LUMIRACOXIB
LINKED TO DEATHS IN AUSTRALIA

Lumiracoxib (Prexige), a COX-2 inhibitor anti-inflammatory drug, has been withdrawn in Australia due to the emergence of serious adverse reactions, including liver failure (leading to transplant) and death. In New Zealand, Medsafe has just announced that approval for Prexige 400 mg tablets has been revoked (100 mg tablets are still available).

Lumiracoxib (Prexige) is a selective inhibitor of cyclo-oxygenase-2 (COX-2). As with all COX-2 inhibitors (coxibs), lumiracoxib is not recommended for people at high risk of heart attack or stroke, for those already taking aspirin, or for routine pain relief, except where the person is at high risk of developing a serious gastrointestinal adverse effect from other standard anti-inflammatory drugs.[1]

Lumiracoxib was deregistered from the Australian market on August 11th, 2007 after the Australian Therapeutic Goods Administration (TGA) received eight reports of serious liver adverse reactions, including two deaths and two patients requiring liver transplants. People were advised to stop taking lumiracoxib immediately and consult their doctor for an assessment of any clinical or biochemical evidence of liver damage. All doses of Prexige were withdrawn. Lumiracoxib has been available in Australia since July 2004 but has only become widely used since being listed on the Pharmaceutical Benefits Scheme in 2006. All eight cases have occurred since March 2007, with six of the cases emerging in the last six weeks. While full details are not yet available, it appears that prolonged use of 200 mg tablets is a risk factor.[2]

There are limited data available on the hepatic side-effects of lumiracoxib. However clinical trial data suggested that if a person developed abnormal liver function while on the drug, their results were likely to normalise when the drug was ceased. In several of the Australian cases, the patients did not improve after lumiracoxib was ceased, due to the severity of their hepatic damage.[2]

Lumiracoxib does not have a significant market share in New Zealand and is not subsidised by PHARMAC. Until now, it was indicated for the symptomatic treatment of osteoarthritis, acute pain, primary dysmenorrhoea and acute gout and was available in 100 mg and 400 mg tablets.[3] Medsafe and the Medicines Adverse Reactions Committee (MARC) reviewed safety data from Australia, Singapore and the United Kingdom and concluded that the increased risk of liver damage seen with higher doses of Prexige outweighs any of its potential benefits.[4] Medsafe therefore has revoked consent for the 400 mg Prexige tablet and it is being recalled. According to Medsafe Interim Manager, Dr Stewart Jessamine, this recall is likely to affect around 1000 people who take Prexige 400 mg in New Zealand.[4]

Recommendations:

Patients using Prexige 100 mg tablets for osteoarthritis, should have their liver function checked and monitored monthly. GPs should report any abnormalities found in these tests to CARM (Centre for Adverse Reactions Monitoring).

Patients using Prexige 100 mg tablets for acute pain should be encouraged to use other suitable analgesics, as it is no longer approved for this use.

Patients using Prexige 400 mg tablets should cease use immediately and be assessed for any signs of adverse effects.

Medsafe also reviewed the safety of the 100 mg daily dose but concluded that severe liver damage with this dose is rare.[4] Dr Jessamine said that a review of New Zealand adverse reactions data showed no reports of liver damage associated with Prexige.[5] At this stage, Prexige 100 mg will still remain on the market, however its safety will be closely monitored.

Changes to Prexige approval include;

- Maximum daily dose now decreased to 100 mg
- Approved indication now limited to osteoarthritis
- Warning statements added to prescriber and patient information sheets, advising that patients should have a liver function test prior to starting treatment and every month thereafter

While the association between coxibs and adverse events has been evident for several years, lumiracoxib is the first of this type of drug to have been withdrawn by a government agency. Rofecoxib (Vioxx) was voluntarily withdrawn by its manufacturer in 2004 after it was found to be associated with an increased risk of heart attack and stroke. This was followed by the voluntary withdrawal of valdecoxib (Bextra) in 2005 after reports of serious skin reactions began to emerge.

An assessment of the clinical pharmacology of lumiracoxib found that liver function test abnormalities were more frequent with lumiracoxib (2.57%) than with comparator NSAIDs (0.63%).[6] Information from the Medsafe drug data sheet indicates that one year trials with lumiracoxib 200 mg and 400 mg, were associated with more frequent elevations of ALT/AST (2.6% >3 x ULN) than lower doses, for shorter time periods. Rare cases of hepatitis have been reported.[3]

There is little evidence of clinical reports of hepatic adverse effects of lumiracoxib in the literature. However it is known that all NSAIDs (including coxibs) are associated with an increased risk of hepatotoxicity.

** For more information on cardiovascular risk and coxibs, see BPJ Issue 1, October 2006.*

Doctors in Singapore recently reported that three patients presented with acute hepatitis after being prescribed nimesulide, an NSAID with COX-2 selectivity, for joint pain. One of these patients subsequently died from hepatic failure.[7] Nimesulide has been associated with many reports of adverse reactions and has never been approved for use in New Zealand. There have been rare reports of hepatic injury attributable to coxibs. One report describes two cases in which patients developed severe hepatotoxicity shortly after the initiation of rofecoxib for arthritic pain. In these cases there was rapid improvement in liver function once the drug was discontinued.[8] A case analysis of hepatic disorders in people taking NSAIDs concluded that, the safety profile of coxibs was no worse than that of traditional NSAIDs.[9]

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