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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-307

**Clinical Pharmacology and Biopharmaceutics
Review**

Clinical Pharmacology/Biopharmaceutics Review

NDA Number: 21-307 (Amendment)
Submission Date: 10/05/01 and 11/01/01
Product: Lotrimin Ultra™ (Butenafine HCl Cream, 1%)
Sponsor: Schering-Plough HealthCare Products, New Jersey, 0792
Reviewer: Abimbola Adebowale Ph.D.
Type of Submission: An amendment in response to an approvable letter

Review of an Original NDA Amendment

I. Background and Introduction

This submission is an amendment in response to the approvable (AE) letter (dated July 27, 2001) issued for the original NDA submission. The original NDA provided for the use without prescription of butenafine HCl cream, 1%, for the topical treatment of tinea corporis, tinea cruris and interdigital tinea pedis.

In this submission the applicant stated that the application is being resubmitted and all of the deficiencies listed in the AE letter addressed. In the AE letter there were no deficiencies related to human pharmacokinetics and biopharmaceutics, however one of the clinical deficiencies implied the collection of pharmacokinetic data. The deficiency was stated in the letter as follows:

“Also, you should propose a protocol to satisfy a Post Marketing Commitment to evaluate the safety and efficacy of tinea corporis in the 12 year old and under pediatric population, especially since the dermatophyte species responsible may vary from adults”.

The applicant submitted a request for a meeting on the 26th of September 2001 to specifically discuss this deficiency. In the resubmission (dated 5th of October, 2001) the applicant then submitted the proposed protocol (# CL2001-10) entitled “A clinical study to evaluate the safety and efficacy of butenafine HCl cream 1% vs. vehicle cream in the treatment of tinea corporis in a pediatric population”. A request for a meeting was then submitted by the applicant again on the 1st of November, 2001 and the same protocol in the resubmission was included as well as a copy of the most comprehensive article that the applicant obtained from a literature search to better understand the possible differences between the dermatophyte species responsible for tinea corporis in children and adults. This meeting was conducted as a teleconference on the 28th of November 2001. At the teleconference the following comment was conveyed to the applicant based on a preliminary review of the draft protocol:

“In the draft protocol (No. CL2001-10) entitled “ A Clinical Study to Evaluate the Safety and Efficacy of Butenafine Hydrochloride Cream 1% vs. Vehicle Cream in the treatment of Tinea Corporis in a Pediatric Population” the sponsor did not include any systemic exposure assessment for safety. Currently we have systemic exposure data in

tinea cruris, tinea pedis and healthy adult patients and subjects respectively. However, we do not have any systemic exposure assessment data of butenafine in the pediatric population. In the pediatric population there is the possibility that there may be a higher apparent systemic exposure because of the smaller volume of distribution and/or body surface area to mass ratio. Therefore, in order to assess if there are clinically relevant differences in the systemic exposure of pediatric patients compared with adults the sponsor would need to provide some information on the systemic exposure of butenafine in the pediatric population”.

This information was acceptable to the applicant and they agreed to provide data on systemic exposure of butenafine cream 1% in the pediatric population as part of their Post Marketing Commitment safety evaluation.

II. Recommendations

Since there were no deficiencies raised in the NA letter from a clinical pharmacology and biopharmaceutics perspective, the applicant did not provide any new Human PK and BA information or data in this resubmission. However, a preliminary review of the clinical efficacy and safety protocol indicated a lack of systemic exposure assessment in the pediatric population. This request has already been conveyed to the applicant and also the medical reviewers (Dr. A. Segal and Dr. J. Porres) are incorporating the information into the approval letter. Based on the aforementioned, this application is acceptable from a clinical pharmacology and biopharmaceutics perspective.

/s/

12/3/01

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/s/

12/5/01

RD/FT signed by Dennis Bashaw, Pharm.D. _____

In this study plasma concentrations of butenafine and the major metabolite (M2) were determined following once daily application for 14 days of 6grams of Mentax cream 1% to the posterior trunk (3000cm²) of one group (N=7) and, 20g to the arms, trunks and groin (~10,000cm²) of another group (N=12). This study used the formulation intended for marketing (formulation PD010-C-003, Penederm cream). The mean (\pm SD) steady state plasma concentrations were 1.4 \pm 0.8 ng/mL and 5.0 \pm 2.0 ng/mL and, the mean (\pm SD) time to peak plasma concentration Tmax was 15 (\pm 8) hours and 6 (\pm 6) hours following the application of 6 and 20 g doses respectively.

