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NDA 20-524

1 OF 5

DDA20-524

AP Ltr

Micro

AE Ltr

Chem

MoR

EA + Forst

Pharm/Tax

Memo

Clin. Pharm/Bio

Co. Carres

Bio

Stat

AP Ltr

AE Ltr

OCT 18 1996

NDA 20-524

Penederm Incorporated
Attention: Barry M. Calvarese, M.S.
Executive Director, Clinical/Regulatory Affairs
320 Lakeside Drive, Suite A
Foster City, CA 94404

Dear Mr. Calvarese:

Please refer to your April 4, 1995, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mentax (butenafine hydrochloride cream) Cream, 1%.

Please also refer to our approvable letter dated April 3, 1996.

We acknowledge receipt of your communications dated March 27, April 2, 4, 8, 30, May 8, 30, June 19, August 29, October 3, 8, 16 (2), 17, and 18, 1996.

This new drug application provides for the treatment of interdigital tinea pedis.

We have completed the review of this application as amended, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed revised draft labeling submitted October 18, 1996. Accordingly, the application is approved effective on the date of this letter.

Please be advised that the stability data in your amendment dated October 16, 1996, will only support an expiration dating period of 18 months. The benzy! alcohol assay was out of specification at 24 months. You had proposed a new lower limit for benzyl alcohol of % . We suggest you supplement this application with data justifying this new lower limit and a request that the expiration dating period be extended to 24 months based on this new lower limit.

The final printed labeling (FPL) must be identical to the enclosed revised draft labeling submitted on October 18, 1996. The enclosed revised draft labeling was stated to be acceptable to you in your letter dated October 18, 1996. Marketing the product with FPL that is not identical to enclosed revised draft labeling may render the product misbranded and an unapproved new drug.

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Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-524. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Dermatologic and Dental Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

NDA 20-524

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If you have any questions, please contact:

Frank H. Cross, Jr., M.A., LCDR
Project Manager
(301) 827-2023

Sincerely yours,

M Weintraub 10/14/96

Michael Weintraub, M.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

The reviewers for this application consisted of:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
Linda Katz, M.D., Deputy Division Director, DDDDP, HFD-540
Nancy Slifman, M.D., Medical Officer, DDDDP, HFD-540
R. Srinivasan, Ph.D., Biostatistics Team Leader, DOBIV, HFD-725
Valeria Freidlin, Ph.D., Biostatistician, DOBIV, HFD-725
Abby Jacobs, Ph.D., Pharmacology/Toxicology Team Leader, DDDDP, HFD-540
Kumar Mainigi, Ph.D., Toxicologist, DDDDP, HFD-540
Eric Sheinin, Ph.D., Director, DNDCIII, HFD-830
Wilson DeCamp, Ph.D., Chemistry Team Leader, DNDCIII, HFD-540
Ernie Pappas, Chemist, DNDCIII, HFD-540
Dennis Bashaw, Ph.D., Biopharmaceutics Team Leader, DPEIII, HFD-880
Frank Pelsor, Ph.D., Biopharmaceutics Team Leader, DPEIII, HFD-880
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Peter Cooney, Ph.D., Microbiology Supervisor, ONDC, HFD-805
Paul Stinavage, Ph.D., Microbiologist, ONDC, HFD-805
Maria Rossana R. Cook, M.B.A., Supervisory Project Manager, DOTCDE, HFD-560
Mary Jean Kozma-Fomaro, R.N., M.S.A., Supervisory Project Manager, DDDDP, HFD-540
Frank Cross, Jr., MA, LCDR, Regulatory Management Officer, DDDDP, HFD-540

NDA 20-524

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cc:

Original NDA 20-524
HFD-540/Division File
HFD-540/Derrin File
HFD-2/Lumpkin (with labeling)
HFD-105/Weintraub (with labeling)
HFD-830/Sheinin
DO: San Francisco
HF-2/Medwatch (with labeling)
HFD-80 (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613 (with labeling)
HFD-735/(with labeling)
HFD-222/NCCDD
HFD-540/CHEM/Pappas/10.3.96
HFD-520/MICRO/Dionne/10.2.96
HFD-805/MICRO/Sinavage
HFD-540/PHARM/Mainigi/9.27.96
HFD-725/BIOSTAT/Freidlin/9.30.96
HFD-880/BIOPHARM/Lee/10.1.96
HFD-540/PM/Cross

Concurrence:

HFD-540/DIV DIR/Wilkin/10.11.96
HFD-540/DEP DIR/Katz/10.9.96
HFD-105/Walling/10.14.96
HFD-830/DIV DIR/Sheinin/10.15.96/10.16.96/10.18.96
HFD-540/CHEM SUPV/DeCamp/10.18.96
HFD-540/PHARM SUPV/Jacobs/9.27.96
HFD-520/SUPV MICRO/Sheldon/10.2.96
HFD-805/MICRO/Hussong/10.8.96
HFD-880/BIOPHARM SUPV/Bashaw/10.1.96
HFD-725/BIOSTAT SUPV/Srinivasan/9.30.96
HFD-725/DIV DIR/Harkins/10.1.96
HFD-540/SPM/Kozma-Fornaro/9/27/96
drafted: fhc/September 10, 1996/n20524.ap
revised: 9/27/96, 10/1/96 (label), 10/1/96 (label), 10/7/96 (label), 10/8/96, 10/11/96,
10/17/96, 10/18/96

APPROVAL

NDA 20-524

Penederm Incorporated
Attention: Barry M. Calvarese, M.S.
Executive Director, Clinical/Regulatory Affairs
320 Lakeside Drive, Suite A
Foster City, CA 94404

Dear Mr. Calvarese:

Please refer to your April 4, 1995, New Drug Application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for butenafine hydrochloride cream, 1%.

We acknowledge receipt of your communications dated April 12 and 28, May 18, June 21, August 15, September 29, October 2, 4, 16, and 19, and November 6, 13, 16, and 22, and December 4, 7, and 12, 1995; and, January 3 and 8 (two), February 15, March 1 (two), and 6, 1996.

This new drug application provides for the treatment of interdigital tinea pedis.

We have completed the review of this application, as submitted with draft labeling, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the following:

1. Revised draft labeling for the drug product that is identical to the enclosed draft labeling. Should additional information relating to the safety and effectiveness of this drug become available, further revision of the labeling may be required. Please note that the proposed tradename, submitted on January 3, 1996, is unacceptable because of its similarity to already marketed drug products. The proposed tradename, Mentax, submitted on March 1, 1996, is approved. However, we recommend that you submit the established name of the active ingredient, butenafine HCl, to the USAN Committee.
2. Ail safety information you now have regarding your new drug, in accordance with the requirements of 21 CFR 314.50(d)(5)(vi)(b). Please provide updated information as listed below:

- A. Retabulate all safety data, including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.
 - B. Retabulate drop-outs with new drop-outs identified. Provide discussion where appropriate.
 - C. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.
 - D. Provide details of any significant changes or findings, if any.
 - E. Summarize worldwide experience on the safety of this drug.
3. Please update the new drug application with respect to reports of relevant safety information, including all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.
 4. If not previously reported in the original submission of the NDA, a comprehensive listing of all foreign countries in which butenafine hydrochloride cream, 1%, is marketed, or pending marketing approval, should be submitted.
 5. Data to support the statement that M2 is the primary metabolite in human plasma should be submitted.

6. Regarding the analytical method:

A. Urine sample analysis:

1. The validation results show that the extraction procedure gives a recovery of 69% for M1 itself and 107% for the internal standard, mefenamic acid. The difference in recovery indicates that mefenamic acid is not an ideal internal standard for M1. Additionally, there may be an endogenous compound that interferes with the analysis of M1. An explanation of the high M1 values observed with 2 subjects should be provided.
2. Urine samples appeared to have been stored for an extended period of time before analysis. Data on extended stability at the sample storage temperature should be submitted.

B. Plasma sample analysis:

1. In the analysis, the standard curve was constructed through linear regression using 1/x weighting. Data to demonstrate that this weighting is appropriate should be submitted.
2. The mobile phase for the HPLC/MS/MS analysis used in Study 9425201D should be specified.
3. The assay method and method validations for Study G3 should be provided.

7. The non-confidential Environmental Assessment (EA) is not adequate. Specifically, the sections listed below should be revised and/or clarified:

- A. 2.B.: This section should include either a statement that no proprietary intermediates are used or complete information on the identity, manufacturer, and information regarding introduction of substances to the environment (format item 6) of proprietary intermediates. If proprietary intermediates are manufactured at foreign facilities, certification may be provided instead of information in format item 6 (see Industry Guidance for details).
- B. 4.B.: The last two sentences should be deleted.
- C. 4.D.: The applicant should clarify what materials are disposed of by the companies/facilities listed in Attachments 1 and 2 of the EA; for example, returned goods, rejected batches, manufacturing wastes, etc.

Also the method of disposal, eg., at a licensed incineration and/or landfill, should be specified.

- D. 4.E.: The information included in the confidential EA should be incorporated in its entirety into the non-confidential EA except for deletion of specific confidential information (e.g., identity of the waste disposal sites). Although improperly located in format item 4, this information fulfills the reporting requirements for format item 6.
 - E. 6.C.: The compliance statements should be included in the non-confidential EA.
8. A commitment to comply with the following Phase 4 requests:

Although not required for approval, the following information is requested:

1. Since animal studies suggest disposition of butenafine in the stratum corneum, the dose level may be exaggerated through an increase in total quantity of formulation applied to the skin as well as the amount applied per unit surface area. Therefore, the rationale for using the relatively low amount of (2 mg/cm²) should be provided. It should be noted that the approximate dose for the treatment of tinea pedis would be 1 gram of butenafine cream 1% per foot per application (total of 2 grams of formulation per day; approximately 0.4mg/kg/day [assuming a 50kg patient] of butenafine HCl).
2. The clinical trial protocols stated that butenafine cream was to be applied nightly (see vol. 1.18, p.143 and vol. 1.20, p.144). It was not specified if this was to occur only after bathing. Therefore, it is unclear if the clinical trials were conducted under the conditions of the proposed labeling. If the sponsor desires the medication to remain for a certain period of time before being washed off, then it should be stated as such in the directions for use.
3. It is recommended that additional information be provided to substantiate the diagnosis of familial hyperbilirubinemia for Patient (PDC 010-001). In addition, it is recommended that the sponsor consider re-challenging this patient with the topical administration of butenafine cream to determine if there is a reproducible elevation of bilirubin (with determination of direct and indirect fractions).

4. It is recommended that the results of the Penederm pharmacokinetic study (PDC 010-011) be analyzed by gender.
5. The continued development of an in vitro drug release test method and test specifications for the cream as delineated in Volume 1.2, page 2-0289 of the NDA is encouraged.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD-40
5600 Fishers Lane
Rockville, MD 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In accordance with the policy described in 21 CFR 314.102(d) of the new drug regulations, you may request an informal conference with the members of the Division of Dermatologic and Dental Drug Products to discuss in detail the issues associated with this application. The meeting is to be requested at least fifteen days in advance.

