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APPROVAL PACKAGE FOR:

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

Medical Review(s)

Medical Officer's Review of NDA 20-524/SE1-005

1.1 NDA Submission number/type NDA 20-524/SE1-005

1.2 Applicant identification

Bertex Pharmaceuticals, Inc.
 Research & Development Division
 320 Lakeside Drive, Suite A
 Foster City, CA 94404

1.3 Submission/Review Dates

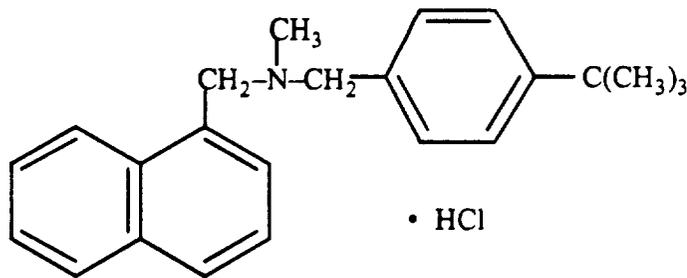
1.3.1	Date of submission (date of applicant's letter)	08-04-00
1.3.2	CDER stamp date	08-07-00
1.3.3	Date submission received by reviewer	08-11-00
1.3.4	Date review initiated	01-10-01
1.3.5	Date review completed	06-04-01

1.4 Drug Identification

1.4.1 Generic name butenafine HCl cream

1.4.2 Proposed trade name Mentax[®] (butenafine HCl cream) Cream, 1%1.4.3 Chemical name *N*-4-*tert*-butylbenzyl-*N*-methyl-1-naphthalenemethylamine hydrochloride

1.4.4 Chemical structure

1.4.5 Molecular formula: C₂₃H₂₇N•HCl

1.4.6 Molecular weight: 353.93

1.5 Pharmacological Category: Antifungal

1.6 Dosage form: Cream

1.7 Route of Administration: Topical

Addendum

The Sponsor is requesting a full waiver of the requirement to assess the safety and effectiveness of Mentax[®] (butenafine HCl cream) Cream, 1% for the claimed indication of tinea versicolor in children under 13 years of age because conducting the necessary studies to obtain data for this population is highly impractical due to the small numbers of such patients.

Reviewer comment:

Tinea versicolor is a disease entity that rarely occurs in pediatric patients below the age of 12 years; therefore, a full waiver of the requirement to assess the safety and effectiveness of Mentax[®] (butenafine HCl cream) Cream, 1% for treatment of tinea

versicolor in pediatric patients below the age of 12 years should be granted. Use of Mentax[®] Cream, 1%, in pediatric patients 12 to 16 years of age is supported by evidence from adequate and well-controlled studies of Mentax[®] Cream, 1%, in adults.

Brenda E. Vaughan, M.D. 6/4/01
Medical Reviewer

cc:

Archival NDA

HFD-540

HFD-540/Division Director/Wilkin 6/5/01

HFD-540/Dermatology Team Leader/Luke 6/4/01

HFD-540/Medical Reviewer/Vaughan

HFD-725/Biostatistics Team Leader/Alosh

HFD-725/Biostatistician/Freidlin

HFD-880/Biopharm/Adebowale

HFD-540/Pharm/Mainigi

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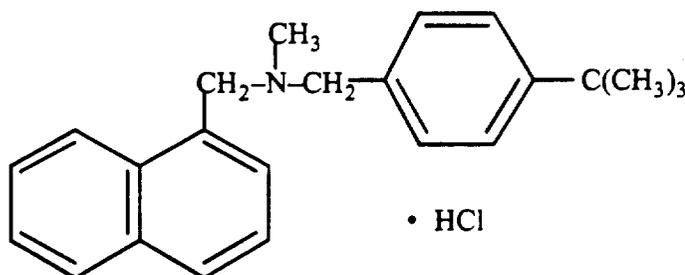
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1.3.5	Date review completed	05-11-01

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1.5 Pharmacological Category: Antifungal

1.6 Dosage form: Cream

1.7 Route of Administration: Topical

1.8 Proposed Indication & Usage section

Mentax[®] (butenafine HCl cream), 1%, is indicated for the topical treatment of the following dermatologic infections: tinea (pityriasis) versicolor due to *Malassezia furfur* (formerly *Pityrosporum orbiculare*), interdigital tinea pedis (athlete's foot), tinea corporis (ringworm) and tinea cruris (jock itch) due to *E. floccosum*, *T. mentagrophytes*, *T. rubrum*, and *T. tonsurans*. Butenafine HCl cream was not studied in immunocompromised patients. (See DOSAGE AND ADMINISTRATION).

1.9 Proposed Dosage & Administration section

Patients with tinea (pityriasis) versicolor should apply Mentax[®] once daily for two weeks.

In the treatment of interdigital tinea pedis, Mentax[®] should be applied twice daily for 7 days OR once daily for 4 weeks (NOTE: in separate clinical trials, the 7-day dosing regimen was less efficacious than the 4-week regimen; see CLINICAL STUDIES. While the clinical significance of this difference is unknown, these data should be carefully considered before selecting the dosage regimen for patients at risk for the development of bacterial cellulitis of the lower extremity associated with interdigital cracking/fissuring).

Patients with tinea corporis or tinea cruris should apply Mentax[®] once daily for two weeks.

Sufficient Mentax[®] Cream should be applied to cover affected areas and immediately surrounding skin of patients with tinea versicolor, interdigital tinea pedis, tinea corporis, and tinea cruris. If a patient shows no clinical improvement after the treatment period, the diagnosis should be reviewed.

1.10 Related Drugs

Table 1 Related NDAs

NDA Number	Drug Name	Indication	Date of Approval
NDA 20-524	Mentax (butenafine HCl cream) Cream, 1%	Topical treatment of the interdigital tinea pedis	10-18-96
NDA 20-633	Mentax (butenafine HCl cream) Cream, 1%	Topical treatment of the following dermal dermatophyte infections: tinea corporis and tinea cruris	12-31-96

Table 2 Related INDs

IND Number	Drug Name	Indication	Date of Submission
IND			

Related Reviews:

Biopharm Review dated: 02-23-01
 Chemistry Review dated: 01-23-01
 Pharm/Tox Review dated: 09-19-00

Microbiology Review dated: 11-08-00
 Statistical Review dated: 04-30-01

1.11.1 NDA Volumes Reviewed

This review is based on the following volumes: 18.1 - 18.8, and 18.15.

1.11.1 Other Documents Reviewed

<u>Document Identification</u>	<u>Source</u>	<u>Date Received</u>
IND	Sponsor	12-04-00

1.11.2 Amendments with Dates

<u>Document Identification</u>	<u>Date Received</u>
NDA 20-524 NC	09-11-00
NDA 20-524 BL	11-03-00
NDA 20-524 BS	11-07-00
NDA 20-524 Y	12-04-00
NDA 20-524 BM	04-09-01
NDA 20-524 BM	04-25-01
NDA 20-524 BZ	05-09-01
NDA 20-524 (Vol. 1.22)	

1.12 Regulatory Background

On August 7, 2000, Bertex Pharmaceuticals Inc. (formally Penederm, Inc.) submitted New Drug Application 20-524, Supplement 005. The application proposes the use of Mentax® (butenafine HCl cream) Cream, 1% in treatment of patients with tinea versicolor. A Pre-IND/End-of Phase 2 (EP2) Meeting was held on January 11, 1999 and a Pre-sNDA Teleconference was held on April 17, 2000 between the Sponsor and the Division. A Biostatistics teleconference discussion as a follow-up to the sNDA Meeting was held on July 10, 2000. The Sponsor was advised at the Pre-IND/EP2 Meeting that microbiological evaluation of a target lesion is not acceptable.

According to the Sponsor there were no amendments to the protocols; however, according to the sponsor (Vol. 2.15, pg. 2-115) several changes were made to the analyses stated in the protocol. These protocol changes included the following: the extent of disease at baseline was never collected therefore an assessment was not performed, new lesions were included among "All Lesions" analyses, and separate analysis not was performed for "New Lesions".

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3 Chemistry/Manufacturing Controls (See Chemistry Review)

The formulation (PD 010-C-003) used in the Phase 3 clinical trials submitted in this application, is unchanged from the formulation approved in NDA 20-524; therefore, no new chemistry, manufacturing or controls information is being submitted. Mentax (PD-010-C-003, lot number: NCC) and vehicle (PD-010-C-004, lot number: NCB) were used.

4 Animal Pharmacology/Toxicology (See Pharm/Tox Review)

No new nonclinical pharmacology or toxicology information is being submitted.

5 Microbiology (See Microbiology Review)

No new clinical microbiology information is being submitted.

6 Human Pharmacokinetics/Pharmacodynamics (See Clinical Pharmacology/Biopharmaceutics Review)

No new clinical human pharmacokinetics or bioavailability information is being submitted. No changes are being made to the human pharmacokinetics or bioavailability information in approved NDA 20-524.

