

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-408

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA Number: 21-408 **Submission Date(s):** 12/14/01, 05/15/02, 06/18/02
Brand Name: Mentax[®]- TC Cream
Generic Name: Butenafine HCl Cream, 1%
Indication: Treatment of tinea versicolor
Reviewer: Abimbola Adebawale Ph.D.
Team Leader: Dennis Bashaw Pharm.D.
OCPB Division: DPEIII
ORM division: HFD-550
Sponsor: Bertek Pharmaceuticals Inc., NC, 27709
Relevant IND(s): 60,471
Submission Type; Code: 3S

1 Executive Summary

In this application the sponsor is seeking approval for Mentax[®]-TC cream, for the topical treatment of tinea (pityriasis) versicolor due to *Malassezia furfur* (formerly *P. orbiculare*). This cream is to be applied once daily for 7 days. This new drug product is an optimized formula of the currently marketed Mentax[®] cream that was the subject of approved NDA's 20-524 and 20-563. Mentax[®] cream is currently indicated for tinea versicolor only, to be applied once daily for two weeks. The approved indications for the prescriptive use of Mentax[®] cream were for the topical treatment of interdigital tinea pedis (athlete's foot [approved NDA 20-524, 10/18/96]), tinea cruris (jock itch), tinea corporis (ringworm; [approved NDA 20-663, 12/31/96]) and, tinea versicolor [approved SNDA 20-524/S-005, 6/6/01]. However, on December 7th, 2001, the indications of topical treatment of interdigital tinea pedis, tinea corporis and tinea cruris with the same dosing regimen as for prescriptive use with Mentax[®] cream was approved for over-the-counter (OTC) use as Lotrimin[®] ultra butenafine hydrochloride cream, 1%.

The new drug product differs from the currently approved formulation primarily by the replacement of — diethanolamine by trolamine (triethanolamine) and the addition of two ingredients, propylene glycol and polyoprepolymer-2 (PP-2). Propylene glycol is used as
PP-2

Provided in the human pharmacokinetics and bioavailability section of this submission is a study report of the *in vivo* assessment of the plasma concentrations of butenafine and its metabolite (M-2) in patients with tinea versicolor (Study # PDC-010-046) following multiple topical applications of Mentax[®]-TC cream. Study reports of two independent *in vitro* studies (PD339:18 and PD356:006) that evaluated the percutaneous absorption of ¹⁴C labeled butenafine

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from Mentax[®] cream and Mentax[®]-TC cream using excised human skin were also provided. Also included were abbreviated reports of two *in vivo* studies conducted in healthy adults and one *in vitro* percutaneous absorption study using excised human skin, which were previously submitted in approved NDA 20-524 and therefore had already been reviewed. The applicant referred to NDA 20-524 for detailed information on these and other *in vivo* and *in vitro* percutaneous absorption studies.

The results of the *in vivo* study following topical application of Mentax[®]-TC cream once daily for seven days to patients with tinea versicolor demonstrated that the plasma concentrations for butenafine ranged from — ng/mL. The mean (SD) butenafine C_{max} was 4.13 (1.85) ng/mL and the AUC₀₋₂₄ was 62.73(28.92) ng/mL. The values for these PK parameters (following dose normalization) are comparable with those obtained following the application of Mentax cream (20g) to healthy volunteers once daily for 14 days. Therefore indicating that a clinically relevant increase in systemic exposure following the application of a similar amount of drug to diseased skin is unlikely. The data from animal dermal studies were also supportive of the data from the human PK study. The mean total plasma concentration obtained in dogs following the topical application of butenafine solution at the no effect dose for local toxicity of 25 mg/kg/day for 12 months was 148 (47) ng/mL which is approximately 19 fold higher than the highest plasma concentration obtained in the human PK study.

Also most adverse events observed during the pivotal clinical studies that were considered possibly related to the drug product were reported in the medical review as dermatological in nature (e.g., itching, warmth at the application site and contact dermatitis).

1.1 Recommendation

The information submitted by the applicant demonstrated that the butenafine pharmacokinetic parameters obtained after clinical use of the Mentax[®]-TC cream in patients with extensive tinea versicolor were comparable to that obtained with currently marketed Mentax[®] cream in healthy patients. Also the plasma concentrations of butenafine were lower than that associated with toxicity in animal dermal studies. Therefore the clinical pharmacology and biopharmaceutics information in this application is acceptable provided that the applicant adequately addresses the labeling comments in section 5.

Comment to be conveyed to the Applicant:

The sponsor is encouraged to develop an *in vitro* drug release test method and test specification for the Mentax[®]-TC cream.

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3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Introduction and Background:

Mentax[®]-TC Cream, 1%, contains the synthetic antifungal agent, butenafine hydrochloride. Butenafine is a member of the class of antifungal compounds known as benzylamines, which are structurally related to the allylamines. Although there is already an approved Mentax[®] cream indicated for tinea versicolor, at a Pre-NDA meeting held on May 21, 2001, the sponsor stated

Clinical Pharmacology: Only the three studies (1 in vivo and 2 in vitro studies) that evaluated the Mentax[®]-TC cream were reviewed. The in vivo study (PDC 010-046) evaluated the systemic absorption of butenafine and its metabolite M2 following the daily topical application of Mentax[®]-TC cream to patients (N = 12) with tinea versicolor (mean treatment area = 5000.33 (2221.92) cm²). On day 7, the mean (SD) butenafine C_{max} was 4.13 (1.85) ng/mL, which occurred at a mean T_{max} of 12.29 (8.47) hrs, and was characterized by a mean AUC₀₋₂₄ of 62.73 (28.92) ng*h/mL. This systemic exposure was much lower than that associated with toxicity in animal dermal studies. The plasma concentrations of the primary metabolite M2

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(identified in rat plasma) which is designated chemically as (N-4- (2-hydroxy-1, 1-dimethylethyl) benzyl-N-methyl-1-naphthalenemethylamine) ranged from — ng/mL.