Within ten days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions regarding this application, please contact:

Frank Cross, Jr., MA, LCDR
Project Manager
(301) 827-2020

Sincerely yours,



Michael Weintraub, M.D.
Director
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosures

The reviewers for this application consisted of:

Jonathan K. Wilkin, M.D., Division Director, DODDDP, HFD-540
Linda Katz, M.D., Deputy Division Director, DODDDP, HFD-540
Nancy Slifman, M.D., Medical Officer, DODDDP, HFD-540
R Srinivasan, Ph.D., Biostatistics Team Leader, DOBIV, HFD-725
Valeria Freidlin, Ph.D., Biostatistician, DOBIV, HFD-725
Abby Jacobs, Ph.D., Pharmacology/Toxicology Team Leader, DODDDP, HFD-540
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Dennis Bashaw, Ph.D., Biopharmaceutics Team Leader, DPEIII, HFD-880
Frank Pelsor, Ph.D., Biopharmaceutics Team Leader, DPEIII, HFD-880
Sue-Chih Lee, Ph.D., Biopharmaceuticist, DPEIII, HFD-880
Albert Sheldon, Ph.D., Microbiology Team Leader, DAIDP, HFD-520
Pete Dionne, Ph.D., Microbiologist, DAIDP, HFD-520
Peter Cooney, Ph.D., Microbiology Supervisory, ONDC, HFD-805
Paul Stinavage, Ph.D., Microbiologist, ONDC, HFD-805
Maria Rossana R. Cook, M.B.A., Supervisory Project Manager, DODDDP, HFD-540
Frank Cross, MA, LCDR, Regulatory Management Officer, DODDDP, HFD-540

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cc:

Orig NDA 20-524

HFD-540

HFD-105/Weintraub

HFD-540/Division File

HFD-2/Lumpkin

HFD-735 (with labeling)

HFA-100

HFC-130

HFD-82 (with labeling)

HFD-800

San Francisco District Office

HF-2/Medwatch (with labeling)

HFD-40/Raymond (with labeling)/3-7-96

HFD-613 (with labeling - Only for applications with labeling.)

HFD-540/Derm File

HFD-540/MO/Slifman/3-6-96

HFD-540/CHEM/Pappas/ 3-8-96/4-2-96

HFD-520/MICRO/Dionne/3-6-96

HFD-160/MICRO/Stinavage/3-7-96

HFD-540/PHARM/Mainigi/3-6-96

HFD-725/BIOSTAT/Freidin/3-6-96

HFD-880/BIOPHARM/Lee/3-6-96

HFD-540/PROJ MGR/Cross/3-6-96/3-8-96/3-12-96/3-13-96

Concurrence:

HFD-540/DIR/Wilkin/3-13-96

HFD-540/DEP DIR/Katz/3-13-96

HFD-830/DIR/Sheinin/3-13-96

HFD-540/CHEM SUPV/DeCamp/3-8-96/4-2-96

HFD-540/PHARM SUPV/Jacobs/3-6-96

HFD-520/SUPV MICRO/Sheldon/3-8-96

HFD-160/SUPV MICRO/Cooney/3-7-96

HFD-880/BIOPHARM SUPV/Bashaw/3-7-96/3-12-96

HFD-725/BIOSTAT SUPV/Srinivasan/3-6-96

HFD-540/PROJ MGT SUPV/Cook/3-6-96

APPROVABLE

mOR

~~MAR 5 1996~~

MAR 12 1996

MEDICAL OFFICER'S REVIEW OF NDA 20-524

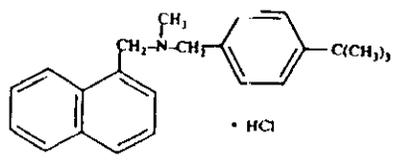
NDA 20-524
M.O. Review #1

Submission date: 4/3/95
Review date: 2/29/96

DRUG NAME:

Generic Name: Butenafine hydrochloride
Proposed Trade Name: Not stated
Chemical Name: *N*-4-*tert* butylbenzyl-*N*-methyl-1-naphthalenemethylamine hydrochloride

Chemical Structure:



Sponsor:

Penederm Incorporated
320 Lakeside Drive, Suite A
Foster City, CA 94404
(415) 358-0100

Pharmacologic Category:

Antifungal
Benzylamine

Proposed Indication:

Treatment of interdigital tinea pedis

Dosage Form and Route of Administration:

1% cream; topical

NDA Drug Classification:

1S

Related Drugs:

Terbinafine HCl cream 1%
Naftifine cream

Related Reviews:

Statistical Review dated: 11/24/95;
Addendum #1: 1/16/96
Addendum #2: 2/20/96
Microbiology Review dated: 7/31/95
Pharmacology Review dated: 8/24/95
Chemistry Review dated: 9/11/95
Biopharm Review dated: 4/4/95; Addendum: 10/16/95

Related Submissions:

IND (Butenafine HCl cream 1%) ✓

Formulation:

<u>Ingredient</u>	<u>Theoretical % w/w</u>
✓ Butenafine HCl	1.0
/ Propylene Glycol Dicaprylate	
✓ Glycerin USP	
✓ Cetyl Alcohol NF	
✓ Glyceryl Monostearate SF	
✓ White Petrolatum USP	
/ Stearic Acid NF	
✓ Polyoxyethylene (23) Cetyl Ether	
/ Benzyl Alcohol NF	
/ Diethanolamine NF	
✓ Sodium Benzoate NF	
✓ Purified Water USP	

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3. MATERIAL REVIEWED Volumes 1.1, 1.16 - 1.23
Updated post-marketing surveillance reports from Japan submitted as new correspondence dated 12/12/95
4. CHEMISTRY/
MANUFACTURING CONTROLS See Chemistry review by E. Pappas
5. ANIMAL PHARMACOLOGY/
TOXICOLOGY See Pharm/Tox review by K. Mainigi.

Dr. Mainigi has recommended that the pregnancy subsection of the proposed labeling be revised to include the pregnancy category of the drug and the studies performed to support the proposed category.

Carcinogenicity studies in animals (oral or dermal) were not performed with this drug.

6. CLINICAL BACKGROUND

6.1 Relevant human experience

Butenafine HCl is a benzylamine derivative which is structurally similar to the allylamine class of antifungal drugs. Other approved allylamine topical antifungal drugs include naftifine and terbinafine. The mechanism of action of butenafine is thought to be by the inhibition of squalene epoxidation with resultant inhibition of ergosterol biosynthesis, a required lipid component of most fungal cell membranes. This is in distinction to the imidazole derivatives which block a later process in the ergosterol biosynthesis pathway involving 14- α -demethylation of lanosterol and are cytochrome P450-dependent.

Butenafine has *in vitro* activity against many pathogenic fungi, including dermatophytes and yeasts. In *in vitro* studies, butenafine may be fungistatic or fungicidal, depending on the fungal species and strain tested and the concentration of butenafine used.

Butenafine HCl has been marketed in Japan since 1992 as a 1% cream and a 1% lotion/gel for the treatment of tinea pedis, tinea cruris and tinea corporis due to dermatophytes, and tinea versicolor.

6.2 Foreign experience

According to the submission, butenafine cream has not been withdrawn from the Japanese market. It is not stated whether butenafine cream is marketed in any other foreign countries or whether any applications are pending.

Reviewer's Comment:

The above information should be submitted to the NDA. In addition, all safety information from foreign markets should be submitted to the NDA.

6.3 Human Pharmacology, Pharmacokinetics, Pharmacodynamics

6.3.1 Pharmacokinetics

Two pharmacokinetic studies were conducted in support of this NDA. These studies are summarized below. In addition, plasma levels of butenafine and its major metabolite (M2) were measured as part of one of the pivotal clinical trials (PDC 010-002) (see section 8.1.2 for review).

Study No. and Title	Dose	Dosage Form	Study Design	No. of Subjects
Study G-3 Single and Multiple Application Study of KP-363, a New Antifungal Agent, in Healthy Adults	5 grams	Butenafine HCl Cream 1% (PD-010-C-001)	Drug was applied to the dorsal skin (20 X 25cm) for 12 hrs. daily, either for 1 day or 7 days (semi-occlusion)	5 - single dose study 5 - multiple dose study
PDC 010-011 A Single Center, Open Label Study to Determine the Plasma Level of Butenafine following Multiple Topical Applications of Butenafine HCl 1% Cream to Normal Volunteers	6 grams and 20 grams	Butenafine HCl Cream 1% (PD-010-C-003)	6 g group: Drug was applied to the posterior trunk daily for 14 days 20 g group: Drug was applied to the arms, trunk, and groin daily for 14 days	7 - 6 g group 12 - 20 g group

Study Title: Single and Multiple Application Study of KP-363, a New Antifungal Agent, in Healthy Adults (Study G-3)

Method: This study was performed at the _____ using butenafine cream 1% (PD-010-C-001).

Single dose: Five grams of material was applied to the dorsal skin (20 X 25 cm) of 5 male subjects. The site was covered with gauze for 12 hours, after which time the drug remaining on the skin was removed and the skin wiped 10 times with moistened cotton to determine the recovered drug.

Multiple dose: The material was applied to the skin of 5 male subjects as described above, once daily for 7 days.

Results: After a single dose of butenafine, plasma levels of butenafine increased until removal from the skin surface at 12 hours. The mean plasma C_{max} was 4.0 ± 1.6 ng/mL. In the multiple dose study, the mean plasma C_{max} ranged from 4.3 ± 3.0 (day 1) to 4.8 ± 2.3 ng/mL (day 7). The $T_{1/2}$ was 26.0 hours (determined after day 7). Assuming complete formulation recovery from the skin surface, **penetration into the stratum corneum represented approximately 20% of the dose.**

Study Title: A Single Center, Open Label Study to Determine the Plasma Level of Butenafine following Multiple Topical Applications of Butenafine HCl 1% Cream to Normal Volunteers (PDC 010-011)

Investigator:

Method: This study was divided into 2 dosing groups. The test material for all subjects was butenafine cream 1% (PD-010-C-003), the formulation intended to be marketed.

Low Dose: Application of 6 grams of butenafine cream 1% to the posterior trunk of normal subjects (approximately 3000 cm²) daily for 14 days.

High Dose: Application of 20 grams of butenafine cream 1% to the arms, trunk, and groin of normal subjects (approximately 10,000 cm²) daily for 14 days.

Blood and urine samples were collected at specified times.

Results: Eight subjects were enrolled into the Low Dose group, of which 7 were evaluable (4M/3F; age range 20 - 44 years). (One patient was not evaluable due to loss of blood samples). Twelve subjects were enrolled into the High Dose group (6M/6F; age range 21 - 65 years). At a daily dose of 6 grams, the mean plasma steady-state C_{max} value for butenafine was 1.43 ± 0.78 ng/mL. At a daily dose of 20 grams, the mean plasma steady-state C_{max} value for butenafine was 5.03 ± 2.04 ng/mL. Extremely low levels of butenafine persisted for > 100 hours following the last dose. Precise estimates of the terminal elimination rate and half-life for butenafine were not able to be calculated due to the lack of sampling timepoints. The effective half-life obtained from plasma concentrations, determined immediately after the steady-state peak, appeared to be about 35 hours. The $T_{max,ss}$ for the 20-gram group was significantly earlier (5.8 hours) than the 6-gram group (15.5 hours).

There were 11 adverse events related to the skin (occurring in 6 patients) in the High Dose group. These consisted of pruritus, "rash," papules, and tingling over the shoulders. In the Low Dose group, there was 1 adverse event reported, and consisted of pruritus. All adverse events related to the skin were considered mild. There were no laboratory abnormalities of clinical significance.

Reviewer's Comment:

1) As noted by the investigator, the actual amount of formulation applied to each subject was less than the theoretical value so that each subject received less than the target concentration of 2mg/cm² (approximately 1.7mg butenafine cream/ cm²).

2) It is recommended that the results of the Penederm pharmacokinetic study be analyzed by gender.

