REPUBLIC OF THE PHILIPPINES
DEPARTMENT OF HEALTH
BUREAU OF FOOD AND DRUGS
Civic Drive, Filinvest Corporate City
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MALAYA AT MALUSOG NA PAMAYANAN

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BUREAU CIRCULAR
No. 8 s. 2005

Re: SELECTIVE COX-2 INHIBITORS

The Selective Cyclooxygenase-2 receptor inhibitors currently registered with the Bureau of Food and Drugs include the following:

Generic Name

Celecoxib
Parecoxib
Valdecoxib
Etoricoxib

These aforementioned COX-2 inhibitors plus the Nonsteroidal Anti-Inflammatory Drugs (NSAIDS) were re-evaluated by various regulatory agencies (US, EU, Australia, Malaysia, New Zealand etc) in the last two months with respect to cardiovascular risk. For clarification, the drugs piroxicam, meloxicam and other oxicams are considered NSAIDs since both COX-1 and COX-2 are inhibited by these drugs.

The BFAD, cognizant of these reviews and in the interest of public safety, thus is recommending the following measures for the compliance and guidance of everyone concerned.

A. Advisory to the industry:

1. For the product insert
   i. Black Box warning on cardiovascular risk of 4 drugs (celecoxib, etoricoxib, parecoxib and valdecoxib)
   ii. Absolute contraindications of COX-2 inhibitors: patients who have had stroke, heart attack or who have undergone angioplasty and Cardiac by-pass graft (CABG) and those with uncontrolled high blood pressure

iii. Warnings regarding potential class effect, however not necessarily in a black box, for all NSAIDS including over-the-counter (OTC) drugs like ibuprofen.

2. Requirement to submit further safety data on COX-2 drugs based on studies whether completed or otherwise to establish sufficient evidence on whether or not there is increased risk of cardiovascular events as class effect or if limited to specific compounds only.

B. Advisory to doctors/prescribers

- The lowest effective dose of COX-2 inhibitor should be used for the shortest necessary period
- Alternative therapies could be evaluated taking into account individual needs and risk factors
- For all patients, the balance between gastrointestinal and cardiovascular risk should be considered before prescribing a COX-2 inhibitor, particularly for those with risk factors for heart disease and those taking low dose aspirin
- A warning could be introduced for prescribers to exercise caution when prescribing COX-2 inhibitors for patients with risk factors for heart disease, such as hypertension, hyperlipidemia, diabetes and smoking, as well as for patients with peripheral arterial disease
- An absolute contraindication for all COX-2 inhibitors in patients with heart attack or stroke and who have undergone angioplasty and CABG

C. Advisory for patients

- Patients who are being treated with a COX-2 inhibitor and who are at high risk of developing a cardiovascular event such as: a previous history of heart attack or stroke, who have a strong family history of heart disease, or have a history of diabetes, smoking, hypertension, or who are on treatment for high cholesterol should be advised to see their doctor to discuss stopping treatment immediately
- All other patients being treated with COX-2 inhibitor medicines should discuss alternative treatment options with their doctors Consumers should be advised that all over-the-counter (OTC) pain medications, including NSAIDS, should be used in strict accordance with the label directions. If use of an (OTC) NSAID is needed for longer than ten days, a physician should be consulted.

D. Action on specific drugs

- To withdraw the indication of management of arthritis of the drug valdecoxib because this drug has been associated with an increased risk of cardiovascular events in cardiac by-pass graft patients
- Prescribers should be reminded that valdecoxib and parecoxib may be associated with higher rates of serious skin reactions (eg Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis) than other COX-2 inhibitors. Treatment should be stopped at the first signs of skin rash or hypersensitivity reaction.
- In the event that rofecoxib would be reintroduced in the market, stronger warnings should be applied to rofecoxib, as well as potentially second-line or third-line use. Reintroduction should be limited to a 12.5 mg dose rather than the previously marketed 25 mg to 50 mg doses.

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