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

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Questions and Answers on COX-2 Inhibitors

This is an updated version of the Q&A document first published in December 2004 and contains new elements relating to the ongoing review of COX-2 inhibitors by the European Medicines Agency and the regulatory actions announced in February 2005.

1. Why is the EMEA providing a further update on COX-2 inhibitors ?

The European Medicines Agency (EMEA) and its scientific committee, the Committee on Medicinal Products for Human use (CHMP) has reviewed all available data on the cardiovascular safety of COX-2 inhibitors. This latest review follows the withdrawal of rofecoxib in September 2004 and new clinical trial data on celecoxib in December 2004.These data indicate that an increased risk of heart attack and stroke may be a class effect of all COX-2 inhibitors. Based on these findings the EMEA/CHMP is now providing further advice on these medicines.

2. What are COX-2 inhibitors ?

Anti-inflammatory medicines have been available for many years and are important in the treatment of arthritis and other painful conditions. Celecoxib is also indicated as a treatment for the rare bowel condition, familial adenomatous polyposis. One disadvantage of anti-inflammatory medicines is their potential to cause stomach and gut (gastro-intestinal) side effects (e.g. ulcers and bleeding), which in rare cases can be serious or even fatal. COX-2 selective inhibitors are a relatively new type of anti-inflammatory medicine that are considered to produce less in the way of gastro-intestinal side effects than older “non-selective” drugs. Emerging data raise concerns of an increased risk of cardiovascular events (including heart attacks and strokes) for this class of products.

3. Which COX-2 inhibitors have been reviewed ?

Celecoxib, etoricoxib, lumiracoxib, valdecoxib and parecoxib.

4. What are the risks shown by the clinical studies ?

The CHMP has now reviewed detailed data on clinical trials ,including long-term use as well as all available scientific evidence on this class of medicines. In an accelerated review the CHMP found an increased risk of cardiovascular adverse events for COX-2 inhibitors as a class.

Available data also suggest an association between dose and duration of intake and the probability to suffer a cardiovascular event.

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5. Is EMEA restricting the use of COX-2 inhibitors based on CHMP findings ?

Based on the available scientific evidence the CHMP recommended that product information of the COX-2 inhibitors should be urgently revised to introduce new contraindications and warnings for use of these medicines.

6. What is the new advice from EMEA and CHMP ?

Prescribers and patients are advised that these products should not be used in patients with ischaemic heart disease or stroke.

An additional contraindication has also been introduced for etoricoxib in patients with hypertension (high blood pressure) whose blood pressure is not under control.

7. What are the additional warnings regarding COX-2 inhibitors ?

Caution is needed when COX-2 inhibitors are to be used in patients with risk factors for heart disease. These include high blood pressure, high cholesterol, diabetes and smoking. The balance of cardiovascular and gastrointestinal risks should be carefully considered for patients who do not have heart disease but are taking low dose aspirin. Evidence suggests that any gastrointestinal safety advantage for COX-2 inhibitors is substantially reduced when given with aspirin.

The cardiovascular risk may increase with duration of treatment and with high doses. Doctors should use the lowest effective dose of the COX-2 medicine for the shortest possible duration of treatment.

8. Should patients switch from COX-2 inhibitors to conventional NSAIDs ?

The choice of treatment with COX-2 inhibitors or other analgesics/ anti-inflammatory medicines is made depending on individual patient characteristics. All treatment decisions should take into account previous medical history and identified risk factors. Prescribers should consider alternative therapy for those patients with ischaemic heart disease or stroke. Patients and healthcare providers are advised to follow the latest recommendations and guidelines for the use of COX-2 inhibitors provided by the national authorities in the Member States.

9. What advice is EMEA/CHMP issuing now ?

- These medicines should not be used in patients with ischaemic heart disease or stroke.
- Etoricoxib should additionally be contraindicated in patients with hypertension whose blood pressure is not yet under control.
- Prescribers should exercise caution when using COX-2 inhibitors in patients with risk factors for heart disease such as hypertension, hyperlipidaemia, diabetes mellitus and smoking, or peripheral arterial disease.
- Doctors should use the lowest effective dose of the COX-2 medicine for the shortest possible duration of treatment.

10. What is the advice for patients taking COX-2 inhibitors ?

- Patients treated with COX-2 inhibitors who have previously been diagnosed as having a stroke, mini-stroke or heart disease, should make a non-urgent appointment to see their doctor who will review their medication and recommend alternative treatment.

- Patients are advised that stopping COX-2 treatment will not cause any harm, but they are likely to need alternative treatment to control symptoms.

- Patients who have risk factors for heart disease or stroke (high blood pressure, high cholesterol, diabetes or those who smoke) do not need to stop treatment, but should discuss their treatment with their doctor at their next routine appointment. He/she will consider whether it would be better to continue with their COX-2 inhibitor or change to another type of treatment, depending on their overall cardiovascular (heart, blood vessel) risks and risks of suffering gastrointestinal (stomach, gut) problems.

11. Is the Europe-wide review of COX-2 inhibitors now complete ?

The Europe-wide review is not yet final. The advice being issued is interim, pending the final outcome of the review; however it is based on a comprehensive review by the CHMP of the cardiovascular safety data for COX-2 inhibitors.