7 Human Clinical Experience**7.1 Foreign Experience**

The identical 1 % cream formulation as approved in NDA 20-524, has been marketed in Canada since April 1997 under the name Dr. Scholl's® Athlete's Foot Cream. An almost identical 1 % formulation () has been marketed in Japan for tinea pedis, tinea corporis, tinea cruris, and tinea versicolor since 1992 under the trade name Mentax®. Foreign marketing history for butenafine HCL cream, 1% is listed in Table 3 that follows:

Table 3 (Sponsor's Table 1, Attachment 1, Foreign Marketing History, Revised Sept. 8, 2000, Submission SE1-005):

Foreign Marketing History of 1% Topical Butenafine HCL Products

Country	Approval Date	Marketing Date	Trade Name (Company)	(Dosage Form) Indication
Japan	Jan. 21, 1992	April 1992	Mentax (Kaken)	(Cream & Lotion) Tinea pedis Tinea cruris
			Volley (Hisamitu)	Tinea corporis Tinea Versicolor
South Korea	Jan. 17, 1994	Mar. 1995	Mentax (Yungjin)	(Cream & Lotion) Tinea pedis Tinea cruris Tinea corporis Tinea Versicolor
	July 6, 1996			July 1997
Canada	Apr. 15, 1997	Sept. 1997	Dr. Scholl's (Schering-Plough Healthcare Products)	(Cream) Tinea pedis

Indonesia			Dermax (Pt.Kalbe)	(Cream) Tinea pedis Tinea Manus Tinea cruris Tinea corporis Tinea Versicolor
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7.2 Post-Marketing Experience

A Foreign marketing update, submission SE1-005 (NC), was received by the Agency on 09-11-00. According to the Sponsor, since approval of Mentax in Japan, no measures such as change of approved items (effect and indication, administration and dosage, formulation), discontinuation or restriction of manufacture and marketing, discontinuation of clinical trials, or recall of the products have been taken for safety reason by regulatory or Marketing Authorization Holder (MAH). MAH is Kaken Pharmaceutical Company Limited in Japan.

8 Clinical Studies

8.1 Introduction

Tinea (pityriasis) versicolor is a superficial, chronically recurring infection of the glabrous skin caused by *Pityrosporum orbiculare* (*Malassezia furfur*). This commensal organism is part of the normal skin flora. In susceptible individuals the condition is often recurrent and may give rise to hyperpigmented and/or hypopigmented patches most commonly on the trunk and upper arms. The most common areas of involvement are the upper back, upper chest, shoulders and upper arms. Initially lesions are discrete, scaly macules that sometimes coalesce into large patches. Treatment of the infection may not immediately result in restoration of pigment to the affected sites. Normalization of pigment following successful therapy is variable and may take months, depending on individual skin type and sun exposure. The rate of recurrence is variable.

Mentax® (butenafine HCl cream) Cream, 1% (Mentax) is a cream formulation with a 1% concentration of butenafine hydrochloride (butenafine), a benzylamine derivative with a chemical structure and mode of action similar to that of the allylamine class of antifungal drugs. Mentax is marketed in the United States and is indicated for the treatment of tinea pedis, tinea corporis and tinea cruris. Butenafine hydrochloride 1% in cream and lotion formulas has been marketed in Japan since 1992 for the treatment of tinea infections (pedis, corporis, cruris and versicolor).

Two clinical trials were conducted by the Sponsor to support this efficacy supplement to NDA 20-524 for use of Mentax® (butenafine HCl cream) Cream, 1% for treatment of tinea (pityriasis) versicolor. PDC 010-031 and PDC 010-032 were two identically conducted multicenter, randomized, double blind, parallel group, vehicle controlled Phase 3 trials conducted in by the sponsor in the US. Two open-labeled trials (Kaken G-4 and Kaken G-5) and one active comparator trial conducted by Kaken Pharmaceuticals in Japan have previously been submitted to NDA 20-524.

8.2 Indication #1 Treatment of Tinea (Pityriasis) Versicolor

The study is to compare the safety and efficacy of Mentax (butenafine HCl cream) Cream, 1% versus its vehicle formulation when used topically once daily for two weeks to treat tinea versicolor.

8.2.1 Reviewer's Trial #1 Sponsor's Protocol PDC 010-031

(Study Dates: April 21, 1999 to October 8, 1999)

Title: "A Multicenter, Double-Blind, Vehicle-Controlled Study To Evaluate The Safety And Efficacy Of Mentax® (Butenafine Hcl) Cream 1% In The Treatment Of Tinea Versicolor"

8.2.1.1 Objective Rationale

The objective of this study was to compare the safety and efficacy of Mentax (butenafine HCl cream) Cream, 1% versus its vehicle formulation when used topically once daily for two weeks to treat tinea versicolor.

8.2.1.2 Design

This was a multicenter, double blind, randomized, two-treatment-arm, parallel group study.

8.2.1.3 Protocol Overview**Diagnosis & Significant Inclusion/Exclusion Criteria**

Subjects were eligible if male or female, at least twelve years of age. Females of child-bearing potential must have been willing to practice an acceptable form of birth control for the duration of their study participation. A clinical diagnosis of tinea versicolor confirmed by microscopy (KOH wet mount of skin scrapings positive for the presence of hyphae; yeast cells may or may not also have been present) was required. (Note: It was recognized that subjects evaluated in this study would be most likely to have yeast forms present along with hyphae. This criterion was worded to emphasize that the presence of yeast forms alone would not be sufficient, and the presence of the pathogenic hyphal form was required, to confirm the diagnosis of tinea versicolor). Total severity score ≥ 3 for clinical signs and symptoms of tinea versicolor (erythema, scaling, pruritus) was needed.

Reviewer's comments:

- 1. Both yeast cells and hypae of M. furfur should be present for the characteristic "spaghetti and meatballs" appearance to diagnose tinea versicolor with use of microscopy alone.*
- 2. Percent involvement at baseline involvement should be specified as an entry criterion. According to the Sponsor, extent of disease at baseline analysis was planned for this study; however, these data were never collected and this covariate was not used in any analysis. After review of a small subset of Baseline Body Diagrams, it was noted that some patients had very limited disease at baseline. For example, out of six Baseline Body Diagrams examined for other reasons, 5 of 6 (e.g., Subjects T104, T116, T407, T416, and T529) subjects appeared to have limited disease.*

Significant exclusion criteria were known sensitivity to allylamine derivatives or to any of the formulation ingredients and pregnant or lactating females. Also excluded were

patients who received radiation therapy or systemic therapy with cytostatic or immunosuppressive drugs within 30 days prior to the start of study medication (Day 1), or used topical antifungals (including medicated shampoos) within 28 days or systemic antifungals within 60 days prior to Day 1.

Concomitant Medication

Subjects were queried at each visit regarding use of any concomitant medications and this information was recorded on the case report form. Application of any topical product other than the study treatment to the affected area was to be avoided during the treatment and follow-up phases. Use of systemic cytostatic or immunosuppressive drugs or topical or systemic antifungals during the treatment and follow-up phases of the study was proscribed.

Investigational Drug Product

Mentax and its vehicle formulation were supplied in 30-gram tubes with identical packaging. One lot of each was used throughout the study: Mentax (PD-010-C-003, lot number: NCC), Vehicle (PD-010-C-004, lot number: NCB).

Method of Randomization/Stratification

Subjects were randomly assigned to one of two treatment arms: Mentax or the vehicle control formulation. Treatments were allocated in blocks of three with a 2:1 ratio in favor of active treatment. Randomization was stratified by site and randomization codes were generated for each site.

Study Procedures

Subjects were evaluated clinically for the presence and severity of signs and symptoms of tinea versicolor and mycologically for the presence of the pathogenic form of *Malassezia furfur*. Subjects were examined by the investigator at Day 1, Day 15 (Week 2), Day 28 (Week 4) and Day 56 (Week 8) for signs and symptoms of tinea versicolor. At each visit for each subject the following were performed:

- thorough examination of trunk, face, neck and extremities, guided by a Wood's lamp, as an aid in identifying these sub-clinical lesions to identify lesions
- microscopic evaluation of skin scrapings in KOH to detect presence of hyphae
- clinical assessment and scoring of signs and symptoms

A summary study schedule follows:

Table 4 (Sponsor's Table of Procedures, Vol. 2.15, pg. 2-049): Study Schedule

Procedure	Baseline			
	Day 1	Day 15	Day 28	Day 56*
Informed consent	X			
Inclusion/Exclusion criteria check	X			
Concomitant medication check	X	X	X	X
Rapid urine pregnancy test	X			
Wood's lamp exam	X	X	X	X
Clinical assessments including signs and symptoms scoring	X	X	X	X
KOH	X	X	X	X
Complete medical history	X			
Brief physical exam	X			
Complete baseline lesion diagram	X			

Dispense study medication	X			
Dispense subject instructions including lesion diagram and diary	X			
Adverse event query		X	X	X
Collect study medication and diary		X		
Compliance check		X		
Collect new lesion body diagram		X		
Subject discharged				X

^a or early termination

Treatments Administered

Subjects were treated with Mentax or its vehicle formulation once daily for 14 days during the study. Study medication was to be rubbed onto all identified lesions and onto at least four inches of skin beyond the affected skin area. The amount of study treatment to be applied depended on the extent of affected skin for each subject. At baseline, the areas affected by tinea versicolor were identified by the investigator and recorded on a Baseline Body Diagram. The investigator instructed each subject to apply sufficient study medication to each affected area, using enough cream to cover the area identified on the diagram, as well as all skin within four inches of the affected area.

Reviewer comment: *The lesions of tinea versicolor are often widespread (e.g., multiple lesions involving the trunk and/or proximal upper extremities). An anatomical approach to therapy is more clinically meaningful and consistent with the Wood's lamp directed search for sub-clinical lesion to demonstrate efficacy.*

Timing of Doses for Each Subject

Subjects were instructed to apply the study medication once daily after bathing from study Day 1 to Day 14. They were instructed not to bathe the affected skin areas for at least 12 hours prior to a study visit, as this would interfere with the Wood's Lamp diagnosis. They were instructed to continue applying the study medication for the full 14 days, even if the tinea versicolor condition appeared to be healed.