3) It is of note that the Kaken study, in which 5 grams of material was applied to each subject, showed the mean plasma C_{max} to be approximately 4.8 ng/mL whereas the Penederm study showed in the 6-gram group, the mean plasma steady-state C_{max} was approximately 1.4 ng/mL. The difference between the 2 studies may have been due to the difference in the amount of drug material applied per cm²: in the Kaken study, 10mg of formulation was applied per cm² in contrast to the Penederm study in which 2mg of formulation was applied per cm². It is possible that the thickness of the layer of applied drug may have affected the percutaneous absorption of the drug material.

4) It should be noted that the approximate dose for the treatment of tinea pedis would be 1 gram of butenafine cream 1% **per foot per application** (total of 2 grams of formulation per day; approximately 0.4mg/kg/day of butenafine HCl [assuming a 50kg patient]). In the Penederm study, the plasma C_{max} obtained in the 20-gram group (4mg of butenafine HCl/kg/day) was approximately 5 ng/mL. In a 12-month study in dogs, the mean serum C_{max} was 352 ng/mL after daily application of 100mg of butenafine HCl/kg/day. There was no reported systemic toxicity at this dose level (see vol. 1.1, p.88). The systemic no-adverse effect dose level after topical administration of butenafine HCl to intact skin of rats was 15mg/kg/day (mild systemic effects were seen at doses of 50mg/kg and greater).

5) **The design of the Penederm study did not enable the determination of percent percutaneous absorption.**

6.4 Directions for Use

The sponsor has proposed that the directions for use in the label state: "... apply to cover the affected and immediately surrounding skin once daily after bathing for 4 weeks."

Reviewer's Comment:

The clinical trial protocols stated that butenafine cream was to be applied nightly (see vol. 1.18, p.143 and vol. 1.20, p.144). It was not specified if this was to occur only after bathing. Therefore, it is unclear if the clinical trials were conducted under the conditions of the proposed labeling (i.e., after bathing).

7. DESCRIPTION OF CLINICAL DATA SOURCES

The data that serve as the basis for this review were obtained from the applicant's original NDA submission. In addition, updated post-marketing surveillance from Japan was submitted as to the original NDA on December 12, 1995.

Sixteen clinical studies were conducted to evaluate the safety and efficacy of butenafine cream 1%. These include 7 studies of cutaneous safety, 2 pharmacokinetic studies, and 2 Phase 3 controlled clinical trials conducted in patients with tinea pedis. The remaining 5 studies were uncontrolled clinical trials which were conducted in Japan and Europe.

CLINICAL STUDIES

Study #	Study Description	# of Subjects	Duration
1. Study G-1 Japan	Primary irritation	36	48 hrs.
2. PDC 010-009	Primary irritation	17	24 hrs.
3. PDC 010-010	21-day cumulative irritation	24	21 days
4. PDC 010-006	Contact sensitization (Repeat Insult Patch Test)	204	3 wks./ Rechallenge after 2 wks.
5. Study G-2 Japan	Phototoxicity	30	48hrs/Evaluation after 24 hrs.
6. PDC 010-007	Phototoxicity	27	24hrs/Evaluation after 48 hrs.
7. PDC 010-008	Photoallergy Potential	31	3 wks./ Rechallenge after 2 wks.
8. Study G-3 Japan	Pharmacokinetics	5: single dose 5: multiple dose	24hrs. and 7 days
9. PDC 010-011	Pharmacokinetics	7: 6 grams/appl. 12: 20 grams/appl.	14 days
10. PDC 010-001	Efficacy study in tinea pedis (Butenafine/Veh control)	53 But 52 Veh	4 wks. therapy/ 4 wks. post-Rx
11. PDC 010-002	Efficacy study in tinea pedis (Butenafine/Veh control)	40 But 40 Veh	4 wks. therapy/ 4 wks. post-Rx

8. CLINICAL STUDIES

UNCONTROLLED CLINICAL STUDIES

The following studies are categorized as uncontrolled clinical studies because they were open label, did not utilize a vehicle control, did not require a culture after the baseline visit as the criterion for mycological cure, and/or did not assess efficacy after the cessation of therapy (no follow-up visit).

Uncontrolled Clinical Studies

Protocol Number	Design	No. Patients	Study Duration	Indication	Results
Study G-4	Open label No vehicle control No culture at end of treatment Majority of baseline cultures were <i>T. mentag</i>	Study conducted in Japan. 206 tinea pedis/manuum 113M 93F 175 evaluable	QD X 4 weeks for tinea pedis/manuum, 2 weeks for other tinea	Tinea pedis/manuum Tinea cruris Tinea corporis Candidiasis Tinea versicolor	39% of tinea pedis/manuum pts had response of "Excellent" (markedly improved + negative KOH) at week 4. Local adverse events: Irritation - 6pts Contact dermatitis - 6pts Erythema - 6pts Itching - 2pts
Study G-5	Double-blind No vehicle control Active control (bifonazole cream) No culture at end of treatment Baseline cultures approx. 50% <i>T. mentag</i> and approx. 50% <i>T. rubrum</i>	Study conducted in Japan. 126 butenafine 62M 64F 99 evaluable 103 evaluable bifonazole	QD X 4 weeks for tinea pedis, 2 weeks for other tinea	Tinea pedis Tinea cruris Tinea corporis Candidiasis Tinea versicolor	46% butenafine and 40% bifonazole tinea pedis pts showed "Excellent" response at week 4. Local adverse events: Erythema - 2pts Itching - 3pts Papules - 1pt
Study G-6	Open label No vehicle control Active control (clotrimazole cream) No culture at end of treatment Majority of baseline cultures were <i>T. rubrum</i>	Study conducted in Japan. 25 butenafine 14M 11F 19 evaluable 17 evaluable clotrimazole	QD X 4 wks for butenafine versus BID X 4 wks for clotrimazole	Tinea pedis	52% butenafine and 53% clotrimazole pts showed "Excellent" response at week 4. Local adverse events: None reported
Study G-7	Open label No vehicle control No culture at end of treatment Approx. 60% of baseline cultures were <i>T. mentag</i>	Study conducted in Japan 20 tinea pedis (gender not reported)	QD X 4 weeks for tinea pedis, 2 weeks for other tinea	Tinea pedis Tinea cruris Tinea corporis Candidiasis Tinea versicolor	40% of tinea pedis pts showed "Excellent" response at week 4 Local adverse events: Contact dermatitis - 1pt

Protocol Number	Design	No. Patients	Study Duration	Indication	Results
Study 90 BUT 02	Double blind No vehicle control Active control (bifonazole cream) Repeat culture 1 week post treatment Majority of baseline cultures were <i>T rubrum</i>	Study conducted in Europe 60 evaluable butenafine 64 evaluable bifonazole	QD X 2 - 5 weeks (1 week after clinical cure)	Tinea pedis	"Overall cure" rate at 1 week post-treatment was 37% for butenafine and 39% for bifonazole. Local adverse events None reported

CONTROLLED CLINICAL STUDIES

In support of this NDA, 2 multicenter (Protocol PDC 010-001 and Protocol PDC 010-002), double-blind, parallel group, vehicle-controlled studies using identical protocols were conducted in patients with interdigital tinea pedis in which the drug product was applied nightly for 4 weeks followed by a 4-week post-treatment period (total length of study was 8 weeks).

Objective/Rationale:

The objective of each study was to evaluate the efficacy and safety of butenafine cream 1% in the treatment of interdigital tinea pedis.

Study Design:

Each study was a multicenter, randomized, double-blind, vehicle-controlled, parallel group study in which patients received treatment for 4 weeks, followed by a 4-week post-treatment follow-up period. Each study was conducted on an outpatient basis.

PROTOCOL

Inclusion Criteria:

- 1) Male or female
- 2) Age over 12 years
- 3) Symptomatic interdigital tinea pedis with the target site characterized by:

(1) **Erythema** with a score of at least 2 where 0 = absent, 1 = mild (barely perceptible), 2 = moderate (definitely present), and 3 = severe (marked, intense)

AND

(2) **Scaling or pruritus** with a score of at least 2 (moderate) using the above grading scale.

Thus, the **minimum total score for inclusion**, based on these clinical parameters, was 4.

- 4) Positive KOH
- 5) Positive fungal culture
- 6) Signed informed consent

Reviewer's Comment:

*The sponsor should be aware that the "positive fungal culture" at baseline must be **positive for a dermatophyte**, since it is those organisms for which the labeled indication is being sought.*

Exclusion Criteria:

- 1) Confluent, diffuse moccasin-type tinea pedis of the entire plantar surface
- 2) Presence of onychomycosis
- 3) Presence of concomitant fungal infections
- 4) Use of any topical antifungal treatment during the previous 2 weeks
- 5) Use of systemic antifungal treatment in the previous 3 months
- 6) Use of immunosuppressive drugs during the previous 3 months
- 7) Current use of antihistamines, antibiotics, or immunosuppressive drugs
- 8) Known hypersensitivity to allylamine derivatives or to any ingredients in the formulation
- 9) Pregnancy or lactation
- 10) For women of childbearing potential, not using adequate contraception to prevent pregnancy
- 11) Any significant disease of the hepatic, renal, endocrine (e.g., diabetes mellitus), or immune systems
- 12) Clinically significant abnormal laboratory results (suggested to be >2X the upper limit of normal, although the final determination was made by each investigator)
- 13) Presence of atopic dermatitis or contact dermatitis of the foot, psoriasis, or any other disease that could interfere with the evaluation
- 14) Use of any investigational drug in the previous 30 days
- 15) Previous enrollment in this protocol

Dosage and Duration of Treatment:

The study medication was applied to the infected areas between each toe of the target foot and to the immediately surrounding skin every night for 4 weeks. Patients were allowed to treat both feet, if infected. The 4-week treatment phase was followed by an additional 4-week post-treatment period.

Study Procedures:

At the baseline visit, a medical history and physical examination were performed. A dermatologic examination was performed to confirm the presence of interdigital tinea pedis and a target lesion was selected for clinical assessment and mycologic sampling throughout the study. If the patient had clinical evidence of tinea pedis on both feet, both feet were allowed to be treated, but the more severe target lesion and foot were selected for treatment during the study. Patients were allowed to enter the study based on the clinical findings and KOH examination, with results of the fungal culture pending. At the end of week 2, if the fungal culture was negative, the patient was not considered evaluable for efficacy (see "Statistical Considerations" section below). Baseline laboratory studies were performed and, for women of childbearing potential, a urine pregnancy test was obtained. After meeting the entry criteria, patients were randomized and one, 30-gram tube of medication was dispensed. The patients were instructed to apply the medication as noted above under "Dosage and Duration of Treatment." Repeat clinical evaluations, KOH examinations, and fungal cultures were performed at weeks 1, 2, 4, and 8. The post-baseline fungal cultures were held for 4 weeks before being declared negative. Repeat laboratory studies were obtained at weeks 2 and 4. Adverse events were recorded at all follow-up visits.

Reviewer's Comment:

As previously discussed with the sponsor, in order to reduce investigator bias, reading of the KOH slide by an investigator other than the one performing the clinical evaluation would be preferred.

Endpoints:

The following procedures/examinations were performed at baseline, weeks 1, 2, 4, and 8 except for the Investigator's Global Response and the Patient Perception of Response which were performed at all visits except baseline.

