CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-408

MEDICAL REVIEW(S)

Addendum to Medical Officer's Review of NDA 21-408 Date: October 10, 2002

1. The sponsor's request for a partial pediatric waiver for subjects of 11 years or less is acceptable since tinea versicolor is rarely seen in the pre-adolescent age group, and the drug is unlikely to be used in this population.
2. The wavelengths employed in the phototoxicity and photoallergenicity studies (UVB and UVA) were appropriate for the absorption spectrum of the drug substance. According to the sponsor, butenafine hydrochloride absorbs at — , and — nm (Volume 1.1 p. 115).
3. Subjects G303, G305 and G306 were confirmed to have received study drug as assigned by the randomization schedule (per review of "Randomization Schedule," Vol. 10, p. 3362 and Listing 7, "Drug Accountability," Vol. 10, p. 3478)

Brenda Carr, M.D.
Medical Officer/Dermatology

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/s/

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Medical Officer's Review of NDA 21-408

Submission date: December 14, 2001

Review completed date: July 15, 2002

Generic name: butenafine HCl cream 1%

Trade name: Mentax®-TC

Sponsor: Bertek Pharmaceuticals, Inc.

Pharmacologic Category: synthetic benzylamine antifungal

Proposed Indication: tinea versicolor

Dosage Form and Route of Administration: cream for topical administration

NDA Drug Classification: 3S

Important Related Drugs: Mentax® (butenafine HCl 1% cream)

Related Reviews: Biostatistics, Microbiology, Chemistry, Pharmacology/Toxicology

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Executive Summary

I. Recommendations

A. Recommendation on Approvability

From a clinical perspective, the new formulation of butenafine HCl cream, 1% is approvable for the treatment of tinea versicolor, once daily for seven days. In two randomized, double-blind, vehicle-controlled studies, Mentax®-TC was more effective than vehicle at Day 49 for the primary endpoint "Effective Treatment," and for the secondary endpoints, "Negative Mycology" and Complete Cure."[1] While application site reactions were reported in one of the two studies, as well as in the supportive safety data from the tinea pedis studies, the dermal safety studies did not appear to reveal any significant evidence for the Sponsor's drug to act as an irritant or contact sensitizer. In the risk-benefit analysis, Mentax®-TC appears to be acceptable for use in the treatment of tinea versicolor, once daily for seven days.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

There are no recommendations for phase 4 studies or risk management steps at this time.

I I. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The subject of this application is a new formulation of the topical antifungal cream, Mentax® (butenafine HCl cream 1%), proposed for the treatment of tinea versicolor once daily for seven days, under the trade name Mentax®-TC.[2] The new butenafine HCl cream 1% formulation differs from Mentax® primarily by the addition of polyolprepolymer-2, said to [redacted] The Sponsor makes no marketing claims for the presence of the polyolprepolymer-2.

The Sponsor conducted two trials in which the new formulation was evaluated in the treatment of tinea versicolor once daily for seven days, studies PDC 010-033 and PDC 010-036. All study subjects were ≥ 12 years of age. A total of 346 subjects was enrolled in the two trials, 229 subjects were randomized to butenafine treatment, and 117 were randomized to vehicle. A total of 337 subjects from the two studies was included in the safety population (223 randomized to butenafine treatment, and 114 to vehicle). The Sponsor also considered an additional 802

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[1] Effective Treatment = Negative Mycology + Total Signs and Symptom score ≤ 1 at Day 49, with score for scaling of zero
Negative Mycology = absence of hyphae in a KOH preparation of skin scrapings, i.e. no fungal forms seen or the presence of yeast cells (blastospores) only in the KOH
Complete Cure = Negative Mycology + Total Signs and Symptom score of zero at Day 49

[2] The "Mentax®" cream formulation was approved for Rx-to-OTC switch (NDA 21-307), and is now marketed under the proprietary name Lotrimin®Ultra™ (Schering-Plough HealthCare Products) for "athelete's foot," "jock itch," and "ringworm."

[3] Penederm Topicare Technical Manual

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subjects, who used the new formulation for tinea pedis, to be part of the safety database (a tinea pedis indication is not being sought in this application).

B. Efficacy

Studies PDC 010-033 and PDC 010-036 employed the same inclusion and exclusion criteria, treatment regimens, and primary efficacy variables. In both studies, primary efficacy was assessed at Day 49, and measured by "Effective Treatment."

The Sponsor defined "Effective Treatment" as Negative Mycology plus signs/symptom score ≤ 1. However, for purposes of the review, "Effective Treatment" was defined as Negative Mycology plus signs/symptom score ≤ 1, where the score for scaling must be zero. The latter definition is considered to be more clinically relevant, since the presence or absence of scaling is the clinical indicator of the status of the tinea versicolor (active and inactive, respectively). "Negative Mycology" was defined by the absence of hyphae on potassium hydroxide (KOH) smear, and the signs and symptom scored were scaling, erythema, and pruritus.

Efficacy was demonstrated for the primary endpoint "Effective Treatment," both as defined by the Agency (p= 0.0176), and as defined by the Sponsor (p=0.0065).

There are no known studies directly comparing the new formulation to other treatments for tinea versicolor, and existing studies have not shown that the new formulation offers any unique advantage over existing therapies.

C. Safety

For studies PDC 010-033 and PDC 010-036, the safety population was taken as a subset of the intent-to-treat population, and was defined as "all subjects who were dispensed study medication and who subsequently provided information either at a post-baseline visit or by another route such as telephone contact." In the combined studies, six subjects (3%) in the butenafine group, and three subjects (3%) in the vehicle group provided no post-baseline data and were excluded from the safety population. Thus, the safety population consisted of 223 subjects in the butenafine group [mean use over the treatment period of 23.9 gm (range 0 to 87.6 gm)] and 114 subjects in the vehicle group [mean use of 21.0 gm (range 0 to 79.5 gm)]. Most subjects in both treatment groups applied all seven doses of study drug.

Seven adverse events were considered to have been at least possibly related to study treatment, six of which were in the butenafine group. All but one of these seven adverse events, were application site reactions, and all but one of the seven adverse events were reported in study PDC 010-036. Five of six treatment-related adverse events in the butenafine group, occurred in study PDC 010-036, and all were application site reactions which ranged from mild to severe in severity. The remaining treatment-related adverse event from the butenafine group, and the only treatment-related adverse event, reported from study PDC 010-033, was a "taste disturbance," considered possibly related to treatment. Systemic safety was not assessed in the two trials; however, a pharmacokinetic study revealed low systemic absorption of butenafine.

For much of the non-clinical information, the Sponsor referenced the application for Mentax®, NDA 20-524. There is no marketing experience with the new formulation. However, pertaining to Mentax®, the Sponsor reports the incidence of side effects (pre- and post-approval) to range from 1.2% to 3.67%. Irritation, pruritus, and contact dermatitis have been the side effects most frequently reported. The Sponsor reports that none of the butenafine formulations

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marketed in foreign countries have been withdrawn or suspended. In the dermal safety studies, there did not appear to be any evidence for the study drug to act as an irritant, contact sensitizer, phototoxic agent or photoallergen.

The Sponsor also included combined safety information from two additional phase 3 trials, in which the new formulation was studied in the treatment of tinea pedis. In both of these tinea pedis trials, the study drug was applied twice daily for ten days, to all interdigital spaces, and the immediately surrounding skin of each affected foot. Because of the different indication and treatment site, tinea pedis efficacy data would not be considered applicable to the indication sought in this application; however, the safety data may be contributory.

The relevant safety population from the tinea pedis studies totals 397 in the butenafine group, and 405 in the vehicle group. Six (1.5%) subjects in the butenafine group reported a total of nine adverse events considered to be at least possibly related to treatment. Five (1.2%) subjects in the vehicle group reported a total of 11 adverse events considered to be at least possibly related to treatment. Systemic safety was assessed in the tinea pedis studies, and no clinically significant differences among treatment groups in the mean changes from pre- to post-treatment for any laboratory test were reported.

The tinea versicolor trials, PDC 010-033 and PDC 010-036, excluded subjects under the age of 12 years; however, this exclusion would not appear to significantly impact the safety profile of the drug, as the indication sought is not typically seen in the pre-adolescent population. Both trials also excluded pregnant and lactating women. While tinea versicolor can be seen in pregnancy and in nursing women, it is felt unlikely that a need for treatment would arise during these periods, since the condition is largely of cosmetic significance.

D. Dosing

Mentax® was approved for tinea verisicolor, once daily for 14 days, on June 7, 2001 (NDA 20-524). For the new formulation, the Sponsor proposes a treatment regimen for tinea versicolor of once daily for seven days.

The Sponsor did not conduct dose-ranging studies with the new formulation believing that previous animal and human experience with related butenafine HCl formulations provided the basis for use of the 1% concentration in the new formulation. Further, the Sponsor selected the once-daily, seven-day treatment regimen based on their clinical experience with Mentax® cream in the treatment of tinea versicolor. Based on their experience with Mentax®, the Sponsor hypothesized that the new formulation of butenafine HCl cream 1% would be effective with a shorter duration of treatment.

As dose-ranging studies were not conducted, it is unclear that the dosage proposed for the new formulation actually represents the optimal dosage for the new formulation.

E. Special Populations

The clinical trials were conducted in all geographic regions of the US, i.e. northern, southern, eastern, western regions. While various age groups, and multiple racial groups were included in the studies, the vast majority of study subjects were Caucasians 18 years and older. Pertaining to studies PDC 010-033 and PDC 010-036, the Sponsor states in the application that, "The studies were not powered to demonstrate statistically significant differences when results were stratified by age, gender, and race. Indeed, the numbers of subjects in many of the various categories were

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too few for meaningful statistical comparison." Thus, while subgroup analyses were performed for both studies, the Sponsor reasonably concluded that limited inferences could be drawn from them.

