ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR REVOCATION OF THE MARKETING AUTHORISATIONS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF MEDICINAL PRODUCTS CONTAINING LUMIRACOXIB (see Annex I)

Lumiracoxib is a non-steroidal anti-inflammatory drug (NSAID) belonging to the group of the selective cyclooxygenase-2 (COX-2) inhibitors indicated for symptomatic relief in the treatment of osteoarthritis of the knee and hip.

Medicinal products containing 100 mg lumiracoxib were authorised in the United Kingdom (UK) in 2003 and are authorised in a number of EU Member States via mutual recognition (see Annex I for the list of lumiracoxib containing medicinal products authorised in the EU). They are available under the invented names Frexocel, Hirzia, Prexige and Stellige as film coated tablets for oral administration.

On 9 November 2007, the United Kingdom Competent Authority (MHRA) issued a Rapid Alert informing the Member States, the EMEA and the European Commission in accordance with Article 107 of Directive 2001/83/EC, as amended, of the intention to suspend the Marketing Authorisations for lumiracoxib containing medicinal products in its Member State. In its assessment the MHRA concluded that lumiracoxib at the 100 mg dose was associated with an increased risk of hepatotoxicity.

The CHMP discussed the matter at its November 2007 plenary meeting and the procedure in accordance with Article 107(2) of Directive 2001/83/EC, as amended was started.

Safety

There is evidence from clinical trials that lumiracoxib is associated with a higher risk for hepatic adverse reactions compared with naproxen, ibuprofen and celecoxib. Furthermore, a number of spontaneous reports of hepatic disorders associated with use of lumiracoxib (up to 15 November 2007, in total 181) have been received, including 74 reports which were judged to be related to lumiracoxib, and to be serious. Although the majority of these events were reported for 200 or 400 mg, there have been reports also for the 100 mg dose, which is the dose approved in the EU. It is not possible to reliably estimate the magnitude of the risk based on spontaneous reporting rates. The available data (clinical trial results and spontaneous reporting) suggest a dose and possibly duration dependant effect, although some cases (even at the 100 mg dose) were observed after short duration of treatment.

It is acknowledged that lumiracoxib 100 mg once daily offers a gastrointestinal safety advantage compared with naproxen 1000 mg and ibuprofen 2400 mg. However, it is unknown and questionable if these advantages would be maintained if the NSAID was co-administered with a proton pump inhibitor, or in patients concomitantly taking low dose acetylsalicylic acid. No gastrointestinal advantage of lumiracoxib has been demonstrated against celecoxib, another COX-2 inhibitor.

Several risk minimisation measures are presently in place, including a contraindication in patients with present or previous hepatic dysfunction or being treated with other hepatotoxic medicines; and recommendations for baseline and on treatment liver test monitoring. However, the available evidence (based on the latest analysis of adverse reaction reports) suggests that existing monitoring requirements and other risk minimisation measures may be inadequate to sufficiently guarantee patient safety.

Additional risk minimisation measures proposed by the marketing authorisation holder included a restriction of pack size to 2 weeks of treatment, the implementation of a treatment registry, and a long-term epidemiological cohort study. However, such short treatment duration is not compatible with the effective management of a chronic disease (osteoarthritis of the knee and hip), and taking the characteristics of the disease into account, readministration of lumiracoxib would be necessary.

Importantly, the interval between treatment periods and the frequency of liver test monitoring which would be needed to sufficiently reassure the safe use is unknown. Furthermore, the risk for 'off-label' use of higher doses than that approved, for longer periods than recommended raised additional concerns, due to the potential dose and duration dependent increase of the risk. To conclude, the present and newly proposed restrictions are not considered sufficiently reassuring to prevent the risk for adverse hepatic reactions such as the ones which have been reported spontaneously.

Benefit/risk

Lumiracoxib is indicated in the treatment of osteoarthritis of the knee and hip, which is a chronic, but not life-threatening disease, where long-term treatment is usually needed. Lumiracoxib has demonstrated a gastrointestinal advantage compared with high doses of NSAIDs. However, there are alternatives with a comparable gastrointestinal safety profile including other COX-2 inhibitors or NSAID given together with gastroprotection. An increased risk for serious hepatotoxic adverse drug reactions has been identified with lumiracoxib, for which an early onset cannot be excluded. The proposed risk minimisation measures are neither considered to assure adequate patient safety, nor to be realistic given the approved clinical indication.

Taking all these elements into account, the CHMP concluded that the benefit/risk balance for lumiracoxib is not considered favourable and recommended the revocation of the Marketing Authorisations for the medicinal products referred to in Annex I.

GROUNDS FOR THE REVOCATION OF THE MARKETING AUTHORISATIONS

Whereas

The Committee considered the procedure under Article 107 of Directive 2001/83/EC, as amended, for medicinal products containing lumiracoxib at the 100 mg dose.

The Committee considered that lumiracoxib is indicated for symptomatic relief in the treatment of osteoarthritis of the knee and hip and that this is a not a life-threatening condition. Furthermore, the Committee noted that alternative treatments are available.

The Committee concluded that there is increasing evidence for lumiracoxib-associated risk of hepatotoxicity at the 100 mg dose, and in some cases a short time to onset cannot be excluded.

The Committee considered that the proposed risk minimisation measures cannot assure adequate patient safety, and are not considered realistic given the approved clinical indication.

The Committee, in light of the above findings, concluded that the benefit/risk balance of lumiracoxib containing medicinal products at the 100 mg dose is not favourable.

Following the provisions under Article 107 (2) of Directive 2001/83/EC, as amended, the Agency's Committee for Medicinal Products for Human Use (CHMP) prepared an Opinion on 13 December 2007 recommending the revocation of the Marketing Authorisations for all lumiracoxib containing medicinal products in Annex I. The CHMP also recommended that temporary measures are needed in order to protect public health and therefore recommends to the European Commission that the marketing and the use of lumiracoxib containing medicinal products be suspended forthwith in all concerned EU Member States awaiting the adoption of final measures.