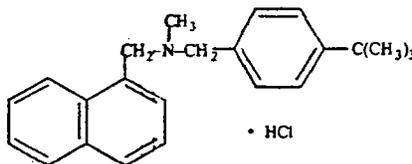
Biopharmaceutics: Two independent in vitro studies (PD339:18 and PD356:006) that evaluated the percutaneous absorption of ¹⁴C labeled butenafine from Mentax[®]-TC cream and Mentax[®] cream using excised human skin were included in this submission. Although different skin donors were used across studies, each study used skin from the same donor. Similar methodology was used in both studies. Since the in vitro deposition and penetration of butenafine was not consistent across studies for both formulations, no conclusions could be reached on the clinical relevance of the data. However, evaluations of the effect of polyolprepolymer-2 (PP-2) in study PD339:18 did not indicate a statistically significant difference in the deposition or penetration of radiolabeled butenafine between the two formulations.

4 Review

4.1 General Attributes

Chemistry and physical-chemical properties of the drug substance:

Butenafine HCl is designated chemically as N-4- tert-butylbenzyl-N-methyl-1-naphthalenemethylamine hydrochloride. Butenafine HCl is a white crystalline powder, odorless or with a faint characteristic odor. It is freely soluble in methanol (— mL), ethanol, and chloroform (— mL), and slightly soluble in water (— mL). The compound has the empirical formula C₂₃H₂₇N•HCl, a molecular weight of 353.93, and the following structural formula:



Formulation of Mentax[®]-TC cream 1%:

| % w/w | |
|------------------------------|--------------|
| Ingredients | PD 010-C-009 |
| Purified water USP | |
| Propylene glycol dicaprylate | |
| Propylene glycol | |
| Glycerine USP | |
| Cetyl alcohol USP | |
| Glyceryl monostearate | |
| White petrolatum USP | |
| Stearic acid NF | |
| Polyoxyethylene cetyl ether | |
| Butenafine HCl | 1.00 |
| Polyolprepolymer-2 | |
| Benzyl alcohol NF | ✓ |
| Trolamine | |
| Diethanolamine NF | 0.00 |
| Sodium benzoate NF | |

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Mechanism of action and therapeutic indication:

Butenafine HCl is a benzylamine derivative with a mode of action similar to that of the allylamine class of antifungal drugs. Butenafine HCl is hypothesized to act by inhibiting the epoxidation of squalene, thus blocking the biosynthesis of ergosterol, an essential component of fungal cell membranes. Mentax[®] - TC cream is indicated for the topical treatment of tinea (pityriasis) versicolor, a superficial, chronically recurring infection of the skin caused by *Malassezia furfur* (formerly *Pityrosporum orbiculare*). This commensal organism is part of the normal skin flora. In susceptible individuals the condition may give rise to scaly, hyperpigmented or hypopigmented patches on the trunk which may extend to the neck, arms and upper thighs.

Proposed dosage regimen:

Patients with tinea (pityriasis) versicolor are to apply Mentax[®]-TC once daily for seven days. Sufficient Mentax[®] - TC cream should be applied to cover affected areas and immediately surrounding skin of patients.

What efficacy and safety information contributes to the assessment of the clinical pharmacology and biopharmaceutics study data?

Two pivotal studies (PDC010-033 and PDC 010-036) conducted in patients with tinea versicolor were included in this submission for the evaluation of safety and efficacy. PDC 010-033 was a multicenter, double-blind, vehicle-controlled study (N = 129; 86 for butenafine and 43 for vehicle) to evaluate the treatment of tinea versicolor with butenafine HCl cream, 1% applied once daily for seven days. PDC 010-036 was a multi-center, double-blind, vehicle-controlled study (N = 217; 143 for butenafine and 74 for vehicle) to evaluate the safety and efficacy of butenafine HCl Cream, 1% applied once daily for seven days in the treatment of tinea versicolor. In the first study a total of seven adverse events were reported by six subjects (7.1%) in the butenafine group and three adverse events in three subjects (7.3%) in the vehicle group. Only taste disturbance was considered by the investigator to be at least possibly related to the study treatment in the butenafine group and none in the vehicle group.

In the second study 15 subjects (10.8 %) in the butenafine group reported a total of 18 adverse events. A total of 18 adverse events were reported by 12 subjects (16.4%) in the vehicle control group. Five adverse events in the butenafine group and one in the vehicle group were considered by the investigator to be at least possibly related to study medication. The treatment related adverse events were application site reactions including itching, warmth at the application site and contact dermatitis. The one treatment related adverse event experienced in the vehicle group was reported as pruritus.

4.2 General Clinical Pharmacology

Were the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships?

Yes, the active moieties, butenafine and the metabolite M2 were appropriately identified and measured (refer to the Analytical Section in 4.4).

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What is the systemic exposure to butenafine under maximum use conditions that are consistent with the proposed dose and duration of Mentax[®] - TC cream in the target population?

In study (PDC 010-046) the systemic exposure of butenafine and its metabolite (M2) following the daily topical application of Mentax[®]-TC cream to patients with tinea versicolor for seven days was evaluated. The plasma concentrations of butenafine were below LOQ in all subjects on Day 1 at pre-dose, however all subjects had plasma concentrations of butenafine above LOQ on day 7 at pre-dose with a mean of 2.47 ± 1.14 ng/mL and a range of _____ ng/mL. On day 7 at post-dose (at sampling times between 0.5-24 hrs), butenafine plasma concentrations ranged from _____ ng/mL. The amount of drug applied in this study ranged from 14.1 - 48.9 grams (mean = 25 ± 11 g) at a dose of 5 mg/cm² and, the treatment area was quite extensive ranging from 2820-9787 cm² (including the lesions and surrounding areas). Reproduced below is a graphical presentation of the plasma concentration versus time for butenafine on Day 7 showing a wide variability between subjects probably due to the wide range of doses applied. The patient with the highest plasma concentration (subject No. 6) was the one given the highest daily dose (48.9g).



The plasma concentrations of butenafine as shown in the graph above are much lower than that obtained with the no effect dose for local and systemic toxicity in animal dermal studies. In the non clinical studies, the applicant stated that following repeated topical doses of 25 mg/kg/day (no effect dose for local toxicity) of a butenafine solution to dogs for 12 months, mean plasma concentration collected at six and twelve months were 229 ± 118 ng/mL and 148 ± 47 ng/ml, respectively. These plasma concentrations are ~19-30 fold higher than the highest concentration obtained in the human PK study. The applicant also reported the mean plasma concentration collected at six and twelve months following repeated topical doses of 100 mg/kg/day (no effect dose for systemic toxicity) of a butenafine solution to dogs for 12 months as 284 ± 81 ng/mL and 352 ± 95 ng/ml. However, the drug is reported as being extensively bound to plasma proteins (>90%) in rats, but no information was provided on plasma protein binding in humans so a comparison based on systemic toxicity in animals is difficult to interpret.