- 1) **Fungal culture**
- 2) **KOH examination**
- 3) **Signs and symptoms** of the target lesion site and the target foot excluding the target lesion, including:
 - Cracking/fissures
 - Erythema
 - Scaling
 - Maceration
 - Pruritus
 - Burning/stinging

Each sign/symptom was scored using the following 4-point scale:

- 0 = absent (none)
- 1 = mild (barely perceptible)
- 2 = moderate (definitely present)
- 3 = severe (marked, intense)

4) The **Investigator's Global Response** of the target foot was graded using the following 7-point scale:

- Cleared = 100% remission of clinical signs and symptoms compared to baseline
- Excellent = 80% - 99% improvement of clinical signs and symptoms compared to baseline
- Good = 50% - 79% improvement of clinical signs and symptoms compared to baseline
- Fair = 25% - 49% improvement of clinical signs and symptoms compared to baseline
- Poor = < 25% improvement of clinical signs and symptoms compared to baseline
- Unchanged = Unchanged clinical signs and symptoms compared to baseline
- Worse = Deterioration of clinical signs and symptoms compared to baseline

5) The **Patient Perception of Response**, when asked the question "How does your athlete's foot condition appear to you now versus when you began the study," was graded using the following 5-point scale:

- 5 = Greatly improved
- 4 = Somewhat improved
- 3 = No change
- 2 = Somewhat worse
- 1 = Much worse

The **primary efficacy variables** were defined by the sponsor as below. The primary efficacy endpoint was at **week 8** (4 weeks post-treatment).

- 1) **Mycological Cure** - Negative KOH and negative culture
- 2) **Effective Treatment** - Mycological Cure **and** a score of "Cleared" **or** "Excellent" on the Investigator's Global Response
- 3) **Overall Cure** - Mycological Cure **and** a score of "Cleared" on the Investigator's Global Response

The secondary efficacy variables were defined by the sponsor as the following:

- 1) Effective Clinical Response - A score of "Cleared" or "Excellent" on the Investigator's Global Response
- 2) Total Signs and Symptoms Score
- 3) Patient Perception of Response

Reviewer's Comment:

1) In previous discussions with the sponsor, the sponsor was informed that the preferred **primary efficacy variable** in support of an NDA for this drug product for the indication of tinea pedis would be "Overall Cure" as defined above (see Memorandum of Teleconference dated March 13, 1995, in response to the minutes of the pre-NDA meeting). A Total Signs and Symptoms score of 0, when used with Mycological Cure, should support the above definition of "Overall Cure."

2) As previously discussed with the sponsor, "Effective Treatment," as defined above, would be considered a **secondary efficacy variable** and only supportive in the determination of efficacy. In the clinical trials submitted in support of this NDA for butenafine cream, because the definition of "Excellent" allows a lower limit of 80% improvement, a "Total Signs and Symptoms Score of 0 or 1" (plus "Mycological Cure") may be a more stringent, and preferable, measure to support efficacy of this drug product. However, because the efficacy of butenafine cream is assessed at week 8, in my opinion, this should provide sufficient time to ensure essentially complete healing of the skin, if the therapy is effective, thus supporting the use of "Overall Cure" as the primary efficacy variable for these studies of interdigital tinea pedis.

3) "Mycological Cure," although necessary, would not be sufficient by itself as a primary efficacy variable.

4) For purposes of this review, since the proposed indication is the treatment of dermatophytes, only those patients with a baseline fungal culture positive for a dermatophyte will be considered in the efficacy analyses.

Statistical Considerations:

Patient Population

Patients were conditionally enrolled pending the results of their baseline fungal culture and laboratory studies. Patients whose baseline fungal culture was negative or who had a significantly abnormal laboratory result were terminated early from the study. Patients with a **delayed positive culture** were considered evaluable. A delayed positive culture was defined as a baseline fungal culture that was negative, but a positive culture that had been obtained at either week 1 or week 2.

Statistical Methods

Definitions

According to the sponsor, a **modified intent-to-treat (MITT)** study population was defined as the following:

- 1) Patients who met all inclusion/exclusion criteria and were randomized to the study medication at baseline
- 2) Patients with a positive baseline culture or delayed positive culture
- 3) Patients without clinically significant abnormal baseline laboratory results
- 4) Patients without protocol violations
- 5) Patients with at least 1 post-baseline follow-up visit

Data from visits that were missed at weeks 1, 2, or 4 was imputed by carrying forward from the last preceding non-missed visit. Visits at weeks 1, 2, or 4 that occurred outside the specified window of ± 3 days of the scheduled visit were handled in the following way:

- a) if the patient was early by more than 3 days for the visits at week 1, 2, or 4, the data for that visit were entered as if the visit had occurred at the appropriate time
- b) if the patient was late by more than 3 days for the week 1 or 2 visit, the data were excluded and the data from the preceding visit carried forward
- c) if the patient was late by more than 3 days for the week 4 visit, but it could be documented that the patient discontinued the medication within ± 3 days of the scheduled visit, then the data was retained as if the visit had occurred at the appropriate time
- d) if documentation could not be provided, then the data for the week 4 visit was excluded and data from the immediately preceding visit were carried forward

If the "week 8" visit occurred early, then the data was carried forward as if it had occurred at week 8. If the "week 8" visit occurred after the scheduled week 8 visit, then the data was carried back to week 8 as if it had occurred at the scheduled visit. If the week 8 visit was missed, data from the most recent visit was carried forward and imputed to week 8.

The "sponsor's per protocol" study population was defined by the sponsor as being identical to the MITT population **with the exception of the week 8 data**. The "window" for the week 8 visit was defined as from **5 days early to 16 days late** from the scheduled week 8 visit. Visits that did not occur within this window were not included in the week 8 analysis.

The "original per protocol" study population was identical to the sponsor's per protocol population except that the "window" for the week 8 visit was defined as ± 3 days from the scheduled week 8 visit.

Patients who were terminated early due to a treatment-related adverse event or lack of efficacy were categorized as failures.

Reviewer's Comment:

1) It should be noted that the original protocol stated that a window of ± 3 days would be used for all visits (see vol 1.18, pp. 22 and 140). Although a long "window" for the week 8 visit might theoretically allow for a greater chance of relapse, it may also allow for a greater chance of achieving a "cleared" score. A reanalysis of the week 8 data using the original window of ± 3 days will be performed by the FDA biostatistician to address this question.

2) The week 8 visit was calculated to be 4 weeks after the date of last use of the medication, as noted on the SAS data listing. In most instances, the last use of medication was the evening prior to the week 4 visit. However, in some instances, according to the submitted line listings, the week 4 visit and date of last use of medication were identical. This is most likely an error, since the patients were instructed to discontinue use of the medication prior to the evaluation. These patients are noted with an asterisk in the listing of Appendix 1.

Methods

The Wilcoxon rank-sum test was used to statistically analyze the parameter of age; the Fisher's exact test was used to analyze race and gender. The primary efficacy variables (defined above in the section "Endpoints") were analyzed using the Cochran-Mantel-Haenszel (CMH) test of response by treatment partialled on investigator. 95% confidence intervals for the difference between butenafine cure rate and vehicle cure rate were computed using the formula for the difference between 2 binomial proportions. The Total Signs and Symptoms Scores were summed and analyzed using the Wilcoxon rank-sum test. Laboratory data were grouped into Low, Normal, and High according to normal ranges provided by the central laboratory. Shift tables were used to display change from baseline. The sign test was used to test for a shift in the median of the test distribution.

8.1.1

STUDY #1

Title:

A Double-Blind Evaluation of Butenafine HCl Cream 1% and Vehicle in the Treatment of Tinea Pedis (Protocol PDC 010-001)

Investigators:

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8.1.1.1 Study Design

See Section 8.0

8.1.1.2 PROTOCOL

8.1.1.2.1 Population/Procedures

A total of 150 patients were enrolled at 6 sites and were randomized to either the butenafine or the vehicle treatment groups. The "Study Procedure" is described above in section 8.0.

8.1.1.3 RESULTS

8.1.1.3.1 Population Enrolled/Analyzed

Of the 150 patients enrolled, 77 were enrolled in the butenafine treatment group and 73 patients in the vehicle group. Of these 150 patients, 40 (23 butenafine/17 vehicle) were excluded because of lack of a positive fungal culture at baseline or lack of a "delayed positive" culture at week 1 or week 2. An additional 5 patients were excluded as follows: abnormal baseline laboratory results (2 vehicle patients), lost-to-follow-up at baseline (2 vehicle patients), and misdiagnosis of moccasin-type tinea pedis (1 butenafine patient). Thus, there were 105 patients (53 butenafine and 52 vehicle) who were considered evaluable (See Table 1).

Table 1 - - Patients Enrolled and Evaluability (at baseline)

	Butenafine	Vehicle	All patients
# of Patients Enrolled	77	73	150
Not evaluable			
Negative baseline fungal culture	22 (30%)	17 (23%)	39 (26%)
Abnormal baseline laboratory results*	1	2	3
No post-baseline follow-up visit	0	2	2
Moccasin-type tinea pedis	1	0	1
Total # not evaluable	24 (32%)	21 (29%)	45 (30%)
Total # Evaluable (MITT population)	53 (67%)	52 (71%)	105 (70%)

* Includes Patient [REDACTED] (butenafine) with elevated SGOT/PT, Patient [REDACTED] (vehicle) with unstated laboratory abnormality, and Patient [REDACTED] (vehicle) with elevated SGOT/PT

Reviewer's Comment:

A relatively large percent of patients, in both treatment arms, were excluded from the evaluable patient population due to negative baseline fungal cultures. This is of interest, since these patients met the other study criteria of positive KOH and minimal clinical findings. For future studies of topical antifungal drug products, it may be of interest to include those patients with a negative fungal culture (but who meet the other study criteria by having a positive KOH and clinical findings) in the study to determine their response, since, in practice, the diagnosis of tinea pedis is frequently made on clinical grounds alone.

The demographics of the evaluable population is shown in Table 2.

Table 2 - - Demographics of Evaluable Patients (MITT population)

	Butenafine	Vehicle	p-value
No. of Patients	53	52	
Male	40 (75%)	37 (71%)	0.663*
Female	13 (25%)	15 (29%)	
Age Mean yrs ± SD Range (yrs)	36.8 ± 13.3	39.5 ± 13	0.290†
Caucasian	20 (38%)	27 (52%)	0.440*
Hispanic	19 (36%)	16 (31%)	
African-American	12 (23%)	7 (13%)	
Asian	2 (4%)	2 (4%)	

* Fisher's Exact Test (2-tailed)

† Wilcoxon rank-sum test

Reviewer's Comment:

There were more males than females in the study. However, the numbers of males and females were balanced between both treatment arms, as shown by the Fisher's Exact test (2-tailed) in Table 2.

The number of evaluable patients is shown in Table 3, listed by investigator, treatment group, and type of statistical analysis.

Table 3 - - Patient Enrollment and Evaluability

Investigator	Treatment Group	Patients Enrolled	Evaluable (wk 8) (MITT)	Evaluable (wk 8) (per protocol*)
Beutner	Butenafine	2 (3%)	1 (2%)	1 (2%)
	Vehicle	0 (0%)	0 (0%)	0 (0%)
	Total	2 (1%)	1 (1%)	1 (1%)
Cullen	Butenafine	13 (23%)	12 (23%)	12 (24%)
	Vehicle	18 (25%)	15 (29%)	12 (26%)
	Total	36 (24%)	27 (26%)	24 (25%)
Reyes	Butenafine	19 (25%)	17 (32%)	15 (30%)
	Vehicle	17 (23%)	14 (27%)	13 (29%)
	Total	36 (24%)	31 (30%)	28 (30%)
Rosen	Butenafine	15 (19%)	10 (19%)	9 (18%)
	Vehicle	16 (22%)	9 (17%)	8 (18%)
	Total	31 (21%)	19 (18%)	17 (18%)
Shupack	Butenafine	14 (18%)	9 (17%)	9 (18%)
	Vehicle	13 (18%)	7 (13%)	6 (13%)
	Total	27 (18%)	16 (15%)	15 (16%)
Weinstein	Butenafine	9 (12%)	4 (8%)	4 (8%)
	Vehicle	9 (12%)	7 (13%)	6 (13%)
	Total	18 (12%)	11 (10%)	10 (10%)
Total	Butenafine	77	53	50
	Vehicle	73	52	45
TOTAL		150	105	95

* The definition of "per protocol" is based on the sponsor's definition as stated in the section above under "Statistical Considerations."