As tinea versicolor is rarely seen in the pre-adolescent age group, and the drug is unlikely to be used in this population, the Sponsor is seeking a partial pediatric waiver for patients younger than 12 years.

As discussed, studies PDC 010-033 and PDC 010-036 excluded pregnant and lactating women.

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Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Mentax®, butenafine HCl cream 1%, is a synthetic benzylamine antifungal. The Sponsor proposes a new formulation of Mentax® for the treatment of tinea versicolor, once daily for seven days, in subjects 12 years of age and older. The new formulation differs from Mentax®, by the addition of propylene glycol and polyolprepolymer-2 and by the addition of trolamine (triethanolamine) which replaces the diethanolamine. The propylene glycol while the polyolprepolymer-2 [4] The Sponsor is not making any marketing claims for the contribution of polyolprepolymer-2. As no efficacy is being attributed to the polyolprepolymer-2, it is considered an excipient. Trolamine is

The proposed name for the new formulation is Mentax®-TC, where "TC" stands for "topical cream," The Sponsor's second choice for the proprietary name is where is for In the course of its development, the new formulation has been referred to as butenafine HCl Optimized Cream. and PD-010-C-009.

B. State of Armamentarium for Indication

Tinea versicolor is a superificial fungal infection of the skin caused by *Malassezia furfur (Pityrosporum orbiculare)*. While the organism is part of the normal skin flora, in susceptible individuals it may give rise to the condition of tinea versicolor. Clinically, tinea versicolor is characterized by hyper- or hypopigmented, scaly patches generally on the trunk, and typically not extending beyond the neck, arms, and upper thighs. The condition is largely of cosmetic significance, but can sometimes be accompanied by pruritus.

While there is no treatment of choice for tinea versicolor, there are a number of effective antifungal therapies for this condition, some approved, but others anecdotal. Treatments include systemic agents and topical agents in a variety of formulations, e.g creams, solutions, shampoos. Treatment of the infection may not result in restoration of normal pigmentation to the affected sites. Normalization of pigment following successful therapy is variable. The condition is more likely to recur than not; however, the frequency of recurrences is variable, and it is not clear that frequency of recurrence is influenced by choice in treatment of the active infection. Factors which potentially influence the choice of therapy include the extent of involvement, patient convenience, and frequency of recurrence.

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[4] Penederm Topicare Technical Manual PP-2, p. 5

C. Important Milestones in Product Development

The regulatory history is somewhat complicated, and is presented below:

In a correspondence dated May 18, 2000 (serial 060), the Sponsor stated their intention to open a new IND with a new formulation of their drug, Mentax®, for an indication of tinea versicolor. In the same correspondence, the Sponsor requested an end-of-phase 2 (EP2) meeting for IND 42,762.

Review of IND 42,762 revealed that a pre-IND/EP2 meeting had been held on January 11, 1999 for Mentax®, for discussion of a new indication of tinea versicolor. (The Sponsor of the product at that time was Penederm, Inc.; it is unclear when Bertek assumed ownership). This new indication would be filed as a supplement to the Mentax® application, NDA 20-524. On June 7, 2001, Mentax® was approved for tinea versicolor under NDA 20-524. The treatment regimen approved was once daily for 14 days.

On June 5, 2000, the Agency received a new phase 3 protocol from the Sponsor, study PDC 010-036. This new submission was assigned the IND number 60,471. At the time of the submission of the protocol for study PDC 010-036, a study numbered PDC 010-033, had already been completed. Study PDC 010-033 had been conducted under IND 42,762, the IND discussed above.

The Sponsor had submitted the protocol for study PDC 010-033 to IND 42,762 as a phase 2, proof-of-concept study of the once daily use of the new formulation in the treatment of tinea versicolor. The original protocol called for enrollment of approximately 72 subjects; however, during the course of the study, the Sponsor amended the protocol to expand the planned number of study subjects from 72 to approximately 130. The amendment, dated November 16, 1999, stated the rationale for increasing enrollment was because the "Sponsor and investigators were initially conservative in estimating the number of tinea versicolor subjects eligible for enrollment due to the seasonal nature of the disease and the timing of the initiation of the study. The increase in number of subjects will allow an increase of statistical power from 50% to 80% to detect a 30% cure rate difference between active and vehicle groups." Additionally, because of the increased sample size, the Sponsor then considered that study PDC 010-033 qualified as a phase 3, pivotal trial. The original protocol for study PDC 010-033 did not pre-specify a statistical analysis plan for the efficacy endpoints; the statistical analysis plan was filed on February 10, 2000.

As discussed, the Sponsor had requested an EP2 meeting for IND 42,762 in the May 18, 2000 correspondence. According to the Sponsor, on June 21, 2000, they were advised by the Division, that since one phase 3 trial had already been completed (study PDC 010-033), it would be more appropriate to have their proposed EP2 questions answered as part of the review process of protocol PDC 010-036 (filed under the new IND 60,471).

On July 10, 2000, the Sponsor received notification that it was safe to proceed with study PDC 010-036, and that the protocol for the study was still under review. On July 20, 2000, the Sponsor was advised that the protocol remained under review. The Sponsor states that they never received clinical comments on the protocol for study PDC 010-036, and proceeded with the trial.

The Sponsor had a pre-NDA meeting for IND 60,471 on May 21, 2001. At the time of the preNDA meeting, trials PDC 010-033 and PDC 010-036 had both been completed. The Sponsor was given clinical advice which included:

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- It appeared that they had conducted an appropriate number of phase 3 studies required for NDA submission.
- There was no EP2 meeting for this formulation for this indication.
- The Agency had made no commitments for this formulation for this indication.
- Statistical plans not stated *a priori* are considered post hoc and may not meet the Agency's requirement for NDA approval.
- Since there was no control arm to isolate the contribution of polyolprepolymer-2 (PPP-2), there will likely be [redacted], if the application is approved.
- Percent involvement at baseline should be specified as an entry criterion, data collected and tabulated.
- Since the area of involvement might be inferred from the amount of drug applied, the amount of drug applied by each subject should be provided.
- Any new lesions occurring on or adjacent to the same anatomical location of prior treatment should be considered a treatment failure.
- The score for scaling should be 0 at the end of treatment, and at study endpoints "Effective Treatment" and "Complete Cure."
- KOH should be negative at the end of treatment and at each post-treatment assessment.

Also at the May 21, 2001 pre-NDA meeting, the statistical reviewer advised the Sponsor that the efficacy results for study PDC 010-033 would be considered post hoc and might not be acceptable for efficacy and safety claims to be made, since the statistical analysis plan had not been pre-specified. During the meeting, the Sponsor stated that the statistical plan had been finalized prior to unblinding the data. Additionally, in Vol.1, Sec. 3.4.3 of this application, the Sponsor states that the general principles of the statistical plan for study PDC 010-033 were finalized before the study was conducted, and were described in the statistical section of the protocol. The Sponsor also stated that the intent-to-treat, per protocol, and safety populations were defined in the protocol. The primary and secondary efficacy variables ("Effective Treatment," "Negative Mycology," Complete Cure, and mean change from baseline in Total Signs and Symptoms Score) were also defined in the protocol.

At the May 21, 2001 pre-NDA meeting, the Sponsor also expressed their intention to include safety data from two tinea pedis studies in the Integrated Safety Summary of the tinea versicolor application. They inquired whether it was acceptable to the Agency to combine the data from the tinea pedis studies, but keep it separate from the tinea versicolor data. The Agency's response was that the proposed format was acceptable.

Reviewer's comments: For purposes of this review, the advice given by the Agency at the pre-NDA meeting was interpreted as follows:

- *The occurrence of new lesions on or adjacent to the treatment areas was not considered a treatment failure.*
- *The score for scaling should be zero at the Day 49 assessment for study endpoints Effective Treatment and Complete Cure. Note: The scaling score of zero at Day 49, is captured in the analysis that the Sponsor terms "Effective Treatment post hoc."*
- *The KOH should be negative at the Day 49 assessment.*

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D. Other Relevant Information

Worldwide, the Sponsor currently markets two formulations of butenafine HCl 1% cream (if approved, the new formulation would make the third). Butenafine HCl 1% creams have been approved and marketed in Japan, South Korea, the United States (U.S.), Canada, Indonesia, the Republic of China, Israel and the Philippines. According to the Sponsor, the cream formulation marketed in the U.S. as Mentax®, has been marketed in Canada for tinea pedis since April 1997, under the trade name "Dr. Scholl's®Athlete's Foot Cream."

In Japan, a butenafine HCl cream 1% has been marketed as Mentax® by Kaken Pharmaceuticals, Inc. since 1992, for treatment of tinea pedis, tinea coproris, tinea cruris, and tinea versicolor.[5,6] The Mentax® formulation marketed in the U.S. differs from the Kaken formulation by inclusion of benzyl alcohol

Kaken Pharmaceuticals, Inc. has also marketed a butenafine HCl lotion 1% since 1992.

Based on information available to the Sponsor, butenafine HCl 1% cream has not been withdrawn or suspended from marketing in any country.

E. Important Issues with Pharmacologically Related Agents

List of IND's for Butenafine HCl

IND 42,762: Butenafine HCl Skin Formulations (topical)

IND 57,959: Mentax® (butenafine HCl cream) Cream 1% for the treatment of tinea versicolor

IND 60,471: Butenafine HCl Optimized Cream, 1% for the treatment of tinea versicolor (topical)

List of NDA's for Butenafine HCl

NDA 20-524: Mentax® Cream, 1% for the treatment of tinea pedis and tinea versicolor
NDA 20-663: Mentax® Cream 1% for the treatment of tinea corporis and tinea cruris
NDA 21-307: Butenafine HCl Cream 1% (Schering-Plough HealthCare Products Application) for OTC treatment of interdigital tinea pedis, tinea corporis and tinea cruris

Mentax® butenafine HCl 1% cream was approved for the topical treatment of interdigital tinea pedis, under NDA 20-524 (October 18, 1996) and for the topical treatment of tinea corporis and tinea cruris, under NDA 20-663 (December 31, 1996). On June 7, 2001, as an efficacy supplement to NDA 20-524, Mentax® was approved for tinea versicolor, for a treatment regimen of once daily for two weeks.