Methods of Assessing Treatment Compliance

Compliance was measured by number of doses recorded in Subject Diary Card and difference in tube weight between the day the tube was dispensed and the day it was returned. Full compliance was defined as the application of 14 doses; non-compliance was defined as the application of fewer than 7 (50%) of the doses.

8.2.1.3.2 Evaluability criteria

8.2.1.3.3 Endpoints, Efficacy, and Safety Variables

Patients were evaluated clinically for the presence of signs and symptoms of tinea versicolor and mycologically for the presence of hyphae.

Scoring Scale

At each visit the severity of erythema, scaling and pruritus was graded on a scale from 0 to 3 described in Table 5. Total Signs and Symptoms (TSS) score was a composite of these three individual scores and could range from 0 to 9.

**Table 5 (Sponsor's Table 1, Vol. 2, Pg. 2-103)
Severity of Erythema, Scaling and Pruritus: Definitions of Scores**

Score	Severity	Erythema, Scaling	Pruritus
0	Absent	Absent	Absent
1	Mild	minimal involvement	at least occasionally present but not bothersome to subject
2	Moderate	distinctive presence	present and bothersome some of the time
3	Severe	marked, intense	present and so bothersome that the subject thinks about it much of the time

Assessments of all lesions and a single target lesion were performed separately. The all lesion score represented the most severe score of any lesion for that sign or symptom; if the target lesion had the most severe score, then the all lesions score would equal the target lesion score. Erythema was evaluated independently of the hyperpigmentation or hypopigmentation characteristic of tinea versicolor.

Reviewer's comments: *As previously mentioned under Regulatory Background, the Sponsor was advised at the Pre-IND/EP2 meeting that microbiological evaluation of a target lesion is not acceptable.*

Body Diagrams

Using the Baseline Body Diagram, the Investigator was to indicate the location of each tinea versicolor lesion by encircling a corresponding area on the most appropriate Baseline Body Diagram view, i.e., front, back, left side, right side. A single lesion may appear on more than one body view, for example, a lesion on the subject's back that wraps around his left side would be drawn on both the back and left side views of the body diagram. The Baseline Body Diagram served as a reference guide at the subject's subsequent study visits to aid the Investigator in checking the condition of all lesions present at Baseline. Additionally, a copy of the completed Baseline Body Diagram was given to the subject when his/her study medication was dispensed so that the subject will be able to easily identify all areas to be treated with study medication.

Reviewer's comments: *Instructions for use of Baseline Body Diagram to indicate the location of each tinea versicolor lesion by encircling a corresponding area on the most appropriate Baseline Body Diagram view (i.e., front, back, left side, right side) is tedious. As previously mentioned a regional approach to therapy rather than "spot" treatment is more consistent with the efficacy endpoint that is based on a global assessment.*

At the Baseline visit, a blank New Lesion Body Diagram was provided to the subject to allow recording of any new tinea versicolor lesions not evident at Baseline and thus not charted on the Baseline Body Diagram. Any new lesions the subject detects and treats during his/her 14 day treatment period, or any new lesions that appear after treatment is completed, must be charted on the New Lesion Body Diagram. The date of new lesion appearance as well as the date treatment was begun, if applicable, was recorded.

Reviewer's comments:

Any new lesions occurring on or adjacent to the same anatomical location of prior treatment should be considered a treatment failure.

Mycological Assessment

For mycological assessment, skin scrapings were taken from tinea versicolor lesions and a KOH wet mount was made using Chlorazol Black E Fungal Stain. The choice of which lesion(s) to be sampled was made by the investigator. Multiple lesions may have been sampled to obtain the KOH prep that was examined for the presence of hyphae. Additionally, at each study visit, the investigator performed a KOH exam on skin scrapings from the "target" lesion selected at baseline. If the target lesion was the only lesion present, or if all other skin areas sampled were negative for the presence of hyphae, then the target lesion provided the mycological results for all lesions as well as the "target" lesion.

Negative Mycology was defined as the absence of hyphae in a KOH preparation of skin scrapings, i.e., no fungal forms seen or the presence of yeast cells (blastospores) only. The investigator collected samples for mycological examination on Study Days 1, 14, 28 and 56 or early termination (study exit).

Reviewer's comments: *The presence or absence of yeast cells was not provided. A rationale for persistence of the yeast cells at the end of therapy should be provided. With active therapy it would seem logical that susceptible normal flora should be altered (absent or reduced) for some period of time during and/or after treatment.*

Safety Assessments

Safety was assessed based on adverse events. At each visit, subjects were asked if they had experienced any medical problems since the last visit. The investigator recorded the adverse events observed or reported by the subject during and following study medication treatment. Information collected on the Case Report Form (CRF) included severity, seriousness, study drug relationship, start date, action taken and outcome. Brief physical examinations were performed. Rapid urine pregnancy tests were performed where appropriate. No urinalysis, systemic chemical, or hematological laboratory assessments were performed.

8.2.1.3.4 Statistical Considerations**Efficacy Variables****Primary Efficacy**

The primary efficacy variable is the proportion of subjects with Effective Treatment considering all lesions, defined as Negative Mycology plus total signs and symptoms score equal to or less than 1 at Day 56. Negative Mycology is defined as the absence of hyphae in a KOH prep of skin scrapings, i.e., no fungal forms seen or the presence of yeast cells (blastospores) only in the KOH prep.

Secondary Efficacy

Complete Cure and Negative Mycology for all lesions at Week 8 in the ITT population were the Sponsor's secondary efficacy endpoints. Complete Cure is defined as negative

mycology plus sign/symptoms score is equal 0. Negative Mycology is defined as the absence of hyphae in a KOH preparation of skin scrapings, i.e., no fungal forms seen or the presence of yeast cells (blastospores) only.

Reviewer's comments: *Total signs and symptoms score equal to or less than 1 for erythema, scaling, and pruritus were permitted at Day 56. Generally for tinea versicolor, scaling is a consistent feature in active disease; therefore, unless confirmatory cultures are performed, the score for scaling should be 0 at the end of the treatment and study endpoint.*

Populations:

For the purpose of this review, the primary population for efficacy analysis is the Intent-to-Treat (ITT) population, defined as all subjects with confirmed tinea versicolor who were dispensed study medication (active or vehicle). A Last Observation Carried Forward (LOCF) algorithm will be applied to this population to supply any missing efficacy data at the end-of-study time point (week 8/Day 56). Adverse events will be analyzed for the Safety Population, which is 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.

Financial Disclosure

According to the Sponsor, no investigator participating in the study received compensation that was dependent on favorable study outcome, has ownership in or stock in the company that cannot be readily determined through reference to public prices, nor has a proprietary interest in the drug product.

8.2.1.4 Study Results (Protocol PDC-010-031)

Five United States sites participated in this. A total of 129 subjects were randomized into Protocol PDC-010-031, 87 receiving Mentax and 42 receiving the vehicle. All randomized subjects had confirmed diagnoses of tinea versicolor and all were dispensed study medication. All 129 randomized subjects were included in the Intent-to-Treat population.

8.2.1.4.1 Demographics, Evaluability

Table 6 (Sponsor's Table 1, Vol. 2.5, pg. 2-094): List of Investigators

Site #	Site	Investigator	Location	# of Subjects Enrolled
1	International Dermatology Research, Inc.	D. Rodriguez	Miami, Florida	36
2	Private Practice	L. Kaminester	North Palm Beach, Florida	12
3	MedaPhase, Inc.	M. Ling	Newnan, Georgia	19
4	J&S Studies	T. Jones	Bryan, Texas	26
5	Central California Medical Research	D. Tashjian	Fresno, California	36

Table 7 (Modified Sponsor's Table 6, Vol.2.15, pg. 2-122): Baseline Demographic and Clinical Characteristics by Treatment-All Randomized Subjects

	Mentax (N=87)	Vehicle (N=42)	p-value ^a
Age (years)			
Mean (sd)	33.0 (11.9)	32.6 (17.1)	0.879
Range	15, 65	15, 77	
Gender			
Male	46 (53%)	24 (57%)	0.708
Female	41 (47%)	18 (43%)	
Race			
Caucasian	62 (71%)	28 (67%)	0.807
Non-Caucasian	25 (29%)	14 (33%)	
Black	2 (2%)	1 (2%)	
Asian	2 (2%)	0 (0%)	
Hispanic	21 (24%)	13 (31%)	

^aFisher's exact Test performed for gender and race (unpooled);
t-test performed for age, weight, height, blood pressure and pulse rate

Demographic and other baseline characteristics between active and vehicle groups were similar. Physical examination clinical parameters (e.g., height, weight, pulse, etc.) were similar between the two groups.

Disposition Of Subjects

Seventy-nine (91%) subjects receiving Mentax and 35 (83%) subjects receiving the vehicle completed the protocol. Three (3.4%) Mentax-treated subjects and four (9.5%) vehicle-treated subjects did not complete the study due to treatment failure. No subject failed to complete the study due to an adverse event. A listing of all subjects presented by site, including any reasons for discontinuing the study and the number of subjects that completed the study is summarized in Table 8.