2. ***Kaken Study G3 entitled "Single and Multiple application of KP-363 (butenafine HCl), a new antifungal agent, in healthy adults"***: This study was conducted in Japan using a formulation (Formulation PD-010-C-001, Kaken cream) slightly different from that intended for marketing. A daily dose of 5 grams was applied once (N=5) for the single dose study and for 7 days (N = 5) in the multiple dose studies to the back (500cm²). The application region was covered with gauze for 12 hours and then removed along with any remaining drug on the skin. The mean Cmax was 4.1 \pm 1.7 ng/mL for day 1 and 4.8 \pm 2.3 ng/mL for day 7.

3. ***Penederm Clinical Study PDC 010-002 entitled "Double-blind evaluation of butenafine HCl 1% cream and vehicle in the treatment of Tinea pedis"***: During treatment, there were a total of 25 samples from 11 patients and the mean plasma butenafine concentration was found to be 0.12 \pm 0.10 ng/mL following application of 1% Penederm cream (Formulation PD-010-C-003, Penederm cream) to the affected area and surrounding skin areas once daily for 4 weeks. The plasma levels ranged from undetectable to — ng/mL in blood samples collected 10 to 20 hours after dosing at 1, 2, and 4 weeks after treatment. (In Beagle dogs, the threshold of toxicity was determined to be greater than 100 ng/mL).

4. ***Penederm Clinical Study PDC 010-005 entitled "A multicenter, double-blind study to evaluate butenafine HCl 1% cream and vehicle in the treatment of Tinea cruris"***: In 24 male patients plasma concentrations of butenafine were determined in blood samples collected at pre-dose, and on days 14 and 42 following the application of butenafine HCl cream 1% (Formulation PD-010-C-003, Penederm cream) to the affected area and immediate surrounding skin area once daily for two weeks (mean average daily dose was 1.3 \pm 0.2g). A single blood sample was collected between 0.5 and 65 hours after the last dose and the mean (\pm SD) plasma concentration of butenafine was 0.91 \pm 0.15 ng/mL (range — ng/mL). Four weeks after cessation of treatment (day 42), the plasma butenafine HCl concentration ranged from — ng/mL. (This study was actually submitted in NDA 20-663).

5. ***In vitro Percutaneous absorption of butenafine hydrochloride from Kaken cream and Penederm cream***: This study was conducted to characterize the deposition and penetration of ¹⁴C radiolabelled butenafine into and through human cadaver skin from Kaken cream (Formulation PD-010-C-001) and Penederm cream (Formulation PD 010-C-003) evaluated in clinical trials and some preclinical studies. The Kaken cream is almost identical to Penederm cream, but does not contain 0.5% benzyl alcohol. The penetration of radiolabeled butenafine from the two formulations was found not to be statistically significant (p> 0.05). This study demonstrated that the inclusion of 0.5% benzyl alcohol as a

preservative does not affect the deposition and penetration of butenafine following topical application.

III. Comments:

1. The results of the studies outlined in the synopsis above indicated that systemic exposure to butenafine is low under conditions of exaggerated dosing in healthy volunteers and, therapeutic use in patients at the recommended dose. The mean maximum plasma concentrations of butenafine obtained in the pharmacokinetic studies (5 ± 2 ng/mL) were substantially less than the threshold of toxicity determined in beagle dogs (>100 ng/mL).
2. The systemic exposure from the OTC marketing would not be expected to be different from that obtained in the studies conducted for the prescription product since the OTC indication, strength, duration of use, dose, route of administration and the dosage form are identical to that which was studied for the original Rx 1% cream product (with the exception of the once daily 4-week dosing regimen for athlete's foot).
3. Also all adverse events observed during the human pharmacokinetic studies that were considered possibly related to the drug product were reported in the review as mild and dermatological in nature (e.g. burning/stinging and itching at site of application).

IV. Recommendation

This application for OTC marketing represents a partial move of a product from prescription to OTC status. As the OTC indication, population to be treated, strength, duration of use, dose, route of administration and the dosage form are identical to that which was studied for the original Rx 1% cream product and, there are no outstanding clinical pharmacology and biopharmaceutics commitments from the 1% cream approval, the marketing of the product is acceptable from a clinical pharmacology and biopharmaceutics perspective.

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