[5] In this review, "Mentax®" refers to the U.S. formulation, unless otherwise noted.
[6] is the manufacturer of the drug substance.

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The new formulation is proposed for the indication of tinea versicolor in a treatment regimen of once daily for seven days. In the clinical trials, the vehicle differed from the active formulation only by the increase in the volume of water to replace the 1% butenafine, and appeared to be identical in appearance to the active.

The Sponsor indicated at the pre-NDA meeting (May 21, 2001), that Mentax® was being reviewed for Rx-to-OTC switch. On December 7, 2001, the Rx-to-OTC switch was approved (NDA 21-307). Sponsorship had been transferred to Schering-Plough HealthCare Products, which now markets the Mentax® formulation over-the-counter, under the proprietary name "Lotrimin®Ultra™." Lotrimin®Ultra™ is marketed for tinea pedis, tinea cruris, and tinea corporis.

If the current application is approved, the Sponsor intends to [redacted] While Mentax® is indicated for tinea versicolor, tinea cruris, and tinea corporis (once daily for two weeks), and for interdigital tinea pedis (twice daily for seven days or once daily for four weeks), the new formulation would be marketed only for the indication of tinea versicolor (once daily for seven days). The new formulation would be marketed Rx under the proposed trade name Mentax®-TC. The Sponsor also reiterated an agreement made at the pre-NDA meeting, that [redacted]

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

The Sponsor states that all relevant nonclinical pharmacology and toxicology study reports on the drug substance, that were available at the time of submission of this NDA were previously submitted to NDA 20-524 (April 4, 1995), and cross references NDA 20-524 for those reports.

The clinical microbiology information submitted in the application is the same as that submitted in the approved NDA 20-524, Mentax®(butenafine HCl) Cream, 1%.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

The Sponsor conducted a single-center, open-label study (PDC 010-046) to determine the plasma levels of butenafine, and a primary metabolite, M-2, following multiple topical applications of the new formulation to the skin of patients with severe tinea versicolor. The objective of this study was to evaluate the systemic absorption of butenafine following the daily topical application of the new drug product, butenafine HCl cream 1% (PD-010-C-009) to subjects, with severe tinea versicolor treated once daily for seven days. Twelve healthy, normal men and women with severe tinea versicolor received seven daily topical applications of at least six grams butenafine HCl cream 1%, applied to a minimum of 300 cm^2 of tinea versicolor lesions, and the four inches of clear skin surrounding the margins of the lesions. Extent of butenafine absorption was assessed by determining the blood levels of butenafine and its major metabolite, M-2.

Low levels of butenafine were reported in all subjects, while M-2 levels were absent or negligible. Cmax was 4.13 ng/mL, while the Tmax was 12.29 hours. The Sponsor considers that

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these data corroborate other data presented in the nonclinical pharmacology section of this NDA, and are, therefore, suggestive of low absorption of butenafine.

The Sponsor states that detailed information on the pharmacokinetics of butenafine HCl in Mentax® were submitted in NDA 20-524, and are incorporated in the current application by reference.

Reviewer's comment: 1) While "severe" tinea versicolor was not defined, the treatment regimen was the same as that proposed in the current application, i.e. once daily for seven days. 2) These data are subject to biopharmaceutics review.

B. Pharmacodynamics

Butenafine HCl (butenafine) is a benzylamine antifungal agent with a reported mode of action similar to that of the allylamine class of antifungal drugs. Allylamine antifungal drugs may act by suppressing the biosynthesis of ergosterol, an essential lipid component of fungal cell membranes, by inhibiting squalene epoxidase. Depending on the concentration of the drug and the fungal species tested, the antifungal benzylamines and allylamines are reported to have fungistatic and fungicidal activity.

IV. Description of Clinical Data and Sources

A. Overall Data

The data reviewed were generated by clinical trials conducted by the Sponsor. Nine clinical trials have been conducted with the new formulation:

- Two studies in tinea versicolor, PDC 010-033 and PDC 010-036
- Two studies in tinea pedis, PDC 501-005 and PDC 501-006 (safety data submitted in this application;
- One cumulative irritation study, PDC 010-037
- One repeat insult patch test, PDC 010-038
- One phototoxicity study, PDC 010-047
- One photoallergy study, PDC 010-048
- One absorption study, PDC 010-046

All clinical trials were conducted in the United States. The trials conducted in support of this application are presented in tabular form on the following page.

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B. Tables Listing the Clinical Trials

Protocol #, Investigators, Location	*Completion Status (Starting Date)*	*Formulations**	*Study Design*	*Treatment Regimen*	*Number of Tinea Versicolor Subjects Entered for Each Treatment*	*Age Range (mean)*	*% Male/Female Black/White/ Other*
PDC 010-033 Tashjian Ling Rodriguez Stough Bruce	Complete 12/28/99 (9/3/99)	PD 010-C-009	Multicenter, double-blind, vehicle-controlled	Once daily For 7 days	Butenafine: 86 Vehicle: 43	12-65	51.9% Male 48.1% Female 11/87/31
PDC 010-036 Pariser Butterwick Whiting Horwitz Jarratt Jones Savin Shavin	Complete 11/20/00 (7/24/00)	PD 010-C-009	Multicenter, double blind, vehicle-controlled	Once daily For 7 days	Butenafine: 143 Vehicle: 74	12-65	53.9% Male 46.1% Female 17/178/22
PDC 010-037	Complete 6/22/00 (6/1/00)	PD 010-C-003 PD 010-C-009 PD 501-C-007	21-Day cumulative irritation	21 consecutive applications of test articles, under occlusion, for 24± hours	31 for all test articles and controls	18 or older	8 Male 23 Female
PDC 010-038	Complete 8/11/00 (6/26/00)	PD 010-C-003 PD 010-C-009 PD 501-C-007 PD 010-A-003 PD 010-A-004	Repeated insult patch test	Repetitive and continuous patch application to same site for approx. 3 weeks	215	18 or older	49 Male 166 Female
PDC 010-046	Complete 9/23/01 (9/30/01)	PD 010-C-009	Open-label	Once daily for 7 days	12	19-42 (26.7)	5 Male 7 Female 4 White 8 Other
PDC 010-047	Complete 10/26/01 (10/8/01)	PD 010-C-009 PD 501-C-007 PD 010-A-005 PD 010-A-004	Evaluation of phototoxicity in humans	Test patches in contact with skin for approx. 24 hours	26 All Treatments	18 - 65 years	7Male 19 Female All White
PDC 010-048	Complete 11/2/01 (9/19/01)	PD 010-C-009 PD 501-C-007 PD 010-A-004 PD 010-A-005	Evaluation of human photoallergy by repeated insult patch test	Six single applications contacting skin for 24 (* 2) hours over 3-wk. period; 2 week rest; challenge of duplicate application of each test article for 24 (±)2 hrs	28 All Treatments	20 - 64 (46.8)	3 Male 25 Female All White

*Formulations: PD 010-A-004 Butenafine Solution Vehicle
PD 010-A-005 Butenafine Solution 1%
PD 010-C-003 Butenafine HCl Cream 1% (Mentax®)
PD 010-C-004 Cream Vehicle for PD 010-C-003
PD 010-C-009 Butenatine HCl Cream 1% (with Mentax TC)
PD 501-C-007 Vehicle for Mentax TC .

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The Sponsor has completed two independent, multicenter, double-blind, parallel-group, vehicle-controlled phase 3 trials in the U.S., evaluating the safety and efficacy of the new formulation in the treatment of tinea pedis:

PDC 501-005: A Multicenter, Double-Blind, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of Butenafine HCl Cream/Betamethasone Dipropionate Cream the Treatment of Tinea Pedis"
PDC 501-006: A Multicenter, Double-Blind, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of Butenafine HCl Cream/Betamethasone Dipropionate Cream the Treatment of Tinea Pedis"

C. Postmarketing Experience

There is no marketing experience with the new formulation, and the Sponsor does not plan to conduct any postmarketing studies. However, pertaining to the Mentax® formulation marketed in the U.S., the Sponsor reports the incidence of side effects (pre- and post-approval) to range from 1.2% to 3.67%. Irritation, pruritus, and contact dermatitis have been the side effects most frequently reported. No additional information was provided as to the specific nature of the contact dermatitis, i.e. irritant or allergic.

D. Literature Review

The Sponsor frequently referenced NDA 20-524, particularly as pertains to the nonclinical pharmacology and toxicology, human pharmacokinetics, and clinical microbiology sections of this application. The Sponsor also referenced publications on the allylamine antifungals (1), butenafine hydrochloride (1), and tinea versicolor (2).

V. Clinical Review Methods

A. How the Review was Conducted

Each tinea versicolor trial was reviewed separately, and with the same emphasis. As stated, the Sponsor included safety data from two tinea pedis studies which employed the new formulation.

B. Overview of Materials Consulted in Review

IND 42,762 and IND 60,471 were reviewed. Additionally, the Medical Officers' reviews of NDA 20-524 and NDA 21-307 were consulted. The Sponsor submitted some sections of the application electronically.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

The case report forms submitted in the application were reviewed. Additional case report forms were requested from the Sponsor, including randomly selected ones from each investigational site. Additionally, to assess compliance, several patient diary cards were requested for review. However, in response to the request (Sponsor's Amendment 006, dated

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April 10, 2002), the Sponsor stated that, "The diary cards are not available, as they were subject aids that were not collected by the study sites."