Plasma concentrations of the metabolite M2 were below LOQ for all subjects on day 1 at pre-dose as expected and only 3/12 subjects had levels above LOQ on day 7 at pre-dose ranging from ——— ng/mL. Three subjects had levels below LOQ from 0-24 hrs. The remaining 9 subjects had scattered plasma concentrations ranging from — ng/mL. The applicant did not provide any information on the activity of M2 so the clinical significance of these results is unknown. Reproduced in the Table below are the pharmacokinetic parameters obtained in study PDC 010-046 on Day 7 for butenafine and M2.

Table: Mean (SD) pharmacokinetic parameter values for butenafine and the metabolite (M2) on Day 7

| Pharmacokinetic parameter (N = 12) | Butenafine | M2 |
|------------------------------------|---------------|-------------|
| C _{max} (ng/mL) | 4.13 (1.85) | 0.12 (0.08) |
| T _{max} (h) | 12.29 (8.47) | 8.72 (6.00) |
| AUC ₀₋₂₄ (ng*h/mL) | 62.73 (28.92) | 1.33 (1.27) |

The data in the table above show that the mean T_{max} was long suggesting a slow process of absorption into the systemic circulation. Also there was quite a wide variability in the values of the PK parameters between subjects for both butenafine and M2. The possible sources of this variability could have been the large differences in the daily dose administered as well as the diseased skin condition.

How does the systemic exposure of butenafine in patients compare to that in healthy volunteers?

The applicant did not conduct any studies using the Mentax[®]-TC cream in healthy volunteers. However, the approved Mentax[®] cream that is also indicated for tinea versicolor was studied in healthy volunteers. Although these studies have already been reviewed for that application the exposure data is reproduced in the table below for comparison purposes only.

Table: Comparison of the mean (SD) pharmacokinetic parameters obtained in tinea versicolor patients with new Mentax[®]-TC cream and that obtained in healthy subjects with approved Mentax[®] cream

| Formulations | Mentax [®] -TC Cream, 1% | Mentax [®] -TC Cream, 1% | Mentax [®] Cream, 1% | Mentax [®] Cream, 1% |
|---|---|--|-------------------------------|--------------------------------------|
| Population | Tinea Versicolor patients | Tinea Versicolor patients | Healthy | Healthy |
| N | 12 | 12 | 7 | 12 |
| Dose/duration | 14.1-48.9g (mean =25 (11)g) QD for 7 days | Individual data was dose normalized for 20 G | 6g QD for 14 days | 20g QD for 14 days |
| Treatment area/[range of total surface area (cm ²)] | 2820-9787 | 2820-9787 | Dorsal skin/[3,000] | Arms, trunk and groin areas/[10,000] |
| C _{max} (ng/mL) | 4.13 (1.9) | 5.67 (4.8) | 1.43 (0.8) | 5 (2.0) |
| T _{max} (hr) | 12.29 (8.5) | 12.29 (8.5) | 15.48 (8) | 6 (6.0) |
| AUC (ng*hr/mL) | 62.73 (28.9) | 80.35 (89.0) | 23.89 (11.3) | 87.8 (45.3) |

The data in the table above indicate that a gross comparison of the PK parameters obtained following application of Mentax[®]-TC cream to patients with tinea versicolor for 7 days is consistent with that obtained with the application of 20g of approved Mentax[®] cream to healthy volunteers for 14 days. Dose Normalization of the C_{max} and AUC obtained in the tinea versicolor patients also shows similarity to the values (with larger variability) obtained in the healthy patients. Although the formulations were slightly different, and the comparisons are not totally robust due to the differences in doses and area of application, overall the data suggests that the potential for a clinically relevant increase in systemic exposure following application of a similar amount of drug to diseased skin is minimal.

What other factors are important in understanding the safety and efficacy of butenafine in Mentax[®]-TC cream?

Safety

The amounts used in the PK study ranging from 14.1-48.9 grams/day were much higher (~4-12 fold) than that used in the clinical studies. The average actual usage of the formulation in the clinical studies PDC 010-033 and PDC 010-036 were 2.9 g/day and 4.0 g/day, respectively (confirmed with Dr. B. Carr, the medical reviewer). Also the no effect dose for systemic effects and local effects obtained in dermal animal studies after 90 days and 1 year topical application of butenafine HCl 1% cream, was 100mg/kg and 25 mg/kg respectively. The mean weight of the patients in the PK study was 70.6 kg and the average daily dose of drug product was 25g (=250 mg of butenafine). Therefore the dose applied was about 3.54 mg/kg/day (~115 mg/m²) of butenafine. This implies that the no effect dose for systemic effects and local effects obtained in animals is ~ 28 times and 7 fold higher than the average amount applied in the PK study or 14 and 3.5 fold higher than the maximum amount (48.9g) applied.

4.3 General biopharmaceutics

What is the in vitro percutaneous absorption of butenafine and how does this relate to the in vivo systemic exposure?

In vitro studies:

Two independent in vitro studies (PD339:18 and PD356:006) that evaluated the percutaneous absorption of ¹⁴C labeled butenafine from Mentax[®]-TC cream and Mentax[®] cream using excised human skin were included in this submission. Although different skin donors were used across studies, each study used skin from the same donor. Similar methodology was used in both studies. Basically, both cream formulations were spiked with (¹⁴C)-butenafine to achieve a radiolabel concentration of 1.0 µCi/3.2 mg dose (= 0.31µCi/mg of formulation). The human dermatomed cadaver skin was mounted on Bronaugh flow-through diffusion cells. Approximately 3.2 mg of formulation was spread over a skin area of 0.64 cm² to achieve a level of 5 mg/cm². The flow rate of the receptor fluid, phosphate-buffered saline containing 0.01% sodium azide with 1.5% Oleth-20 was set at 1mL/hr at 37 °C. The receptor samples were collected at 6-hr intervals for a total of 24 hours. Following a 24-hour exposure, test material was removed from the skin surface by wiping with two, dry cotton swabs (only this was used in Study PD 356:006), or 3 mild detergent washes or 1 strong detergent wash. The residual cream and the outer layers of the skin were removed from the epidermis by a single tape strip and the

epidermis was then separated from the dermis. Quantity of radioactivity in the wipes, tape-strip, epidermis, dermis and receptor samples was evaluated by liquid scintillation counting techniques to determine ¹⁴C-butenafine percutaneous absorption. Inserted below is a tabular summary of the percent of the applied dose of radiolabeled butenafine in the tape strip, epidermis, dermis and receptor from both studies.

