Title: Incidence of Hepatic Toxicity for Lumiracoxib

Date: August 29, 2007

Research question:

What is the incidence of hepatic toxicity, with dose considerations, for lumiracoxib (Prestige)?

Methods:

A literature search was conducted on key health technology assessment resources, including PubMed, University of York Centre for Reviews and Dissemination (CRD) databases, ECRI’s HTAIS, and a focused Internet search. Results include English language publications from 2002 to date. Links to online full-text or abstracts are provided when available.

Results:

This report focuses exclusively on incidence of hepatic toxicity and hepatic impairment for lumiracoxib. No relevant health technology assessments, systematic reviews, meta-analyses, or randomized controlled trials were identified.

Observational Studies


The aim of this study was to evaluate the influence of hepatic impairment on the pharmacokinetics (PK) of the novel cyclooxygenase-2 (COX-2) selective inhibitor
lumiracoxib (Prexige), so that dose recommendations for clinical use can be provided. This was an open-label, single dose, case-controlled study in which eight subjects with liver cirrhosis classed as moderate hepatic impairment (Child-Pugh score: 7-9) and eight demographically-matched healthy subjects received a single oral 400 mg dose of lumiracoxib. Routine safety assessments were made and blood samples were taken for determination of lumiracoxib concentrations for 96 h post dose. The ex vivo binding of lumiracoxib to plasma proteins was determined pre dose and at 2 and 12 h post dose. An analysis of variance was used to detect differences in PK parameters (AUC, Cmax and Tmax) between the treatment groups. There were no significant differences between subjects with moderate hepatic insufficiency and healthy subjects in the area under the lumiracoxib plasma concentration-time curves (AUC(0-infinity)): 29.2 +/- 6.7 microg h ml(-1) versus 28.7 +/- 6.3 microg h ml(-1). The rate of absorption of lumiracoxib was not significantly altered by hepatic impairment based on Cmax and Tmax. The protein-bound fraction of lumiracoxib exceeded 98% both in healthy control subjects and in those with moderate hepatic insufficiency. A single dose of 400 mg lumiracoxib was well tolerated. In conclusion, no dose adjustments appear to be required when lumiracoxib is administered to patients with either mild or moderate hepatic impairment.

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Appendix – Further information:

Guidelines

See: pg. 290-295: Renal and hepatic events

Additional references

Canada:


See: 2. Notice of Decision and 3.3.4 Clinical Study


Australia and New Zealand:

See: pg.15 – Hepatic effects


United Kingdom:


Abstract: According to a report by Marketwatch, the Therapeutic Goods Administration (TGA) - Australia's drugs regulator – has cancelled the registration of Prexige® (lumiracoxib), due to concerns over hepatic toxicity. The TGA has received eight reports of serious liver-related adverse reactions to lumiracoxib, including two deaths and two patients requiring liver transplants. All these reports have been received since March 2007, with 6 reports received in the last 6 weeks. The TGA has issued a safety alert in Australia, which can be viewed at the link above.

Novartis has issued a UK press release (see attached) regarding this action by the TGA. This notes that the majority of cases of liver failure followed treatment with higher doses of lumiracoxib (exact doses not stated), and that “the 100mg dose of lumiracoxib, which is the recommended dose worldwide for treatment of osteoarthritis, has not been associated with an unexpected incidence of liver-related side effects for an osteoarthritis population treated with NSAIDs”. The press release goes on to say that “we continue to believe that the way in which lumiracoxib is used in the UK has a positive benefit/risk profile in the treatment of appropriate patients, especially those at risk of serious gastrointestinal side effects”. Patients taking lumiracoxib who have any concerns about their medication are advised to consult their healthcare provider.
