IRISH MEDICINES BOARD

Drug Safety NEWSLETTER

20th EDITION

Cyclo-oxygenase-2 (COX-2) selective inhibitors

Arcoxia (etoricoxib), Bextra (valdecoxib), Celebrex (celecoxib), Dynastat (parecoxib) and Vioxx (rofecoxib)

Further to withdrawal of rofecoxib (Vioxx) in September 2004, an EU wide review of COX-2 inhibitors, the class of products to which rofecoxib belongs was initiated. In December 2004, new clinical trial data on celecoxib became available which suggested that an increased risk of non-fatal myocardial infarction and stroke may be a class effect of all COX-2 inhibitors. This information was immediately communicated to healthcare professionals through "Dear Healthcare Professional" letters, issued by the relevant pharmaceutical companies. In view of this data, it was agreed to accelerate the EU wide evaluation of the COX-2 inhibitors, with the aim of finalising the review as soon as possible.

Analysis of the data for all products is on-going, with the issues reviewed and discussed at EU and national level. However, on the basis of the currently available data an increased risk of cardiovascular adverse events for COX-2 inhibitors appears to be a class effect. The data also suggest an association between duration and dose of intake and the probability of suffering a cardiovascular event. As a result, interim, urgent regulatory measures were recently taken in respect of all currently authorised COX-2 inhibitors available in the European Union to update the product information. Again, these changes were immediately communicated to healthcare professionals through "Dear Healthcare Professional" letters, issued by the relevant pharmaceutical companies.

On 7th April, 2005, sales and marketing of Bextra were voluntarily suspended by the company as a precautionary measure, because of concerns regarding serious skin reactions in addition to the known cardiovascular class effects.

The IMB is actively involved in the on-going EU wide review and will keep healthcare professionals informed of its progress and outcome.

A summary of the prescribing information and new advice for each product is included in this edition of the Drug Safety Newsletter.

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IRISH MEDICINES BOARD

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Arcoxia (etoricoxib) 60mg, 90mg & 120mg tablets

Arcoxia (etoricoxib) is indicated for the symptomatic relief of osteoarthritis, rheumatoid arthritis and the pain and signs of inflammation associated with acute gouty arthritis.

- In osteoarthritis, the recommended daily dose is 60mg once daily and should not be exceeded.
- In rheumatoid arthritis the recommended daily dose is 90mg once daily and should not be exceeded
- In acute gouty arthritis, the recommended dose is 120mg once daily and should not be exceeded.
  Arcoxia (etoricoxib) 120mg should be used only for the acute symptomatic period, limited to a maximum of 8 days treatment
- The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically, especially in patients with osteoarthritis.
  The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks
- As the cardiovascular risk may increase with duration of exposure and with high doses, the lowest effective dose should be used for the shortest duration necessary.
- For patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) or those with peripheral arterial disease, the balance of risks should be considered before prescribing a selective COX-2 inhibitor.
- Similarly, careful consideration should be given to the balance of these risks for patients who are taking low dose aspirin for (primary) prevention of cardiovascular events, as a clear gastrointestinal safety advantage has not been established when COX-2 inhibitors are combined with aspirin.

The following additional contra-indications and warnings now apply to Arcoxia (etoricoxib).

- **Arcoxia is now CONTRAINDICATED in patients with established ischaemic heart disease, cerebrovascular disease and congestive heart failure (NYHA II-IV).**
- **Arcoxia (etoricoxib) treatment should not be initiated in patients whose hypertension is not under control.**
- **Arcoxia (etoricoxib) may be associated with more frequent and severe effects on blood pressure than some other COX-2 inhibitors and NSAIDs, particularly at high doses. Therefore careful monitoring of blood pressure is advised for all patients taking Arcoxia (etoricoxib).**

Patients with these conditions who are currently taking etoricoxib should be switched to alternative treatments.

Bextra (valdecoxib) 10mg, 20mg and 40mg Film Coated Tablets

Bextra (valdecoxib) is a selective COX-2 inhibitor which was authorised for use in Ireland following an EU assessment procedure in 2003 and was indicated for the symptomatic relief in the treatment of osteoarthritis, rheumatoid arthritis and primary dysmenorrhoea. On 7th April 2005, sales and marketing of Bextra were voluntarily suspended by the company as a precautionary measure.