The results in the table below show that in study PD339:18, a statistically greater

Table 2:
***In Vitro* Percutaneous Absorption of Butenafine from Mentax Cream and Mentax Plus Cream**
Values in Percent of Applied Dose, Mean ± SD (% CV), n = 4 to 6

| | Mentax Cream | Mentax Plus Cream |
|--------------------------|--------------|-------------------|
| Single Tape-Strip | | |
| PD356:06 | 11 ± 2.5* | 8.0 ± 1.4 |
| PD339:18 | 9.9 ± 4.2 | 14 ± 2.8 |
| Epidermis | | |
| PD356:06 | 4.2 ± 1.3 | 4.1 ± 1.2 |
| PD339:18 | 3.6 ± 0.8 | 5.7 ± 2.1 |
| Total Epidermis | | |
| PD356:06 | 15 ± 3.6 | 12 ± 2.5 |
| PD339:18 | 14 ± 4.3 | 20 ± 4.4* |
| Dermis | | |
| PD356:06 | 3.0 ± 0.7 | 3.3 ± 0.8 |
| PD339:18 | 1.9 ± 0.4 | 2.8 ± 1.0 |
| Penetration | | |
| PD356:06 | 0.4 ± 0.1 | 0.4 ± 0.1 |
| PD339:18 | 0.6 ± 0.1 | 1.3 ± 0.3* |
| % Recovery | | |
| PD356:06 | 100 ± 4.1 | 97 ± 8.6 |
| PD339:18 | 113 ± 6.4 | 111 ± 4.6 |

*Statistically (p < 0.05, Student-Newman-Keuls and unpaired t-test) greater

[*Mentax plus cream is the same as Mentax-TC cream.]

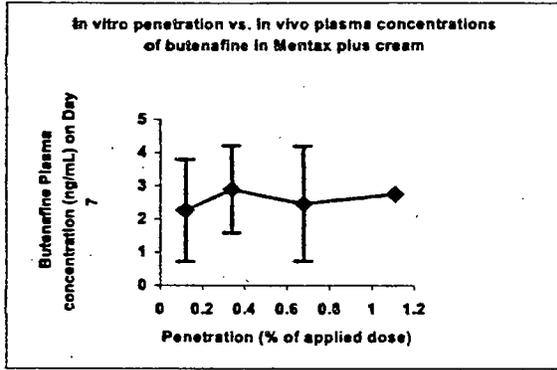
(p < 0.05) deposition of butenafine in the total epidermis (i.e. tape strip plus remaining epidermis) and skin penetration was observed for Mentax[®]-TC cream relative to Mentax[®] cream. However, this was not consistent across studies using human skin because in study PD356:06 a statistically greater deposition of butenafine was only observed in the single cellophane tape-strip for Mentax[®] cream relative to Mentax[®]-TC cream. The results indicate that in study PD339:18 there was a higher percentage recovery, which suggests that there might have been some calibration differences. Because of the discordance across studies a conclusion cannot be reached.

However, the data on the evaluation of the addition of PP-2 did not result in a statistically significant difference in the deposition or penetrations of radiolabeled butenafine between the two formulations in study PD:339:18.

In vitro–*In vivo* relationship:

Reproduced below is a graphical presentation of the relationship between the in vitro penetration results (study PD339:18) and the in vivo plasma concentration for the 6, 12, 18 and 24 hr time-points.

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The graph above suggests that as the skin penetration increased, any change in the plasma concentration in vivo after 7 days application was minimal.

4.4 Analytical

How were the active moieties identified and measured in plasma in the clinical pharmacology and biopharmaceutics studies?

Were the analytical methods used for the determination of butenafine and M2 in biological fluids validated?

| Compound | | Butenafine | M2 |
|----------------------|--------------------|-----------------------------------|-----------------------------------|
| Assay Method | | LC-MS-MS | LC-MS-MS |
| Accuracy | <i>Between-Day</i> | _____ | _____ |
| Precision (CV%) | <i>Between-Day</i> | _____ | _____ |
| Standard curve range | | _____ ng/mL (r = _____, N = 2) | _____ ng/mL (r = _____, N = 4) |
| Stability | | _____ | _____ |
| Selectivity | | _____ | _____ |

The method validation results as shown in the table above demonstrate that the LC-MS-MS analytical method used for the quantitative measurement of butenafine and its major metabolite (M2) in human plasma was accurate and reproducible for the intended use.

5 Detailed Labeling Recommendations

Since it is not only the dose but also the surface area (and the resultant amount of formulation applied per unit surface area) that can affect the percutaneous absorption of the drug, the labeling should also indicate the surface areas used in the study as shown below:

The deletions are strikeouts and the changes/additions are bolded italics

CLINICAL PHARMACOLOGY

Pharmacokinetics

In 12 patients with ~~_____~~ *extensive* tinea versicolor, a range of 14 to 49 grams of Mentax®-TC Cream, 1% was applied ~~_____~~ *using* 5 mg/cm² to ~~_____~~ cover each lesion and ~~_____~~ *10.2 centimeters margin* of ~~_____~~ surrounding *clear skin*, (*mean total area of application: 5,000.3 ± 2,221.9 cm²*). ~~_____~~ *On the 7th day* of applications, the ~~_____~~ mean peak plasma butenafine HCl concentration, (C_{max}) ~~was~~ ~~_____~~ *± 1.7* 9 ng/mL. ~~_____~~ *The* mean time to peak plasma concentration, (T_{max}) ~~was~~ ~~_____~~ *12.3 ± 8.5* hours. ~~_____~~ The mean area under the plasma- concentration-time curve, (AUC₀₋₂₄) was 62.7 ~~± 28.~~ ~~_____~~ ng-hr/mL.