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Table 8 (Sponsor's Table 2 (Vol. 2.15, pg. 2-117): Subject Disposition

Treatment	Site	Number Enrolled	Lost to Follow-up	Treatment Failure	Other	Number (%) Completed
Mentax	1	24	2			22 (92%)
	2	8			1*	7 (88%)
	3	13	1	1		11 (85%)
	4	18		2		16 (89%)
	5	24	1			23 (96%)
All Sites		87	4	3	1	79 (91%)
Vehicle	1	12				12 (100%)
	2	4				4 (100%)
	3	6	1	1		4 (67%)
	4	8		3		5 (63%)
	5	12	2			10 (83%)
All Sites		42	3	4		35 (83%)

*Subject chose to withdraw from study

Protocol Deviations

Eighteen subjects had major protocol violations and were excluded from the Per-Protocol population. Fourteen were in the Mentax group and four were in the vehicle group.

- Seven subjects (T108, T125, T205, T303, T308, T504, and T535) were excluded from the safety population because they did not provide any post-baseline data.
- Two additional subjects (T301, T513) had evidence that at least one dose of medication had been applied, but the actual total number of doses was unknown.
- One subject (T312) applied 6 doses of the medication, which was less than 50% of doses, and this subject was eliminated from the Per-Protocol population.
- Seven additional subjects (T204, T313, T425, T510, T516, T522, and T525) had the Week 8 visit not in the visit window and this was the only major protocol deviation for this group. These seven subjects were excluded from the Per-Protocol population.
- One additional subject (T316) used methyl-prednisolone, a disallowed medication, for bronchitis. This subject was excluded from the Per-Protocol population.

Problem Encountered with the Sponsor's Data Presentation

Nine additional subjects were excluded from efficacy analysis and are discussed below.

Problems encountered with the Sponsor's data presentation fell into two categories:

1) mycology results at the end of study and at Week 4 that makes a result of cure at Week 8 unreliable and 2) development of new lesions in an area in or near previously treated areas. The following KOH results (e.g., +, -, +, - at baseline, Weeks 2, 4, & 8 respectively and +, +, +, - at baseline, Weeks 2, 4, & 8 respectively) were found to be problematic.

These mycology results appear inconsistent with cure as a result of treatment (tinea versicolor infections can also wax and wane due to environmental changes). The assumption of this reviewer was that post-treatment "test-of-cure" time point was generally used to eliminate inhibitory effects of the drug (to rule out false negatives at the end of treatment).

The following 8 subjects (T104, T116, T404, T407, T411, T416, T103, and T418) were excluded from efficacy analysis because variable mycology. In addition to Week 8, KOH results should have been negative at the end of treatment (Week-2) and maintained throughout the designated post-treatment evaluation evaluations.

Development of so-called "new lesions" was also problematic. This reviewer excluded one subject (Patient T529) from efficacy analysis because it appeared that a new lesion noted at Week 8 had developed near an area of prior treatment. Baseline Lesion and New Lesion Diagram lesion entries were practically the same (New Lesion Diagram should have been blank except for new lesion documentation); however, there appears to be an additional area of involvement noted left of the umbilicus.

Reviewer's comments: A rationale for the inconsistent mycology results was requested from the Sponsor. The response received on 04-24-01 indicated that there is probably more than one reason. The Sponsor hypothesized that these variable results were perhaps due to sampling errors and/or false positive or false negative KOH results, etc.

Unless there is some unique mechanism of action for the drug product, a basic assumption made by this reviewer is that mycology should be negative at the end of study and remain negative through a pre-designated endpoint chosen by the Sponsor to claim "cure". However, other than baseline and study endpoint (Week 8), no agreements between the Sponsor and the Division specifically addressing the status of mycological results were made; therefore, after Divisional discussions, it was felt that Sponsor should not now be penalized for these interim positive mycology results. The same applies to new lesion assessment.

8.2.1.4.2 Efficacy Results

8.2.1.4.2.1 Clinical

The regressing clinical outcome subsets evaluated for this review will be the patients who achieve Complete Cure, Effectively Treated, and Mycological Cure. The Sponsor's agreed upon primary efficacy end point is Effective Treatment of all lesions at Week 8.

Effective Treatment

Sponsor's primary efficacy variable was proportion of patients with Effective Treatment, defined as defined as negative mycology for all lesions plus total signs and symptoms ψ 1 at Day 56 (Week 8/study exit). At Week 8, 55% of the Mentax-treated group and 36% of the vehicle treated group achieved Effective Treatment. The Division's Statistical Reviewer's analysis indicated that Mentax was significantly better than vehicle with $p=0.039$ and $p=0.038$ in the pooled and non-pooled analyses, respectively. The Sponsor's Fisher's exact test ($p=0.041$) was not statistically significant.

However, in the alternative analysis (excluding the 9 subjects), Mentax was only numerically better than vehicle with $p=0.084$ and $p=0.041$ in the pooled and non-pooled analyses, respectively.

Table 9 (Statistical Reviewer's Table 3-A): Primary Efficacy Analysis in Study 31 Effective Treatment of All Lesions at Week 8, by Treatment [Number Achieved (% achieved)] – ITT Population of Study 31

	Mentax	Vehicle	Difference	Fisher's Exact Test P-value	Model ^a P-value	CMH-test ^b P-value
Original analysis (the ITT population)	48/87 (55%)	15/42 (36%)	19%	0.041	0.028	0.039 0.038(pooled) ^d
Alternative analysis excluding 9 subjects ^c	40/79 (51%)	14/41 (34%)	17%	0.121	-	0.084 0.082 (pooled) ^d

^a Logistic regression model controlling for site, tinea versicolor duration, age, gender, race, and baseline Total Signs and Symptoms (sponsor's analysis).

^b CMH test controlling for site (reviewer's analysis).

^c Eight Mentax subjects (T103, T104, T116, T404, T407, T411, T418, and T529) and one Vehicle subject (T416) were excluded by the medical reviewer because variability in the KOH results and conflicting records made their negative mycology at Week 8 unreliable.

^d Analysis with small sites #2 and #3 pooled.

Analysis of Target Lesion

Since a treatment effect was noted in Study 32, analysis of the Target Lesion was performed for supportive evidence of efficacy. At Week 8/study exit, 60% of the Mentax-treated patients and 38% of the vehicle-treated patients achieved statistical significance ($p=0.023$ in the CMH test).

Table 10 (Statistical Reviewer's Table 3-T: Supportive Efficacy Analysis in Study 31 Effective Treatment of Target Lesions at Week 8, by Treatment [Number Achieved (% achieved)] – ITT Population of Study 31

	Mentax	Vehicle	Difference	Fisher's Exact Test P-value	Model ^a P-value	CMH-test ^b P-value
Original analysis (the ITT population)	52/87 (60%)	16/42 (38%)	22%	0.025	0.011	0.023
Alternative analysis excluding 7 subjects ^c	47/82 (57%)	14/40 (35%)	22%	0.033	-	0.022

^a Logistic regression model controlling for site, tinea versicolor duration, age, gender, race, and baseline Total Signs and Symptoms (sponsor's analysis).

^b CMH test controlling for site (reviewer's analysis).

^c Five Mentax subjects (T116, T404, T407, T410, and T411) and two Vehicle subjects (T109 and T416) were excluded by the medical reviewer because variability in the KOH results and conflicting records made their negative mycology at Week 8 unreliable.

Reviewer's comments: *After review of the Baseline Lesion and New Lesion Body diagrams, 3 additional (T104, T418, and T529) patients should have been excluded from target lesion efficacy analysis. CRF was not available for one patient and an exclusion determination could not be made. Statistical significance of Mentax over vehicle would not have changed with exclusion of these additional patients.*

However during review of the Baseline Body Diagrams for target lesions, it became apparent to this reviewer that the target lesion assessments might not be clinically relevant in support of efficacy. For instance, target lesions varied in size from minute areas or apparently a single lesion (e.g., subjects T212, T527, and T529) to larger target areas (e.g., T104, T407, and T411).

Complete Cure

A numerically greater percentage of patients in the Mentax- treated group achieved Complete Cure (defined, as negative mycology plus sign/symptoms score is equal 0) at Week 8/study exit (51% vs. 36%) in the Sponsor's and FDA's analyses. This difference was not statistically significant in the Division's Statistical Reviewer's CMH test ($p=0.113$). Additionally, this difference was not statistically significant in the Sponsor's Fisher's exact test ($p=0.133$), or in the logistic regression analysis ($p=0.066$).

Table 11 (Statistical Reviewer's Table 4) Secondary Efficacy Analysis in Study 31 Complete Cure of All Lesions at Week 8, by Treatment [Number Achieved (% achieved)] – ITT Population of Study 31

	Mentax	Vehicle	Difference	Fisher's Exact Test P-value	Model ^a P-value	CMH test ^b P-value
Original analysis (the ITT population)	44/87 (51%)	15/42 (36%)	15%	0.133	0.066	0.113

^a Logistic regression model controlling for site, tinea versicolor duration, age, gender, race, and baseline Total Signs and Symptoms (sponsor's analysis).

^b CMH test controlling for site (reviewer's analysis).

Negative Mycology

Table 12 (Statistical Reviewer's Table 5-A: Secondary Efficacy Analysis in Study 31 Negative Mycology at Week 8, by Treatment [Number Achieved (% achieved)] – ITT Population of Study 31

	Mentax	Vehicle	Difference	Fisher's Exact Test P-value	Model ^a P-value	CMH-test ^b P-value
Original analysis (the ITT population)	48/87 (55%)	15/42 (36%)	19%	0.041	0.028	0.039
Alternative analysis excluding 9 subjects ^c	40/79 (51%)	14/41 (34%)	17%	0.121	-	0.084

^a Logistic regression model controlling for site, tinea versicolor duration, age, gender, race, and baseline Total Signs and Symptoms (sponsor's analysis).