In addition to the cardiovascular risks of COX-2 inhibitors, valdecoxib is associated with a risk of serious skin reactions, including Stevens-Johnson syndrome (SJS), erythema multiforme, exfoliative dermatitis and toxic epidermal necrolysis (TEN). The number of reports of serious skin reactions has been greater in the US, where use of valdecoxib has been much higher than in Europe. However, in context of this concern, together with the evidence of cardiovascular risks associated with the class of COX-2 inhibitors, a suspension of the sale and marketing of Bextra was implemented. Prior to suspension, it is estimated that approximately 3000 patients in Ireland were undergoing treatment with Bextra. To date, the IMB has received two reports of SJS associated with the use of Bextra, since the product was first marketed in 2003.

Healthcare professionals are advised as follows:

- **Not to initiate treatment of any new patients.**
- **No repeat prescriptions for Bextra should be issued.**
- **No further prescriptions for Bextra should be dispensed.**

Celebrex (celecoxib) 100mg & 200mg capsules

Celebrex (celecoxib) is indicated for symptomatic relief in the treatment of osteoarthritis and rheumatoid arthritis.

- In osteoarthritis: the recommended daily dose is 200 mg taken once daily, or in two divided doses.
- For rheumatoid arthritis: the initial recommended daily dose is 200 mg taken in two divided doses.
- In both indications the dose may be increased to 400 mg per day (in divided doses) if needed. In the absence of increased therapeutic benefit after two weeks, other therapeutic options should be considered.
- In all cases the patient's response to therapy should be re-evaluated periodically. The decision to prescribe celecoxib should be based on an assessment of the individual patient's overall risk.
- Cardiovascular risks of treatment may increase with dose and duration of exposure, therefore the lowest effective daily dose should be used for the shortest duration possible.
- **Celebrex is now CONTRAINDICATED in patients with established ischaemic heart disease or cerebrovascular disease. In addition Celebrex is now contraindicated in class II-IV NYHA congestive heart failure. Celebrex should not be prescribed to such patients.**
- Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) or peripheral arterial disease should only be treated with celecoxib after careful consideration.

Dynastat (parecoxib sodium) 40 mg powder for injection

Dynastat is indicated for the short-term treatment of postoperative pain.

- The recommended dose is 40 mg administered intravenously (IV) or intramuscularly (IM), followed every 6 to 12 hours by 20 mg or 40 mg as required, not to exceed 80 mg/day.
- The decision to prescribe Dynastat should be based on an assessment of the individual patient's overall risk
- **Dynastat is now CONTRAINDICATED in patients with established ischaemic heart disease or cerebrovascular disease.**
- **In addition Dynastat is now contraindicated in class II-IV NYHA congestive heart failure.**
  Dynastat should not be used in the treatment of post-operative pain following coronary artery bypass graft (CABG) surgery. Dynastat should not be prescribed to such patients.
- Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) or peripheral arterial disease should only be treated with Dynastat after careful consideration.

Update on Adverse Drug Reaction Reporting

The IMB monitors the safety of all authorised medicinal products available on the Irish market on an on-going basis. Part of this monitoring is carried out through review and evaluation of suspected adverse drug reactions (ADRs) and the IMB encourages all healthcare professionals to notify suspected ADRs observed during their practice. The IMB greatly appreciates the interest in reporting and acknowledges the enormous contribution of busy healthcare professionals to the continued surveillance of the safety of medicines through the voluntary reporting system. While the burdensome nature of form filling is recognised and acknowledged, the collection of ADR reports is essential to ensure continued, effective surveillance of the safety of licensed medicines.

In addition to the standard "Yellow Cards" for notification of suspected ADR reports, a copy of the IMB's ADR report form is also available from the IMB's webside (www.imb.ie) under the heading "Pharmacovigilance". Downloaded forms should be completed and posted in an envelope marked 'Freepost' to the address below.

You are particularly reminded to report:

- All suspected adverse reactions to new medicinal products (i.e. those available on the market for less than two years).
- Serious suspected reactions to established medicines. A serious reaction is defined as one which is fatal, life threatening, results in persistent or significant disability/ incapacity, results in or prolongs hospitalisation. This definition also includes congenital abnormalities or birth defects and serious adverse clinical consequences.
- Any suspected increase in the frequency of minor reactions.
- Any suspected teratogenic effects.
- Any suspected reactions associated with the use of vaccines.