Nursing Mothers

It is not known if butenafine HCl is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised in prescribing Mentax® - TC Cream, 1%, to a nursing woman. ~~_____~~

PRECAUTIONS

General

6 Appendix

6.1 Proposed Draft Package Insert

Mentax® - TC (butenafine HCl cream) Cream, 1%

Rx Only

DESCRIPTION

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5 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

In provocative testing in 215 subjects, there was no evidence of allergic contact sensitization for either the cream or vehicle base for Mentax - TC Cream, 1%. In 26 subjects in a phototoxicity study and 31 subjects in a cumulative irritation study, there was no evidence of phototoxicity or cumulative irritation, respectively. Of 26 subjects in a photoallergy study, one subject had a response suggestive of photoallergy.

OVERDOSAGE

Overdosage of butenafine HCl in humans has not been reported to date.

DOSAGE AND ADMINISTRATION

Patients with tinea (pityriasis) versicolor should apply Mentax[®] - TC once daily for seven days.

Sufficient Mentax[®] - TC Cream should be applied to cover affected areas and immediately surrounding skin. If a patient shows no clinical improvement after the treatment period, the diagnosis and therapy should be reviewed.

HOW SUPPLIED

Mentax[®] - TC (butenafine HCl cream) Cream, 1%, is supplied in tubes in the following sizes:
15-gram tube (NDC 62794-161-02)

30-gram tube (NDC 62794-161-03)

STORE BETWEEN 5°C and 30°C (41° and 86°F).

Manufactured By: DPT Laboratories
San Antonio, TX 78215

Distributed By: BERTEK PHARMACEUTICALS INC.
Research Triangle Park, NC 27709-4149 PN516.01A

December 2001

6.2 Individual Study Reviews

6.2.1 NDA 21-408 (Study PDC010-046)

| | | |
|---|---|--|
| Name of Investigational Product: Mentax [®] -TC Cream 1% | Name of Active Ingredient: Butenafine Hydrochloride | Indication: Topical treatment of tinea versicolor due to the organism <i>Malassezia furfur</i> |
| Sponsor: Bertek Pharmaceuticals, Inc., 530 Davis Drive Durham, NC 27713 | | |
| Title of Study: A single center, open label study to determine the plasma levels of butenafine and primary metabolite, M-2, following multiple topical applications of butenafine HCl cream, 1%, to patients with severe tinea versicolor | | |
| Objectives: | | |

To determine the absorption of butenafine from Butenafine HCl cream, 1% (PD 010-C-009) in subjects with severe tinea versicolor, by determining the blood levels of butenafine and its major metabolite, M-2, which resulted following the daily topical administration of a dose of at least 6 gm/day, at a rate of 5 mg/cm² to at least 300 cm² of tinea versicolor lesions and the four inches of clear skin surrounding the margins of the lesions.

Phase: I

Principal Investigators; Study Centers:

Analytical Methods Laboratory:

Design of Study:

Open-label, randomized study in healthy men and women infected with tinea versicolor.

Study Schedule:

September 23, 2001 to September 30, 2001

Study Population Demographics:

Twelve (5M, 7F) subjects were enrolled and, completed the study. The age of the subjects ranged from 19-42 years old with a mean of 26.7 years old. Their weight ranged from 51-100 kg (mean = 70.6) and, the height ranged from 147.3 - 182.9 cm (mean = 164.6 cm). There were 4 Caucasians, 7 Hispanics and one "other".

Study Population Characteristics:

The severity of tinea versicolor was evaluated as a function of area of involvement, and degree of severity of three signs and symptoms of tinea versicolor infection (using a four point scale), i.e. erythema, scaling, and pruritus therefore in order to ensure that enrolled subjects have maximal tinea versicolor severity, the minimum total tinea versicolor lesion area required for eligibility for this study was set at 300 cm². The area of tinea versicolor involvement, total application area, and weight of drug applied was measured for each subject.

The area of tinea versicolor involvement and total application area are as follows:

Baseline Lesion Area (cm²): Ranged from 322-9787 (mean = 1910.67±2657.39) (~10% of BSA)

Treatment Area (cm²): Ranged from 2820-9787 (mean = 5000.33 ± 2221.92) (~ 30% of BSA)

Day 7 lesion Area (cm²): Ranged from 118-1503 (mean = 509.17 ± 412.74)

Above suggests there is a decrease of ~ 73% in lesion area when comparing day 1 and day 7 indicating some efficacy.

Treatment (s) Administered:

Butenafine HCl Cream 1% (PDC-010-C-009, Lot PEGF-2). This is the same formulation as that was used in the clinical studies (lot # is NEEC) and intended for marketing. This Lot PEGF-2 was also used in the phototoxicity study and the photoallergy study. Batch size was — for Lot #'s PEGF-2 and NEEC respectively.

Dose Selection:

The minimum lesion area was selected after careful consideration of information obtained from the clinical trials conducted in patients with tinea versicolor for this formulation and the previous Mentax formulation. The mean amount applied in all 4 studies was 4.2, 3.0, 3.1 and 3.2 g respectively. The amount of drug applied in this study ranged from 14.1- 48.9 grams (mean = 25± 11g) at a rate of ~ 5 mg/cm². (What is the usual dose for the proposed indication? Discussions with Dr. Brenda Carr, I was told this would vary a lot, maximum would be ~ 45% of BSA).

Dosing Regimen :

Daily topical application of at least 6g/day to the tinea versicolor lesions (~ 300 cm²) and the 4 inches of clear skin surrounding the margins of the lesions for seven consecutive days.

Mode of Administration:

Study drug product was applied by SFBCFM personnel to each subject early in the morning on study days 1 through 7. Subjects were instructed not to wash the areas to which the study drug was applied for 12 hours post-dosing. Subjects were dosed sequentially at irregular hours on day 7 to insure that subsequent blood samples would be collected precisely as scheduled following the last daily dose.

Criteria for Evaluation:

Pharmacokinetic Sampling and Handling: Pre-dose blood samples were taken prior to the first day (day 1) and last day (day 7) daily doses and a series of blood samples were taken during the 24 hours following the last daily dose. On day 7 blood samples (10 mL) were collected in heparinized glass tubes at the following times: 0.5, 1, 3, 6, 9, 12, 15, 18, 21 and 24 hours after study drug administration. Tubes were centrifuged at 2500 rpm for 15 minutes and then plasma transferred to separate screw-cap tube and frozen at -70°C or colder until analysis.

Analytical Methods: A reproducible (the between day precision did not exceed — of the coefficient of

Results

The comparison of the different washing procedures demonstrated that the amount of radiolabeled butenafine observed in the tape-strip, epidermis and dermis after performing the mild and strong detergent washes (Procedure B and C) was much lower (~ 45-95%) than that obtained with the dry wipe wash (procedure A). These results suggest that the mild and strong detergent washes may have extracted drug out of the skin. The deposition (single-tape strip, epidermis, dermis) and penetration (receptor) of ¹⁴C-butenafine was highest with Mentax plus cream 1% (PD-010-C-009) followed by Mentax plus cream, 1% butenafine devoid of PP-2 (PD333:099) and then Mentax cream, 1% butenafine (PD-010-C-003). The applicant stated that the deposition of butenafine observed in the total epidermis was statistically greater (p < 0.05, unpaired t-test) between PD-010-C-003 and PD-010-C-009 (14 (4.3)% and 20 (4.4) % respectively. The applicant stated that radiolabeled penetration from PD-010-C-003 at 6,12,18 and 24 hrs was statistically (p < 0.05, Student-Newman-Keuls and unpaired t-test) lower when compared to PD-010-C-009 and PD333:099. However this analysis was based on all cells dosed with a respective formulation, irrespective of washing technique (i.e. n=17-18). An evaluation of the penetration results with the dry washing technique only is consistent with the above in that the mean percent of applied dose that penetrated the dermatomed skin was highest for Mentax plus cream followed by Mentax plus cream devoid of PP2 and then Mentax cream.

The addition of PP-2 did not appear to affect the *in vitro* deposition or penetration of ¹⁴C-butenafine because there was no statistical difference (p > 0.05, Student-Newman-Keuls) in ¹⁴C deposition or penetration between the two formulations.

Conclusions

The *in vitro* percutaneous absorption of Mentax plus cream 1% was statistically higher than those of Mentax cream 1%. Also the addition of PP-2 in Mentax plus cream does not appear to influence the *in vitro* percutaneous absorption of radiolabeled butenafine.

In vitro disposition using the dry wipe washing technique

| Formulation | Percent of applied dose, mean (SD) n = 4 ≤ n ≤ 6 | | | | | | |
|--------------|--|-------------------|-----------|------------------|-----------|------------------------|------------|
| | Wipe | Single-Tape strip | Epidermis | *Total Epidermis | Dermis | Penetration (Receptor) | % Recovery |
| PD-010-C-003 | 96 (4.3) | 9.9 (4.2) | 3.6 (0.8) | 14 (4.3) | 1.9 (0.4) | 0.6 (0.1) | 113 (6.4) |
| PD-010-C-009 | 82 (10) | 14 (2.8) | 5.7 (2.1) | 20 (4.4) | 2.8 (1.0) | 1.3 (0.3) | 111 (4.6) |
| PD333:099 | 92 (3.0) | 12 (2.0) | 5.3 (0.5) | 17 (2.0) | 2.3 (0.5) | 0.9 (0.1) | 115 (2.8) |

*Total epidermis is the tape strip following wash plus remaining epidermis

Table 2:
In Vitro Penetration of (14C)-Butenafine from PD-010-C-003, PD-010-C-009** and PD333:099****
(values in percent of applied dose, mean ± SD, 17 ≤ n ≤ 18)

| Duration of Exposure (hr) | PD-010-C-003 | PD-010-C-009 | PD333:099 |
|---------------------------|--------------|--------------|-------------|
| 6 | 0.08 ± 0.02 | 0.12 ± 0.03 | 0.11 ± 0.03 |
| 12 | 0.21 ± 0.06 | 0.34 ± 0.10 | 0.30 ± 0.09 |
| 18 | 0.41 ± 0.12 | 0.68 ± 0.19 | 0.57 ± 0.17 |
| 24 | 0.68 ± 0.21 | 1.11 ± 0.30 | 0.96 ± 0.27 |

Penetration based on all cells dosed with a respective formulation, irrespective of washing procedure

* Penetration of radiolabeled butenafine from PD-010-C-003 was statistically (p < 0.05, Student-Newman-Keuls) lower than PD-010-C-009 and PD333:099

- * PD-010-C-003 (Mentax cream, 1% butenafine)
- ** PD-010-C-009 (Mentax Plus cream, 1% butenafine)
- *** PD333:099 (Mentax Plus cream, 1% butenafine devoid of PP-2)

6.2.3 NDA 21-408 (PD356:006)

| | | |
|--|---|--|
| Name of Investigational Product: Mentax [®] -TC Cream 1% | Name of Active Ingredient: Butenafine Hydrochloride | Indication: Topical treatment of tinea versicolor due to the organism <i>Malassezia furfur</i> |
| Sponsor: Bertek Pharmaceuticals, Inc., 530 Davis Drive Durham, NC 27713 | | |
| Title of Study: | | |

In Vitro Percutaneous Absorption of (¹⁴C)-Butenafine from Mentax Cream and Butenafine Solution Formulations using Human Skin

Objectives:

To determine the in vitro percutaneous absorption of (¹⁴C)-butenafine HCl from cream and solution formulations containing 1.2% butenafine HCl. This study also evaluated the effect of propylene glycol (PG) addition to solution on butenafine HCl percutaneous absorption. Lamisil solution was spiked with a tracer level of (¹⁴C)-butenafine HCl for evaluation of butenafine HCl percutaneous absorption from this commercial formulation.

