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Questions and answers

Refusal of a change to the marketing authorisations for Ariclaim, Cymbalta and Xeristar (duloxetine)

Outcome of re-examination

On 21 July 2011, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of a change to the marketing authorisations for the duloxetine-containing medicines Ariclaim, Cymbalta and Xeristar. The change concerned the addition of a new indication, the treatment of moderate to severe chronic somatic pain in patients not taking NSAIDs regularly. The company that applied for the change to the authorisation is Eli Lilly.

The applicant requested a re-examination of the opinion. After considering the grounds for this request, the CHMP re examined the initial opinion, and confirmed the refusal of the change to the marketing authorisations on 17 November 2011.

What are Ariclaim, Cymbalta and Xeristar?

Ariclaim, Cymbalta and Xeristar are medicines containing the active substance duloxetine. They are available as gastroresistant capsules.

Ariclaim is used to treat pain due to diabetic peripheral neuropathy (damage to the nerves in the extremities that can occur in patients with diabetes).

In addition to pain due to diabetic peripheral neuropathy, Cymbalta and Xeristar are also used in major depression and generalised anxiety disorder (long-term anxiety or nervousness about everyday matters).

What were the medicines expected to be used for?

In addition to their approved uses, the three medicines were expected to be used to treat moderate to severe chronic (long-term) somatic pain in patients not regularly taking NSAID pain killers (non-

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steroidal anti-inflammatory drugs). Somatic pain is from the body surfaces (such as skin) or musculoskeletal tissues (such as skeletal muscles, bone and joints). It does not include pain from internal organs such as the stomach and intestines.

How are they expected to work?

The medicines are expected to work in the same way they do in diabetic peripheral neuropathy. The active substance duloxetine, is a serotonin-noradrenaline re-uptake inhibitor. It works by preventing the neurotransmitters 5-hydroxytrypamine (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 involved in reducing the sensation of pain, blocking their re-uptake into nerve cells may improve the symptoms of pain.

What did the company present to support its application?

The company presented results of five main studies in 839 patients with chronic somatic pain: two studies in patients with knee pain caused by osteoarthritis (swelling and pain in the joints) and three in patients with chronic low back pain. Patients in the studies were treated with duloxetine or placebo (a dummy treatment) with some patients taking them in combination with NSAIDs. The main measure of effectiveness was the change in the severity of pain, as recorded by the patients on an 11-point scale after 12 or 13 weeks of treatment.

What were the CHMP's main concerns that led to the refusal of the change to the marketing authorisations?

The CHMP noted that the studies had not proven that duloxetine would provide a relevant benefit in the indication applied for. There was also insufficient evidence that its effect could be maintained over time, which is important when treating a long-term condition. In addition, more information was needed on the effects of duloxetine in elderly patients and its safety in the intended patients including the elderly. The CHMP therefore concluded that the benefits of duloxetine in the treatment of moderate to severe chronic somatic pain in patients not regularly taking NSAIDs had not been shown to outweigh its risks.

During the re-examination, the Committee considered the use of duloxetine in a smaller group of patients: patients with chronic low back pain or osteoarthritis (swelling and pain in the joints) of at least moderate severity who cannot use NSAIDS. The Committee concluded however that its concerns had still not been adequately addressed and confirmed its initial negative opinion recommending the refusal of a change to the marketing authorisations.

What consequences does this refusal have for patients in clinical trials or compassionate use programmes?

The company informed the CHMP that there are currently no ongoing clinical trials with Ariclaim, Cymbalta and Xeristar in chronic somatic pain patients in Europe.

What is happening with Ariclaim, Cymbalta and Xeristar for in their approved indications?

There are no consequences on the use of these medicines in their approved indications, for which the balance of benefits and risks remains unchanged.

The full European Public Assessment Report for Ariclaim, Cymbalta and Xeristar can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports.