Annex II

Scientific conclusions and grounds for the amendments of the Summary of Product Characteristics and Package Leaflet presented by the EMA

Scientific conclusions

Overall summary of the scientific evaluation of nimesulide-containing medicinal products for systemic use (see Annex I)

Nimesulide is a non-steroidal anti-inflammatory drug (NSAID) with preferred COX-2 inhibition authorised in Europe since 1985. It is indicated as second line treatment for acute pain, symptomatic treatment of painful osteoarthritis and primary dysmenorrhoea. The recommended dosage is 100 mg twice daily and the maximum duration of treatment is 15 days with the shortest duration of treatment recommended to minimise the occurrence of side effects.

Nimesulide was subject of an Article 31 referral to the CHMP in 2002, following national suspension of the Marketing Authorisations for nimesulide-containing medicinal products in Finland, and subsequently in Spain due to concerns regarding hepatotoxicity.

Further to consideration of all data available at that time, it was concluded that the incidence of hepatic reactions associated with nimesulide treatment was slightly higher when compared to other NSAIDs but that there was no increased incidence in severe hepatic reactions. It was concluded that the risk-benefit balance remained positive subject to amendments to the Marketing Authorisations, including introduction of restrictions for the safe use of the products.

Restriction of the maximum dose to 100 mg twice daily (with withdrawal of the marketing authorisations for the 200 mg), restriction of the therapeutic indications to the three above mentioned and warnings, precaution for use and contraindications were introduced. This referral procedure was concluded in 2004 (European Commission decision issued on 26 April 2004) and the product information was subsequently updated.

In May 2007, following new information regarding cases of fulminant hepatic failure associated with the use of nimesulide, Ireland suspended the marketing authorisations for all systemic medicinal products containing nimesulide and a procedure under Article 107 was started.

The reported cases showed an association with non-A non-B non-paracetamol-related fulminant hepatic failure requiring liver transplantation in Ireland higher with nimesulide than with any other medicinal product. Some of these cases were considered to be confounded by concomitant disease/hepatotoxic medication and a clear causal relationship with nimesulide could not be concluded. It was noted that the majority of hepatic disorders (56%) occurred after two weeks of treatment. Overall and further to consideration of the data submitted, it was concluded that a small increase in the absolute risk for hepatotoxic reactions, including severe hepatic reactions, associated with nimesulide could not be excluded.

In the context of this review, limited information on the gastrointestinal toxicity profile of nimesulide in comparison to other NSAIDs, and the possible consequences of switching to other NSAIDs with a higher gastrointestinal toxicity risk was considered. In view of the uncertainties regarding the magnitude and the determinants of possible nimesulide-induced harm, the risk-benefit balance was considered positive subject to amendments to the product information and conditions to the Marketing Authorisations for all products containing nimesulide for systemic use.

Moreover, considering that the review and assessment of the available data for nimesulide under the Article 107 focused on the hepatic safety of nimesulide and that only limited information regarding the gastrointestinal toxicity profile of nimesulide was considered, it was agreed that a full risk-benefit assessment should be conducted in the framework an Article 31 procedure, where the risks of nimesulide should be weighted vis-à-vis the gastrointestinal risks of other NSAIDs.

The additional measures would contribute to minimising the risks associated with the use of nimesulide whilst awaiting the full risk-benefit assessment of the Article 31 referral.

On 19 January 2010, the European Commission triggered a referral under Article 31 of Directive 2001/83/EC requesting the CHMP to give its opinion on whether the marketing authorisations for medicinal products containing nimesulide for systemic use should be maintained, varied, suspended or withdrawn.

The CHMP reviewed the data submitted by the marketing authorisation holders from clinical and non-clinical studies, epidemiological studies and spontaneous reports.

Nimesulide-containing medicinal products for systemic use are currently authorised in 17 Member States on prescription only and marketed in 15 Member States (Bulgaria, Czech Republic, Cyprus, France, Greece, Hungary, Italy, Latvia, Lithuania, Malta, Poland, Portugal, Romania, Slovakia and Slovenia). Patient's exposure has been decreasing over the recent years following the outcomes of the previous reviews under Article 31 and Article 107. Overall the highest exposure is seen in Italy,

Poland, France and Greece. In the remaining Member States the exposure appears relatively stable over time.

Efficacy

Nimesulide efficacy in the treatment of pain associated with several inflammatory and painful disorders has been shown in mostly short-term studies (up to four weeks) with limited numbers of patients. Although there are some results of clinical studies that may suggest rapid onset of analgesic action associated with the use of nimesulide compared with other NSAIDs, the clinical relevance of the measured differences in onset of pain relief is doubtful.

Based on available data, it is concluded that the proven efficacy of nimesulide in short-term clinical studies is consistent with the indication for short-term use only (i.e. maximum 15 days of treatment) as previously restricted to minimise the risks for hepatoxicity. No unequivocal and clinically meaningful advantage over other NSAIDs has been demonstrated and, therefore the Committee considered the efficacy of nimesulide to be similar to other NSAIDs available.

Safety

Nimesulide is associated with an increased risk of hepatotoxicity versus no-use or past use. Further to the review of all available data, it is overall concluded that nimesulide seems to have a worst safety profile for hepatotoxicity compared to diclofenac and naproxen, both for severe liver injury requiring transplant and for hospitalisation for liver injury. The hepatotoxic profile compared to ibuprofen varies from worse in spontaneous reports, to comparable with respect to hospitalisations for liver injury or slightly better with respect to severe liver injury requiring transplant.