According to the sponsor, there were 3 patients who terminated early from the study (see Table 4). It should be noted that patient [redacted], who withdrew because of lack of efficacy, **was included in the sponsor's per protocol analysis for week 8** by carrying forward the data from the last non-missed visit. The other 2 patients were excluded from the per protocol analysis at week 8. There were no patients who were discontinued early from the study due to an adverse event.

Table 4 - - Reasons for Early Termination

Patient #	Investigator	Treatment Group	Reason for withdrawal	Included in sponsor's per protocol analysis at wk 8?
	Reyes	Butenafine	Lost to follow-up. Withdrew after 1 wk.	No
	Cullen	Vehicle	Lack of efficacy. Withdrew after wk 2.	Yes
	Cullen	Vehicle	Death in family. Withdrew after wk 1.	No

* The results of this patient were "carried-forward" because the early termination was due to lack of efficacy.

There were 8 additional patients (2 butenafine/6 vehicle) whom the sponsor included in the MITT analysis, but were considered unevaluable at week 8 in the sponsor's per protocol analysis. As shown in Table 5, these patients were considered unevaluable at week 8 either because their visit occurred more than 5 days before the scheduled week 8 visit (4 patients: 1 butenafine/3 vehicle) or because of a negative culture at baseline (4 patients: 1 butenafine/3 vehicle). (See Appendix 1 for line listing of evaluability of patients).

Table 5 - - Reasons for Unevaluable Patients at Week 8 (not included in sponsor's per protocol analysis)*

Patient #	Investigator	Treatment Group	Reason for Unevaluable at Week 8	Time of Termination from Study
	Reyes	Butenafine	Baseline culture incorrectly reported as negative. Later found to be positive for <i>T. rubrum</i> .	Pt. terminated after wk 2.
	Rosen	Butenafine	Week 8 visit occurred 10 days early.	
	Cullen	Vehicle	Week 8 visit occurred 7 days early.	
	Cullen	Vehicle	Baseline culture negative. Positive culture from wk 1 (delayed positive culture).	Pt. terminated after wk 4.
	Reyes	Vehicle	Baseline culture negative. Positive culture from wk 1 (delayed positive culture).	Pt. terminated after wk 4.
	Rosen	Vehicle	Week 8 visit occurred 7 days early.	
	Shupack	Vehicle	Week 8 visit occurred 6 days early.	
	Weinstein	Vehicle	Baseline culture negative. Positive culture from wk 2 (delayed positive culture).	Pt. terminated after wk 2.

* Based on Table B, vol. 1.18, p.28

There were 15 patients (6 butenafine/9 vehicle) who were considered by the sponsor to have had protocol deviations, but were retained in the analyses. These patients are summarized in Table 6.

Table 6 - - Summary of Protocol Deviations

Patient #	Investigator	Treatment Group	Reason
	Cullen	Butenafine	Enrolled in study on 5/12/94. Began amoxicillin for URI on 5/29 for 1 wk. until 6/5. Last day of study medication on 6/7.
	Cullen	Butenafine	Enrolled in study on 9/14/94. Reported not having used study medication at time of wk 1 visit. Still had signs/symptoms and positive KOH (repeat culture was not performed, but culture from 9/14 was positive). Pt. re-enrolled on 9/20.
	Rosen	Butenafine	Week 4 culture discarded after 2 weeks (negative for fungus at that time). Should have been held for 4 weeks before being declared negative.
	Rosen	Butenafine	Enrolled in study on 8/30/94. Started applying Lotrimin™ cream bid to the face on 9/14 for seborrheic dermatitis. Stopped Lotrimin™ on 9/21. Last day of study medication on 10/14.
	Rosen	Butenafine	Lost wk 1 culture.
	Shupack	Butenafine	Elevated bilirubin at wks 2, 4, and 6.
	Cullen	Vehicle	Enrolled in study on 5/25/94. Did not start using study medication until 5/27. Baseline enrollment date changed to 5/27.
	Cullen	Vehicle	Used study medication for only 24 days (instead of 28 days as specified in protocol).
	Cullen	Vehicle	Inadequate birth control, as specified in protocol.
	Cullen	Vehicle	Baseline culture was negative and pt. should have been terminated from study. However, culture from wk 1 was positive. Patient had completed 4 weeks of treatment with study medication.
	Reyes	Vehicle	Enrolled in study on 5/3/94. Started applying Temovate™ cream to an insect bite on the leg on 5/11 for 3 days. Last day of study medication on 5/31.

Patient #	Investigator	Treatment Group	Reason
	Reyes	Vehicle	Enrolled in study on 9/6/94. Started nitrofurantoin on 9/8 for UTI for 9 days until 9/17. Last day of study medication on 10/5.
	Rosen	Vehicle	Baseline culture sent to Fungus Testing Lab after 2-week time period specified in protocol.
	Shupack	Vehicle	Enrolled in study on 6/3/94. Last day of study medication 6/30. Started oral antibiotic (not specified) for UTI on 7/21. Wk 8 visit on 7/27.
	Weinstein	Vehicle	Concomitant tinea versicolor. Not treated during the study.

Comparability of the treatment groups at baseline of pathogens, previous tinea pedis episodes, and the Total Signs/Symptoms Score is shown below (Tables 7 and 8).

Table 7 - - Baseline Distribution of Pathogens, Combined Investigators*

Pathogen	Butenafine (n=53)	Vehicle (n=52)
<i>T. rubrum</i>	42 (79%)	46 (88%)
<i>T. mentagrophytes</i>	7 (13%)	5 (10%)
<i>E. floccosum</i>	4 (8%)	1 (2%)

* Based on Table 4a, vol. 1.18, p.56

* One patient had *T. mentagrophytes* at baseline and *T. rubrum* at week 8. See Comment #1 below.

Reviewer's Comment:

1) It should be noted that the above table is different from that submitted by the sponsor (vol 1.18, p.56). The sponsor noted that 1 patient (vehicle) had a baseline culture of *T. mentagrophytes* and a week 8 culture of *T. rubrum*. For the above table, this patient was considered to have only *T. mentagrophytes* at baseline.

2) The p-value (Fisher's Exact test) was 0.3 (see Biostatistics review, p. 6). It should be noted that this lack of statistical significance may be because of the small sample size. There is a potential difference in therapeutic response depending on the pathogen, with some authors feeling that *T. rubrum* is more difficult to cure than the other dermatophytes.

3) Examination of the distribution of pathogens by investigator shows that both Dr. Cullen and Dr. Rosen had more a greater percentage of patients with *T. rubrum* in the vehicle treatment group vs. the butenafine treatment group as shown below:

	Butenafine	Vehicle
Cullen		
<i>T. rubrum</i>	9 (75%)	15 (100%)
<i>T. mentag</i>	2 (17%)	0
<i>E. floccosum</i>	1 (8%)	0
Rosen		
<i>T. rubrum</i>	7 (70%)	9 (100%)
<i>T. mentag</i>	1 (10%)	0
<i>E. floccosum</i>	2 (20%)	0

Table 8 - - Other Baseline Variables, Evaluable Patients

	Butenafine (n = 53)	Vehicle (n = 52)	p-value
Previous tinea pedis episodes			
Yes	34 (64%)	36 (69%)	0.680*
No	19 (36%)	16 (31%)	
Total Signs/Symptoms Score of target lesion (median)	8 Range: 5 - 17	8.5 Range: 5 - 16	0.344†

* Fisher's Exact Test (2-tailed)

† Wilcoxon rank-sum test

Reviewer's Comment:

These results indicate that there was not a statistically significant difference in the number of previous episodes of tinea pedis or the median Total Signs/Symptoms score at baseline between the butenafine and vehicle treatment groups.

8.1.1.3.2 Efficacy Endpoint Outcomes

The following results are for the modified intent-to-treat (MITT) population with last-observation-carried-forward and the sponsor's per protocol population, as defined under section 8.0 "Statistical Considerations." The endpoint of the study was week 8. However, as noted under the section "Statistical Considerations," patients were included in the MITT analysis who had missed the theoretical date of the week 8 visit by being late as many as 16 days. Statistical analyses using the originally-defined per protocol population (i.e., ± 3 days) were performed by the FDA biostatistician and are referred to in this review as the "original per protocol."

The primary efficacy variable was considered to be "Overall Cure" as defined by "Mycological Cure" (negative culture and KOH) + Investigator's Global of "Cleared". The results for "Overall Cure" and "Mycological Cure" are shown below in Tables 9 and 10. Results for each of the statistical populations are presented for week 8.

Table 9 - - Overall Cure ("Mycological Cure" + Investigator's Global of "Cleared")

	Wk 1	Wk 2	Wk 4	Wk 8		
				MITT	Sponsor's per protocol	Original per protocol
Butenafine	0/53 (0%)	3/53 (6%)	7/53 (13%)	11/53 (21%)	11/50 (22%)	9/41 (22%)
Vehicle	0/52 (0%)	1/52 (2%)	5/52 (10%)	4/52 (8%)	4/5 (9%)	4/37 (11%)
p-value*	1.0	0.492	0.802	0.035	0.056	0.14
95% CI	Not defined	-3.5%, 11.0%	-8.5%, 15.7%	0.0%,26.2%	-1.1%,27.3%	

* Cochran-Mantel Haenszel test

Reviewer's Comment:

1) These results indicate that in the MITT population, at week 8, there was a statistically significant difference between the butenafine and vehicle treatment groups. However, it should be noted that the percent of patients in the butenafine group who exhibited "Overall Cure" was very small, even though significantly different from the vehicle treatment group.

2) In the sponsor's per protocol analysis, the results at week 8 showed marginal statistical significance ($p=0.056$). As shown in Table 9, analysis of the **original per protocol population** (performed by the FDA biostatistician) failed to show that there was a statistically significant difference between the butenafine and vehicle treatment groups ($p=0.14$). The difference between these 2 study populations was the window for the week 8 visit (-5 days to +16 days for the sponsor's per protocol population; ± 3 days for the original per protocol population), resulting in fewer evaluable patients in the original per protocol population. This may have resulted in a loss of statistical power to detect a significant difference between the 2 treatment groups in the original per protocol population (see "Statistical Methods" section).

3) Examination of the results by investigator shows that Dr. Cullen contributed 6/11 (55%) of the butenafine patients who were considered "Overall Cure." Of interest, Dr. Cullen also contributed 2/4 (50%) of the vehicle patients who were considered "Overall Cure." Drs. Beutner, Shupack, and Weinstein did not have any patients in either treatment arm who were considered "Overall Cure."

The number and percent of patients achieving "Mycological Cure" (negative culture and negative KOH) at the indicated timepoints are shown in Table 10.

