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: 15 November 2007

Reviewer: David Scott

Reviewer’s report:

General

This paper is a straightforward account of a one year trial comparing two doses of lumiracoxib with celecoxib in patients with osteoarthritis. It involves leading experts in the field.

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

1. The introduction about osteoarthritis is overlong; this paper will be read by experts who know most of the general background and are interested in the specific issues raised by this trial.

2. The current report is rather naïve in its approach to issues around liver toxicity. Within the EU there have been major concerns on this point and in August 2007, following consultation with the European regulatory authorities, the manufacturer wrote to healthcare professionals to inform them of new prescribing restrictions on lumiracoxib. Concern was raised worldwide after rare reports of severe liver reactions; mostly relating to daily doses higher than licensed in the EU. In the present paper the authors note that “elevations in liver enzymes of more than 3 x ULN, submitted for adjudication and considered to be related to the study drug, occurred in 1.5% of patients treated with lumiracoxib 100 mg o.d. This incidence is greater than previously observed for ALT/AST elevations >3 x ULN with lumiracoxib 100 mg o.d. in long-term clinical trials (0.91%) (Novartis: data on file, Studies 2360 [core plus extension] and 2361 [core plus extension] pooled). However, the incidence rate for lumiracoxib 100 mg o.d. is similar to that reported in the prescribing information for many NSAIDs (1% or less), such as naproxen and ibuprofen [35,36], and less than that observed with diclofenac, which has been associated with ALT and AST abnormalities in 3.2% and 1.8% of patients, respectively [37]”. They also report that ALT/AST elevations >3 x ULN occurred at a higher frequency in patients treated with lumiracoxib 100 mg b.i.d. (twice the recommended dose) (2.3%) than with lumiracoxib 100 mg o.d. (1.5%) or celecoxib 200 mg o.d. (0.4%) in the results section but not in the discussion. I suspect that the general public would think this level of hepatotoxicity is a potentially major problem against the background of the letter to healthcare professionals and the concerns by regulatory bodies. I am not certain it is wise to
minimise its importance. If liver function tests indicate problems with an
anti-inflammatory drug why use an agent with substantially higher risks? I am not
implying that there is a correct or incorrect response to this difficult question, only
that a cautious response is required in the discussion. I also think it might be
wise to temper the final overall conclusions of the study.

3. The inclusion of patients from a centre that fell below the mark for Good
Clinical Practice is challenging. I do not think I can reach a conclusion on what
should be done. My inclination is not to publish such work at all, though I realise
this is potentially incorrect as many patients have been involved and we should
all be committed to open publication. In any event I suspect more discussion is
required on the pros and cons of publishing. At the very least I suspect we need
to know what had gone wrong; not meeting GCP standards could be due to
many reasons and not all will give rise to equal concern. Although I am certain
the answer will be straightforward it would be sensible to give some indication
about the standards observed in the other centres and how these were judged.

4. The data on the 10 most common adverse events is not helpful. The frequency
of common, minor problems is not of great interest; it would be more relevant to
report serious adverse events.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of
a term, which the author can be trusted to correct)

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 of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a
statistician.

Declaration of competing interests:

I declare that I have no competing interests