22 September 2011
EMA/877413/2011
Patient Health Protection

Assessment report pursuant to Article 29(4) of Directive 2001/83/EC, as amended

Canazole Clotrimazole cream 1% w/w

International non-proprietary name: clotrimazole

Marketing authorisation holder: Pinewood Laboratories Ltd.

Procedure no: EMEA/H/A-29/1286

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Mutual recognition procedure (MRP) and CMD(h) 60 day procedure

The marketing authorisation holder (MAH) Pinewood Laboratories Ltd. submitted an application for mutual recognition of Canazole Clotrimazole cream 1% w/w, on the basis of the marketing authorisation granted by Ireland on 8 December 2000.

The application was submitted to the concerned Member State (CMS): United Kingdom.
The mutual recognition procedure IE/H/141/01/MR started on 16 June 2010.

On day 90, major issues regarding the requirement of therapeutic equivalence, raised by the United Kingdom, remained unsolved; hence the procedure was referred to CMD(h), under Article 29, paragraph 1 of Directive 2001/83/EC, as amended, by Ireland on 15 September 2010. The CMD(h) 60 day procedure was initiated on 27 September 2010.
Day 60 of the CMD(h) procedure was on 26 November 2010, and since there could be no agreement the procedure was referred to the CHMP.

1.2. Notification of an official referral for arbitration

Notification of a referral for arbitration, under Article 29(4) of Directive 2001/83/EC as amended, to the CHMP was made by Ireland on 25 November 2010 . The United Kingdom raised public health objections on the grounds that a therapeutic equivalence study for the formulation was needed to show bioequivalence.

2. Scientific discussion during the referral procedure

2.1. Introduction

Canazole Clotrimazole Cream 1% w/w is an anti-fungal agent, indicated for the treatment of superficial fungal skin and mucous membrane infections. Clotrimazole is an imidazole derivative, which acts against fungi by inhibiting ergosterol synthesis. Its mode of action is fungistatic or fungicidal depending on the concentration of clotrimazole at the site of infection.

Canazole clotrimazole cream was first authorized in Ireland on 8 December 2000 for the treatment of candida, dermatophytoses, and commensal yeast infections. The marketing authorisation application was submitted in accordance with Article 4.8 (a) (iii) of Directive 65/65/EEC. The reference product was Canesten 1% Cream marketed by Bayer.

At the time of the initial authorisation, the marketing authorisation was granted in the absence of supporting pre-clinical or clinical data on the basis of the applicant's argument that essential similarity to the reference product could be demonstrated on the basis of the similarity of the manufacturing processes, and the quantity and quality of the active substance and excipients. Both products - Canazole clotrimazole cream and the reference product Canesten contained the same active and inactive ingredients at the same concentrations, with the exception of benzyl alcohol.

However, in the mutual recognition application review, objections were raised. The formulation of the product was considered to be complex and a clinical study showing therapeutic equivalence or other validated models were considered necessary to demonstrate bioequivalence.

The procedure was therefore referred to the CHMP. Further to the initial assessment of the matter, a list of questions was adopted. In particular, the MAH was asked questions related to the need to prove therapeutic equivalence for the formulation.

Critical evaluation

In the initial marketing authorisation application the MAH provided quality data to justify that there is essential similarity between Canazole Clotrimazole cream and the reference product. The data aimed to demonstrate that the proposed formulation is similar to the reference product with respect to formulation, pH and viscosity of the cream, globule size of the dispersed oil phase and size of the active present as particles.

Upon receipt of the mutual recognition procedure comments, the MAH undertook an *in house* comparative testing of Canazole Clotrimazole cream and the reference product, Canesten cream. Two batches of Canazole Clotrimazole Cream and one batch of Canesten of similar age were tested. Conventional testing methods, as per currently approved analytical methods and in line with finished product specifications, were used.

Overall the results showed that the physico-chemical properties of the test and reference products were similar and the quantitative difference in benzyl alcohol was not considered relevant.

The CHMP noted that viscosity for the test product ranged from 23640 to 35190 cPs with a mean of 27024 cPs. The viscosity of the single sample of reference product was given as 27513 cPs, which was within the range of the test product; however, the viscosity of one of the batches of Cotrimazole (test product) manufactured in May 2008 was given as 43100 cPS. No explanation was provided. It is noted that viscosity may influence the ease of application (spreadibility) and possibly skin penetration and is therefore an important physical property.

Regarding globule size of the dispersed oil phase and size of the active present as particles, the MAH compared the partitioning of clotrimazole in the test and reference products, and results are shown below.

