European Medicines Agency
Evaluation of Medicines for Human Use

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OPINION OF THE COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE PURSUANT TO ARTICLE 5(3) OF REGULATION (EC) No 726/2004, FOR NON-SELECTIVE NON STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

Basis for opinion

On 21 September 2006, France presented a request to the CHMP for an opinion under Article 5(3) of Regulation (EC) No 726/2004 on the cardiovascular risks of non-selective non-steroidal anti-inflammatory drugs (NSAIDs) in the context of their overall benefit/risk profile. This was due to newly available data on cardiovascular safety of non-selective NSAIDs stemming from clinical and epidemiological studies and concerns on the impact on the benefit-risk balance of these products. The grounds for this request are appended to this opinion (Appendix 1).

On the basis of the request made by France, the CHMP considered that there were sufficient grounds to start the procedure.

The procedure started on 21 September 2006.

Opinion

The CHMP, having considered the matter as set out in the appended assessment report (Appendix 2), is of the opinion that no public health concerns have been identified that are considered as being of Community interest, which would warrant an Article 31 referral. However, the CHMP agrees that the recommendations for use of non-selective NSAIDs should adequately reflect the current level of knowledge on thrombotic risk. To this effect, the CHMP has recommended that its Pharmacovigilance Working Party (PhVWP) consider whether there is a need to revise the previously agreed key elements[1] related to cardiovascular safety. Furthermore, the CHMP recommends that the outcome of the MEDAL[2] programme should be analysed in more depth once complete results are available. Possibilities for further epidemiological studies to obtain additional data on pertinent safety aspects of non-selective NSAIDs will be explored.

The CHMP agrees that the general prescribing advice and the advice to patients for NSAIDs remains as follows:

- Prescribers and patients should continue to use NSAIDs at the lowest effective dose for the shortest possible duration to control symptoms.
- Prescribers should continue to choose any NSAID on the basis of the overall safety profile of the product, as set out in the product information, and the patient's individual risk factors.
- Prescribers should not switch between NSAIDs without careful consideration of the overall safety profile of the products and the patient's individual risk factors, as well as the patient's preferences.

[1] Adopted key elements for the prescribing information of non-selective NSAIDs published in October 2005 and adopted key elements for the prescribing information of the non-selective NSAIDs piroxicam, ketoprofen and ketorolac published in September 2006

[2] Multinational Etoricoxib versus Diclofenac Arthritis Long-term

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

This opinion is without prejudice to the outcome of the ongoing Article 31 referral procedure for piroxicam[3].

The Icelandic and the Norwegian CHMP members agree with the above-mentioned recommendation of the CHMP.

The scientific conclusions are set out in Annex I.

This opinion is forwarded to France, the European Commission, all other Member States, Iceland and Norway, together with its annex and appendices.

The opinion is published on the EMEA website with its annex and appendices.

London, 18 October 2006

On behalf of the CHMP
Dr Daniel Brasseur, Chairman

[3] EMEA/H/A-31/763

ANNEX I

SCIENTIFIC CONCLUSIONS

SCIENTIFIC CONCLUSIONS

The reason for this review under article 5(3) is new data and analyses stemming from clinical and epidemiological studies, which signal a potentially increased arterial thrombotic risk (such as myocardial infarction or stroke) for non-selective NSAIDs, especially when used at high doses and in long-term treatment. These new data include (i) the MEDAL clinical trial programme comparing etoricoxib and diclofenac, (ii) updated meta-analyses of clinical and epidemiological studies of NSAIDs and COX-2 inhibitors, (iii) new epidemiological data for meloxicam (iv) updated analyses for Cox-II inhibitors from the APPROVe[4], APC[5] and PreSAP [6]studies. The CHMP has reviewed these data sets taking into account previous NSAIDs and COX-2 inhibitors reviews.

The CHMP agrees the following on the arterial thrombotic risk:

- Data from the MEDAL programme indicate that the overall thrombotic risk for diclofenac (150 mg/d) and etoricoxib (60 or 90 mg/d) is similar. However, there are issues that need to be further analysed before the results of the programme can be considered conclusive (e.g. review of individual studies, subgroups, dose effects). When the full data set is available, these issues will be further assessed.

  Taking all available clinical trial and epidemiological data into account, diclofenac, particularly at a high dose (150 mg/d), may be associated with an increased risk of arterial thrombotic events (for example myocardial infarction or stroke).

- Clinical trial data suggest that ibuprofen at a high dose (2400 mg/d) may be associated with an increased risk of thrombotic events (for example myocardial infarction or stroke). Overall, epidemiological studies do not suggest that low dose ibuprofen (e.g. ≤1200 mg/daily) is associated with an increased risk of myocardial infarction.

- Clinical trial and epidemiological data suggest that naproxen (1000 mg/d) may be associated with a lower risk for arterial thrombotic events than COX-2 inhibitors, but a small risk cannot be excluded. Overall, the data do not support a cardioprotective effect.

- For all other non-selective NSAIDs, there are insufficient data to conclude on thrombotic risk. Therefore, an increased risk cannot be excluded.

- New epidemiological evidence and updated clinical trial data (APC, PreSAP, APPROVe and meta-analyses) continue to point towards an increased thrombotic risk with COX-2 inhibitors compared to non-use (in epidemiological studies) and compared to placebo (in clinical studies) possibly accounting for about 3 extra events per 1000 patient-years. This relates mainly to myocardial infarction, and includes cerebrovascular and peripheral vascular events in some studies. For the majority of patients, the potential increase in thrombotic risk is small. However, in subjects with pre-existing risk factors for cardiovascular disease or history of cardiovascular disease, the risk may be higher.

[4] Adenomatous Polyp Prevention with VIOXX

[5] Adenoma Prevention with Celecoxib

[6] Prevention of Colorectal Sporadic Adenomatous Polyps

After review of all data currently available to the CHMP, the Committee concludes:

- Non-selective NSAIDs are important treatments for arthritis and other painful conditions.

- It cannot be excluded that non-selective NSAIDs may be associated with a small increase in the absolute risk for thrombotic events especially when used at high doses for long-term treatment.

- The overall benefit-risk balance for non-selective NSAIDs remains favourable when used in accordance with the product information, namely on the basis of the overall safety profile of the respective non-selective NSAID, and taking into account the patient's individual risk factors (e.g. gastrointestinal, cardiovascular and renal).

- Based on this latest review, no public health concerns have been identified that are considered as being of Community interest, which would warrant an Article 31 referral.

- The CHMP agrees that the recommendations for use of the above compounds should adequately reflect the current level of knowledge on thrombotic risk.

- The CHMP recommends that the Pharmacovigilance Working Party should consider whether there is a need to revise previously agreed key elements related to cardiovascular safety for the non-selective NSAID prescribing information.

- The complete results from the MEDAL programme should be analysed in depth when available. Following these analyses, the current recommendations on the cardiovascular safety of COX-2 inhibitors may be reconsidered.

- Possibilities for further epidemiological studies to obtain additional data on pertinent safety aspects of non-selective NSAIDs will be explored by a joint ad hoc group between the CHMP and the PhVWP.

The CHMP agrees that the general prescribing advice and the advice to patients for NSAIDs remains as follows:

- Prescribers and patients should continue to use NSAIDs at the lowest effective dose for the shortest possible duration to control symptoms.

- Prescribers should continue to select any NSAID on the basis of the overall safety profile of the product, as set out in the product information, and the patient's individual risk factors.

- Prescribers should not switch between NSAIDs without careful consideration of the overall safety profile of the products and the patient's individual risk factors, as well as patient's preferences.