

ANNEX V

DETAILED EXPLANATION OF THE REASONS FOR THE ADDITIONAL CONDITIONS AND RESTRICTIONS TO THE CHMP OPINION

BACKGROUND:

The opinion adopted by the Committee for Medicinal Products for Human Use on 20 September 2007 recommended the maintenance of the national marketing authorisations for nimesulide-containing medicinal products with the introduction of several risk minimisation measures (limitation of the maximum duration of treatment, safety warnings in the product information, additional safety studies). A significant number of members of the Committee expressed however a divergent opinion, sustaining that the benefit/risk profile of these products should be considered negative and that the marketing authorisations should rather be revoked.

The Standing Committee for Medicinal Products for Human Use discussed the matter on 20 January 2008. In the course of the meeting, it became clear that there would be neither a qualified majority in support of a draft Commission decision following the opinion of the CHMP nor a qualified majority against it.

It also appeared that a fundamental disagreement persisted among Member States competent authorities on whether risk minimisation measures were capable of addressing the risk of hepatotoxicity of the product. Moreover, the relevance of new information was discussed in the meeting. It also appeared from the discussions that certain Member States were applying at national level measures not reflected in the harmonised product information and intended to further reduce the risks associated with nimesulide. These relate in particular to restrictions to the indications (with a limitation to second line treatment) and to conditions of use and prescription practices. It was furthermore noted that alternative products also present some risks, namely of gastrointestinal bleeding.

In view of this situation, the Commission chairman decided not to submit the draft decision to a vote by the Standing Committee during the meeting but to refer the matter to the CHMP for further examination of any new reports of suspected hepatotoxicity related to nimesulide and identification and consideration of existing national measures, such as guidelines or recommendations, in relation to the use of nimesulide with a view to recommending necessary risk minimisation measures.

By letter dated 26 June 2008, the Chairman of the CHMP has informed the Commission that following the assessment of the new additional reports and consideration of other risk minimisation measures, the assessment report was updated with the new factual information and a CHMP opinion containing the same recommendations as the September opinion was put to a vote in the CHMP. The CHMP could not reach a majority for the adoption of the opinion with the same recommendations.

It follows from the above:

- Nimesulide presents a risk of hepatotoxicity, including risk of fulminant hepatic failure.
- On the other hand, the switching from nimesulide to other Non-Steroidal Anti-inflammatory drugs may lead to an increase of gastrointestinal toxicity occurrences. Therefore, an increase in gastrointestinal toxicity events may occur if nimesulide ceases to be available.
- There are divergent views within the CHMP on the assessment of whether this risk may be addressed through risk minimisation measures allowing maintenance of the products on the market or whether the risk is such that the authorisation should be revoked.
- This disagreement was also observed in the Standing Committee meeting of 20 January 2008.

Upon recommendation from the CHMP, given that an assessment of the gastrointestinal toxicity of nimesulide was outside the scope of the review procedure under Article 107, the Commission will initiate a referral under Article 31 of Directive 2001/83/EC, under which a full risk-benefit assessment will be undertaken.

PRESENT DECISION:

The European Commission considers it appropriate to maintain the marketing authorisation for medicinal products containing nimesulide. The majority view within the CHMP sustained such maintenance when the committee adopted its opinion of 20 September 2007 and it appears adequate to follow this majority view. This approach is strengthened by the fact that a full risk-benefit assessment

is to be conducted in the framework an Article 31 procedure, where the risks of nimesulide will be weighted vis-à-vis the gastrointestinal risks of other products.

The risk minimisation measures proposed by the CHMP shall also be introduced as it is uncontested that the maintenance of the product in the market has to be accompanied by measures aiming at lowering the possibility of adverse events.

However, in view of the severity of the adverse events, these measures should in the Commission's perspective be further intensified by (1) limiting the prescription of nimesulide to second line treatment and by (2) introducing a clear obligation upon the marketing authorisation holder to inform healthcare professionals of the safety risks associated with this product.

The restriction of the indication to second line treatment is intended to ensure that nimesulide is not used as a routine pain killer where other treatment options which present a reduced hepatotoxic risk are available. The use of nimesulide in second line treatment is already recommended in some Member States via prescription guidelines. The restriction of the indication in the summary of the product characteristics should ensure that this prescription practice is followed in all Member States where the product is authorised.

These additional measures should contribute to minimising the risks associated with the use of nimesulide whilst awaiting the results of the Article 31 referral.

The relevant sections of the Summary of Product Characteristics and Package Leaflet of systemic formulations of nimesulide and of the Conditions of the Marketing Authorisation are amended as set out in Annexes III and IV of this Decision.