ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE MAINTENANCE OF THE MARKETING AUTHORISATIONS AND AMENDMENTS OF THE SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLET PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF NIMESULIDE CONTAINING MEDICINAL PRODUCTS (SYSTEMIC FORMULATIONS) (see Annex I)

Nimesulide is a non-steroidal anti-inflammatory drug (NSAID), available only on prescription and authorised in Europe since 1985.

Nimesulide-containing medicinal products are currently marketed in more than 50 countries world-wide, particularly in Europe and South America.
In Europe, nimesulide is nationally authorised in 16 Member States (Austria, Belgium, Bulgaria, Czech Republic, Cyprus, France, Greece, Hungary, Italy, Latvia, Lithuania, Malta, Portugal, Romania, Slovakia and Slovenia).

Nimesulide was the subject of an Article 31 referral to the CHMP in 2002, following national suspension of its licence in Finland, and subsequently Spain, due to concerns regarding hepatotoxicity. This referral concluded, with divergent positions submitted by Finland, Spain and Ireland, that the benefit/risk profile of nimesulide for systemic use remained positive, subject to revision of the product information, including a restriction of the maximum oral dose to 100 mg twice daily. This decision was endorsed by the European Commission in April 2004 and the product information was subsequently amended to contraindicate its use in patients with hepatic impairment, and to include warnings about the risk of hepatitis, fulminant hepatitis (including fatal cases), jaundice and cholestasis. The harmonised product information were implemented in the Member States end of 2004-beginning of 2005.

On 15th May 2007, following new safety information regarding cases of fulminant hepatic failure associated with nimesulide, the Irish Medicines Board suspended the national marketing authorisations for all systemic medicinal products containing nimesulide available in Ireland. The Irish Medicines Board informed the EMEA, other Member States and the Marketing Authorisation Holders in accordance with Article 107(2) of Directive 2001/83/EC, as amended.

During its plenary meeting in May 2007, the CHMP considered the emerging safety data from Ireland on the risk of fulminant hepatic failure associated with nimesulide, as well as data available from published literature, and concluded that hepatotoxicity data on nimesulide should be reviewed in accordance with Article 107(2) of Directive 2001/83/EC, as amended.

The CHMP reviewed the data presented, including answers provided by the Marketing Authorisations Holders (MAHs), pharmacovigilance data provided by the Member States, data provided by the EMEA and literature review. This review focused on the hepatic safety of nimesulide in light of the significant concern arising from the Irish data and within the defined scope of the Article 107.

The hepatotoxic signal seen in Ireland showed that nimesulide was associated with more cases of non-A non-B non-paracetamol-related fulminant hepatic failure requiring liver transplantation in Ireland than any other medicinal product. Some of the cases reported were however confounded by concommittant disease/hepatotoxic medication and a clear causal relationship with nimesulide could not be concluded.

The assessment of overall post-marketing spontaneous reporting data, clinical studies, and epidemiological data, show a higher frequency of severe adverse hepatic reactions with nimesulide compared with other NSAIDs. However, with the exception of the signal of serious hepatic adverse reactions raised by Ireland, the review of the overall data submitted do not modify the safety profile of nimesulide as established after the previous CHMP opinion.

The CHMP considered the gastrointestinal toxicity profile of nimesulide as compared to other NSAIDs, and the possible consequences of switching to other NSAIDs with a higher gastrointestinal risk. The assessment of these consequences were supported by a simulation of the possible impact of

nimesulide withdrawal in Italy. This simulation showed a notable reduction of hospitalisation due to liver injuries whilst hospitalisation due to gastroinstestinal toxicity might increase.

Finally, according to the data submitted by the Marketing Authorisation Holder the majority of hepatic disorders (56%), occurred after two weeks of treatment, therefore a treatment period of not longer than 15 days may limit the risk of acute liver injury.

Having considered all of the available evidence, the CHMP concluded that the data did not support a suspension of all marketing authorisations in Europe.

The CHMP agreed, that the risk minimisation measures adopted at the end of the first referral have been able to contain the incidence of the most serious liver injuries. The use of nimesulide in strict accordance with the Product Information recommendations has been shown to be equally effective in reducing hepatic toxicity. The additional Product Information restrictions together with a limitation of duration of treatment and withdrawal of the pack sizes above 30 units aim at further minimising such risk, together with the conditions (see Annex IV) and the effort of national competent authorities in education and information activities on both prescribers and patients.

The review concluded that a small increase in the absolute risk for hepatotoxic reactions associated with nimesulide cannot be excluded although the overall risk benefit/balance remains positive.

Overall, the benefit-risk profile of nimesulide-containing medicinal products for systemic use remains favourable and the Marketing Authorisations for products containing nimesulide for systemic use should be maintained with the following restrictions:
- The decision to prescribe nimesulide should be based on an assessment of the individual patient's overall risks.
- The maximum duration of a treatment course with nimesulide is 15 days. Therefore pack sizes above 30 units should be withdrawn and not authorised
- New contraindications and strengthened warnings have been added to the Summary of Product characteristics and Package Leaflet in order to limit exposure of nimesulide to those patients without risk factors for hepatic reactions.

Furthermore the maintenance of the Marketing Authorisations is linked to the conditions, below:
- Submission of 6-monthly PSURs
- Implementation of a retrospective study, followed by a prospective study in transplant centres
- Update of Risk Management Plan
- Information of healthcare professional via a ‘Direct Healthcare Professional Communication’ letter

GROUNDS FOR THE MAINTENANCE OF THE MARKETING AUTHORISATIONS AND THE AMENDMENTS OF THE SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGE LEAFLET

Having reviewed all available data on hepatotoxicity, the CHMP concluded the following.

- Nimesulide showed a higher frequency of severe adverse hepatic reactions but the overall safety profile of nimesulide is not modified.

- The CHMP considered the gastrointestinal toxicity profile of nimesulide and the possible consequences of switching to other NSAIDs.

- The limitation of treatment with nimesulide not longer than 15 days may limit the risk of acute liver injury.

The CHMP has recommended the maintenance of the Marketing Authorisations for all medicinal products referred to in Annex I of the Opinion and to amend the relevant sections of the Summary of Product Characteristics and Package Leaflet of systemic formulations of nimesulide, as set out in Annex III of the Opinion in accordance with Article 107(2) of Directive 2001/83/EC, as amended. Conditions of the Marketing Authorisations are identified in Annex IV of this Opinion.