European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

London, 27 October 2005
Doc. Ref. EMEA/358234/2005

EMEA PUBLIC STATEMENT ON THE SUSPENSION OF THE MARKETING AUTHORISATION FOR BEXTRA (valdecoxib) IN THE EUROPEAN UNION

The European Commission issued a Commission Decision to suspend the Marketing Authorisation of Bextra on 13 October 2005, confirming the European Medicines Agency's recommendation made in June 2005.

In the context of the review of COX-2 inhibitors the EMEA's Committee for Medicinal Products for Human Use (CHMP), had assessed the safety data of valdecoxib, in particular with regard to cardiovascular safety and serious skin reactions, and recommended in its Opinion that the marketing authorisation be suspended (see http://www.emea.eu.int/pdfs/human/press/pr/20776605en.pdf).

The CHMP was of the opinion that Bextra can no longer be safely used in view of the occurrence of severe and unpredictable cutaneous adverse reactions. This affects the overall benefit/risk balance of valdecoxib and makes it unfavourable in the authorised indications. Furthermore it was not possible to restrict the indications or add adequate contra-indications to permit its safe use. Therefore, the CHMP recommended the suspension of the Marketing Authorisation for Bextra.

On the basis of the CHMP Opinion, the European Commission issued a Commission Decision for suspension of the Marketing Authorisation of Bextra on 13 October 2005.

For background information and scientific discussion, please refer to the annex below.

For further information contact:
M. Noël Wathion
Head of Unit of Evaluation of Medicines for Human Use
Tel: +44 207 418 8411/ Fax: +44 207 418 8668

ANNEX

BACKGROUND INFORMATION

Rofecoxib withdrawal

In September 2004, the Marketing Authorisation Holder (MAH) of rofecoxib (a selective Cox-2-inhibitor) informed the EMEA that new clinical trial (APPROVe) data for rofecoxib have revealed a risk of thrombotic cardiovascular (CV) events. These data resulted in the worldwide withdrawal of Vioxx (rofecoxib) from the market on 30 September 2004 by the MAH and raised questions regarding the cardiovascular safety of other Cox-2 inhibitors.

COX-2 review

Further to discussions at the plenary meeting of the CHMP in October 2004, the European Commission recommended that this public health issue on all aspects of cardiovascular safety including thrombotic events and cardio-renal events is the subject of Community referrals under Article 31 of Directive 2001/83/EC, as amended regarding decentrally authorised products containing celecoxib, etoricoxib and lumiracoxib and subject to a review procedure under Article 18 of Council Regulation (EEC) No 2309/93, as amended regarding the centrally authorised products containing celecoxib (Onsenal), parecoxib (Dynastat/Rayzon) and valdecoxib (Bextra/Valdyn); these procedures were started in November 2004.

During the CHMP meeting of February 2005, discussions on cardiovascular safety took place. The CHMP agreed that an Urgent Safety Restriction (USR) on cardiovascular safety was needed to introduce new contraindications and strengthen warnings and information on side effects in the SPC and the Package Leaflet (PL). This USR was initiated on 16 February 2005 and finalised on 17 February 2005.

Bextra voluntary withdrawal

On 7 April 2005, the EMEA requested that Pfizer voluntarily withdraw Bextra (valdecoxib) from the market and Pfizer agreed to suspend sale and marketing of Bextra pending further discussions on the unfavourable risk versus benefit due to data on serious skin reactions.

On 20 April 2005, Pfizer presented data on serious skin reactions for valdecoxib during a hearing. Further to a request from the European Commission, the scope of the ongoing class review was broadened to include the assessment of serious skin reactions in addition to the cardiovascular safety aspects.

SCIENTIFIC DISCUSSION

CHMP assessment of the safety of Bextra

Between November 2004 and June 2005, the MAH made oral explanations to the CHMP on cardiovascular and skin safety aspects for Bextra on 18 January, 20 April, and 25 May 2005.

- **Cardiovascular aspects.**

On 23 June 2005, the CHMP concluded that further to the assessment of:

- the new data provided on rofecoxib by the APPROVe clinical study, which revealed a risk of thrombotic CV events,
- the data on celecoxib presented in the APC study, which suggested a dose-related increased risk of serious CV events,
- the data on valdecoxib and parecoxib presented in the CABG (Coronary Artery Bypass Graft) and in the CABG II studies, which showed a higher rate of serious CV

thromboembolic events in the parecoxib/valdecoxib treatment arm compared to the group of patients receiving placebo,
- the data on etoricoxib in the EDGE study and pooled analyses of other clinical trials, which suggested an association with a higher thrombotic risk than naproxen,
- the data on lumiracoxib in the Target study, which suggested a small increase in thrombotic events (especially myocardial infarction) versus naproxen,

all available data show an increased risk of CV adverse reactions for Cox-2 inhibitors as a class and agreed that there is an association between duration and dose of intake and the probability of suffering a CV reaction.

- **Serious skin reactions safety aspects.**

The propensity for valdecoxib to cause Severe Cutaneous Adverse Reactions (SCAR) is higher than that of other COX-2 inhibitors. In comparison to celecoxib the event rate of SCAR is 3 to 4-fold higher. Review of the reporting rates for the two compounds by annual quarters indicate that the rate for valdecoxib has on occasion been 12 to 14 times higher than celecoxib, though this is likely to be in part due to stimulated reporting for valdecoxib. However, even in the 'trough' reporting periods the rate for valdecoxib is 3 to 4 times that for celecoxib. Furthermore, some data suggested that over the first two years of marketing for each product, valdecoxib had a SCAR reporting rate 8.6 times that of celecoxib and 18.2 times that of rofecoxib.

The CHMP concluded, that there is a clear causal association between the use of valdecoxib and severe cutaneous adverse reactions (e.g. Erythema Multiforme; Stevens-Johnson Syndrome; Toxic Epidermal Necrolysis).

The occurrence of severe cutaneous adverse reactions, associated with valdecoxib is unpredictable and no preventive measures have been identified. This risk of skin toxicity constitutes an unacceptable hazard if not balanced by a high beneficial therapeutic effect.

Considering the safety data on SCAR available today, the CHMP concluded that there is strong evidence of a disadvantage of valdecoxib versus the other Cox-2 inhibitors and that the severe cutaneous adverse reactions reporting rate with valdecoxib was too high to keep the product on the market.

The MAH proposed to limit the indications in the European Union to the treatment of patients unresponsive or intolerant of other COX-2 inhibitors/NSAIDS. The CHMP discussed whether potential advantages for patients unresponsive or intolerant of other COX-2 inhibitors/NSAIDS could be identified. However, considering the available data, no evidence could allow the identification of such a "niche" indication where the benefit would outweigh the known and unpredictable occurrence of severe cutaneous adverse reactions associated with the use of valdecoxib.

Therefore the CHMP considered that, further to the assessment of the data provided by the MAHs, the benefit/risk balance of valdecoxib for symptomatic relief in the treatment of osteoarthritis or rheumatoid arthritis and the treatment of primary dysmenorrhoea was not favourable and the Marketing Authorisations should be suspended.