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APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
20-524/S-005**

**Clinical Pharmacology and Biopharmaceutics
Review**

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA: 20-524 (SE1-005) **Submission Date:** 8/4/00

Product: Mentax[®] (butenafine HCl cream) 1%

Sponsor: Bertex Pharmaceuticals **Reviewer:** Abimbola Adebowale Ph.D.
Foster City, CA

Review of a Clinical Efficacy Supplemental NDA

I. Background and Introduction

Butenafine is a benzyl derivative closely related in structure and mode of action to the allylamine antifungal agents. It exerts its action by inhibiting epoxidation of squalene, thus blocking the biosynthesis of ergosterol, an essential component of fungal cell membranes. Mentax[®] (butenafine HCL 1% cream) is currently marketed for the indications of *Tinea pedis* (Approved NDA 20-524 10/18/96), *Tinea cruris* and *Tinea corporis* (Approved NDA 20-663 12/31/96). In the current SNDA the applicant is proposing to use the same formulation for the indication of *Tinea versicolor*, applied once daily for two weeks. *Tinea versicolor* is an infection of the smooth skin caused by *Pityrosporum orbiculare* (*Malassezia furfur*). The condition is recurrent and may give rise to hyperpigmented or hypopigmented patches on the trunk that may extend to the neck, arms and upper thighs.

The applicant has not provided any new human pharmacokinetic or bioavailability information in this application but has cross-referenced the previously submitted data in approved NDA 20-524 and 20-663 (reviewed by Dr. S. Lee).

II. Synopsis of Studies Included in and Reviewed under NDA 20-524 and 20-663

1. ***Penederm Study No. 9425201D entitled "A single-center, open-label study to determine the plasma level of butenafine following multiple topical applications of butenafine HC 1% cream to normal volunteers (protocol PDC-010-011):***

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 (±SD) steady state plasma concentrations were 1.4 ± 0.8 ng/mL and 5.0 ± 2.0 ng/mL and, the mean (±SD) time to peak plasma concentration T_{max} was 15 (± 8) hours and 6 (±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 C_{max} was 4.1 ± 1.7 ng/mL for day 1 and 4.8 ± 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 ± 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 0.3 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 ± 0.2g). A single blood sample was collected between 0.5 and 65 hours after the last dose and the mean (± SD) plasma concentration of butenafine was 0.91 ± 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 radiolabeled 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 %. 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 % as a does not affect the deposition and penetration of butenafine following topical application.

III. Comments:

1. The formulation, dosing regimen and duration of treatment studied for NDA 20-663 for patients with *Tinea cruris* and *Tinea corporis* are identical to that proposed for patients with *Tinea versicolor*.
2. The results of the studies outlined in the synopsis above indicated that systemic exposure to butenafine is low under conditions of therapeutic use in patients with

Tinea cruris at the recommended dose and also, exaggerated dosing in healthy volunteers. 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).

3. Although the pattern of use in the patients with *Tinea versicolor* might be more extensive than in patients with *Tinea cruris* and *Tinea corporis*, the human pharmacokinetics and bioavailability studies conducted in NDA 20-524 in healthy volunteers involved very extensive areas of application with exaggerated doses.
4. All adverse events observed during the human pharmacokinetic studies that were considered possibly related to the drug product were reported in the reviews as mild and dermatological in nature (e.g. burning/stinging and itching at site of application).

III. Recommendation

Since the formulation, dosing regimen and duration of treatment and, the pharmacokinetics portion of the label are identical to that which was originally studied in NDA 20-663, and, there are no outstanding clinical pharmacology and biopharmaceutics commitments from the 1% cream approval for the approved NDA 20-524 and 20-663, the application is acceptable from a clinical pharmacology and biopharmaceutics perspective.


2/23/01

Abimbola O. Adebawale Ph.D.
Office of Clinical Pharmacology /Biopharmaceutics
Division of Pharmaceutical Evaluation III


2/23/01

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