^b CMH test controlling for site (reviewer's analysis).

^c Eight Mentax subjects (T103, T104, T116, T404, T407, T411, T418, and T529) and one Vehicle subject (T416) were excluded by the medical reviewer because variability in the KOH results and conflicting records made their negative mycology at Week 8 unreliable.

As noted in Table 12 above, statistical significance was reached for negative mycology at study exit (Week 8) between the active and vehicle groups in the original analysis

Sponsor's Fisher's exact test ($p=0.041$) and the Division's CMH test ($p=0.039$). At study exit, 55% of the Mentax-treated group and 36% of the vehicle-treated group achieved Negative mycology. In the alternative analysis (excluding the 9 subjects), Mentax was only numerically better than vehicle, CMH test ($p=0.084$).

8.2.1.4.3 Safety

Total Exposure

Drug usage ranged from 3.1 to 113.6 grams in the Mentax-treated group and from 1.6 to 115.4 grams in the vehicle-treated group. According to the submission, more than three-quarters of the subjects in both treatment groups applied the full course of 14 doses. The Mentax group used an average of 42.8 grams per subject (3.1 grams per day), and the vehicle group used an average of 42.9 grams per subject (3.1 grams per day) over 14 days of dosing.

The safety population consisted of 122 subjects, 83 in the Mentax group and 39 in the vehicle group. Seven subjects did not provide any post-baseline data, four from the Mentax group and three from the vehicle group. A total of 13 (16%) patients in the Mentax group and 5 (13%) in the vehicle group experienced at least one adverse event. The only serious adverse event, hyperglycemia, occurred in the Mentax group; however, was not related to the study drug.

Table 13 (Sponsor's Table 22, Vol. 2.15, pg. 2-155):
Summary of All Adverse Events by Treatment and Body System [N(%)]- Safety Population

	Mentax (N=83)	Vehicle (N= 39)	Fisher's Exact Test <i>p</i> -value
No Adverse Event	70 (84%)	34 (87%)	0.789
Any Adverse Event	13 (16%)	5 (13%)	
Gastrointestinal Disorders	1 (1%)	0 (0%)	1.000
Tooth impacted	1 (1%)	0 (0%)	
General Disorders	1 (1%)	0 (0%)	1.000
Pain NOS*	1 (1%)	0 (0%)	
Immune System Disorders	0 (0%)	1 (3%)	0.319
Allergy to insect sting	0 (0%)	1 (3%)	
Infections and Infestations	10 (12%)	1 (3%)	0.171
Bladder infection NOS	2 (2%)	0 (0%)	
Bronchitis NOS	1 (1%)	0 (0%)	
Nasopharyngitis	1 (1%)	0 (0%)	
Pneumonia NOS	1 (1%)	0 (0%)	
Sinusitis NOS	3 (4%)	0 (0%)	
Upper respiratory tract infection NOS	1 (1%)	0 (0%)	
Urinary tract infection NOS	1 (1%)	1 (3%)	
Injury and Poisoning	1(1%)	1 (3%)	0.538
Injury NOS	0 (0%)	1 (3%)	
Joint sprain	1 (1%)	0 (0%)	

*Not otherwise specified

**Table 13 (Sponsor's Table 22) (cont.):
Summary of All Adverse Events by Treatment and Body System [N(%)]- Safety
Population**

	Mentax (N=83)	Vehicle (N= 39)	Fisher's Exact Test p-value
Metabolism and Nutrition Disorders	1 (1%)	0 (0%)	1.000
Hyperglycemia NOS ^a	1 (1%)	0 (0%)	
Nervous System Disorders	2 (2%)	0 (0%)	1.000
Headache NOS	2 (2%)	0 (0%)	
Sinus headache	1 (1%)	0 (0%)	
Psychiatric Disorders	1 (1%)	0 (0%)	1.000
Depression NEC ^b	1 (1%)	0 (0%)	
Renal and Urinary Disorders	0 (0%)	1 (3%)	0.319
Calculus, renal NOS	0 (0%)	1 (3%)	
Respiratory, Thoracic and Mediastinal Disorders	1 (1%)	1 (3%)	0.538
Cough	1 (1%)	0 (0%)	
Sinus Congestion	0 (0%)	1 (3%)	
Skin and Subcutaneous Tissue Disorders	0 (0%)	2 (5%)	0.100
Dermatitis, contact	0 (0%)	1 (3%)	
Drug eruption, NOS	0 (0%)	1 (3%)	

^a Not otherwise specified

^b Not elsewhere classified

Deaths, Other Serious Adverse Events And Other Significant Adverse Events

There were no deaths reported for subjects in this study. No subjects withdrew from the study due to an adverse event. One serious adverse event was reported for one subject in the Mentax-treated group. Subject T510, a 23-year-old Hispanic male with a history of diabetes, was hospitalized for hyperglycemia during the treatment period. The physician considered this serious adverse event not related to the study treatment.

Clinical Laboratory Evaluation

Data were not collected on clinical laboratory parameters.

Vital Signs, Physical Findings, and Other Observations Related to Safety

Data were collected for these parameters only at baseline.

Safety Conclusions

No statistically significant difference between treatments was observed for adverse event rates between the Mentax-treated group (16%) and the vehicle-treated group (13%). There were no reported study treatment related on-treatment or post-treatment adverse events.

8.2.1.5

Reviewer's Comments/ Conclusions of Study Results

Effective Treatment of all lesions in the ITT population was the agreed upon primary efficacy. Effective Treatment of all lesions is defined as Negative Mycology with a Total

Signs and Symptoms Score of $\psi 1$ at Week 8/study exit. The Division's Statistical Reviewer's statistical analysis was the CMH test controlling for center.

This reviewer had concerns regarding the reliability of negative KOH results (probable false negative results or if negative, not a treatment effect) at Week 8 in 9 patients. Lesions designated as "new" developing after the end of study (Week 2) in or near an area of prior treatment were also problematic. Division's Statistician performed an alternative analysis based on exclusion of nine patients that fell into these categories. The nine patients were excluded rather than considered failures; thereby according to the Statistician, the analysis was performed under more favorable conditions. For the Sponsor's primary efficacy endpoint, Effective Treatment, in the alternative analysis excluding 9 patients, Mentax was only numerically better than vehicle with $p=0.084$ and $p=0.082$ in the non-pooled and pooled analyses, respectively. Mentax did not demonstrate statistical significance over vehicle ($p=0.084$) in achieving negative mycology. Mentax was only numerically better than vehicle with 51% of the Mentax-treated group and 34% of the vehicle treated group achieving negative mycology.

However, after internal discussions, it was felt that Sponsor should not now be penalized for these interim positive mycology results. Other than baseline and study endpoint (Week 8), no discussions or agreement between the Sponsor and the Division specifically addressing the status of interim mycological results had been made. The Divisional is not accepting the analysis excluding the 9 patients for establishing efficacy. Although to this reviewer, negative mycology at study end and at post-treatment follow-up assessments should be a given. Additionally, there had not been prior discussions concerning the definition of "new" lesions (just that they were to be noted).

Based on prior agreement, for Effective Treatment of all lesions, the primary efficacy endpoint, Mentax was found to be statistically significantly better than vehicle with $p=0.039$ and $p=0.038$ in the non-pooled and pooled analyses, respectively in the ITT population. The Sponsor's analysis in the ITT population using Fisher's exact test ($p=0.041$) and logistic model controlling for site, tinea vericolor duration, age, gender, race, and baseline Total Signs and Symptoms ($p=0.028$) demonstrated statistical significance for Mentax over vehicle.

Statistical significance was reached for Negative Mycology (defined as the absence of hyphae in a KOH preparation of skin scrapings, i.e., no fungal forms seen or the presence of yeast cells (blastospores) only) at study exit (Week 8) $p=0.039$ in the Division's original statistical analysis in the ITT population. At study exit (Week 8), 55% of the Mentax-treated group and 36% of the vehicle treated group achieved negative mycology.

For Complete Cure of all lesions, defined as Negative mycology plus Total Signs and Symptoms score of 0 at Week 8/Day 56, statistical significance was not reached in either the Division's nor Sponsors analyses in the original ITT population.

Based on the Division's analyses of the original ITT population as agreed upon, the Sponsor demonstrated statistical superiority of Mentax over vehicle in Study PDC-010-031 in the primary efficacy endpoint, Effective Treatment.

Financial Disclosure

According to the Sponsor, no investigator participating in PDC-010-032 received compensation that was dependent on favorable study outcome, has ownership in or stock in the company that cannot be readily determined through reference to public prices, nor has a proprietary interest in the drug product.

Indication #1 Treatment of Tinea (Pityriasis) Versicolor

This study was designed to compare the safety and efficacy of Mentax® (butenafine HCl cream) Cream, 1% versus its vehicle formulation when used topically once daily for two weeks to treat tinea versicolor.

8.2.2 Reviewer's Trial #2**Sponsor's Protocol # PDC-010-032**

(Study Dates: 04/29/99 to 11/11/99)

Title: "A Multicenter, Double-blind, Vehicle-controlled Study to Evaluate the Safety and Efficacy of Mentax® (Butenafine HCl) Cream, 1% in the Treatment of Tinea Versicolor"

8.2.2.1 Objective Rationale

The objective of this study is to compare the safety and efficacy of Mentax® (butenafine HCl cream) Cream, 1% versus its vehicle formulation when used topically once daily for two weeks to treat tinea versicolor

8.2.2.1.1 Design

This was a multicenter, double-blind, randomized, two-treatment-arm, parallel group study to compare the safety and efficacy of Mentax versus its vehicle control formulation when applied topically once daily for two weeks to treat tinea versicolor.

