Annex II

Scientific conclusions and grounds for refusal and suspension presented by the European Medicines Agency

Isotretinoin is a vitamin A derivative indicated for the treatment of severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring) resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy. Isotretinoin is effective against severe acne via a direct effect on the size and activity of sebaceous glands, plus a probable dermal anti-inflammatory effect.

Isotretinoin Ranbaxy 10 mg & 20 mg, capsules (soft) was authorised in the reference member state (UK) under Article 10 of Directive 2001/83/EC and the application was submitted in the concerned member states (France and Spain) under the mutual recognition procedure.

At the time of the initial authorisation, bioequivalence was shown under fasting conditions (study No 237/00). However, during the mutual recognition procedure, demonstration of bioequivalence in fed state was considered essential by the Concerned Member States and the matter was referred to the CHMP. Having regard to the fact that the absorption of Isotretinoin in fed state is larger than that observed in fasted state (which motivates the SPC recommendation of intake with food (as clearly mentioned in the Posology section of the SPC), the CHMP agreed that a study in the fed state was essential.

Results of a study in healthy adult human male subjects under fed conditions (study No 122_ISOTR_10) were subsequently provided by the marketing authorisation holder. However, the results failed to show that the Isotretinoin Ranbaxy generic is bioequivalent to the originator product in real conditions of use (fed conditions), as the 90% confidence intervals (CI) fell outside the predefined interval of 80-125%, which constitutes a risk to public health.

The totality of data submitted does not support the conclusion that the product is bioequivalent. It is therefore considered that the particulars submitted in support of the application do not comply with article 10 of Directive 2001/83/EC as amended. The Committee further considered that it is not possible, on the basis of the data submitted in support of this application, to establish a positive benefit-risk balance for this product and, in these circumstances, the marketing of the product constitutes a risk to public health.

GROUNDS FOR NEGATIVE OPINION

The CHMP considered that the data submitted in support of this application failed to show bioequivalence between the test and the reference product, and that therefore the product is not approvable for the sought indications.

Based on:

- the results of the bioequivalence study in fed conditions provided by the MAH,
- the rapporteur's and co-rapporteur's assessment reports
- and scientific discussion within the Committee

the CHMP was of the opinion that the particulars submitted in support of the application do not comply with article 10 of Directive 2001/83/EC as amended. The Committee further considered that it is not possible, on the basis of the data submitted in support of this application, to establish a positive benefit-risk balance for this product and that, in these circumstances, the marketing of the product constitutes a risk to public health.

Therefore, the Committee adopted an opinion recommending the refusal of the marketing authorisations in the concerned member states and the suspension of the marketing authorisations in the reference member state, subject to the conditions outlined in annex III of the Opinion.