



QSM/MC/IEA.111

28 February 2005

Information Exchange System

Cyclooxygenase-2 (COX-2) Inhibitor Medicines

Following the withdrawal of rofecoxib in September 2004 on account of an increased risk of myocardial infarction and stroke being demonstrated in a clinical trial, several drug regulatory agencies worldwide have undertaken a full review of all available data on the cardiovascular safety of all cyclooxygenase-2 (COX-2) inhibitors. COX-2 inhibitors belong to a relatively new class of non-steroidal anti-inflammatory medicines used in the treatment of arthritis. In particular, celecoxib, etoricoxib, lumiracoxib, valdecoxib and parecoxib are being investigated. The Australian Therapeutic Goods Administration (TGA), the European Medicines Agency (EMA) and the New Zealand Medicines and Medical Devices Safety Authority (MEDSAFE) have all completed preliminary accelerated reviews of the COX-2 inhibitors and, pending a full review, have announced interim regulatory restrictions on the use of these medicines. Preliminary analyses suggest a class-effect, with an increased risk of cardiovascular adverse events for all COX-2 inhibitors.

Australia:

The Australian Drug Evaluation Committee (ADEC) made a number of recommendations to restrict the use of these drugs in Australia.

The TGA will immediately require manufacturers of COX-2 inhibitors to place new highlighted explicit warnings in product information about the increased risk of cardiovascular adverse events from this group of drugs. The new warning statements are to be highlighted with a black boxed margin.

The TGA is also advising people who are taking more than 200 mg a day of celecoxib (Celebrex) or more than 15 mg a day of meloxicam (Mobic; Movalis) to review their treatment regime with their doctors.

The TGA has also accepted a number of other recommendations of ADEC and has given notice to the relevant companies.

- It is proposed to cancel the registration of the drug parecoxib (Dynastat) because of the risk of cardiovascular events. Dynastat **is marketed in Australia** and is approved as a single dose at the time of surgery to reduce post-operative pain.
- It is proposed to withdraw the indication of management of arthritis of the drug valdecoxib (Valdyne, Dynoral - known in some countries as Bextra) which is converted to parecoxib in the body. Valdecoxib **has not been marketed in Australia**. Valdecoxib has been associated with an increased risk of cardiovascular events in cardiac bypass graft patients. The use of valdecoxib for five days as an analgesic in patients without increased cardiovascular risk will remain.
- It is proposed to greatly limit the approved uses of two other COX-2 inhibitors which **have not yet been marketed in Australia**. They are etoricoxib and lumiracoxib. In both instances, ADEC was not sufficiently assured of the safety of these drugs for anything other than short term use in patients without increased cardiovascular risk.

People who are concerned about their use of COX-2 inhibitors should discuss their treatment with their medical practitioner.

European Medicines Agency:

The following urgent safety restrictions have been taken for COX-2 inhibitors available in the European Union.

- A contra-indication is introduced for all COX-2 inhibitors in patients with ischaemic heart disease or stroke.
- As a further measure, a contra-indication is introduced for etoricoxib in patients with hypertension (high blood pressure) whose blood pressure is not under control.
- A warning is introduced for prescribers to exercise caution when prescribing COX-2 inhibitors for patients with risk factors for heart disease, such as hypertension, hyperlipidaemia (high cholesterol levels), diabetes and smoking, as well as for patients with peripheral arterial disease.
- 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.

These are interim measures pending the finalization of the class review, expected in April 2005. The Agency's Committee for Medicinal Products for Human Use (CHMP) also concluded that more research is needed in the field to evaluate the cardiovascular safety of COX-2 inhibitors, and that ongoing cardiovascular trials should continue as planned.

New Zealand:

The Ministry of Health advises that anyone taking a COX-2 inhibitor should follow the advice provided by the Ministry's expert committee, released in December last year, that COX-2 agents are not recommended:

- for routine use in patients with rheumatoid arthritis or osteoarthritis except where the patient is at "high risk" of developing a serious gastrointestinal adverse effect from other standard non-steroidal anti-inflammatory agents;
- for patients at high risk of heart attack or stroke;
- for patients already taking aspirin;
- for routine relief of post-operative pain.

Patients already taking COX-2 inhibitors on a regular basis should discuss the continuing use of these medicines with their general practitioner or specialist. Prescribers should discuss with their patients the available alternatives, and review the risks and benefits of these alternatives compared with the emerging clinical concerns about the COX-2 inhibitors, before deciding on the best course of treatment for that individual. If the patient and prescriber decide that continued use of a COX-2 inhibitor is appropriate, use of the lowest effective dose is prudent.

USA:

After three days of deliberations, an advisory panel to the US Food and Drug Administration decided that the widely used COX-2 inhibitors rofecoxib, celecoxib and valdecoxib all carry serious risks of heart attack and stroke. The panel recommended that these products should carry strongly worded 'black box' warnings about these risks.

References:

1. TGA Media Statement, 10 February 2005. Available on the Internet at <http://www.tga.gov.au>
2. EMEA Public Statement, EMEA/62838/2005, 17 February 2005. Available on the Internet at <http://www.emea.eu.int>
3. MEDSAFE Alert/Letter, 22 February 2005. Available on the Internet at <http://www.medsafe.govt.nz>
4. News, British Medical Journal 2005; 333:440 (26 February).