European Medicines Agency
Press office

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Press release

European Medicines Agency concludes action on COX-2 inhibitors

Concluding its review of the class of COX-2 inhibitors, the European Medicines Agency (EMEA) has recommended the suspension of the marketing authorisation for Bextra (valdecoxib) and recommended new contraindications and warnings for other COX-2 inhibitors that continue to be available in the European Union (EU). This builds on earlier regulatory actions taken in February 2005.

COX-2 inhibitors are part of a broader class of medicines called non-steroidal anti-inflammatory drugs (NSAIDs), whose safety profile will now also be examined.

At its 20-23 June 2005 meeting the Agency's Committee for Medicinal Products for Human Use (CHMP) said that additional warnings and contraindications are necessary for all COX-2 inhibitors due to the cardiovascular risks, but concluded that the additional risks of serious and potentially fatal skin reactions associated with the use of Bextra outweigh its benefits. The suspension of Bextra will be reviewed within one year, during which time Pfizer has the opportunity to provide further safety and other relevant data before the Committee can consider the re-introduction of the product in the EU. At the request of the EMEA, Pfizer voluntarily agreed in April 2005 to withdraw the product from the market in the EU.

For the other COX-2 inhibitors (celecoxib, etoricoxib, lumiracoxib and parecoxib), the Committee agreed that the available data show an increased risk of thrombotic adverse cardiovascular reactions, such as heart attacks and strokes. The CHMP confirmed its February 2005 finding of an association between duration and dose of intake and the probability of suffering such cardiovascular reactions. The Committee also confirmed that serious skin reactions occur with other COX-2 inhibitors, but have been reported at lower rates than with Bextra. In concluding its review, the CHMP recommended the following contraindications and precautions for these products:

- Contraindications stating that COX-2 inhibitors must not be used in patients with established ischaemic heart disease and/or cerebrovascular disease (stroke), and also in patients with peripheral arterial disease
- Reinforced warnings to healthcare professionals to exercise caution when prescribing COX-2 inhibitors to patients with risk factors for heart disease, such as hypertension, hyperlipidaemia (high cholesterol levels), diabetes and smoking
- Given the association between cardiovascular risk and exposure to COX-2 inhibitors, doctors are advised to use the lowest effective dose for the shortest possible duration of treatment
- Additional or strengthened warnings to healthcare professionals and patients that hypersensitivity reactions and rare, but serious and sometimes fatal, skin reactions can occur with all COX-2 inhibitors. In the majority of cases these occur in the first month of use, and prescribers are warned that patients with a history of drug allergies may be at greater risk.

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When prescribed in accordance with these additional contraindications and precautions, the Committee concluded that the balance of benefits and risks remains positive for these COX-2 inhibitors used in their target patient populations. In addition to any ongoing studies, the CHMP emphasised the importance for the authorisation holders for COX-2 inhibitors in the EU (Merck Sharp & Dohme, Novartis and Pfizer) to continuously and carefully monitor and assess cardiovascular safety and serious skin reactions.

The Committee assessed safety data for COX-2 inhibitors versus some conventional NSAIDs during the course of the review procedure for the COX-2 inhibitors. On the basis of these data and following a request from the European Commission, the Committee has now decided to look at the safety profile of NSAIDs to determine the need for further steps. This will build on a review already started by the Committee's Pharmacovigilance Working Party on the safety of the most commonly used NSAIDs.

It is unclear if the findings for COX-2 inhibitors are also relevant for conventional NSAIDs. Pending any future recommendations, healthcare professionals and patients should closely follow the product information for conventional NSAIDs (whether prescription or non-prescription products) and COX-2 inhibitors. Patients who have concerns or questions should talk to their doctor or pharmacist.

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NOTES:

1. The EMEA review of the COX-2 inhibitor class of medicines was announced on 22 October 2004 and can be found [here]. The EMEA issued further statements on 17 December 2004 [here], 22 December 2004 [here], 20 January 2005 [here], 17 February 2005 [here] and 7 April 2005 [here].
2. An updated question and answer document can be found [here].
3. The revised product information of celecoxib, etoricoxib, lumiracoxib and parecoxib can be found [here].
4. The COX-2 inhibitors that were reviewed are celecoxib, etoricoxib, lumiracoxib, parecoxib and valdecoxib.
5. Lumiracoxib is currently only authorised in the United Kingdom and is not yet being marketed.
6. Valdecoxib was authorised in the European Union as Bextra and Valdyn in March 2003. The marketing authorisation holders are Pfizer and Pharmacia-Pfizer respectively. The recommendation for suspension also applies to Valdyn.
7. The suspension of a marketing authorisation is a temporary measure in response to public health concerns, usually for a renewable period of one year, during which time a marketing authorisation holder may conduct additional studies to provide data and/or analysis in support of the benefits and risks of the product.
8. This press release, together with other information about the work of the EMEA, may be found on the EMEA web site at http://www.emea.eu.int

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