The absolute risk for acute liver failure indicated for transplantation is 5.64 [2.43-11.11] per million person-years and 5.90 per billion DDDs (defined daily doses). The absolute risk for hospital admission for hepatoxicity is approximately 30-35 per 100,000 person-years and the absolute risk for abnormal liver function tests is approximately 1%.
The hepatoxicity of nimesulide was previously assessed under the Article 107 procedure triggered by the new information regarding cases of fulminant hepatic failure associated with its use in Ireland and the consequent suspension of the marketing authorisations for nimesulide in that Member State. At that time the magnitude of the increased risk of severe hepatic adverse reactions with nimesulide compared to other NSAIDs seen in spontaneous reporting, clinical and epidemiological studies seemed slight, with the exception of the signal raised by Ireland. Further to that the results of the SALT study became available. In this regard the SALT study was a key piece of data expected to provide further insight. As discussed throughout the assessment report, the SALT study presented several limitations such as small number of identified cases, all severe cases are of acute liver failure and very wide confidential intervals making the results not being robust. Nevertheless, the SALT study did confirm the signal seen in Ireland which was not seen in any other country involved in the study. This signal could possibly be due to environmental, genetic factors involved and it remains to be explained.

Data available including a new epidemiological study (FVG GI study) confirms that all NSAIDs can induce damage to the gastroduodenal mucosa and increase the risk of upper gastrointestinal complications (UGIC). The risk of gastrointestinal complications due to nimesulide is lower than for ketorolac, piroxicam, indomethacin and azopropazone, but not proven to be consistently different from other NSAIDs such as celecoxib, ibuprofen, naproxen, ketoprofen, diclofenac, sulindac and meloxicam. However, it must be noted that no direct comparisons are available, and confidence intervals are overlapping considerably.

Overall, gastrointestinal toxicity of nimesulide is regarded to be comparable to other available NSAIDs. When combining both liver injury and GI toxicity nimesulide falls in the mid range of the other NSAIDs. The safety profile in terms of hepatotoxicity and gastro intestinal toxicity for nimesulide is shown as worse than alternative NSAIDs such as diclofenac and naproxen.

No new safety issue with respect to cardiovascular disorders, renal safety, skin, immunological and nervous system safety has arisen from the data submitted during this review. It seems that the risk profile of nimesulide is not better than for other NSAIDs with regards to cardiovascular disorders. Data suggests that that the renal safety for nimesulide is comparable to other NSAIDs and also comparable or slightly favourable with regards to skin, immunological and nervous system safety.

Benefit / risk balance

Nimesulide efficacy is proven in short-term clinical studies which is consistent with the indication for short-term use (i.e. maximum 15 days of treatment) previously introduced to minimise the risks for hepatoxicity. Overall nimesulide is at least as effective as other NSAIDs in short-term use indications for pain.

There is an increased risk of hepatoxicity associated with nimesulide whose magnitude still raises uncertainties. It is noted that 23% of the hepatic cases reported for nimesulide involved patients treated for more chronic indications. Therefore the committee concluded that nimesulide use should be restricted to acute conditions only i.e. treatment of acute pain and primary dysmenorrhoea. In view of the risk of chronic use in the treatment of osteoarthritis and aiming further minimisation of the risks associated with nimesulide, the CHMP concluded that nimesulide has no longer a positive risk- benefit in this indication.

Grounds for amendment of the summary of product characteristics and package leaflet

Whereas

- The Committee considered the referral made under article 31 of Directive 2001/83/EC, for medicinal products containing nimesulide for systemic use.
- The Committee considered all the available data submitted on the safety and the efficacy of nimesulide-containing products for systemic use.
- The Committee considered that evidence of the clinically efficacy of nimesulide-containing products for systemic use in the indications for short-term treatment has been shown. No unequivocal and clinically meaningful advantage over other NSAIDs has been demonstrated and, therefore the Committee considered the efficacy of nimesulide to be similar to other NSAIDs available.
- The Committee considered that nimesulide overall gastrointestinal toxicity is comparable to other NSAIDs but that nimesulide is associated with an increased risk for hepatotoxicity. The combined safety profile in terms of hepatotoxicity and gastro intestinal toxicity for nimesulide is shown as worse than some other alternative NSAIDs such as diclofenac and naproxen. Furthermore, the limitations of the current available data lead to uncertainties on hepatotoxicity, and concerns remain especially with prolonged use of nimesulide.
- Considering the maximum duration of 15 days of treatment to minimise the risk for hepatotoxicity and aiming a further minimisation of the risks associated with nimesulide, the Committee considered that nimesulide use should be restricted to acute conditions only i.e. treatment of acute pain and primary dysmenorrhoea.
- The Committee, in light of the above, considered that there is a risk of chronic use of nimesulide in "symptomatic treatment of painful osteoarthritis" and concludes that the risk-benefit balance of nimesulide-containing medicinal products for systemic use is no longer favourable in this indication.

Therefore, the CHMP recommended the variation to the terms of the Marketing Authorisations for nimesulide-containing medicinal products for systemic use referred in Annex I, subject to the conditions set out in Annex IV and for which the amendments of the Summary of Product Characteristics and Package Leaflet are set out in Annex III.