8.2.2.4.1 Study Results

Five study sites located in the United States participated in Study PDC-010-032. The list of investigators, location, and number of subjects enrolled at each site follows in Table 14 below.

Table 14 (Sponsor's Table 1, Vol. 5.15, pg. 5-059): List of Investigators

Site #	Site	Investigator	Location	Number of Subjects Enrolled
1	Gwinnett Clinical Research Center	J. Shavin	Snellville, Georgia	23
2	Louisiana State University Medical Center	D. Greer	New Orleans, Louisiana	25
3	DermResearch	M. Jarratt	Austin, Texas	26
4	Savin Dermatology Center	R. Savin	New Haven, Connecticut	38
5	Baylor College of Medicine	S. Bruce	Houston, Texas	17

A total of 129 subjects were randomized into Protocol PDC-010-032, 86 receiving Mentax and 43 receiving the vehicle. All randomized subjects had confirmed diagnoses of tinea versicolor and all were dispensed study medication. All 129 randomized subjects were included in the Intent-to-Treat population.

**Table 15 (Sponsor's Modified Table 6, Vol. 5, pg. 5-087):
Baseline Demographic and Clinical Characteristics by Treatment-All Randomized Subjects**

	Mentax (N=86)	Vehicle (N=43)	p-value ^a
Age (years)			
Mean (sd)	35.7 (12.9)	32.1 (14.5)	0.160
Range	13, 75	14, 75	
Gender			1.000
Male	50 (58%)	25 (58%)	
Female	36 (42%)	18 (42%)	
Race			0.639
Caucasian	66 (77%)	34 (79%)	
Non-Caucasian	20 (23%)	9 (21%)	
Black	14 (16%)	7 (16%)	
Asian	0 (0%)	1 (2%)	
Hispanic	5 (6%)	1 (2%)	
Other	1 (1%)	0 (0%)	

^aFisher's exact test performed for gender and race (unpooled);
t-test performed for age, weight, height, blood pressure and pulse rate.

Demographic and other baseline characteristics between active and vehicle groups were similar. Physical examination clinical parameters (e.g., height, weight, pulse, etc.) were similar between the two groups.

Disposition Of Subjects

A listing of all subjects with reasons for discontinuing the study is presented by site. Seventy-seven of 86 (90%) subjects receiving Mentax and 40 of 43 (93%) subjects receiving the vehicle completed the protocol. No subject failed to complete the study due to treatment failure or an adverse event.

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Table 16 (Sponsor's Table 4, vol. 5, pg. 5-082): Subject Disposition

Treatment	Site	Number Enrolled	Lost to Follow-up	Treatment Failure	Other	Number (%) Completed
Mentax	1	15	1		2*	12 (80%)
	2	17	3			14 (82%)
	3	17				17 (100%)
	4	25	1		1*	23 (92%)
	5	12	1			11 (92%)
All Sites		86	6		3	77 (90%)
Vehicle	1	8			1	7 (88%)
	2	8				8 (100%)
	3	9			1	8 (89%)
	4	13	1			12 (92%)
	5	5				5 (100%)
All Sites		43	1		2	40 (93%)

* includes 1 non-compliant subject

The following eighteen subjects were listed as having major protocol violations and were excluded from the Sponsor's Per-Protocol population. Fifteen were in the Mentax group and three were in the vehicle group.

- Seven subjects (V105, V106, V113, V203, V209, V211, and V412) did not provide post-baseline data. These seven subjects, five receiving Mentax and two receiving vehicle, were excluded from the Per-Protocol population.
- Four subjects (V121, V324, V416, and V503) did not complete the protocol and had the Week 8 visit outside the visit window, three received Mentax and one received vehicle.
- One subject (V418) did not complete the protocol, had the Week 8 visit outside the visit window and applied less than 50% of the scheduled doses (6 doses) and was eliminated from Per-Protocol population. This subject received Mentax.
- One subject (V434) did not apply treatment to all lesions and this was considered a major protocol deviation. This subject received Mentax.
- Two additional subjects (V321, V511) had the Week 8 visit out of window and this was the only major protocol deviation. These two subjects received Mentax.
- One subject (V315) had the Week 8 visit out of the visit window and used a proscribed medication (cortisone injection for poison ivy). This subject received Mentax.

- Two additional subjects (V214, V308) used proscribed medications and this was the only major protocol deviation. One used prednisone for arthritis and the second used cortisone cream, 1% for a heat rash. Both these subjects received Mentax.

Problem Encountered with the Sponsor's Data Presentation

As noted in Study 31, problems were also encountered with the Sponsor's data presentation falling into same two categories: variable mycology that makes a result of cure at Week 8 unreliable and development of new lesions in or near areas of prior therapy. Eight subjects (V102, V111, V207, V401, and, V242) with variable mycology and three subjects with new lesions (V210, V218, and V505) were excluded from efficacy analysis.

After review of New Lesion Diagrams, the following patients should were considered failures because new lesions were noted near previously treated areas:

- **V 210** – new lesions right shoulder area at Week 8. These lesions were not treated; however, occurred in an area that was noted as involved at baseline. It is unclear to this reviewer how this patient could be considered a success.
- **V218** – New lesion developed and noted at Week-8. The New Lesion documentation for this patient is confusing in that there are markings on the diagram dated 10-27-99. An additional New Lesions Body Diagram report indicates in writing that the patient the new lesions occurred on the lower back; however, the diagram does not support this claim. Although considered a complete cure on 10-27-99, it is interesting to note that on 11-04-99, the patient was treated systemically for t. versicolor (not wanting anymore cream).
- **V505**- new lesion developed near previously treated area noted at Week 2 and Week 4, was not treated and was negative at Week 8.

Effective Treatment

Sponsor's primary efficacy variable was proportion of patients with Effective Treatment, defined as defined as negative mycology for all lesions plus total signs and symptoms ψ 1 at Day 56 (Week 8/study exit). At Week 8, 43% of the Mentax-treated group and 26% of the vehicle treated group achieved Effective Treatment in the ITT population. The Division's Statistical Reviewer's analysis indicated that Mextax was marginally significantly better than vehicle ($p=0.051$). The Sponsor's results were as follows: Fisher's exact test ($p=0.057$) and $p=0.086$ in the logistic regression model. In the alternative analysis (excluding the 8 subjects), Mentax was statistically significantly better than vehicle (40% vs. 20%, $p=0.030$) as noted in Table 17.

**Table 17 (Statistical Reviewer's Table 9-A):
Effective Treatment of All Lesions at Week 8, by Treatment [Number Achieved (% achieved)] – ITT Population of Study 32**

	Mentax	Vehicle	Difference	Fisher's Exact Test P-value	Model^a P-value	CMH- test^b P-value
Original analysis (the ITT population)	37/86 (43%)	11/43 (26%)	17%	0.057	0.086	0.051
Alternative analysis excluding 8 subjects ^c	32/81 (40%)	8/40 (20%)	20%	0.040	-	0.030

^a Logistic regression model controlling for site, tinea versicolor duration, age, gender, race, and baseline Total Signs and Symptoms (sponsor's analysis).

^b CMH test controlling for site (reviewer's analysis).

^c Five Mentax subjects (V111, V218, V401, V424, and V508) and three Vehicle subjects (V207, V210, and V505) were excluded by the medical reviewer because variability in the KOH results and conflicting records made their negative mycology at Week 8 unreliable.

Statistical significance was achieved for active over vehicle for Target Lesion assessment as displayed in Table 18 that follows.

**Table 18 (Statistical Reviewer's Table 9-T): Supportive Efficacy Analysis in Study 32
Effective Treatment of Target Lesions at Week 8, by Treatment [Number Achieved (% achieved)] – ITT Population of Study 32**

	Mentax	Vehicle	Difference	Fisher's Exact Test P-value	Model^a P-value	CMH-test^b P-value
Original analysis (the ITT population)	50 /86 (58%)	14/43 (33%)	25%	0.009	0.013	0.007
Alternative analysis excluding 5 subjects ^c	46/82 (56%)	13 /42 (31%)	25%	0.013	-	0.008

^a Logistic regression model controlling for site, tinea versicolor duration, age, gender, race, and baseline Total Signs and Symptoms (sponsor's analysis).

^b CMH test controlling for site (reviewer's analysis).

^c Four Mentax subjects (V401, V424, V504, and V507) and one Vehicle subject (V505) were excluded by the medical reviewer because variability in the KOH results and conflicting records made their negative mycology at Week 8 unreliable.

As in Study 31, wide variations in the size and location of the target lesions from minute (e.g., V505 and V508), uncertain (V102), to larger designated areas were observed in a subset of Baseline Body Diagrams for target lesions in Study 32.

Complete Cure

Numerically greater percentages of subjects in the Mentax-treated group achieved Complete Cure at Week 8 (35% vs. 23%) for the ITT population. This result was not

statistically significant in the Division's Statistical Reviewer's CMH test ($p=0.16$). This result was also not statistically significant in the Sponsor's Fisher's exact test ($p=0.23$).