Because of several similarities noted in the demographics of the study populations for studies PDC 010-031 (NDA 20-524) and study PDC 010-033 from the current application, a Division of Scientific Investigation's consult was initiated. Additionally, three investigators were common to both studies. In an Information Request, the Sponsor was requested to provide a list of subjects who participated in more than one of the pivotal trials for NDA 20-524 (trials PDC 010-031, and PDC 010-032), and NDA 21-408 (trials PDC 010-033 and PDC 010-036). In Amendment 006, the Sponsor stated that there were no duplicate participants in studies PDC 010-031 and PDC 010-033. However, there were 19 subjects who participated in study PDC 010-032 (NDA 20-524), and were subsequently enrolled in study PDC 010-036 (this application). On review of the list of subjects, the dates of the duplicates' participation in study PDC 010-032 did not preclude any of their enrollment in study PDC 010-036.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

The trials appear to have been conducted in accordance with accepted ethical standards. The investigators' Institutional Review Board approved the protocols and the informed consent forms. Written informed consent was obtained from study participants prior to the undertaking of study procedures.

E. Evaluation of Financial Disclosure

The Sponsor certified that they had not entered into any financial arrangement with the listed clinical investigators for studies PDC 010-033 and PDC 010-036 whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2 (a). The Sponsor further certified that none of the listed clinical investigators disclosed any proprietary interests in the product or a significant equity in the Sponsor as defined in 21 CFR 54.2 (b). Lastly, the Sponsor certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f). Thus, there do not appear to be any financial arrangements which might cast doubt on the findings.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

In the intent-to-treat (ITT) population, statistically significant differences were shown between active-treated and vehicle-treated subjects at Day 49, for the primary efficacy variable Effective Treatment, defined as Negative Mycology + Total Signs and Symptom score ≤ 1, with the score for scaling of zero. When this definition of Effective Treatment is applied, the magnitude of the treatment effective stated in the proposed label claims is lessened; however, the effect remains statistically significant.

Efficacy assessments consisted of clinical assessments of lesional skin for scoring of scaling, pruritus, and erythema, and scraping of lesional skin for potassium hydroxide preparations to assess for the presence of hyphae.

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B. General Approach to Review of the Efficacy of the Drug

The efficacy database was considered to be the ITT population, defined as all subjects with confirmed tinea versicolor who were dispensed study medication. For purposes of the review, efficacy was based on the proportion of subjects who had Effective Treatment at Day 49, where "Effective Treatment" was defined as Negative Mycology + Total Signs and Symptoms score ≤ 1, with the score for scaling being zero. This differed from the Sponsor's definition of Effective Treatment in that Total Signs and Symptoms score was to be ≤ 1, but the score for scaling did not have to be zero (additional definitions are discussed later in the review).

ITT Populations

Demographics	PDC 010-033		PDC 010-036		Combined	
	Butenafine (N=86)	Vehicle (N=43)	Butenafine (N=143)	Vehicle (N=74)	Butenafine (N=229)	Vehicle (N=117)
Age (years)						
12-17	5(6%)	4(9%)	10(7%)	4(5%)	15(7%)	8(7%)
18-30	29(34%)	16(37%)	67(47%)	28(38%)	96(42%)	44(38%)
31-64	52(61%)	22(51%)	65(46%)	40(54%)	117(51%)	62(53%)
≥65	0(0%)	1(2%)	1(1%)	2(3%)	1(0%)	3(3%)
Gender						
Male	46(54%)	21(49%)	77(54%)	40(54%)	123(54%)	61(52%)
Female	40(47%)	22(51%)	66(46%)	34(46%)	106(46%)	56(48%)
Race						
Caucasian	61(71%)	26(61%)	121(85%)	57(77%)	182(80%	83(71%)
Black	6(7%)	5(12%)	9(6%)	8(11%)	15(7%)	13(11%)
Hispanic	18(21%)	10(23%)	10(7%)	5(7%)	28(12%)	15(13%)
Other	1(1%)	2(5%)	3(2%)	4(5%)	4(2%)	6(5%)

Based on Table 8.2 (Vol. 13) and the Demographics Listings (Listing 1) in Vols. 10 and 11

Reviewer's comment: The review will consider only the ITT population in analysis of efficacy.

C. Detailed Review of Trials by Indication

Study #1: Protocol Number: PDC 010-033: "A Multicenter, Double-Blind, Vehicle Controlled Study to Evaluate the Treatment of Tinea Versicolor with Butenafine HCl Cream 1% for Seven Days"

Center/Investigator	Butenafine (N=86)	Vehicle (N=43)	Total # Enrolled (N=129)
G1 David Tashjian, M.D.	17(20%)	8(19%)	25 (19%)
G2 Mark Ling, M.D.	12(14%)	6(14%)	18 (14%)
G3 David Rodriguez, M.D.	18(21%)	9(21%)	27 (21%)
G4 Dow Stough, M.D.	21(24%)	11(26%)	32 (25%)
G5 Suzanne Bruce, M.D.	18(21%)	9(21%)	27 (21%)

Based on Table B.3.1.1, Vol. 13

First subject enrolled: September 3, 1999
Last subject completed: December 28, 1999
Amendment 1 to protocol issued November 16, 1999
Final protocol with Statistical Analysis Plan: February 10, 2000

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Study #2: Protocol Number: PDC 010-36: "A Multicenter, Double-Blind, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of Butenafine HCl Cream 1% in the Treatment of Tinea Versicolor"

Center/Investigator	Butenafine (N=143)	Vehicle (N=74)	Total # Enrolled (N=217)
B1 Robert J. Pariser, M.D.	16(11%)	8(7%)	24 (11%)
B2 Kimberly Butterwick, M.D.	12(8%)	7(6%)	19 (9%)
B3 David Whiting, M.D.	20(14%)	11(9%)	31 (14%)
B4 Stephen Horwitz, M.D.	10(7%)	5(4%)	15 (7%)
B5 Michael Jarratt, M.D.	18(13%)	9(8%)	27 (12%)
B6 Terry M. Jones, M.D.	22(15%)	12(10%)	34 (16%)
B7 Ronald Savin, M.D.	23(16%)	11(9%)	34 (16%)
B8 Joel Shavin, M.D.	22(15%)	11(9%)	33 (15%)

Based on Table B.3.1.1, Vol. 13

First subject enrolled: July 24, 2000
Last subject completed: November 20, 2000

The two trials were very similar in design and will therefore be discussed together. Differences will be noted in the text of the discussion. Both were multicenter, double-blind, randomized, two-treatment arm, parallel group trials, with stated objectives to compare the safety and efficacy of butenafine HCl cream 1% and its vehicle, applied topically, once daily for seven days, in the treatment of tinea versicolor. Inclusion and exclusion criteria were the same for both studies and are entirely presented in Appendix XI.

At the Day 1 baseline visit, subjects with a clinical diagnosis of tinea versicolor had their lesions scraped for potassium hydroxide (KOH) preparations using the reagent Chlorazol Black E Fungal Stain. Because *M. furfur* is part of the normal cutaneous flora, the yeast (blastospore) form can be observed on the KOH in the absence of disease. Therefore, the presence of yeast alone was insufficient to confirm the clinical diagnosis; confirmation of the diagnosis required the presence of hyphae (mycelial phase). The presence of hyphae defined a "KOH positive" result, while the absence of hyphae indicated a " KOH negative" result. Several lesions could be sampled to obtain a KOH positive, while this was not stated for KOH negative (i.e. multiple lesions being scraped to confirm a negative result).

Reviewer's comment: It is possible that there could have been bias in the selection of which lesion to scrape for the KOH testing at efficacy assessment. Since neither protocol specified that multiple lesions had to be KOH negative at the efficacy assessment, it is possible that a single, non-scaly lesion might have been selected for the KOH preparation. However, this potential for bias was negated by the Agency's requirement for a score of zero for scaling at efficacy assessment.

A total sign/symptoms score of ≥ 3 was required for study eligibility, according to the scale below. If a subject had several lesions of different severity scores, the lesion with the most severe score was recorded:

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Severity Scale for Sign/Symptoms (NOTE: 0= "absent" for all three parameters)

	Scaling	Erythema	Pruritus
1=mild	Powdery, seen only after scratching	Barely perceptible, pinkish	Occasional, but not bothersome
2=moderate	Powdery, seen without scratching	Distinctive pink, light red	Bothersome
3=severe	Marked, coarser (flaky)	Deep red	So bothersome it's thought of much of the time

KOH-positive subjects, who had the appropriate sign/symptom score (≥ 3), and who met all other entry criteria were enrolled into the study. Exclusion criteria included subjects who had used topical antifungals within 28 days or systemic antifungals within 60 days prior to Day 1. Also excluded were subjects who had been involved in an investigational drug study within 8 weeks prior to entry into this study or who had previously been enrolled in this study.

Reviewer's comment: Extent of disease was not specified at baseline (or any other time point in the study).

Enrolled subjects were subsequently examined under Wood's lamp to identify subclinical lesions of tinea versicolor. Subjects had been advised not to bathe for at least 12 hours prior to examination so as not to wash off the water soluble yellow fluorescing pigment. All lesions, both clinical and subclinical, were to have been documented on the most appropriate view of the baseline body diagram, where investigators were to draw in lesions which corresponded to the subject's lesions in location and relative size. Additionally, in study PDC 010-036, investigators were to sequentially number the lesions on the baseline diagram.