Test Formulations:

1% butenafine HCl or 1% terbinafine HCl were spiked with ¹⁴C-butenafine HCl to achieve a radiolabel concentration of 1 μ Ci/dose. The final concentration of butenafine was 1.2% and 0.2 % in lamisil (PG = propylene glycol)

1. Mentax cream (formulation PD-010-C-003, Lot # NC C-1)
2. Mentax plus cream (formulation PD-010-C-009, Lot # NEEC-1)
3. PD353:047 solution
4. PD353:041 solution containing PG
5. PD353:047 solution containing PG
6. PD353:047 solution containing PG
7. Lamisil (terbinafine)solution (commercial, lot # 040A-6189)

Experimental:

The cream and solution formulations were spiked with (¹⁴C)-butenafine to achieve a radiolabel concentration of 1.0 μ Ci/3.2 mg dose (= 0.31 μ Ci/mg of formulation). The final concentration of butenafine was 1.2% in cream and solution formulations and 0.2% in Lamisil solution. The human dermatomed cadaver skin (obtained from the same donor) was mounted on Bronaugh flow-through diffusion cells. Approximately 3.2 mg of formulation was spread over a skin area of 0.64 cm² to achieve a level of 5 mg/cm². The flow rate of the receptor fluid, phosphate-buffered saline containing 0.01% sodium azide with 1.5% Oleth-20 was set at 1mL/hr at 37 °C. The receptor samples were collected at 6-hr intervals (i.e. 6, 12, 18 and 24 hrs) for a total of 24 hours. Following a 24-hour exposure test material was removed from the skin surface by wiping with two, dry cotton swabs (Wash procedure A). The residual formulation and the outer layers of the skin were removed from the epidermis by a single tape strip that was then dissolved in tetrahydrofuran (THF). The epidermis was then separated from the dermis and each component was dissolved in 2N KOH separately. Each diffusion cell cap was soaked in 95% EtOH for at least 3 hours and then wiped with one dry swab. For each cap, the EtOH wash and the corresponding swab were pooled.

Criteria for Evaluation:

All wipes, tape-strips, epidermis, dermis, receptor samples and cap wash were analyzed for radioactivity by liquid scintillation counting techniques using _____ for receptor and tissue samples and _____ for all other samples. A student Newman-Keuls test and an unpaired t-test were performed on butenafine levels in the single tape-strip, epidermis, dermis and receptor fluid. A difference between formulations was considered to be statistically significant when p < 0.050.

Results

_____ solution (containing no PG) and lamisil solution demonstrated statistically (p<0.05, Student-Newman-Keuls test) greater dermal deposition relative to cream formulations.

Varying the concentration of PG in _____ solution did not effect butenafine HCl deposition and penetration.

The only statistically significant difference (p<0.05) between Mentax cream and Mentax Plus cream was more butenafine in the single tape-strip from mentax cream. These results are different from Study PD339:18, in which Mentax Plus cream exhibited statistically (p<0.05) greater total epidermal deposition and skin penetration relative to Mentax cream.

Conclusions

The in vitro percutaneous absorption of Mentax cream 1% was statistically higher than that of Mentax Plus cream 1%, not consistent with previous findings. Lamisil appears to give higher deposition, however results not comparable due to differences in butenafine spiked concentrations compared to the other formulations (~6-fold difference).

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Table 1:
In Vitro Percutaneous Absorption of Butenafine from Mentax Cream and Butenafine Solution Formulations
 Values in Percent of Applied Dose, Mean \pm SD (% CV), n = 4 to 6

| Formulation | Single Tape-Strip | Epidermis | Total Epidermis | Dermis | Penetration | % Recovery |
|-------------------|---------------------------------------|--------------------------------------|---------------------------------------|---------------------------------------|--------------------------------------|--------------------------|
| Mentax Cream | 10.7 \pm 2.5 ^a (23.2) | 4.2 \pm 1.3 ^c (31.1) | 14.9 \pm 3.6 (24.3) | 3.0 \pm 0.7 (25.1) | 0.4 \pm 0.1 (24.5) | 100.3 \pm 4.1 (4.0) |
| Mentax Plus Cream | 8.0 \pm 1.4 (16.9) | 4.1 \pm 1.2 ^c (30.1) | 12.1 \pm 2.5 (20.6) | 3.3 \pm 0.8 (25.4) | 0.4 \pm 0.1 (18.9) | 97.1 \pm 8.6 (8.9) |
| Solution | 8.9 \pm 3.4 (37.7) | 16.1 \pm 7.0 (43.3) | 25.0 \pm 8.7 ^d (34.8) | 9.9 \pm 5.5 ^e (55.1) | 0.4 \pm 0.3 (66.3) | 97.2 \pm 6.2 (6.4) |
| Solution (PG) | 8.6 \pm 1.0 (11.3) | 14.9 \pm 4.1 (27.3) | 23.6 \pm 3.3 ^e (13.9) | 7.1 \pm 1.2 (16.3) | 0.2 \pm 0.1 (23.3) | 96.7 \pm 2.5 (2.6) |
| Solution (PG) | 6.2 \pm 1.4 (22.9) | 11.8 \pm 6.0 (50.4) | 18.0 \pm 6.6 (36.7) | 6.8 \pm 3.4 (50.9) | 0.4 \pm 0.3 (69.9) | 95.6 \pm 2.2 (2.3) |
| Solution (PG) | 7.6 \pm 1.9 (24.4) | 11.2 \pm 5.1 (45.6) | 18.8 \pm 5.3 (28.0) | 7.3 \pm 3.9 (53.9) | 0.5 \pm 0.4 (70.4) | 96.3 \pm 3.8 (3.9) |
| Lamisil Solution | 12.2 \pm 2.1 ^b (17.6) | 16.2 \pm 2.9 (18.0) | 28.3 \pm 4.9 ^f (17.4) | 13.8 \pm 7.5 ^g (54.3) | 0.8 \pm 0.2 ^h (19.3) | 96.2 \pm 3.9 (4.1) |