Table 19 (Statistical Reviewer's Table 10): Secondary Efficacy Analysis in Study 32 Complete Cure of All Lesions at Week 8, by Treatment [Number Achieved (% achieved)] – ITT Population of Study 32

	Mentax	Vehicle	Difference	Fisher's Exact Test p-value	Model p-value	CMH-test p-value
Original analysis (ITT population)	30/86 (35%)	10/43 (23%)	12%	0.227	0.006	0.16

^aLogistic regression model controlling for site, tinea versicolor duration age gender, race, and baseline Total Signs and Symptoms (Sponsor's analysis)

^bCMH test controlling for site (Stat Reviewer's analysis)

Negative Mycology

For the ITT population, a total of 50% of the Mentax-treated patients and 28% of the vehicle-treated patients achieved negative mycology in Study 32 at Week 8. The difference was statistically significant in the Division's statistical analysis ($p=0.015$) and in the Sponsor's analysis ($p=0.023$ in the Fisher's exact test, and $p=0.034$ in the logistic regression model).

Table 20 (Statistical Reviewer's Table 11): Secondary Efficacy Analysis in Study 32 Negative Mycology at Week 8, by Treatment [Number Achieved (% achieved)] – ITT Population of Study 32

	Mentax	Vehicle	Difference	Fisher's Exact Test P-value	Model ^a P-value	CMH-test ^b P-value
Original analysis (the ITT population)	43/86 (50%)	12/43 (28%)	22%	0.023	0.034	0.015

^a Logistic regression model controlling for site, tinea versicolor duration, age, gender, race, and baseline Total Signs and Symptoms (sponsor's analysis)

^b CMH test controlling for site (reviewer's analysis).

8.2.2.4.3 Safety

Of 129 subjects randomized into the study, 122 (95%) provided post-baseline data and were included in the Safety Population. Fourteen subjects (8 [10%]) in the Mentax group and 6 [15%] in the vehicle group) experienced adverse events. There were no reported deaths or serious adverse events. One of the reported adverse events was considered by the physician to have a possible relationship to study treatment. This was a case of itching in the Mentax-treated group (subject V318). No subject withdrew from the study due to an adverse event. No statistically significant ($p=0.548$) treatment differences in the proportion of subjects with any adverse events were observed with Fisher's exact test

Extent Of Exposure

Drug usage ranged from 0.4 to 116.0 grams in the Mentax-treated group and from 3.0 to 111.6 grams in the vehicle-treated group. The Mentax group used an average of 44.7 grams per subject (3.2 grams per day), and the vehicle group used an average of 46.8 grams per subject (3.3 grams per day) over 14 days of dosing.

Adverse events are summarized by treatment and body system in Table 21 that follows. Each subject with the event is counted in this table. A subject could be included in multiple categories, depending on the number of adverse events.

Table 21 (Sponsor's Table 3, Vol. 5, pg. 5-121):

**Summary of All Adverse Events by
Treatment and Body System [N(%)]- Safety Population**

	Mentax (N=81)	Vehicle N=(41)	Fisher's Exact Test p-value*
No Adverse Event	73 (90%)	35 (85%)	0.548
Any Adverse Event	8 (10%)	6 (15%)	
General Disorders and Administration Site Conditions			
Influenza-like Illness	1 (1%)	1 (2%)	1.000
Infections and infestations	5 (6%)	3 (7%)	1.000
Ear infection NOS ^a	0 (0%)	1 (2%)	
Lice Infestation	1 (1%)	0 (0%)	
Nasopharyngitis	2 (2%)	2 (5%)	
Pneumonia NOS	1 (1%)	0 (0%)	
Sinusitis NOS	1 (1%)	0 (0%)	
Tooth Infection	0 (0%)	1 (2%)	
Musculoskeletal, Connective Tissue and Bone Disorders			
Muscle Disorder NOS	0 (0%)	1 (2%)	0.336
Nervous System Disorders	1 (1%)	1 (2%)	1.000
Headache NOS	1 (1%)	1 (2%)	
Skin and Subcutaneous Tissue Disorders	4 (5%)	0 (0%)	0.299
Dermatitis, Contact	1 (1%)	0 (0%)	
Dermatitis, NOS	1 (1%)	0 (0%)	
Heat Rash	1 (1%)	0 (0%)	
Pruritus NOS	1 (1%)	0 (0%)	

*Not otherwise specified

Similar adverse event rates were reported for both treatment groups, 8 (10%) Mentax-treated subjects and 6 (15%) vehicle-treated subjects reported adverse events during or after the two-week treatment phase of the study. The most common body system category was infections and infestations, experienced by 5 (6%) Mentax and 3 (7%) vehicle-treated subjects.

Deaths Other Serious Adverse Events Other Significant Adverse Events

There were no deaths, serious adverse events or withdrawals due to adverse events. One reported adverse event was considered to have a possible relationship to the study treatment by a physician. This related adverse event was an incidence of itching reported in a subject in the Mentax-treated group.

Clinical Laboratory Evaluation

Data were not collected on clinical laboratory parameters.

Vital Signs, Physical Findings, and Other Observations Related to Safety

Data were collected for these parameters only at baseline.

Drug-Drug and Drug-Disease Interactions

Drug-drug and drug-disease interactions were not investigated in this study. However, the use of prior and concomitant medications was recorded for each subject. The most common indication for concomitant use was contraception (female) followed by cold and sinus, headache, hypercholesterolemia/hyperlipidemia and hypertension. No drug-drug or drug-disease interactions were apparent.

Safety Conclusions

Adverse events were reported Mentax-treated group (10%) and the vehicle-treated group (15%). No statistically significant difference between treatments was observed. There were no reported deaths, no withdrawals due to an adverse event and no reported serious adverse events. Itching was the one reported on-treatment adverse event in the Mentax treatment group that was considered to be possibly related to the study treatment.

8.2.2.5 Reviewer's Comments/ Conclusions of Study Results (Study 32)

As in Study 31, reliability of negative KOH results at Week 8 and so-called "new" lesions developing after the end of study (Week 2) in or near an area of prior treatment in 8 patients were problematic for this reviewer. In the Division's alternative analysis excluding 8 patients that were in these categories, Mentax was statistically significantly better than vehicle (40% vs. 20%, $p=0.030$). In contrast, the Sponsor's analysis only demonstrated marginal statistical significance in the Fisher's exact test ($p=0.051$) and $p=0.086$ in the logistic regression model.

The primary efficacy variable, proportion of patients with Effective Treatment, Mentax was marginally significantly better than vehicle (43% vs. 26%, $p=0.051$) in the CMH test controlling for center in the ITT population. In the Sponsor's Fisher's exact test, $p=0.057$ and $p=0.086$ in the logistic regression model.

For negative Mycology, the difference was statistically significant in the Division's statistical analysis ($p=0.015$) and in the Sponsor's analysis ($p=0.023$ in the Fisher's exact test, and $p=0.034$ in the logistic regression model).

For Complete Cure, the Mentax-treated group achieved numerically greater percentages of subjects at Week 8 (35% vs. 23%) than vehicle for the ITT population. This result was

not statistically significant in the Division's Statistical Reviewer's CMH test ($p=0.16$) and also not statistically significant in the Sponsor's Fisher's exact test ($p=0.23$).

9 Overview of Efficacy

Data from Studies PDC 010-031 and PDC 010-032 were submitted by the Sponsor in support of Mentax Cream in treatment of tinea versicolor. The agreed upon primary efficacy variable is the proportion of subjects with Effective Treatment considering all defined as negative mycology (KOH only) plus total signs and symptoms score for erythema, pruritus, and scaling equal to or less than 1 at day 56. Secondary efficacy was Complete Cure and Negative Mycology for all lesions at Week 8 in the ITT population.

A total of 129 subjects were randomized into Protocol PDC-010-031, 87 receiving Mentax and 42 receiving the vehicle. Mentax was found to be statistically significantly better than vehicle with $p=0.039$ and $p=0.038$ in the non-pooled and pooled analyses, respectively in the ITT population in Study PDC-010-031 for Effective Treatment of all lesions (based on prior agreement). The Sponsor's analysis in the ITT population using Fisher's exact test ($p=0.041$) and logistic model controlling for site, tinea vericolor duration, age, gender, race, and baseline Total Signs and Symptoms ($p=0.028$) demonstrated statistical significance for Mentax over vehicle.

A total of 129 subjects were randomized into Protocol PDC-010-032, 86 receiving Mentax and 43 receiving the vehicle. All randomized subjects had confirmed diagnoses of tinea versicolor and all were dispensed study medication. All 129 randomized subjects were included in the Intent-to-Treat population. Mentax was marginally significantly better than vehicle (43% vs. 26%, $p=0.051$) in the CMH test controlling for center in the ITT population in Study PDC-010-032. In the Sponsor's Fisher's exact test, $p=0.057$ and $p=0.086$ in the logistic regression model.

In the Division's ITT analyses based on the original agreement between the Sponsor and the Division, statistical significance of Mentax over vehicle was demonstrated in Study PDC-010-031 and a trend in efficacy was noted in Study PDC-010-032.

10 Overview of Safety Significant/Potentially Significant Events

The safety population consisted of 122 subjects, 83 in the Mentax group and 39 in the vehicle group in Study PDC 010-031. Seven subjects did not provide any post-baseline data, four from the Mentax group and three from the vehicle group. A total of 13 (16%) patients in the Mentax group and 5 (13%) in the vehicle group experienced at least one adverse event. The only serious adverse event, hyperglycemia, occurred in the Mentax group; however, was not related to the study drug. No statistically significant difference between treatments was observed for adverse event rates between the Mentax-treated group (16%) and the vehicle-treated group (13%). There were no reported study treatment related on-treatment or post-treatment adverse.