The completed baseline diagram was to serve as a reference to aid the investigator in assessing the baseline lesions when subjects presented for subsequent study visits. Additionally, a copy of the completed baseline diagram was given to the subject to aid in identifying all areas to be treated with study medication. In study PDC 010-036, a blank body diagram was also provided to subjects at the baseline visit onto which subjects were to record the location of any new lesion that arose during the seven-day treatment period, i.e. lesions that appeared after the baseline visit. In study PDC 010-033, subjects noted the date of appearance of new lesions, and the date on which treatment of new lesions was begun on their copy of the baseline diagram.

Subjects were instructed to treat all of the new lesions, in addition to the lesions identified at baseline. Study medication was to be applied once daily, and the treatment area was to include a minimum four-inch margin of clear skin area surrounding each tinea versicolor lesion. Depending on the extent of the tinea versicolor identified at baseline, subjects were dispensed one or two tubes of study medication (or more if the extent of disease warranted and after contacting the Sponsor). Subjects were to return at Day 8 for the first post-treatment assessment. Subsequent post-treatment assessments were at Day 28 and Day 49 (primary efficacy assessment and final visit).

At all post-treatment assessments (Days 8, 28, and 49), lesions identified at baseline were scraped for KOH and scored for signs/symptom. Scoring was again based on the worst lesion. The KOH results and signs/symptom scores for treatment-emergent lesions were considered separately from the baseline lesions. New lesions that appeared after the seven-day treatment

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period were recorded, but not scored in study PDC 010-033. In study PD010-036, lesions that appeared post-treatment were not recorded or scored.

Full compliance was defined as the application of seven doses; non-compliance was defined as fewer than three or more than seven doses. Compliance was assessed by:

- comparison of the weights of the medication tubes when issued pre-treatment, to their weight on return, post-treatment.
- review of subject diary cards, where the time and date of dosage applications were to have been recorded.

A treatment failure was considered to be:

- a subject who voluntarily withdrew from the study prior to completion stating lack of response.
- a subject who, in the opinion of the investigator, required alternative therapy prior to Day 49.

These subjects (treatment failures) were encouraged to complete the 49-day study period if there were no serious health concerns.

Efficacy endpoints:

Primary efficacy variable: proportion of subjects with Effective Treatment at Day 49/Week 7

Secondary efficacy variables (termed "Other variables of interest" in study PDC 010-036):

- proportion of subjects with Negative Mycology
- proportion of subjects with Complete Cure
- mean change from baseline in signs and symptom scores
- percent change from baseline in signs and symptom scores (measured only in study PDC 010-036)

At the preNDA meeting, the Sponsor was advised that the score for scaling should be zero at study endpoints "Effective Treatment" and "Complete Cure." Since scaling would be considered the most important clinical indicator of active tinea versicolor, its complete absence, as indicated by a score of zero, would be considered the most appropriate score at efficacy assessment. Therefore, for purposes of this review, the primary efficacy endpoint was defined as follows:

Effective Treatment (Agency): Negative Mycology + Total Signs and Symptoms score ≤ 1 at Day 49, where the score for scaling must be zero

The Agency's definition of the primary endpoint differed from that presented by the Sponsor:

Effective Treatment (Sponsor): Negative Mycology + Total Signs and Symptom score ≤ 1 at Day 49 (the signs/symptom score was termed "Effective Clinical Response" in study PDC 010-036)

The Sponsor's definitions of other efficacy measusres were acceptable and are presented below:

Negative Mycology: absence of hyphae in a KOH preparation of skin scrapings, i.e. no fungal

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forms seen or the presence of yeast cells (blastospores) only in the KOH

Complete Cure: Negative Mycology + Total Signs and Symptom score of zero at Day 49

The review will consider the primary endpoint of "Effective Treatment" as defined by the Agency, and the secondary endpoints of "Negative Mycology" and "Complete Cure." Efficacy assessments at Day 49 will be considered for all three endpoints.

RESULTS

Baseline Sign/Symptom Severity ITT Population (Modified Sponsor Table 8.3, Vol. 13)

	PDC 010-033		PDC 010-036		Combined -033 and -036		
	Butenafine (N=86)	Vehicle (N=43)	Butenafine (N= 143)	Vehicle (N=74)	Butenafine (N=229)	Vehicle (N=117)	p-value*
Mean Total Signs and Symptoms Score	4.90	5.00	4.45	4.35	4.62	4.59	0.8702
Erythema	1.73	1.49	1.50	1.51	1.59	1.50	0.2819
Scaling	1.84	1.84	1.75	1.82	1.78	1.83	0.4871
Pruritus	1.33	1.67	1.20	1.01	1.24	1.26	0.9060

Reference: ISE statistical Table B.2.
*p-value compares pooled butenafine versus pooled distributions; from ANOVA

In study PDC 010-033, subjects used an average of 3.8 gm of medication per day, enough to cover approximately 760cm^2 of BSA. In study PDC 010-036, subjects used an average of 2.9 gm of medication per day, enough to cover approximately 580cm^2 of BSA. For both studies, the Sponsor assumed the medication was applied in the amount of 5mg/cm^2.

Efficacy Results at Day 49 -ITT Population (Sponsor Table 8.4, Vol. 13)

	PDC 010-033			PDC 010-036			Combined		
Criterion	Butenafine	Vehicle	p- value*	Butenafine	Vehicle	p-value*	Butenafine	Vehicle	p-value*
Effective treatment (Agency)	37/86 (43%)	10/43 (23%)	0.0176	77/143 (54%)	25/74 (34%)	0.0033	114/229 (50%)	35/117 (30%)	0.0002
Effective treatment (Sponsor)	40/86 (47%)	10/43 (23%)	0.0065	83/143 (58%)	25/74 (34%)	0.0005	123/229 (54%)	35/117 (30%)	<.0001
Negative Mycology	44/86 (51%)	10/43 (23%)	0.0010	87/143 (61%)	25/74 (34%)	0.0001	131/229 (57%)	35/117 (30%)	<.0001
Complete cure	34/86 (40%)	8/43 (19%)	0.0110	74/143 (52%)	23/74 (31%)	0.0021	108/229 (47%)	31/117 (26%)	0.0001

*p-value from Cochran-Mantel-Haenszel test adjusted for centers

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Sponsor's Subgroup Analysis by Center ITT Population LOCF

Study PDC 010-033

Site/Investigator	Effective Treatment (Agency's defintion) p-value 0.0002		Effective Treatment (Sponsor's defintion) p< 0.0001		Negative Mycology p< 0.0001		Complete Cure p=0.0001	
	Butenafine	Vehicle	Butenafine	Vehicle	Butenafine	Vehicle	Butenafine	Vehicle
G1 Tashjian	11/17 (65%)	3/8 (38%)	11/17 (65%)	3/8 (38%)	11/17 (65%)	3/8 (38%)	9/17 (53%)	1/8 (13%)
G2 Ling	0/12 (0%)	2/6 (33%)	2/12 (17%)	2/6 (33%)	2/12 (17%)	2/6 (33%)	0/12 (0%)	2/6 (33%)
G3 Rodriguez	10/18 (56%)	3/9 (33%)	11/18 (61%)	3/9 (33%)	13/18 (72%)	3/9 (33%)	10/18 (56%)	3/9 (33%)
G4 Stough	14/21 (67%)	2/11 (18%)	14/21 (67%)	2/11 (18%)	16/21 (76%)	2/11 (18%)	13/21 (62%)	2/11 (18%)
G5 Bruce	2/18 (11%)	0/9 (0%)	2/18 (11%)	0/9 (0%)	2/18 (11%)	0/9 (0%)	2/18 (11%)	0/9 (0%)

Study PDC 010-036

Site/Investigator	Effective Treatment (Agency's defintion) p-value 0.0002		Effective Treatment (Sponsor's defintion) p< 0.0001		Negative Mycology p< 0.0001		Complete Cure p=0.0001	
	Butenafine	Vehicle	Butenafine	Vehicle	Butenafine	Vehicle	Butenafine	Vehicle
B1 Pariser	9/16 (56%)	3/8 (38%)	10/16 (63%)	3/8 (38%)	10/16(63 %)	3/8 (38%)	8/16 (50%)	3/8 (38%)
B2 Butterwick	2/12 (17%)	2/7 (29%)	3/12 (25%)	2/7 (29%)	3/12 (25%)	2/7 (29%)	2/12 (17%)	1/7 (14%)
B3 Whiting	4/20 (20%)	3/11 (27%)	7/20 (35%)	3/11 (27%)	8/20 (40%)	3/11(27 %)	4/20 (20%)	2/11 (18%)
B4 Horwitz	4/10 (40%)	1/5 (20%)	5/10 (50%)	1/5 (20%)	5/10 (50%)	1/5 (20%)	4/10 (40%)	1/5 (20%)
B5 Jarrat	12/18 (67%)	3/9 (33%)	12/18 (67%)	3/9 (33%)	13/18 (72%)	3/9 (33%)	11/18 (61%)	3/9 (33%)
B6 Jones	17/22 (77%)	7/12 (58%)	17/22 (77%)	7/12 (58%)	17/22 (77%)	7/12 (58%)	17/22 (77%)	7/12 (58%)
B7 Savin	10/23 (43%)	2/11 (18%)	10/23 (43%)	2/11 (18%)	11/23 (48%)	2/11 (18%)	9/23 (39%)	2/11 (18%)
B8 Shavin	19/22 (86%)	4/11 (36%)	19/22 (86%)	4/11 (36%)	20/22 (91%)	4/11 (36%)	19/22 (86%)	4/11 (36%)

Source for both tables: Table B 3.1.1, Vol. 13
All p-valules from Cochran-Mantel-Haenszel test adjusted for center

Reviewer's comment: Pertaining to study PDC 010-033, the Breslow-Day test was significant for the Agency's definition of Effective Treatment (p=0.0121) and for Complete Cure (p=0.0082). Pertaining to study PDC 010-036, the Breslow-Day test was not significant for any cure category.

