Annex II

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

Scientific conclusions

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Canazole Clotrimazole Cream 1% w/w is an anti-fungal agent indicated for the treatment of superficial fungal skin and mucous membrane infections, such as candidiasis, dermatophytoses and commensal yeast infections.

Canazole clotrimazole cream was authorised in Ireland on 8 December 2000 under Article 4.8 (a) (iii) of Directive 65/65/EEC. At the time of the initial authorisation, the need for therapeutic equivalence studies was waived based on quality data demonstrating that the proposed formulation was similar to the reference product with respect to formulation (except the benzyl alcohol concentration), pH and viscosity of the cream, globule size of the dispersed oil phase and size of the active substance present as particles.

The application was submitted in the concerned member state (UK) under the mutual recognition procedure. However, the need for a therapeutic equivalence study or other validated model for the formulation to prove equivalence was considered essential by the concerned member state and the matter was referred to the CHMP.

The CHMP considered the comparative quality data and a preservative efficacy test *(in vitro*) to demonstrate comparable anti-fungal activity provided.
The CHMP noted that inconsistent data were provided regarding the state of the drug substance in the drug product and critical quality attributes were not satisfactorily addressed. Key pharmaceutical parameters, such as the dissolution of drug substance in the oily phase were not appropriately validated. Differences in droplets size and their possible effect in tissue penetration were not explained. An appropriate skin permeation or similar *in vitro* studies should have been performed to investigate this matter.
It was not possible to discuss variability between and within batches of the test and reference products as information on the necessary batches of each product was not provided. In addition, the CHMP considered that the preservative efficacy test lacked the methodological details which would allow a correct interpretation. Comparative *in vitro* microbial tests to investigate the antimicrobial nature of the drug product were not provided.

The comparative quality data provided and the preservative efficacy test were, therefore, not considered sufficient to justify a waiver of the need to demonstrate therapeutic equivalence by clinical studies or other validated model, and these were therefore deemed necessary in this case to prove equivalence.

The totality of data submitted does not support the conclusion that the product is therapeutically equivalent. 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.