- a. Mentax Cream is statistically greater than Mentax Plus Cream (p = 0.040, unpaired t-test) and Solution (PG) (p < 0.050, Student-Newman-Keuls test)
- b. Lamisil Solution is statistically greater than Mentax Plus Cream, Solution (PG), and Solution (PG) (p < 0.050, Student-Newman-Keuls test)
- c. Cream Formulations are statistically less than Solution Formulations (p < 0.050, Student-Newman-Keuls test)
- d. Solution is statistically greater than Cream Formulations (p < 0.050, Student-Newman-Keuls test)
- e. Solution (PG) is statistically greater than Mentax Plus Cream (p < 0.050, Student-Newman-Keuls test)
- f. Lamisil Solution is statistically greater than Cream Formulations, Solution (PG) and Solution (PG) (p < 0.050, Student-Newman-Keuls test)
- g. Solution and Lamisil Solution demonstrate statistically greater dermal deposition relative to Cream Formulations (p < 0.050, Student-Newman-Keuls test)
- h. Lamisil Solution is statistically greater than Solution (PG) (p < 0.050, Student-Newman-Keuls test)

Table 6.1
Composition of Butenafine HCl Creams, 1%

| Ingredients | % w/w | |
|------------------------------|--------------|--------------|
| | PD 010-C-009 | PD 010-C-003 |
| Purified water USP | / | / |
| Propylene glycol dicaprylate | / | / |
| Propylene glycol | / | 0.00 |
| Glycerine USP | / | / |
| Cetyl alcohol USP | / | / |
| Glyceryl monostearate | / | / |
| White petrolatum USP | / | / |
| Stearic acid NF | / | / |
| Polyoxyethylene cetyl ether | / | / |
| Butenafine HCl | 1.00 | 1.00 |
| Polyolprepolymer-2 | / | 0.00 |
| Benzyl alcohol NF | / | / |
| Trolamine | / | 0.00 |
| Diethanolamine NF | 0.00 | / |
| Sodium benzoate NF | / | / |

Text Table 3.6.5
Safety Factors from Nonclinical Dermal Toxicity Studies with Butenafine HCl

| Species | Study Length | No-Effect Dose for Systemic Effects mg/kg | Safety* Factor | No-Effect Dose for Local Effects mg/kg | Safety* Factor |
|---------|--------------|---|----------------|--|----------------|
| Rat | 90 Days | 15 mg/kg | 4 | 15 mg/kg | 4 |
| Dog | 90 Days | 100 mg/kg | 28 | 25 mg/kg | 7 |
| Dog | 1 Year | 100 mg/kg | 28 | 25 mg/kg | 7 |

* Safety Factor = Nonclinical Dose (mg/kg)/Human Dose (3.6 mg/kg)

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6.3 OCPB Filing/Review Form

| Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form | | | | |
|---|----------------------------------|-----------------------------|-------------------------------|--------------------------|
| General Information About the Submission | | | | |
| | Information | | Information | |
| NDA Number | 21-408 | Brand Name | Mentax-TC cream | |
| OCPB Division (I, II, III) | III | Generic Name | Butenafine 1% | |
| Medical Division | HFD-540 | Drug Class | Antifungal | |
| OCPB Reviewer | Abi Adebowale | Indication(s) | Treatment of tinea versicolor | |
| OCPB Team Leader | Dennis Bashaw | Dosage Form | Cream | |
| IND Number | 60,471 | Dosing Regimen | Once daily for seven days | |
| Date of Submission | 17 December, 2001 | Route of Administration | Topical | |
| Estimated Due Date of OCPB Review | 25 th June, 2001 | Sponsor | Bertek Pharmaceuticals, Inc. | |
| PDUFA Due Date | 17 th , October, 2002 | Priority Classification | 3S | |
| Division Due Date | 26 th June, 2002 | | | |
| Clin. Pharm. and Biopharm. Information | | | | |
| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
| STUDY TYPE | | | | |
| Table of Contents present and sufficient to locate reports, tables, data, etc. | X | | | |
| Tabular Listing of All Human Studies | X | | | |
| HPK Summary | X | | | |
| Labeling | X | | | |
| Reference Bioanalytical and Analytical Methods | X | | | |
| I. Clinical Pharmacology | | | | |
| Mass balance: | | | | |
| Isozyme characterization: | | | | |
| Blood/plasma ratio: | | | | |
| Plasma protein binding: | | | | |
| Pharmacokinetics (e.g., Phase I) - | | | | |
| Healthy Volunteers- | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| Patients- | | | | |
| single dose: | | | | |
| multiple dose: | X | 1 | | |
| Dose proportionality - | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| Drug-drug interaction studies - | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |
| Subpopulation studies - | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| PD: | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| PK/PD: | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| Population Analyses - | | | | |
| Data rich: | | | | |

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| | | | | |
|--|---|---|--|--|
| Data sparse: | | | | |
| II. Biopharmaceutics | | | | |
| Absolute bioavailability: | | | | |
| Relative bioavailability - | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | | | | |
| Bioequivalence studies - | | | | |
| traditional design; single / multi dose: | | | | |
| replicate design; single / multi dose: | | | | |
| Food-drug interaction studies: | | | | |
| Dissolution: | | | | |
| In vitro percutaneous absorption studies | X | 2 | | |
| (IVIVC): | | | | |
| Bio-wavier request based on BCS | | | | |
| BCS class | | | | |
| III. Other CPB Studies | | | | |
| Genotype/phenotype studies: | | | | |
| Chronopharmacokinetics | | | | |
| Pediatric development plan | | | | |
| Literature References | | | | |
| Total Number of Studies | | 3 | | |
| Filability and QBR comments | | | | |
| | "X" if yes | Comments | | |
| Application filable ? | X | Reasons if the application <u>is not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one? | | |
| Comments sent to firm? | | Comments have been sent to firm (or attachment included). FDA letter date if applicable. | | |
| QBR questions (key issues to be considered) | What is the systemic exposure to butenafine under maximum use conditions (i.e. dose, duration and body surface area) in the target population following topical application of Mentax-TC cream? | | | |
| Other comments or information not included above | | | | |
| Primary reviewer Signature and Date | Abi Adebowale (06/13/02) | | | |
| Secondary reviewer Signature and Date | | | | |

CC: NDA 21-408, HFD-850 (P. Lee), HFD-860 (M. Mehta), HFD-540 (F. Cross), HFD-880 (D. Bashaw, J.Lazor, A. Selen).

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/s/

Abi Adebawale
7/3/02 01:24:05 PM
BIOPHARMACEUTICS

Dennis Bashaw
7/3/02 04:14:44 PM
BIOPHARMACEUTICS

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