D. Efficacy Conclusions

In the intent-to-treat population, statistically significant differences were shown between active-treated and vehicle-treated subjects at Day 49 for the primary efficacy variable Effective Treatment (defined as Negative Mycology + Total Signs and Symptom score ≤ 1, with the score for scaling =0), and for Negative Mycology, and Complete Cure. The results indicate that the new formulation of butenafine HCl cream, 1% applied once daily for seven days is

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effective in the treatment of tinea versicolor.

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

There were no particular safety concerns raised by any of the clinical trials.

B. Description of Patient Exposure

Considering both PDC 010-033 and PDC 010-036, a combined total of 229 subjects was randomized to butenafine use, and 117 subjects to vehicle use. These subjects constitute the ITT population, and are the population considered in the efficacy analysis. The safety population was a subset of the ITT population, and was defined by the Sponsor as "All subjects who were dispensed study medication and who subsequently provided information either at a post-baseline visit or by another route such as telephone contact." Based on this definition, six subjects (3%) were excluded from the butenafine group, and three subjects (3%) were excluded from the vehicle group. Thus, the Sponsor considered the safety population to consist of 223 subjects in the butenafine group and 114 subjects in the vehicle group. The subject groups were comparable between treatment regimens and across protocols.

In both pivotal studies, subjects were to apply study drug once daily for one week to all tinea versicolor lesions, and to a four-inch margin of skin beyond the lesional skin. Most subjects in both studies were reported to have applied all seven doses called for in the protocol (89% in study PDC 010-033, and 87% in study PDC 010-036). In the butenafine group, the mean usage over the course of the one-week treatment period, was 23.9 grams. In the vehicle group, usage over the treatment period averaged 21.0 grams. Usage ranged from 0 to 87.6 gm over the treatment period.

Extent of Exposure by Study (per Subject)

	Study 033		Study 036	
	Butenafine	Vehicle	Butenafine	Vehicle
Mean gm use/week	29.3	25.1	20.6	18.7
Mean gm use/day	4.2	3.6	2.9	2.7
Range (mean)	0 to 87.6 (22.4)		0.0 to 57.1 (17.5)	

Sources: Vol. 9, Sec. 12.1; Vol. 11. Sec. 12.1; Vol. 13. Sec. 8.5.3

Reviewer's comment: Neither protocol called for investigators to estimate the extent of body surface area involvement during the course of the studies. However, both protocols contained detailed instructions as to how investigators were to document the lesions on the subject body diagrams. The Sponsor submitted case report forms, including the body diagrams for subjects who developed new lesions, subjects who experienced application site reactions, for adverse events associated with study withdrawal, for serious adverse events, and for discontinuations. Review of the available body diagrams revealed variance in the investigators' approaches to documenting the extent of involvement on the body diagrams.

Safety was assessed by monitoring adverse events throughout the course of the study. The investigator was to attempt to establish a diagnosis, and describe adverse events by diagnosis

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(e.g., cold, seasonal allergies, etc. instead of runny nose).

Demographics

The Sponsor excluded nine subjects, who did not have post-baseline visits, from their safety population. In the butenafine group, six of 229 (3%) were excluded, while in the vehicle group three of 117 (3%) were excluded. As there were so few subjects excluded from the ITT population, the Sponsor reasonably considered the demographics of the safety population to be essentially the same as for the ITT group.

Adverse Events

Twenty-one (21) subjects (9.4%) of 223 subjects in the butenafine group reported a total of 25 adverse events of any causality, while 15 subjects (13%) of 114 subjects in the vehicle group reported a total of 21 adverse events. Clinical laboratory evaluations were not done in either of the two studies. Neither the difference between groups in the number of subjects with adverse events, nor the distribution of adverse events within body systems among groups were statistically significant.

One subject was withdrawn from the study prematurely because of an adverse event. This subject, B106, from study PDC 010-036, developed a contact dermatitis which the investigator considered to compromise the ability to conduct study evaluations. The subject had completed dosing "several" days prior to being discontinued. This adverse event was considered treatment-related.

A report of chest pain in study PDC 010-036 was the only serious adverse event reported (necessitated hospitalization). This adverse event was considered unrelated to study treatment.

Five subjects in the butenafine group reported a total of six adverse events characterized by the investigator as at least possibly related to treatment. All but one of the treatment-related adverse events were application site reactions: subject G119 in study PDC 010-033 reported a taste disturbance of mild severity that began on Day 4 and was one day in duration.

Treatment-Related Adverse Events

Subject	Treatment Group	Adverse Event	Severity	Onset (Duration)	Relationship
G119 (42y/oWF)	Butenafine	Taste disturbance	Mild	Day 4 (one day)	Possible
B106 (37y/oWF)	Butenafine	Contact dermatitis	Moderate	3 days post-treatment (duration of enrollment)	Possible
B120 (27y/oWF)	Butenafine	Pruritus	Moderate	Day 1 (through Day 7)	Possible
B204 (41y/oWF)	Butenafine	1.Pruritus 2.Warm skin	1.Mild 2.Mild	1.Day 1 (through Day 7) 2.?	1.Probable 2.Probable
B409 (16y/oHF)	Butenafine	Pruritus	Severe	Day 2 (one day)	Probable
B510 (40y/oWM)	Vehicle	Pruritus	Mild	Day 25 (duration of enrollment)	Possible

Sources: Vol. 13, Table 8.7 (Integrated Summary of Safety) and Vol. 13, Listing 1

The Adverse Event Summary by Body System and MedDRA Term is presented on the following page.

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Adverse Event Summary by Body System and MedDRA Term
All Adverse Events for Studies PDC 010-033 &-036
Sponsor's Safety Population (modified from Table B 3.1; Vol. 13)

Body System MedDRA Term	Butenafine (n=223)		Vehicle (n=114)		p-value [1]
	#AE	% w/AE	#AE	%w/AE	
Any AE	25	21 (9.4)	21	15 (13.2)	0.2928
Gastrointestinal disorders	2	2 (0.9)	2	2 (1.8)	0.4916
Abdominal pain NOS	1	1 (0.4)	0	0 (0.0)	
Abdominal pain upper	1	1 (0.4)	0	0 (0.0)	
Pancreatic disorder NOS	0	0 (0.0)	1	1 (0.9)	
Sore throat NOS	0	0 (0.0)	1	1 (0.9)	
General disorders and administration site conditions	3	2(0.9)	2	2 (1.8)	0.4916
Application site pruritus	2	2 (0.9)	0	0 (0.0)	
Application site reaction NOS	1	1 (0.4)	0	0 (0.0)	
Chest pain NEC	0	0 (0.0)	1	1 (0.9)	
Influenza like illness	0	0 (0.0)	1	1 (0.9)	
Infections and infestations	12	12 (5.4)	10	9 (7.9)	0.3664
Bladder infection NOS	0	0 (0.0)	1	1 (0.9)	
Gastroenteritis NOS	1	1 (0.4)	0	0 (0.0)	
Nasopharyngitis	3	3 (1.3)	0	0 (0.0)	
Pharyngitis	1	1 (0.4)	0	0 (0.0)	
Sinusitis	0	0 (0.0)	2	2 (1.8)	
Skin papilloma	1	1 (0.4)	0	0 (0.0)	
Tonsillitis NOS	1	1 (0.4)	0	0 (0.0)	
Upper respiratory tract infection NOS	2	2 (0.9)	2	2 (1.8)	
Urinary tract infection NOS	0	0 (0.0)	2	2 (1.8)	
Vaginal candidiasis	1	1 (0.4)	0	0 (0.0)	
Vaginal infection NOS	1	1 (0.4)	0	0 (0.0)	
Vaginitis bacterial NOS	1	1 (0.4)	0	0 (0.0)	
Injury and poisoning	1	1 (0.4)	0	0 (0.0)	0.4739
Back injury NOS	1	1 (0.4)	0	0 (0.0)	
Musculoskeletal, connective tissue and bone disorders	1	1 (0.4)	0	0 (0.0)	0.4739
Back pain	1	1 (0.4)	0	(0.0)	
Nervous system disorders	3	3 (1.3)	5	2 (1.8)	0.7688
Headache NOS	2	2 (0.9)	5	2 (1.8)	
Taste disturbance	1	1 (0.4)	0	0 (0.0)	
Renal and urinary disorders	1	1 (0.4)	0	0 (0.0)	0.4739
Calculus renal NOS	1	1 (0.4)	0	0 (0.0)	
Respiratory, thoracic and mediastinal disorders	0	0 (0.0)	1	1 (0.9)	0.1613
Nasal congestion	0	0 (0.0)	1	1 (0.9)	
Skin & subcutaneous tissue disorders	2	2 (0.9)	1	1 (0.9)	0.9854
Dermatitis contact	1	1 (0.4)	0	0 (0.0)	
Pruritus NOS	1	1 (0.4)	1	1 (0.9)	

[1] from Chi-squared test comparing number of patients with adverse events.
NEC-Not elsewhere classified, NOS-Not otherwise specified
For No. of adverse events, all adverse event occurrences, including multiple occurrences of the same adverse event, were counted.