Table 10 - - "Mycological Cure" (Negative Culture and KOH)

	Wk 1	Wk 2	Wk 4	Wk 8 MITT [*]	Wk 8 Sponsor's per protocol
Butenafine	17/53 (32%)	34/53 (64%)	48/53 (91%)	44/53 (83%)	42/50 (84%)
Vehicle	14/52 (27%)	24/52 (46%)	33/52 (63%)	20/52 (38%)	18/45 (40%)
p-value [*]	0.549	0.113	0.002	<0.001	<0.001
95% CI	12.3%, 22.6%	-0.7%, 36.7%	11.8%, 42.4%	27.9%, 61.2%	26.4%, 61.6%

^{*} Cochran-Mantel-Haenszel test

Reviewer's Comment:

1) These results indicate that there was a statistically significant difference between the butenafine and vehicle treatment groups at weeks 4 and 8.

2) It should be noted that throughout the study, the vehicle treatment group had a very high rate of negative mycology results. This was particularly evident at week 4, with 63% of the vehicle patients showing negative mycology. At week 4, the butenafine treatment group also had a remarkably high percent of patients with negative mycology results. At week 8, 4 weeks post-treatment, the vehicle group still had a high percent of patients with negative mycology, even though there was a statistically significant difference between the butenafine and vehicle treatment groups. This high rate of negative mycology in the vehicle treatment group may have been due to inadequate sampling by the various investigators. Negative mycology does not appear to be a good predictor of "Overall Cure" (see Table 9).

The variable "Effective Treatment," defined as "Mycological Cure" + Investigator's Global of "Cleared" or "Excellent" is considered as a secondary efficacy variable. These results are shown in Table 11.

Table 11 - - Effective Treatment (Mycological Cure + Investigator's Global of "Cleared" or "Excellent")

	Wk 1	Wk 2	Wk 4	MITT	Wk 8 Sponsor's per protocol
Butenafine	7/53 (13%)	13/53 (25%)	31/53 (58%)	36/53 (68%)	34/50 (68%)
Vehicle	3/52 (6%)	8/52 (15%)	16/52 (31%)	13/52 (25%)	12/45 (27%)
p-value*	0.159	0.360	0.005	<0.001	<0.001
95% CI	-3.7%,18.5%	-6.0%,24.3%	9.5%,46.0%	25.7%,60.1%	23.1%,59.6%

* Cochran-Mantel-Haenszel test

Reviewer's Comment:

1) These results indicate that there was a statistically significant difference between the two treatment groups at weeks 4 and 8. Analysis of the data by FDA for week 8 in the original per protocol population confirmed the results shown in Table 11.

2) Examination of the results by investigator at week 8 (end of study) shows that all of the investigators except Dr. Shupack had results that favored the butenafine treatment group. For Dr. Shupack, a higher percent of vehicle patients (29% [2/7]) met the criteria of "Effective Treatment" in comparison to the percent of butenafine patients (11% [1/9]). However, given the very small numbers involved, the interpretation of this finding is not clear.

Efficacy results using the clinical parameter of Total Signs/Symptoms Score for the target plus "Mycological Cure" are shown in Tables 12 and 13.

Table 12 - - Patients with "Mycological Cure" + Total Signs/Symptoms Score of 0 (target lesion)

	Wk 1	Wk 2	Wk 4	Wk 8		
				MITT	Sponsor's per protocol	Original per protocol
Butenafine	1/53 (2%)	4/53 (8%)	13/53 (25%)	17/53 (32%)	17/50 (34%)	15/41 (37%)
Vehicle	0/52 (0%)	2/52 (4%)	6/52 (12%)	6/52 (12%)	5/45 (11%)	5/37 (14%)
p-value*	0.3	0.4	0.1	0.01	0.006	0.016

* Cochran-Mantel-Haenszel test

Reviewer's Comment:

1) *These results indicate that there was a statistically significant difference between the 2 treatment groups at week 8 (end of study). As shown in Table 12, analysis of these results by the FDA biostatistician using the **original per protocol population** showed a p-value of 0.016 (see Biostatistics review, p. 9), and supports the above conclusion.*

2) *It should be noted that, in this study, there were 8 discrepant patients who had a Total Signs/Symptoms Score of 0, but an Investigator's Global of only "Excellent" (80-99% improvement) instead of the expected Investigator's Global of "Cleared."*

Table 13 - - Patients with "Mycological Cure" + Total Signs/Symptoms Score of 0 or 1 (target lesion)

	Wk 1	Wk 2	Wk 4	Wk 8		
				MITT	Sponsor's per protocol	Original per protocol
Butenafine	3/53 (6%)	7/53 (13%)	26/53 (49%)	28/53 (53%)	27/50 (54%)	25/41 (67%)
Vehicle	0/52 (0%)	5/52 (10%)	12/52 (23%)	9/52 (17%)	8/45 (18%)	8/37 (22%)
p-value*	0.05	0.83	0.01	<0.001	<0.001	<0.001

* Cochran-Mantel-Haenszel test

Reviewer's Comment:

1) *These results indicate that at weeks 4 and 8, there was a statistically significant difference between the butenafine and vehicle treatment groups. These results also indicate that there were fewer patients with a Total Signs/Symptoms score of 0 or 1 than those defined by the variable "Effective Treatment" (Investigator's Global of "Cleared or "Excellent"). This may be because a Total Signs/Symptoms score of 1 may have been more difficult to achieve than an Investigator's Global of "Excellent" (80-99% improvement).*

2) *Analysis of this data by the FDA biostatistician using the original per protocol population shows that, for week 8, these results were statistically significant ($p < 0.001$), as shown in Table 13.*

The median of the Total Signs/Symptoms Score for the target lesion for the MITT population is shown below for each timepoint.

Table 14 - - Median Total Signs/Symptoms Score for Target Lesion

	Baseline	Wk 1	Wk 2	Wk 4	Wk 8
Butenafine (n = 53)					
Median Range	8	5	3	2	1
Vehicle (n = 52)					
Median Range	8.5	5	3	3	3
p-value*	0.344	0.494	0.405	0.068	0.001

* Wilcoxon rank-sum test

Reviewer's Comment:

These results indicate that a statistically significant difference between the 2 treatment groups in the Total Signs/Symptoms score for the target lesion was not apparent until week 8 (end of study). Both treatment groups showed marked improvement in comparison to their respective baseline median values. The distribution of scores for the MITT population is shown in Table 15.

The distribution of total scores at baseline and week 8 for each treatment group is shown in Table 15. The number of patients with each score is shown. As indicated, the maximum possible score per patient was 18.

Table 15 - Distribution of Scores for Signs/Symptoms of the Target Lesion

Baseline																			
Score	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
B*						2	9	10	13	5	7	3	1			1	1	1	
V*						1	10	9	6	7	8	1	2	5	2		1		
Week 8																			
Score	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
B*	19	11	6	5	3	2		2	2		3								
V*	6	5	8	8	5	3	7	3	2	1	1	1			2				

* B = butenafine cream

* V = vehicle

The Investigator's Global Scores are shown in Table 16 for each timepoint for the MITT population.

Table 16 - - Investigator's Global Scores, MITT population*

	Cleared 100% improved	Excellent 80-99% improved	Good 50-79% improved	Fair 25-49% improved	Poor <25% improved	Unchange	Worse	'p- value
Week 1								
Butenafine (n = 52)	0 (0%)	10 (19%)	7 (13%)	15 (29%)	11 (21%)	9 (17%)	0(0%)	0.617
Vehicle (n = 50)	0 (0%)	6 (12%)	8 (16%)	18 (36%)	6 (12%)	12 (24%)	0(0%)	
Week 2								
Butenafine (n = 53)	3 (6%)	14 (26%)	18 (34%)	11 (21%)	3 (6%)	4 (8%)	0(0%)	0.198
Vehicle (n = 52)	1 (2%)	11 (21%)	17 (33%)	11 (21%)	4 (8%)	7 (13%)	1(2%)	

	Cleared 100% improved	Excellent 80-99% improved	Good 50-79% improved	Fair 25-49% improved	Poor < 25% improved	Unchange	Worse	'p-value
Week 4								
Butenafine (n=53)	7 (13%)	26 (49%)	14 (26%)	3 (6%)	2 (4%)	1 (2%)	0(0%)	0.03
Vehicle (n=52)	5 (10%)	20 (38%)	11 (21%)	5 (10%)	5 (10%)	3 (6%)	3(6%)	
Week 8								
Butenafine (n=53)	12 (23%)	27 (51%)	6 (11%)	3 (6%)	2 (4%)	3 (6%)	0(0%)	< .001
Vehicle (n=52)	4 (8%)	16 (31%)	7 (13%)	9 (17%)	5 (10%)	7 (13%)	4(8%)	

* From vol. 1.18, pp.90-91

† Cochran-Mantel-Haenszel mean score test

Reviewer's Comment:

These results indicate that, by weeks 4 and 8, there was a statistically significant difference between the butenafine and vehicle treatment groups.

The "Patient Assessment of Response" at weeks 4 and 8 is shown in Table 17.

Table 17 - - Patient Assessment of Response, MITT population

	Greatly improved	Somewhat Improved	No Change	Somewhat Worse	Much Worse	'p-value
Week 4						
Butenafine (n=53)	33 (62%)	19 (36%)	1 (2%)	0 (0%)	0 (0%)	0.022
Vehicle (n=52)	25 (48%)	17 (33%)	6 (12%)	3 (6%)	1 (2%)	
Week 8						
Butenafine (n=53)	40 (75%)	9 (17%)	3 (6%)	1 (2%)	0 (0%)	< 0.001
Vehicle (n=52)	21 (40%)	11 (21%)	16 (31%)	3 (6%)	1 (2%)	

* Cochran-Mantel-Haenszel mean score test

Reviewer's Comment:

These results indicate that there was a statistically significant difference between the butenafine and vehicle treatment groups at weeks 4 and 8.

Those patients who achieved "Overall Cure" in the MITT population and the sponsor's per protocol population are listed in Table 18.

Table 18 - - Patients with "Overall Cure"

Butenafine

<u>Patient #</u>	<u>Investigator</u>	<u>Organism</u>
	Cullen	T. rubrum
	Cullen	E. Floccosum
	Cullen	T. rubrum
	Reyes	T. rubrum
	Reyes	T. rubrum
	Reyes	T. mentagrophytes
	Rosen	T. mentagrophytes
	Rosen	T. rubrum

Vehicle

<u>Patient #</u>	<u>Investigator</u>	<u>Organism</u>
	Cullen	T. rubrum
	Cullen	T. rubrum
	Reyes	T. mentagrophytes
	Reyes	T. rubrum

* These patients would have been excluded if the original per protocol "window" definition for the week 8 visit had been adhered to (i.e., \pm 3 days of the scheduled week 8 visit)

Reviewer's Comment:

1) The visit of Patient [REDACTED] was 8 days beyond the scheduled week 8 evaluation and that of Patient [REDACTED] was 6 days beyond the scheduled week 8 evaluation. These patients were not included in the original per protocol statistical analyses.

2) The majority of the patients in the butenafine treatment group who achieved an "Overall Cure" had been infected with T. rubrum (73%) This organism is presumed to be more difficult to cure than the other 2 organisms studied, and is consistent with the percent of patients enrolled in the study with this organism (see Table 7).

Subgroup analyses were performed for gender, age, and ethnic group. For males, at week 8, in both the MITT population and the sponsor's per protocol population, there was a statistically significant difference between the butenafine and vehicle treatment groups for all efficacy parameters, including "Overall Cure" ($p=0.011$ [MITT] and $p=0.022$ [sponsor's per protocol]). For females, there was not statistically significant difference between the butenafine and vehicle treatment groups for "Overall Cure" or "Mycological Cure"; a statistical difference was achieved for "Effective Treatment" for both the MITT population and the sponsor's per protocol population ($p=0.024$ and $p=0.04$, respectively).