Investigation	Results
1. Direct comparison of simplified Canesten and Canazole emulsions.	Direct comparison of Canesten and Canazole in trial 1 and trial 2 revealed both emulsions to be relatively similar. However, the oil droplets on the surface of the Canazole emulsion appeared to be larger in size. The difference in both top layers may be attributed to the difference in benzyl alcohol concentration
2. The presence of polysorbate 60 in the emulsion made it difficult to distinguish between the phases and was therefore eliminated from trial 2.	
3. Trial 3 was prepared without the presence of surfactant or benzyl alcohol.	No difference observed
4. Trial 4 involved the preparation of an emulsion without the presence of surfactant and an increased concentration of benzyl alcohol.	In trial 4 and 5, the concentration of benzyl alcohol was examined. It was noted that clotrimazole was fully dissolved in both cases. With increased benzyl alcohol concentration (Canazole formulation) it was also observed that the oil phase was more evenly dispersed and less likely to stick to the beaker. The results indicated that the benzyl alcohol concentration had an effect on both clotrimazole solubility and flow properties.
5. Trial 5 involved a more in-depth investigation into the concentration of benzyl alcohol.	
6. Trial 6 examined the effect of water concentration in the aqueous phase.	Increasing or decreasing the concentration of water in the aqueous phase did not result in a dramatic difference.
7. Trial 7 examined the solubility of clotrimazole in equi-molar concentrations of benzyl alcohol and 2-octyldodecanol respectively.	Benzyl alcohol showed a marked ability to dissolve clotrimazole. While 2-octyldodecanol was also capable of dissolving clotrimazole, heating and stirring was required. In comparison no heating was required when using benzyl alcohol as the solvent. Also the final benzyl alcohol solution was clearer than that of 2-octyldodecanol.
8. Trial 8 examined the solubility of clotrimazole in formulations containing only the actual amounts of benzyl alcohol and 2-octyldodecanol.	
9. Trial 9 examined the solubility of clotrimazole in the oil phase of the Canesten and Canazole formulations.	Clotrimazole was seen to be fully dissolved in the complete oil phase prior to mixing with the aqueous phase. These results would suggest that the clotrimazole exists as an oil droplet in both the Canesten and Canazole formulations

The CHMP noted that the MAH's initial dossier and at day 60 of the mutual recognition procedure (MRP) stated that the active substance is only partially dissolved in the oil phase (one part of clotrimazole being dissolved in the cream and the other part in a fine distributed suspension), which could make the extent of dissolution critical to the efficacy of the product. Differences in dissolution of the active in the different phases, and also the manufacturing processes could lead to clinically detectable differences in the efficacy and potentially the safety of the product. However, in answers to questions asked by the Committee, the MAH submitted laboratory data to demonstrate that clotrimazole would dissolve completely in the oil phase and that this is unaffected by benzyl alcohol. The specifications however include a test for particles. This major inconsistency challenged the expected robust and extensive knowledge of the product and was noted by the Committee. Justification should have also been provided for the use of 'simplified emulsions' and the tests that were conducted, in contrast to testing the actual test and reference finished products, including justification for how the results of these studies can be extrapolated to the actual products. In addition it should have also been confirmed that the production method used is comparable to the commercial manufacturing process.

It was previously known that there was a difference in oil droplet size between test and reference products. However, the MAH presented images using light microscopy that showed that most oil droplets from the test product were of comparable size to the reference, but there were also larger droplets present. Although the MAH argued that this was due to aggregation, no information on the possible effect in tissue penetration was provided. An *in vitro* skin permeation or similar studies should have been provided.

The MAH also presented *in vitro* anti-fungal data, to demonstrate comparable anti-fungal activity, based on the preservative efficacy test. The CHMP considered that the data lacked the methodological details which would allow a correct interpretation. No other data was presented and no further justification was provided.

An oral explanation was held on the 14 March 2011. It was acknowledged that the data provided so far were from preliminary studies and that further studies would be necessary to prove therapeutic equivalence. During the discussion with the CHMP, it was also highlighted to the MAH that care should be exercise in a robust description of the method of manufacture, and inconsistencies identified should be carefully considered by the MAH. Further details of the data required to show therapeutic equivalence of Canazole Clotrimazole Cream 1% w/w could be provided through Scientific Advice, if the MAH were to take such an approach. The CHMP considered that the data submitted do not support therapeutic equivalence between Canazole Clotrimazole Cream 1% w/w and the reference product.

2.2. Risk management plan

The CHMP did not require the MAH to submit a risk management plan.

2.3. Recommendation

Data were submitted by the MAH to demonstrate that Canazole Clotrimazole Cream 1% w/w should be considered equivalent to the reference product. Comparisons of physico-chemical characteristics to demonstrate that the formulations are similar (except the benzyl alcohol concentration) were provided; it was argued that both products are manufactured using similar process, have similar pH, viscosity,

appearance and droplet size, solubility and partitioning. A preservative efficacy test *(in vitro*) to demonstrate comparable anti-fungal activity was also provided.

The CHMP considered that the comparative quality data was considered minimal and the description of development pharmaceutics was considered to be unsatisfactory. 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. Information on the necessary batches of each product should have been provided. An appropriate skin permeation or similar *in vitro* studies should have been performed. In addition, 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 note for 'Guidance on the clinical requirements for locally applied; locally acting products (CMP/EWP/239/95)' indicates that clinical trials are in principle necessary to demonstrate therapeutic equivalence but that other models may be used. No such study has been provided with this application. It was therefore not considered sufficient to justify a waiver of the need to demonstrate therapeutic equivalence by clinical studies or other validated model, and a therapeutic equivalence study was therefore deemed necessary in this case to prove equivalence.

2.4. Conclusions and benefit risk assessment

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

Based on:

- the results from the studies 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 authorisation in the concerned member state and the suspension of the marketing authorisation in the reference member state, subject to the conditions outlined in annex III of the Opinion.