Reviewer's comments: According to the Manual of Dermatologic Therapeutics (2002, Lippicott Williams & Wilkins), 1 gram of cream will cover an area of approximately 100 cm^2, i.e. 10 x 10cm (assuming a layer of 100μm in thickness). In the same reference, two grams of topical medication are the approximate amount required to cover the face. Given that the protocol specified application of study medication to a four-inch margin of skin surrounding each lesion,

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it is felt that even if only one lesion were considered, the treatment area would be approximately the size of an adult face. Therefore, to have been in compliance with the protocol, it is felt subjects would need to have used at least two grams of study medication per day. It is believed that this is the minimum amount of study drug that a subject could have used to treat even a single lesion and four-inch, perilesional margins. Considering both studies, 110 subjects used < 14 gm of study medication over the treatment period (73 were randomized to butenafine, 37 to vehicle). Examples of subjects whose reported usage over seven days was < 14 gm include:

Subject # (Treatment)*	*Reported usage over 7 days(gm)*	*Outcome°*
G125 (B)	*1.6*	*S*
G507 (V)	*2.5*	*F*
G521 (B)	*4.9*	*S*
B101 (B)	*0.4*	*S*
B105 (V)	*0.6*	*F*
B524 (B)	*1.9*	*S*
B812 (V)	*0.8*	*S*
B832 (V)	*0.1*	*S*

Sources: Drug Accountability Listings 7, Vol. 10 & 11
**B=butenafine; V=vehicle*
°S=treatment success; F=treatment failure

One of these 110 subjects (B713) was excluded from the safety population by the Sponsor per their definition of the safety population.

The safety population comprised of subjects who used at least14 grams of study medication over the treatment is tabulated below:

Safety Population (>14gm of study medication over the treatment period)

Demographics	PDC 010-033		PDC 010-036		Combined	
	Butenafine (N=61)	Vehicle (N=28)	Butenafine (N=90)	Vehicle (N=49)	Butenafine (N=151)	Vehicle (N=77)
Age (years)						
12-17	4(7%)	3(11%)	5(6%)	2(4%)	9(6%)	5(6%)
18 and older	57(93%)	25(89%)	85(94%)	47(96%)	142(94%)	72(94%)

Based on Tables B.1.1 and 8.2 (Vol. 13) and the Demographics Listings (Listing 1) in Vols. 10 and 11

Twenty-one of 151 subjects (14%) in the butenafine group reported a total of 25 adverse events AE of any causality. Fifteen of 77 subjects (19%) in the vehicle group reported a total of 21 adverse events of any causality.

Five subjects reported six treatment-related adverse events. With the exception of a report of taste disturbance, all treatment-related adverse events were application site reactions. Excluding subject B409 (above), three subjects in the butenafine group (2%) reported a total of four treatment-related adverse events. Three of the butenafine-related adverse events were application site reactions. Three subjects (2%) reported the four butenafine-related application site reactions. One subject in the vehicle group (1%) reported a treatment –related adverse events. Thus, when subjects who applied < 14 gm of study medication are excluded, the incidence of treatment-related adverse events remains low.

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Studies PDC 501-005 and PDC 501-006

In these two studies, the new formulation was evaluated in the treatment of tinea pedis. The new formulation of butenafine HCl cream 1% and its vehicle were two of the four comparator treatment arms in the tinea pedis studies (the other two treatment arms were butenafine HCl cream/betamethasone dipropionate cream combination and betamethasone dipropionate alone). The Sponsor considers data from the butenafine and vehicle arms of these studies to provide additional safety information which are applicable to the current submission. Thus, the Sponsor considers the total safety database for the new formulation to consist of 620 subjects: 223 subjects from the tinea versicolor studies, and 397 subjects from the tinea pedis studies.

Usage was twice a day for ten days to all interdigital spaces, and the immediate surrounding skin of the affected foot. The Sponsor reported that the procedure for identifying and evaluating adverse events in the tinea pedis studies was identical to the method employed in the tinea versicolor studies. Unlike the tinea versicolor studies, the tinea pedis studies included pre- and post-treatment laboratory testing.

The relevant safety population from studies PDC 501-005 and PDC 501-006 consists of a combined total of 397 subjects in the butenafine group and 405 in the vehicle group. The subject groups in the safety population appear to have been comparable between treatments and across protocols. Amount of drug applied ranged from 0.4 to 57.1 gm in the butenafine group and 0.5 to 52.8 gm in the vehicle group. In study PDC 501-005, the average amounts of study drug used were 17.78 gm butenafine, and 17.98 gm of vehicle; in study PDC 501-006, the average exposure was 15.53 gm of butenafine and 16.02 gm of vehicle (information provided in response to an Information Request from the Agency).

Eighty-nine (22.4%) of the 397 subjects in the Safety Population randomized to butenafine reported a total of 126 adverse events of any causality during their seven-week term of study enrollment. Eighty-eight (21.7%) of the 405 subjects randomized to vehicle reported a total of 134 adverse events of any causality. Neither the difference between groups in the number of subjects with adverse events, nor the distribution of adverse events within body systems was statistically significant, except that more subjects in the vehicle group experienced accidental injuries.

Six (1.5%) subjects in the butenafine group reported a total of nine adverse events considered to be at least possibly related to treatment. Five (1.2%) subjects in the vehicle group reported a total of 11 adverse events considered to be at least possibly related to treatment. Neither the difference between groups in the number of subjects with treatment-related adverse events, nor the distribution of adverse events within body systems was statistically significant. Treatment-related adverse events are tabulated on the following page.

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Sponsor's Table of Treatment –Related Adverse Events for Tinea Pedis Studies (PDC 501-005 &-006)*

Subject #	Treatment Group	Adverse Event	Severity	Relationship
0333	Butenafine	1.Hot feet sensation 2.Swollen feet	1.Moderate 2.Moderate	1.Possible 2.Possible
0706	Butenafine	Rash, left foot	Mild	Possible
E608	Butenafine	1.burning, left foot 2.itching, left foot	1.Severe 2.Severe	1.Possible 2.Possible
E0728	Butenafine	Tension	Mild	Possible
E0732	Butenafine	Ingrown toenail	Mild	Possible
E0738	Butenafine	1.Headache 2.Vomiting	1.Severe 2.Moderate	1.Possible
0103	Vehicle	1.Erythema 2.Pruritus 3.Pruritus	1.Severe 2.Severe 3.Mild	1.Possible 2.Possible 3.Possible
0713•	Vehicle	Rash on feet	Moderate	Possible
E0151	Vehicle	Decreased WBC	Mild	Possible
E0153	Vehicle	Decreased WBC	Mild	Possible
E0614•	Vehicle	1.Blistering on feet 2.Itching on feet 3.Redness on feet 4.Stinging on feet 5.Swelling of feet	1.Moderate 2.Moderate 3.Moderate 4.Moderate 5.Moderate	1.Probable 2.Probable 3.Probable 4.Probable 5.Probable

*Table 8.9 from *Integrated Summary* of Safety, Vol. 13; •Withdrew because of the adverse event(s)

Four additional subjects experienced four other adverse events occurred in the foot area and were categorized by the investigator as "not related" to treatment. All four of these adverse events were reported in the butenafine group. No alternate etiology was suggested for these events:

- mild itching of the feet that began three weeks post-treatment and lasted for three days.
- interdigital *Pseudomonas* infection of the right foot that began on treatment Day 6 and lasted for nine days. No additional therapy for the infection was given.
- edema of the left small toe that began on treatment Day 3 and lasted four days.
- redness on top of the foot and toes that began two days post-treatment and lasted for one week.

Three subjects in the Safety Population of studies PDC 501-005 and PDC 501-006 withdrew from the study prematurely due to an adverse event. One subject in the butenafine group withdrew because of two adverse events unrelated to study treatment: dizziness and tachycardia, both of moderate severity. The subject used three applications of study medication prior to withdrawing. Two subjects in the vehicle group withdrew because of adverse events which were considered treatment related: one subject reported five adverse events of moderate severity occurring on both treated feet: redness, swelling, itching, stinging, and blistering. The symptoms lasted for three days and led to the subject's withdrawal from the study. The Investigator considered the events probably related to treatment. The second subject in the vehicle group reported a red rash of moderate severity on the dorsum of both feet. The subject had tinea pedis on both feet and both were treated with study medication. The adverse event was considered by the Investigator as possibly related to treatment. The subject discontinued study medication on Day 5, and after a follow-up visit to monitor the status of the foot rash, the subject was withdrawn from the study.

Two serious adverse events were reported, both or which were considered unrelated to study treatment: one subject in the vehicle group was diagnosed with non-Hodgkins lymphoma; one subject in the butenafine group, was hospitalized for pneumonia.

There were no clinically significant differences among treatment groups in the mean changes from pre- to post-treatment for any laboratory test.

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Reviewer's comments:

While the new formulation was employed in the referenced tinea pedis studies, these data do not appear to be entirely applicable to the indication proposed in the application for the reasons which include:

- *The safety populations were defined differently. For the tinea pedis studies the safety population was comprised of all subjects who were dispensed study medication (Vol. 13, Table E.1.1), and it is thus unclear if all subjects actually had exposure to study medication.*
- *The treatment sites differ.*
- *The mean exposures to study drug were not comparable. Although in the tinea pedis studies medication was used twice as often and for a longer duration, the mean amounts of study drug are less (nearly half that used in study PDC 010-033).*

It is noted that the Sponsor recoded the adverse event data from COSTART, used in the conduct of the trials, to MedDRA used in the tinea versicolor trials. The Sponsor did not specify whether the recoding was done from the verbatim terms or from the COSTART terms.