Mentax group used an average of 42.8 grams per subject (3.1 grams per day), and the vehicle group used an average of 42.9 grams per subject (3.1 grams per day) over 14 days of dosing.

Of 129 subjects randomized into Study PDC 010-032, 122 (95%) provided post-baseline data and were included in the Safety Population. Fourteen subjects (8 [10%]) in the Mentax group and 6 [15%] in the vehicle group) experienced adverse events. There were no reported deaths or serious adverse events. One of the reported adverse events was considered by the physician to have a possible relationship to study treatment. This was a case of itching in the Mentax-treated group (subject V318). No subject withdrew from the study due to an adverse event. No statistically significant ($p=0.548$) treatment differences in the proportion of subjects with any adverse events were observed with Fisher's exact test

Drug usage ranged from 0.4 to 116.0 grams in the Mentax-treated group and from 3.0 to 111.6 grams in the vehicle-treated group. The Mentax group used an average of 44.7 grams per subject (3.2 grams per day), and the vehicle group used an average of 46.8 grams per subject (3.3 grams per day) over 14 days of dosing.

10.1 Deaths

There were no reported deaths.

10.1.2 Other Significant/Potentially Significant Events Other Serious Adverse Events (e.g., Serious adverse events, drop-outs/withdrawals)

No subjects withdrew from either study due to an adverse event. There was one serious adverse event reported for one subject in the Mentax-treated group in Study 31. A 23-year-old Hispanic male with a history of diabetes was hospitalized for hyperglycemia during the treatment period; however, this serious adverse event not related to the study treatment.

One reported adverse event was considered to have a possible relationship to the study treatment by a physician. This related adverse event was an incidence of itching reported in a subject in the Mentax-treated group.

10.2 Other Safety Findings

10.2.1 ADR Incidence Tables

Pooled safety data were not provided; however, they are displayed for each study separately.

10.1.3 Over-dosage exposure

Overdose was not addressed in the submission; however, the likelihood of over-dosage from topical administration is extremely low.

**Table 22, Study 31 (Sponsor's Table 22, Vol. 2.15, pg. 2-155):
Summary of All Adverse Events by Treatment and Body System [N(%)]- Safety
Population**

	Mentax (N=83)	Vehicle (N= 39)	Fisher's Exact Test p-value
No Adverse Event	70 (84%)	34 (87%)	0.789
Any Adverse Event	13 (16%)	5 (13%)	
Gastrointestinal Disorders	1 (1%)	0 (0%)	1.000
Tooth impacted	1 (1%)	0 (0%)	
General Disorders	1 (1%)	0 (0%)	1.000
Pain NOS ^a	1 (1%)	0 (0%)	
Immune System Disorders	0 (0%)	1 (3%)	0.319
Allergy to insect sting	0 (0%)	1 (3%)	
Infections and Infestations	10 (12%)	1 (3%)	0.171
Bladder infection NOS	2 (2%)	0 (0%)	
Bronchitis NOS	1 (1%)	0 (0%)	
Nasopharyngitis	1 (1%)	0 (0%)	
Pneumonia NOS	1 (1%)	0 (0%)	
Sinusitis NOS	3 (4%)	0 (0%)	
Upper respiratory tract infection NOS	1 (1%)	0 (0%)	
Urinary tract infection NOS	1 (1%)	1 (3%)	
Injury and Poisoning	1(1%)	1 (3%)	0.538
Injury NOS	0 (0%)	1 (3%)	
Joint sprain	1 (1%)	0 (0%)	

^aNot otherwise specified

**Table 22 (Sponsor's Table 22) (cont.):
Summary of All Adverse Events by Treatment and Body System [N(%)]- Safety
Population**

	Mentax (N=83)	Vehicle (N= 39)	Fisher's Exact Test p-value
Metabolism and Nutrition Disorders	1 (1%)	0 (0%)	1.000
Hyperglycemia NOS ^a	1 (1%)	0 (0%)	
Nervous System Disorders	2 (2%)	0 (0%)	1.000
Headache NOS	2 (2%)	0 (0%)	
Sinus headache	1 (1%)	0 (0%)	
Psychiatric Disorders	1 (1%)	0 (0%)	1.000
Depression NEC ^b	1 (1%)	0 (0%)	
Renal and Urinary Disorders	0 (0%)	1 (3%)	0.319
Calculus, renal NOS	0 (0%)	1 (3%)	
Respiratory, Thoracic and Mediastinal Disorders	1 (1%)	1 (3%)	0.538
Cough	1 (1%)	0 (0%)	
Sinus Congestion	0 (0%)	1 (3%)	
Skin and Subcutaneous Tissue Disorders	0 (0%)	2 (5%)	0.100
Dermatitis, contact	0 (0%)	1 (3%)	
Drug eruption, NOS	0 (0%)	1 (3%)	

* Not otherwise specified

* Not elsewhere classified

No statistically significant difference between treatments was observed for adverse event rates between the Mentax-treated group (16%) and the vehicle-treated group (13%) in Study 31. There were no reported study treatment related on-treatment or post-treatment adverse events.

Table 23 Study 32(Sponsor's Table 4, Vol. 5, pg. 5-121):

**Summary of All Adverse Events by
Treatment and Body System [N(%)]- Safety Population**

	Mentax (N=81)	Vehicle N=(41)	Fisher's Exact Test p-value*
No Adverse Event	73 (90%)	35 (85%)	0.548
Any Adverse Event	8 (10%)	6 (15%)	
General Disorders and Administration Site Conditions			
Influenza-like Illness	1 (1%)	1 (2%)	1.000
Infections and infestations	5 (6%)	3 (7%)	1.000
Ear infection NOS ^a	0 (0%)	1 (2%)	
Lice Infestation	1 (1%)	0 (0%)	
Nasopharyngitis	2 (2%)	2 (5%)	
Pneumonia NOS	1 (1%)	0 (0%)	
Sinusitis NOS	1 (1%)	0 (0%)	
Tooth Infection	0 (0%)	1 (2%)	
Musculoskeletal, Connective Tissue and Bone Disorders	0 (0%)	1 (2%)	0.336
Muscle Disorder NOS	0 (0%)	1 (2%)	
Nervous System Disorders	1 (1%)	1 (2%)	1.000
Headache NOS	1 (1%)	1 (2%)	
Skin and Subcutaneous Tissue Disorders	4 (5%)	0 (0%)	0.299
Dermatitis, Contact	1 (1%)	0 (0%)	
Dermatitis, NOS	1 (1%)	0 (0%)	
Heat Rash	1 (1%)	0 (0%)	
Pruritus NOS	1 (1%)	0 (0%)	

* Not otherwise specified

Similar adverse event rates were reported for both treatment groups in Study 32. Eight (10%) Mentax-treated subjects and 6 (15%) vehicle-treated subjects reported adverse events during or after the two-week treatment phase of the study. The most common body system category was infections and infestations, experienced by 5 (6%) Mentax and 3 (7%) vehicle-treated subjects.

10.2.2 Laboratory Evaluation Vital Signs, Physical Findings, and Other Observations Related to Safety

Data were not collected on clinical laboratory parameters. Clinical data were collected only at baseline for vital signs, physical finding, etc.

10.2.3 Special Studies

Special studies were not required since this is an approved drug product.

10.2.4 Drug-Demographic Interactions

Comparative inferences for cure rates of subjects at either end of the age spectrum were problematic because the great majority of enrolled subjects were between the ages of 18-38 and 37-64. Effective Treatment rates in the Mentax groups was identical at 51% for these two age groups. There was a relatively small number of Black or Hispanic subjects enrolled in the studies; however, according to the Sponsor there was no indication of a race effect noted.

10.2.5 Drug-Disease Interactions

Drug-disease interactions were not investigated in this study. No drug-disease interactions were apparent.

10.2.6 Drug-Drug

Drug-drug interactions were not investigated in this study. No drug-drug interactions were apparent.

10.2.7 Withdrawal Phenomena/Abuse Potential

Withdrawal phenomena or abuse potential were not addressed in the submission.

10.2.8 Human reproductive Data

Mentax[®] Cream is already approved as a Pregnancy Category B drug. No additional data were submitted.

10.3 Safety Conclusions

Safety has been established for Mentax[®] Cream an approved drug product. Use of Mentax[®] Cream in treatment of tinea versicolor does not appear to present any additional risks.

Resistance

- 11 According to the Sponsor, it is unlikely that it is unlikely that these fungi, *T. mentagrophytes* and , will acquire resistance to butenafine (Vol. 1.15, pg. 1-092); however, it is unknown to this reviewer whether this can be extrapolated to *M. furfur*.

12 Labeling**A. DRAFT PACKAGE INSERT**

8 pages redacted from this section of
the approval package consisted of draft labeling

Pages
35-42

13 Recommendation

It is recommended that NDA 20-524 (SE1-005) be approved for use of Mentax[®] (butenafine HCl cream) Cream, 1%, in treatment of tinea (pityriasis) versicolor applied once daily use for 2 weeks.

Brenda E. Vaughan ~~MD~~ M.D. 5/18/01
Medical Reviewer

cc:

Archival NDA

HFD-540

HFD-540/Division Director/Wilkin 6/5/01

HFD-540/Dermatology Team Leader/Luke 5/18/01

HFD-540/Medical Reviewer/Vaughan

HFD-725/Biostatistics Team Leader/Alosh

HFD-725/Biostatistician/Freidlin

HFD-880/Biopharm/Adebowale

HFD-540/Pharm/Mainigi