsules' contents pass through the stomach without being broken down until they reach the intestine. This prevents the active substance being destroyed by the acid in the stomach.

Cymbalta/Xeristar has been authorised since December 2004. It is used for the treatment of adults with the following diseases:

- episodes of major depression;
- pain due to diabetic peripheral neuropathy (damage to the nerves in the extremities that can occur in patients with diabetes);
- generalised anxiety disorder (long-term anxiety or nervousness about everyday matters).

What was Cymbalta/Xeristar expected to be used for?

Cymbalta/Xeristar was also expected to be used to treat adults with fibromyalgia, a disease causing long-lasting, widespread pain and painful responses to touch. Fibromyalgia can also cause other symptoms such as tenderness, stiffness, tiredness, anxiety and changes in how the patient sleeps, feels and thinks. The cause of fibromyalgia is not known. Cymbalta/Xeristar was expected to be used in fibromyalgia patients with or without depression.

How is Cymbalta/Xeristar expected to work?

The active substance in Cymbalta/Xeristar, duloxetine, is a serotonin-noradrenaline re-uptake inhibitor. It works by preventing the neurotransmitters 5-hydroxytryptamine (also called serotonin) and noradrenaline from being taken back up into nerve cells in the brain and spinal cord. Neurotransmitters are chemicals that allow nerve cells to communicate with one another. By blocking their re-uptake, duloxetine increases the amount of these neurotransmitters in the spaces between these nerve cells, increasing the level of communication between the cells. Since these neurotransmitters are thought to be involved in fibromyalgia, blocking their re-uptake into nerve cells is expected to improve the symptoms of the disease.

What documentation was presented to support this application?

The results of five studies involving a total of 1,718 adults with fibromyalgia were presented to the CHMP to support the application. Four of the studies were short-term, lasting between three and six months, and comparing Cymbalta/Xeristar with placebo (a dummy treatment) in a total of 1,411

patients. The fifth, a long-term study, compared the effects of two doses of Cymbalta/Xeristar over a year in 307 patients.

In all of the studies, the main measures of effectiveness were based on changes in the patients' symptoms, particularly pain levels, and their overall state of health. These were measured using standard scales and questionnaires.

What were the major concerns that led the CHMP to recommend the refusal of the change to the marketing authorisation?

The CHMP was concerned that the effectiveness of Cymbalta/Xeristar in treating fibromyalgia had not been shown sufficiently. In the short-term studies, the CHMP considered that the effect of Cymbalta/Xeristar was too small to be relevant for patients: there was no clear demonstration of improvement in symptoms, and the modest effects of Cymbalta/Xeristar could be due to the medicine's effect of improving the patients' mood. The CHMP also concluded that the long-term study was insufficient to show the effectiveness of the medicine and that a long-term study comparing Cymbalta/Xeristar with placebo would be needed.

At that point in time, the CHMP was of the opinion that the benefits of Cymbalta/Xeristar in the treatment of fibromyalgia did not outweigh its risks. Hence, the CHMP recommended that the change to the marketing authorisation be refused.

What are the consequences of the refusal for patients in clinical trials with Cymbalta/Xeristar?

The companies informed the CHMP that there are currently no ongoing clinical trials with Cymbalta/Xeristar in fibromyalgia patients in Europe.

What is happening for duloxetine used for the treatment of other diseases?

Duloxetine, under the names Aricclaim and Yentreve, is also authorised for use in stress urinary incontinence. There are no consequences on the use of Cymbalta/Xeristar, Aricclaim or Yentreve in their authorised indications, for which the balance of benefits and risks remains unchanged.

Medicinal Product no longer authorised