Reviewer's report

Title: Long-term retention on treatment with lumiracoxib 100 mg once or twice daily compared with celecoxib 200 mg once daily: a randomised controlled trial in patients with osteoarthritis [NCT00145301]

Version: 2 Date: 10 November 2007

Reviewer: Richard Day

Reviewer's report:

General

Lumiracoxib Retention Study.

Retention rate analysis over 1 year has demonstrated non-inferiority of lumiracoxib 100mg OD and BID versus celecoxib 200mg OD in a large number of patients with OA. The study was a parallel, double-blinded, randomised trial.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

There is not enough attention given to the serious AEs – cardiovascular and hepatic and the contrast between lumiracoxib and celecoxib that emerge. The percentage of deaths in the three groups requires more discussion. The relative risks for lumiracoxib 100mg bd versus celecoxib 200mg OD is 5 and although event numbers are small and the difference not statistically significant it needs attention in Discussion. Recall the criticism following the VIGOR publication for a similar relative risk for MI. Similarly, the cardiovascular and hepatic adverse event experiences needs to be better presented – in tables would be better. Then these need to be properly discussed. It looks to be the case that risks are less with celecoxib and although the study is not big enough, what are the implications for use in the community? It is important to deal with the liver toxicity better – the drug has been withdrawn in Australia for serious hepatotoxicity. It has been rejected by FDA recently. Hepatotoxicity is a concern yet it is brushed over in this paper. There is more enzyme elevation seen with lumiracoxib than other NSAIDs except perhaps diclofenac. What are the implications for use? Liver function tests would not be done as often as in this study but the practice lead to identification of elevation of liver enzymes greater than 3 times ULN and in some cases cessation of the drug. And this is in a trial population without comorbidities.

Table 4 would be better replaced with data on the serious AEs notably cardiovascular and hepatic, indicating exactly when they occurred in relation to the study timeline and drug treatments.

There seems to be no reason to contemplate use of lumiracoxib 100mg BID yet this is not stated or discussed in the paper. This is an important practice point.
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

The sentence in the Introduction: “The patient randomisation list was produced using a validated system that automated the random assignment of patient numbers to randomisation numbers in a block formation in order to ensure treatment groups were balanced within centres.” Is extremely convoluted and difficult to follow – a rewrite would be helpful for ease of understanding.

With regard to methods, for those patients with hand or spine OA, how was the SAS scale used – “Patients completed the SAS, which comprises four 11-point scales (pain, global, difficulty with stairs and difficulty with shopping)”? Is it validated for those areas of OA involvement?

In methods, “The analysis was repeated for the per protocol population (all ITT patients without major protocol violations).” Isn’t this the ITT population?

In methods, what does “to adjust for multiplicity” mean?

Was the analysis of secondary efficacy variables performed on the ITT population?

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

Lumiracoxib advisory committee in Australia where the drug has been withdrawn (200mg dose) because of a number of cases of serious hepatotoxicity. Celecoxib
advisory committee member in Australia many years ago. Sitting fees placed in audited trust funds of St Vincent's Hospital Sydney for use in my Clinical Pharmacology Unit for research and some equipment costs.