C. Methods and Specific Findings of Safety Review

The design and summary of findings from the topical safety studies are presented below (table is continued on the following page):

Study/Subjects	Test articles	Methods	Findings/conclusions
PDC 010-037 Cumulative irritation study 31 subjects (23 female, 8 male)	Mentax cream 1% Mentax-TC cream 1% Mentax-TC cream Vehicle 0.9% sodium chloride (NaCl) irrigation Sodium laurel sulfate (SLS)	21 consecutive appliclations of test articles and controls under occlusion for 24±2 hrs; scored for irritation every 24 hrs, immediately prior to reapplication	- 1 subject reported all 3 AE* (of 9 total AE) considered related to test articles ("itching from tape" was "possibly" related to all test articles, "itching at patch sites" was "probably" related to all articles, and "burning at vehicle site was "probably" related to Mentax-TC cream Vehicle) - Mentax-TC cream 1% was significantly less irritating than SLS and less irritating than NaCl (not significant) - Mentax-TC cream vehicle was significantly less irritating than SLS and less irritating than NaCl and Mentax-TC cream (not significant)

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Study/Subjects	Test articles	Methods	Findings/conclusions
PDC 010-038 Repeat insult patch test 215 subjects (166 female, 49 male)	Mentax cream 1% Mentax-TC cream 1% Mentax-TC cream vehicle Butenafine solution 1% Butenafine solution 1% vehicle	Induction: Patches applied to same sites on Mondays (for 48 hrs), Wednesdays (48 hrs), Fridays (72 hrs) for 3 weeks Rest: No patches for approx. 2 weeks. Challenge: One 48-hr patch application of test articles to a naïve site	21 subjects reported 32 AE; 3 AE were considered "possibly" related to test articles (one subject reported "restricted breathing;" a second subject reported "soreness at cream vehicle site and "tingling/numbness" at the same site) Under the conditions of the study, there did not appear to be any evidence of contact sensitization to any of the test materials
PDC 010-047 Phototoxicity study 26 subjects (19 female, 7 male)	Butenafine HCl cream (PD-010-C-009)# 1% Butenafine HCl cream vehicle PD-501-C-007)• Butenafine HCl solution 1% Butenafine HCl solution 1% vehicle Distilled water	Duplicate applications of each test article on lower paraspinal area, applied neat under semi-occluded patches for 24 hrs. Day 2, some patches removed and sites irradiated with 16 Joules/cm^2 of UVA, then 0.5 MED UVB. Patches removed from non-irradiated sites after the UV dosing. All sites evaluated 24, 48, 72 hrs after UV irradiation.	No AE were observed or reported Under conditions of the study, no evidence of phototoxicity was elicited by exposure of the test sites to16 Joules/cm^2 of UVA and 0.5 MED UVB.
PDC 010-048 Photoallergy study 26 subjects (25 female, 1 male)	Butenafine HCl cream (PD-010-C-009)# 1% Butenafine HCl cream vehicle PD-501-C-007)• Butenafine HCl solution 1% Butenafine HCl solution 1% vehicle Distilled water	Induction: Test articles applied (neat,semi-occluded) to paraspinal regions, on Mondays & Thursdays, for 3 consecutive weeks (6 applications total). Removed after 24±2 hrs, and sites irradiated with UVB (2 x MED)/ UVA. Some sites evaluated 48 hrs after patch removal and irradiation, others 72 hrs after removal/irradiation. Rest: no patches or UVL for 2 weeks. Challenge: On the 1st day, duplicate patches of test articles to naïve sites on back. After 24 hrs, half of patches removed, and sites irradiated with 16 Joules/cm^2 of UVA and 0.5 MED UVB. Patches removed from non-irradiated sites (controls) after the UVB dosing. Test sites evaluated 1, 24, 48, 72 hrs following UVL exposures and removal of patches from non-irradiated sites.	No AE were observed or reported. Induction scores for irradiated, butenafine-treated sites exhibited primarily slight to mild erythema with occasional edema, peeling or hyperpigmentation. Challenge scores consisted primarily of none to slight erythema with occasional occurrence of mild erythema. Non-irradiated challenge sites exhibited "sporadic" slight erythema. Two subjects exhibited strong induction and challenge responses c/w photosensitization to the Sponsor's cream and solution, but because of the early emergence of induction scores, the subjects were considered to have pre-existing photosensitization. Sponsor concluded that under the conditions of the study, there was no evidence that the study cream or its vehicle induced photosensitization in any subjects. (Note: one subject treated with butenafine solution showed evidence of photosensitization.)

*Adverse events
code name for the study drug
• code name for the study drug vehicle

D. Adequacy of Safety Testing

There is a question as to the extent of exposure, because of the total amount of usage reported over the seven-day treatment period for a number of subjects in both studies. The possible

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explanations for the low usage would appear to include minimal extent of disease at baseline and non-compliance with the treatment regimen. Discounting these subjects from the safety review was felt to give a more relevant picture of exposure to the study drugs over the study period.

The appropriate topical safety studies were done, and an adequate number of subjects was enrolled in each of the studies. However, the number of subjects in the photoallergy study was barely adequate. Clinical laboratory tests were not done in the tinea versicolor studies. Laboratory tests from the tinea pedis studies, however, revealed no "clinically significant differences among treatment groups in the mean changes from pre- to post-treatment for any laboratory test."

E. Summary of Critical Safety Findings and Limitations of Data

VIII. Dosing, Regimen, and Administration Issues

Dose ranging studies were not done, thus it is unclear whether the dosage the Sponsor proposes actually represents the optimal dosage for the new product. It was the Sponsor's belief that previous animal and human experience with related butenafine HCl formulations provided the basis for use of the 1% concentration in the new formulation. The Sponsor selected the once-daily, seven-day treatment regimen based on their clinical experience with Mentax® cream in the treatment of tinea versicolor, which lead the Sponsor to hypothesize that the new formulation would be effective with a shorter duration of treatment.

There is no known potential for abuse, and the Sponsor reports no overdosage of butenafine HCl in humans to date.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation; Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The Sponsor's subgroup analyses suggest that the response to their drug was most pronounced in males, in subjects 31 to 64, and in Caucasians. However, pertaining to both tinea versicolor studies, the Sponsor states, "The studies were not powered to demonstrate statistically significant differences when results were stratified by age, gender, and race. Indeed, the numbers of subjects in many of the various categories were too few for meaningful statistical comparison" (Vol. 13, Sec. 8.4.4). Thus, while the various subgroup analyses were performed for studies PDC 010-033 and PDC 010-036, the reviewer would agree with the Sponsor that limited inferences could be drawn from these analyses.

B. Evaluation of Pediatric Program

The Sponsor is seeking a partial waiver for pediatric subjects 11 years or younger, because the new drug is not likely to be used in a substantial number of patients in that age group.

When both studies are considered, a combined total of 23 subjects 12 through 17 years of age was enrolled: 15 subjects were randomized to butenafine; eight were randomized to vehicle. None of these subjects experienced application site reactions or serious adverse events.

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While the pediatric database was limited, there appears to be no indication that pediatric subjects 12 years and older would be at particular risk for any adverse event from use of the Sponsor's drug.

C. Comments on Data Available or Needed in Other Populations

The Sponsor did not study their drug in immunocompromised subjects. There is no apparent need identified at this juncture for data in other populations, e.g. renal or hepatic compromised, or use in pregnancy.

X. Conclusions and Recommendations

A. Conclusions

The new formulation has been evaluated in several clinical trials, some of which were specifically intended to assess safety. In the risk-benefit analysis, Mentax-TC® appears to be acceptable for use in the treatment of tinea versicolor, once daily for seven days. In studies PDC 010-033 and PDC 010-036, Mentax®-TC was more effective than vehicle at Day 49 for the primary endpoint "Effective Treatment," and for the secondary endpoints, "Negative Mycology" and Complete Cure." While application site reactions were reported in study PDC 010-036 , as well as in the supportive safety data from the tinea pedis, the repeat insult patch test did not appear to reveal evidence of potential for the Sponsor's drug to cause contact sensitization. While systemic safety was not assessed in the pivotal trials, the pharmacokinetic study suggested low absorption of butenafine.

There has been substantial clinical use of the Sponsor's currently-marketed product, and no safety concerns have been identified to date.

B. Recommendations

It is recommended that Mentax®-TC is approvable for the treatment of tinea versicolor, once daily for seven days, subsequent to labeling revisions.

Brenda Carr, M.D.
Medical Officer/Dermatology

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

___ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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B. Inclusion and Exclusion Criteria

Inclusion Criteria

Potential subjects were eligible to enroll if they met the following inclusion criteria:

1. Male or female, and ≥ 12 years of age. Sexually active females of child-bearing potential were required to practice an acceptable form of birth control for the duration of their study participation.
2. In sufficient good health as to be reasonably expected to be able to complete the protocol, as confirmed by medical history and vital signs.
3. A clinical diagnosis of tinea versicolor confirmed by microscopy (KOH wet mount of skin scrapings positive for the presence of yeast and hyphae). The presence of yeast cells alone was not considered to be diagnostic for tinea versicolor.
4. A total severity score of 2 3 for clinical signs and symptoms of tinea versicolor (erythema, scaling, pruritus).
5. Provision of a signed informed consent form after having received full explanation of the nature of the study; in addition, written informed consent was required from parent or guardian if the individual was under the age of 18.

Exclusion Criteria

Potential subjects were not to be enrolled if they met any of the following exclusion criteria:

1. Radiation therapy or systemic therapy with cytostatic or immunosuppressive drugs within 30 days prior to the start of study medication (Day 1).
2. Use of topical antifungals (including medicated shampoos) within 28 days or systemic antifungals within 60 days prior to Day 1.
3. Known sensitivity to benzylamine or allylamine derivatives or to any of the formulation ingredients.
4. Pregnant or lactating (if female).
5. Presence of psoriasis, folliculitis, atopic or contact dermatitis, or any other skin disease that could interfere with the evaluation of the study results.
6. A history of alcoholism, drug abuse, psychosis, poor motivation, antagonistic personality, or emotional or intellectual problems that would likely make the individual unreliable for the study.
7. Involvement in an investigational drug study within 8 weeks prior to entry into this study or previous enrollment in this study.
8. Presence of concomitant skin or mucocutaneous fungal infections requiring active treatment.

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/s/

Brenda Carr
8/29/02 12:10:42 PM
MEDICAL OFFICER

Susan Walker
8/29/02 02:44:23 PM
MEDICAL OFFICER
Concur with Dr. Carr's review.

Jonathan Wilkin
10/10/02 05:58:37 PM
MEDICAL OFFICER
See Addendum to MOR dated 10/10/02

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