Subgroup analyses by age were performed on age strata of <45 years (41 butenafine patients/35 vehicle patients), 45-65 years (11 butenafine patients/15 vehicle patients), and >65 years (1 butenafine patient/2 vehicle patients). For those less than 45 years old and those 45-65 years old, there was not a statistically significant difference between the butenafine and vehicle treatment groups for "Overall Cure" ($p=0.077$ and $p=0.971$, respectively). There were too few patients over 65 years to statistically analyze.

Analyses stratified by ethnic group showed that for Caucasian patients, at week 8, there was a statistically significant difference between the butenafine and vehicle treatment groups for all of the efficacy parameters, including "Overall Cure," "Mycological Cure," and "Effective Treatment," in both the MITT population ($p=0.003$, $p=0.004$, and $p=0.013$, respectively) and the sponsor's per protocol population ($p=0.012$, $p=0.008$, and $p=0.03$, respectively). For Hispanic patients (19 butenafine/16 vehicle), at week 8, there was a statistically significant difference between the 2 treatment groups for "Mycological Cure" and "Effective Treatment," although a statistically significant difference was unable to be demonstrated between the butenafine and vehicle treatment groups for "Overall Cure." For African-American patients (12 butenafine/7 vehicle), at week 8, there was not a statistically significant difference between the 2 treatment groups for any of the efficacy parameters. There were too few Asian patients to statistically analyze.

Reviewer's Comment:

In summary, the therapeutic effect of butenafine was more apparent in males, those who were less than 45 years old, and in Caucasian patients. However, the relative lack of statistical significance for females and African-American patients may be, in part, due to the small numbers of these patients who were enrolled in the study such that the power of the study may not have been sufficient to detect a statistical difference between the butenafine and vehicle treatment groups. Alternatively, it is possible that those subgroups of patients who showed a poor therapeutic effect (e.g., females, patients over 45 years old, and African-Americans) may have more resistant tinea pedis for unknown reasons.

8.1.1.3.3 Safety Outcomes

Adverse Events

A total of 150 patients were enrolled in this study, with 77 randomized to butenafine and 73 to vehicle. Of these, 149 patients (76 butenafine and 73 vehicle) applied at least one dose of the assigned treatment and were included in the safety analysis. A total of 52 patients were exposed to butenafine for four weeks while 50 were exposed to vehicle for that period. For laboratory studies, 73 butenafine patients and 71 vehicle patients had baseline laboratory results.

There was only 1 patient (butenafine) who was considered by the sponsor to have had a serious adverse event. This was considered to be non-treatment related and consisted of a basal cell carcinoma located on the medial canthus. The patient was able to complete the study. In addition, there was 1 patient (vehicle) who had a CVA, although this was not considered by the sponsor to have been a serious adverse event. No patient withdrew from the study due to an adverse event. One patient (vehicle) withdrew because of lack of efficacy; 1 patient (butenafine) had worsening of her tinea pedis, but completed the study.

All adverse events related to the skin (except for excision of lesions) are shown in Table 19. Adverse events unrelated to the skin reported in greater than 1% of the patients are also listed in Table 19.

Table 19 - - Adverse Events (expressed as number of patients)

Event	Butenafine n = 76 pts.	Vehicle n = 73 pts.
Infection*	5 (6%)	2 (3%)
Headache	2 (3%)	5 (7%)
Hyperbilirubinemia†	1 (1%)	0 (0%)
Worsening of tinea pedis	1 (1%)	0 (0%)
Basal cell carcinoma	1 (1%)	0 (0%)
Seborrheic dermatitis	1 (1%)	0 (0%)

* Includes URIs

† Includes Patient (butenafine) described below

Laboratory Tests

Patients with elevated laboratory values (see footnote to Table 20 for definitions) beyond the baseline visit are listed in Table 20. Those laboratory studies of particular interest were the percent eosinophils, SGPT, SGOT, and total bilirubin.

Table 20 - - Selected Abnormal Laboratory Values

Pt. #	Investigator	Treatment Group Butenafine n=73 Vehicle n=71	Test	Result
	Beutner	Butenafine	% Eos ¹	10% (baseline) 8% (wk 2) 6% (wk 4)
	Cullen	Butenafine	% Eos ¹	7% (wk 2)
	Cullen	Butenafine	% Eos ¹	6% (baseline) 7% (wk 2) 9% (wk 4)
	Reyes	Butenafine	% Eos ¹	4% (baseline) 10% (wk 2) 9% (wk 4)
	Cullen	Butenafine	SGPT ²	86 (baseline) 100 (wk 2) 110 (wk 4)
	Weinstein	Butenafine	SGPT ²	45 (baseline) 58 (wk 2) 36 (wk 4)
	Shupack	Butenafine	T. Bili ³	1.8 (baseline) 2.3 (wk 2)
	Shupack	Butenafine	T. Bili ³	0.8 (baseline) 1.9 (wk 2) 3.0 (wk 4) 2.8 (wk 6) 1.3 (wk 8)

Pt #	Investigator	Treatment Group Butenafine n = 73 Vehicle n = 71	Test	Result
	Cullen	Vehicle	% Eos ¹	6% (baseline) 7% (wk 2)
	Cullen	Vehicle	% Eos ¹	7% (wk 4)
	Reyes	Vehicle	% Eos ¹	6% (baseline) 7% (wk 2) 6% (wk 4)
	Reyes	Vehicle	SGPT ²	40 (baseline) 54 (wk 2)
	Rosen	Vehicle	SGPT ²	53 (wk 2) 70 (wk 4)
			SGOT ³	43 (wk 2) 66 (wk 4)
	Rosen	Vehicle	SGPT ²	22 (baseline) 63 (wk 2)
	Weinstein	Vehicle	SGPT ²	110 (baseline) 101 (wk 2) 74 (wk 4)
	Weinstein	Vehicle	SGOT ³	63 (baseline) 61 (wk 2) 44 (wk 4)

¹ Normal limits 0-4%. Values \geq 7% are listed.

² Normal limits 0-50 IU/mL

³ Normal limits 0-50 IU/mL

⁴ Normal limits 0.1-1.2 mg/dL. Values \geq 1.8 mg/dL are listed.

Reviewer's Comment:

Patient [redacted] (butenafine) had an elevation of bilirubin starting at week 2 which peaked at week 4 (3.0mg/dL) and gradually decreased 4 weeks post-treatment. The remainder of the patient's liver function tests, including alkaline phosphatase, SGOT, and SGPT, were within normal limits. The sponsor reports that this patient has a family history hyperbilirubinemia. However, no other data was submitted to support this diagnosis, such as the fraction of indirect vs. direct bilirubin. In addition, the apparent increase of bilirubin during the treatment period and then decrease during the post treatment period may or may not be causally associated with the use of butenafine. Patient [redacted] (butenafine), the twin sister of patient [redacted] (not stated whether identical), also showed an elevated total bilirubin at baseline and week 2.

This patient was terminated from the study after week 2 because of a negative baseline fungal culture. However, it would have been very helpful to have obtained a repeat bilirubin after having discontinued butenafine to help determine possible causality with use of the drug. It is recommended that additional information be provided to substantiate the diagnosis of familial hyperbilirubinemia. In addition, it is recommended, if possible, that the sponsor consider re-challenging these patients with the topical administration of butenafine cream to determine if there is a reproducible elevation of bilirubin (with determination of direct and indirect fractions).

8.1.1.4 REVIEWER'S CONCLUSIONS REGARDING EFFICACY DATA

Summary of p-values, week 8

	MITT	Sponsor's Per Protocol (-5 to +16 days)	Original Per Protocol (± 3 days)
"Overall Cure" ("Mycological Cure" + Global of "Cleared")	0.035	0.056	0.14
"Mycological Cure" (negative culture and KOH)	<0.001	<0.001	<0.001
"Effective Treatment" ("Mycological Cure" + Global of "Cleared" or "Excellent")	<0.001	<0.001	<0.001
"Mycological Cure" + Total Signs/Symptoms Score of 0 (target lesion)	0.009	0.006	0.016
"Mycological Cure" + Total Signs/Symptoms Score of 0 or 1 (target lesion)	<0.001	<0.001	<0.001

As shown above, for the primary efficacy variable of "Overall Cure" at week 8 (end of study), there was a statistically significant difference between the butenafine and vehicle treatment groups in the MITT population. Using the sponsor's per protocol population, the results showed only marginal statistical significance whereas analysis of the original per protocol population failed to demonstrate a statistically significant difference between the 2 treatment groups. Although, ideally the statistical analysis of the 3 data populations (i.e., MITT, sponsor's per protocol, and original per protocol) should substantially agree, it is

possible that this study lacked sufficient power to detect a difference between the butenafine and vehicle treatment groups in the original per protocol population due to the smaller sample size in comparison to the MITT population. It should also be noted that for all 3 populations, the vehicle effect was marked. This may also have resulted in the necessity of needing a larger sample size than originally calculated in order to detect a statistically significant difference between the 2 treatment arms.

For all of the other efficacy variables, there was a statistically significant difference between the butenafine and vehicle treatment groups in the MITT, sponsor's per protocol, and original per protocol analyses. In particular, the efficacy parameter of "Mycological Cure" + Total Signs/Symptoms Score of 0," although apparently not as stringent a criteria for "cure" as the parameter "Mycological Cure" plus an Investigator's Global grade of "cleared" (i.e., "Overall Cure"), since there were patients who had a score of 0, but an Investigator's Global of only "excellent," I feel, nonetheless, is evidence of therapeutic efficacy of butenafine in comparison to the vehicle.

It should be noted that there was a relatively high vehicle effect seen in all efficacy parameters, particularly the percent of vehicle patients with negative mycology at weeks 4 and 8. As stated by the sponsor, it was expected that the "Mycological Cure" (negative fungal culture and KOH) at week 4 would be no greater than 30% in the vehicle group whereas the actual study results show 63% of vehicle patients with negative mycology. Even at week 8 (4 weeks post-treatment), almost 40% of the vehicle patients had negative mycology. The reasons for this are unclear, but may be related to the conduct of the trial by the investigators (e.g., lack of adequate sampling for the culture or KOH) and/or antifungal efficacy of a component(s) of the vehicle.

8.1.2 STUDY #2

Title: A Double-Blind Evaluation of Butenafine HCl Cream 1% and Vehicle in the Treatment of Tinea Pedis (Protocol PDC 010-002)

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8.1.2.1 Study Design

See Section 8.0

8.1.2.2 PROTOCOL

8.1.2.2.1 Population/Procedures

A total of 119 patients were enrolled at 4 sites and were randomized to either the butenafine or the vehicle treatment groups. The "Study Procedure" is described above in section 8.0.

8.1.2.3

RESULTS

8.1.2.3.1

Population Enrolled/Analyzed

Of the 119 patients enrolled, 60 were enrolled in the butenafine treatment group and 59 patients in the vehicle group. Of these 119 patients, 36 (19 butenafine/17 vehicle) were excluded because of lack of a positive fungal culture at baseline or lack of a "delayed positive" culture at week 1 or week 2. An additional 3 patients were excluded as follows: abnormal baseline laboratory results (1 vehicle patient), lost-to-follow-up at baseline (1 vehicle patient), and ineligible baseline medication (1 butenafine patient). Thus, there were 80 patients (40 butenafine and 40 vehicle) who were considered evaluable (See Table 21).

