European Medicines Agency

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QUESTIONS AND ANSWERS ON THE REVIEW OF ETORICOXIB-CONTAINING MEDICINES

The European Medicines Agency (EMEA) has completed a review of the benefits and risks of etoricoxib-containing medicines. The Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of etoricoxib-containing medicines outweigh their risks when used to treat rheumatoid arthritis (an immune system disease causing inflammation of the joints) or ankylosing spondylitis (a disease causing inflammation and pain in the joints of the spine). However, a number of measures need to be introduced into the prescribing information for these medicines, to minimise the risks associated with their use. This review was carried out under 'Article '6(12)'[1] and 'Article 31' referrals[2].

What is etoricoxib?
Etoricoxib is a non-steroidal anti-inflammatory drug (NSAID). It has been authorised in all European Union Member States for a number of years and is used to relieve the symptoms of the following diseases:

- osteoarthritis (at doses of 30 to 60 mg once a day);
- rheumatoid arthritis (at a dose of 90 mg once a day);
- short-term arthritis due to gout (at a dose of 120 mg once a day).

Etoricoxib is a cyclo-oxygenase enzyme type 2 (COX-2) inhibitor. This means that it blocks the action of COX-2, an enzyme that is involved in the inflammation process. As a result, etoricoxib reduces inflammation and pain. Etoricoxib-containing medicines[3] are authorised by regulatory authorities in Member States.

Why has etoricoxib been reviewed?
The etoricoxib-containing medicine Arcoxia is currently being assessed to determine whether it can also be used to treat ankylosing spondylitis at a dose of 90 mg once a day. During the assessment of this application, concerns were raised over the safety of the medicine when used at this dose for long periods, particularly its side effects affecting the heart, blood and blood vessels, such as high blood pressure and the formation of blood clots. Consequently, the French medicines regulatory agency referred this issue to the EMEA under an 'Article 6(12)' referral, so that a Europe-wide consensus could be reached on whether the new indication should be granted.

As the proposed dose of Arcoxia for ankylosing spondylitis is the same as the dose already used for rheumatoid arthritis, the French medicines regulatory authority also asked the CHMP to carry out a full assessment of the benefits and risks of all etoricoxib-containing medicines in the treatment of both ankylosing spondylitis and rheumatoid arthritis under an 'Article 31' referral. This was intended to determine whether the marketing authorisations for these medicines should be maintained, varied, suspended or withdrawn across the European Union.

Both referrals were concluded during the CHMP's meeting of 23-26 June 2008.

[1] Article 6(12) of Commission Regulation EC No 1083/2003, arbitration procedure initiated by a Member State following disagreement between Member States on a type II variation.
[2] Article 31 of Directive 2001/83/EC as amended, referral under Community interest.
[3] Etoricoxib is available in Algix, Arcoxia, Auxib, Etoricoxib MSD, Exxiv, Ranacox, Tauxib and Turox.

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Which data has the CHMP reviewed?
The CHMP has assessed all of the available information on the long-term benefits and risks of etoricoxib in patients with rheumatoid arthritis or with ankylosing spondylitis. This included information from clinical trials that compared etoricoxib with placebo (dummy treatments) and with other medicines. For rheumatoid arthritis, these studies lasted up to three years, and for ankylosing spondylitis, they lasted for up to a year. The CHMP also reviewed information provided by the company that makes the medicines.

What are the conclusions of the CHMP?
Based on the information available, the CHMP has concluded that:

- the benefits of etoricoxib-containing medicines continue to outweigh their risks for the treatment of rheumatoid arthritis;
- the benefits of etoricoxib-containing medicines outweigh their risks for the treatment of ankylosing spondylitis, when used at a dose of 90 mg once a day. Therefore, the Committee recommended that the extension of indication for Arcoxia to include ankylosing spondylitis should be granted.

However, the CHMP concluded that more information is needed on the effectiveness of lower doses of etoricoxib, such as 60 mg once a day, for the treatment of both diseases. The company that makes etoricoxib-containing medicines will design and carry out studies to investigate this lower dose.

In addition, the CHMP concluded that a number of measures need to be introduced in the prescribing information for etoricoxib-containing medicines to manage the risks associated with their use. The Committee recommended that the existing contraindication on the use of etoricoxib in patients with high blood pressure that is not adequately controlled should be amended to state that patients whose blood pressure is persistently above 140/90 mmHg and has not been adequately controlled must not take the medicine. Warnings on the risk of heart-related side effects should also be added, stating that:

- high blood pressure should be controlled before treatment is begun;
- blood pressure should be monitored for two weeks after the start of treatment and regularly thereafter.

The CHMP also noted that further studies need to be carried out to investigate the effects of these medicines in more detail when they are used for ankylosing spondylitis. In particular, information is needed on their side effects affecting the heart and blood vessels. The company that makes etoricoxib-containing medicines should also look into ways to investigate their safety in patients with ankylosing spondylitis in more depth, such as setting up a registry of patients taking the medicines.

What are the recommendations for patients and prescribers?

- When prescribing etoricoxib-containing medicines in any of their indications, doctors should use the updated prescribing information and be aware of the potential heart-related side effects.
- Doctors should not prescribe etoricoxib-containing medicines to patients whose blood pressure is persistently above 140/90 mmHg and has not been adequately controlled. Blood pressure should be monitored for two weeks after a patient starts to take etoricoxib and regularly thereafter.
- Doctors and patients should watch out for the signs symptoms of side effects affecting the heart and blood vessels, such as fluid retention, high blood pressure, shortness of breath or chest pain.
- Patients who have any questions or concerns should speak to their doctor or pharmacist.