European Medicines Agency

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP) OPINION FOLLOWING AN ARTICLE 31(2) REFERRAL

Etoricoxib containing medicinal products

International non-proprietary name (INN): etoricoxib

BACKGROUND INFORMATION *

Etoricoxib is a selective inhibitor of COX-2 (cyclooxygenase 2) indicated in the symptomatic relief of osteoarthritis (OA, 30-60mg once daily (od)), rheumatoid arthritis (RA, 90mg od) and the pain and signs of inflammation associated with acute gouty arthritis (120mg od).

This referral procedure relates to a request for arbitration concerning the benefit/risk of the 90mg dose of etoricoxib in the treatment of RA and ankylosing spondylitis (AS).

At the end of the mutual recognition procedure for the variation to extend the indication to include AS, there was a discrepancy between different European Union (EU) Member States regarding the safety of etoricoxib at the 90mg dose. As these concerns were not resolved during the course of the procedure, and since the 90mg dose of etoricoxib was used in both RA and AS, a notification of an official referral for arbitration under Article 31(2) of Directive 2001/83, as amended to the CHMP was made by France on 19 September 2007.

The main unresolved areas of concern identified by France were concerns regarding long term safety of a daily dose of 90mg etoricoxib in the view of possible increased cardiovascular (CV) risk related to the use of the 90mg dose in the RA and AS indications. France considered that a review of the benefit/risk profile of etoricoxib containing medicinal products was of Community interest.

The arbitration procedure was discussed by the CHMP at its plenary meeting in September 2007 and a Rapporteur (Dr. Karl Broich) and Co-Rapporteur (Dr. Matthew Thatcher) were appointed. The referral procedure was initiated on 20 September 2007 with the adoption of a CHMP list of questions that were to be addressed by the marketing authorisation holders (MAHs). During the February 2008 plenary meeting Dr. Rafe Survana was appointed Co-Rapporteur, replacing Dr. Matthew Thatcher.

Written explanations were provided by the MAHs on 14 December 2008, 5 May 2008, 12 June 2008 and 20 June 2008.

The CHMP concluded that the data confirmed the known renovascular safety profile of etoricoxib (hypertension, oedema and congestive heart failure). The data further confirmed a similar CV thrombotic risk like diclofenac and some degree of upper gastrointestinal (GI) safety advantage over naproxen and diclofenac (though no particular lower GI safety advantage). There was little direct comparative safety data for individual non-steroidal anti-inflammatory drugs (NSAIDs) other than diclofenac and naproxen. It was therefore difficult to determine risks for etoricoxib compared with ibuprofen, ketoprofen or other less-commonly used NSAIDs.
Drug utilisation data showed that some patients with high blood pressure are being initiated on etoricoxib. The CHMP therefore recommended the strengthening of the contraindication in

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hypertensive patients and alerts prescribers that blood pressure needs to be monitored, especially within 2 weeks of treatment initiation. Healthcare professionals were to be reminded of these measures through a communication letter (Dear Healthcare Professional Letter).

Data from clinical studies showed clinically meaningful treatment effect for the 90mg etoricoxib once daily dose for both RA and AS indications; however, some data are available to indicate that lower doses might also show effect. The CHMP therefore recommended that dose finding studies should be explored to conclude if treatment with 60mg once daily would also be adequate for some patients.

Based on the review of the available data, the CHMP considered that the benefits of etoricoxib outweigh the risks in the treatment of rheumatoid arthritis and ankylosing spondylitis.

On 26 June 2008, the CHMP, having considered the data provided by the MAHs, recommended the granting of the variation to the marketing authorisations.

The list of product names concerned is given in Annex I. The scientific conclusions are provided in Annex II, the amended product information in Annex III and the conditions of the marketing authorisation in Annex IV.

The final opinion was converted into a decision by the European Commission on 9 September 2008.

∗ Notes: the information given in this document and its annexes reflects only the CHMP opinion dated 26 June 2008. The Member States' competent authorities will continue to keep the product under regular review.