Table 21 - - Patients Enrolled and Evaluability (at baseline)

	Butenafine	Vehicle	All patients
# of Patients Enrolled	60	59	119
Not evaluable			
Negative baseline fungal culture	19 (32%)	17 (29%)	36 (30%)
Abnormal baseline laboratory results	0	1	1*
No post-baseline follow-up visit	0	1	1
Ineligible baseline medication	1**	0	1
Total # not evaluable	20 (33%)	19 (32%)	39 (33%)
Total # Evaluable (MITT population)	40 (67%)	40 (68%)	80 (67%)

* Includes Patient [REDACTED] with elevated serum glucose at baseline and at week 1

** Includes Patient [REDACTED] who was taking prednisone

Reviewer's Comment:

As with Study #1, a relatively large percent of patients, in both treatment arms, were excluded from the evaluable patient population due to negative baseline fungal cultures.

The demographics of the evaluable population is shown in Table 22.

Table 22 - - Demographics of Evaluable Patients (MITT population)

	Butenafine	Vehicle	p-value
No. of Patients	40	40	
Male	26 (65%)	30 (75%)	0.465*
Female	14 (35%)	10 (25%)	
Age Mean yrs \pm SD Range (yrs)	34.9 \pm 13	39.3 \pm 13	0.088†
Caucasian	21 (53%)	29 (73%)	0.136*
Hispanic	10 (25%)	5 (13%)	
African-American	7 (18%)	3 (8%)	
Asian	1 (3%)	0	
Other	1 (3%)	3 (8%)	

* Fisher's Exact Test (2 tailed)

† Wilcoxon rank-sum test

Reviewer's Comment:

The butenafine treatment group was slightly younger than the vehicle group. This degree of age difference between the 2 treatment groups would not be expected to affect the efficacy of the product. In regard to ethnic group, there were more Caucasian patients in the vehicle group than the butenafine group whereas the butenafine group had more Hispanic and African-American patients than the vehicle group. It is not known if ethnic group may affect the efficacy of the drug product. As with Study #1, there were more males than females, but balanced between the treatment groups.

The number of evaluable patients is shown in Table 23, listed by investigator, treatment group, and type of statistical analysis.

Table 23 - - Patient Enrollment and Evaluability

Investigator	Treatment Group	Patients Enrolled	Evaluable (wk 8) (MITT)	Evaluable (wk 8) (per protocol)
Elewski	Butenafine	15 (25%)	11 (28%)	9 (4%)
	Vehicle	15 (25%)	10 (25%)	10 (28%)
	Total	30 (25%)	21 (26%)	19 (26%)
Gorsulowsky	Butenafine	14 (23%)	11 (28%)	11 (29%)
	Vehicle	13 (22%)	8 (20%)	8 (22%)
	Total	27 (23%)	19 (24%)	19 (26%)
Pariser	Butenafine	15 (25%)	6 (15%)	6 (16%)
	Vehicle	16 (27%)	9 (23%)	8 (22%)
	Total	31 (26%)	15 (19%)	14 (19%)
Tschen	Butenafine	16 (27%)	12 (30%)	12 (32%)
	Vehicle	15 (25%)	13 (33%)	10 (28%)
	Total	31 (26%)	25 (31%)	22 (30%)
Total	Butenafine	60	40	38
	Vehicle	59	40	36
TOTAL		119	80	74

* The definition of "per protocol" is based on the sponsor's definition as stated in the section above under "Statistical Considerations."

According to the sponsor, there were 4 patients (all vehicle patients) who terminated early from the study (see Table 24). It should be noted that patient [REDACTED] who withdrew because of an adverse event related to the study, **was included in the sponsor's per protocol analysis for week 8** by carrying forward the data from the last non-missed visit. The other 3 patients were excluded from the per protocol analysis at week 8.

Table 24 - - Reasons for Early Termination

Patient #	Investigator	Treatment Group	Reason for withdrawal	Included in sponsor's per protocol analysis at wk 8?
	Pariser	Vehicle	Pregnancy. Withdrew after wk 2.	No
	Pariser	Vehicle	Adverse event consisting of burning, itching, and stinging after application of medication to both feet. Withdrew after 3 days.	*Yes
	Tschen	Vehicle	Lost to follow-up. Withdrew after wk 2.	No
	Tschen	Vehicle	No post-baseline visit. Not included in MITT analysis.	No

* The results of this patient were "carried-forward" because the early termination was due to a treatment-related adverse event.

There were 4 additional patients (2 butenafine/2 vehicle) whom the sponsor considered evaluable for the MITT analysis, but were considered unevaluable at week 8 in the sponsor's per protocol analysis. As shown in Table 25, these patients were considered unevaluable at week 8 either because their visit occurred more than 5 days before the scheduled week 8 visit (3 patients: 2 butenafine/1 vehicle) or because of a negative culture at baseline (1 vehicle patient). (See Appendix 2 for line listing of evaluability of patients).

Table 25 - - Reasons for Unevaluable Patients at Week 8 (not included in sponsor's per protocol analysis)*

Patient #	Investigator	Treatment Group	Reason for Unevaluable at Week 8	Time of Termination from Study.
	Elewski	Butenafine	Week 8 visit occurred 15 days early.	
	Elewski	Butenafine	Week 8 visit occurred 10 days early.	
	Tschen	Vehicle	Week 8 visit occurred 12 days early.	
	Tschen	Vehicle	Negative baseline culture, but subsequent report of positive week 1 culture.	Withdrew after week 3.

* Based on Table B, vol. 1.20, p.28

There were 16 patients (7 butenafine/9 vehicle) who were considered by the sponsor to have had protocol deviations, but were retained in the analyses. These patients are summarized in Table 26.

Table 26 - - Summary of Protocol Deviations

Patient #	Investigator	Treatment Group	Reason
	Elewski	Butenafine	Week 8 visit occurred at week 6 because original protocol was for a 6-week study and IRB approval to extend the study to 8 weeks was not obtained prior to enrolling this patient.
	Elewski	Butenafine	Week 8 visit occurred at week 6 because original protocol was for a 6-week study and IRB approval to extend the study to 8 weeks was not obtained prior to enrolling this patient.
	Gorsulowsky	Butenafine	Enrolled in study on 5/13/94. Started amoxicillin on 5/16 until 6/4/94 for pharyngitis. Last day of study medication on 6/8/94. Week 8 visit on 7/11/94.
	Gorsulowsky	Butenafine	Missed week 2 visit.

Patient #	Investigator	Treatment Group	Reason
	Gorsulowsky	Butenafine	Enrolled in study on 7/19/94. Started penicillin on 8/12/94 until 8/18/94 for an "ear infection." Last day of study medication on 8/15/94. Week 8 visit on 9/14/94.
	Gorsulowsky	Butenafine	Missed week 1 visit.
	Pariser	Butenafine	Missed week 2 visit.
	Elewski	Vehicle	Missed week 1 visit.
	Gorsulowsky	Vehicle	No laboratory studies at weeks 2 and 4
	Pariser	Vehicle	Stopped study medication after only 3 weeks of treatment. Returned for scheduled week 8 visit.
	Pariser	Vehicle	Enrolled in study on 10/14/94. Used DesOwen™ cream topical steroid on the face for irritation for 3 days (11/21 to 11/24). Week 8 visit on 12/8/94.
	Tschen	Vehicle	Enrolled in study on 5/3/94. Hyperglycemia (serum glucose 298 and 238mg/dL) noted at baseline and week 2. Diagnosed as having diabetes mellitus and begun on glyburide tablets on 5/28. Also begun on oral ciprofloxacin and cefadroxil for a leg abscess. Last day of study medication on 5/31. Week 8 visit on 6/28/94.
	Tschen	Vehicle	Enrolled in study on 5/23/94. Begun on cefaclor on 5/27 until 6/6 for URI. Last day of study medication on 6/20. Week 8 visit on 7/19/94.
	Tschen	Vehicle	Enrolled in study on 8/3/94. Started cephalixin on 9/27 for sinusitis. Week 8 visit on 9/28/94.
	Tschen	Vehicle	Week 8 visit 12 days early because patient relocating.
	Tschen	Vehicle	Enrolled in study on 10/20/94. Started clarithromycin on 11/10 for bronchitis. Week 8 visit on 11/11/94.

Reviewer's Comment:

Although there is no objection to retaining Patient # [REDACTED] in the study (even though the patient was diagnosed as having diabetes mellitus which could potentially affect the recalcitrance of tinea pedis infections), it is recommended that for future studies, in order to provide consistency across all investigators, the sponsor provide specific criteria for "abnormal baseline values" leading to exclusion of patients, rather than leaving it to the discretion of each individual investigator. For example, Patient # [REDACTED] (vehicle; Dr. Elewski) was excluded, presumably at the discretion of the investigator, because of a serum glucose of 252mg/dL at baseline whereas Patient # [REDACTED] (vehicle; Dr. Tschen) was retained.

Comparability of the treatment groups at baseline of pathogens, previous tinea pedis episodes, and the Total Signs/Symptoms Score is shown below (Tables 27 and 28).

Table 27 - - Baseline Distribution of Pathogens, Combined Investigators*

Pathogen	Butenafine (n=40)	Vehicle (n=40)
<i>T. rubrum</i>	38 (95%)	35 (88%)
<i>T. mentagrophytes</i>	1 (2.5%)	3 (7%)
<i>E. floccosum</i>	1 (2.5%)	0 (0%)
<i>S. hyalinum</i>	0 (0%)	1 (2.5%)
<i>Yeast (not specified)</i>	0 (0%)	1 (2.5%)

* Based on Table 4a, vol. 1.20, p.55

† Patient # [REDACTED] had *S. hyalinum* at baseline and *T. rubrum* at week 4

Reviewer's Comment:

1) It should be noted that the above table is different from that submitted by the sponsor (vol 1.20, p.55). Patient # [REDACTED] (vehicle) had a positive culture only for *S. hyalinum* at baseline and a positive culture only for *T. rubrum* at week 4. For the above table, this patient was considered to have only *S. hyalinum* at baseline.

2) The p-value (Fisher's Exact test) was 0.2 (see Biostatistics review, p. 13). These results indicate that there was not a statistically significant difference in the distribution of "pathogens" between the 2 treatment groups. Unlike Study #1, there were slightly more patients with *T. rubrum* in the butenafine treatment group, a dermatophyte potentially more difficult to treat than *E. floccosum* or *T. mentagrophytes*.

3) Patient # [REDACTED] (vehicle) had a positive culture for "yeast" at baseline. There was not a positive culture for dermatophytes at any time during the study. In my opinion, this patient does not meet the inclusion criteria to support the labeling indication (i.e., treatment of interdigital tinea pedis due to *E. floccosum*, *T. mentagrophytes*, or *T. rubrum*) and should have been excluded from the efficacy analyses submitted by the sponsor. Consequently, the efficacy analyses will be reanalyzed by the FDA biostatistician with this patient excluded.

4) Patient # [REDACTED] was positive for *S. hyalinum* at baseline and *T. rubrum* at week 4, although the week 8 culture was negative for both organisms. *S. hyalinum* is a nondermatophyte mold which can produce infection of the skin which clinically mimics tinea pedis infections caused by dermatophytes. It is usually recalcitrant to "conventional" topical (and oral) antifungal therapy. Because a dermatophyte was not cultured at baseline and because there were too few patients with *S. hyalinum* to analyze separately for a therapeutic response, the data was reanalyzed by the FDA biostatistician with and without this patient where noted.

Table 28 - - Other Baseline Variables, Evaluable Patients

	Butenafine (n=40)	Vehicle (n=40)	p-value
Previous tinea pedis episodes			
Yes	19 (48%)	16 (40%)	0.652*
No	21 (53%)	24 (60%)	
Total Signs/Symptoms Score of target lesion (median)	11 Range:	12 Range:	0.397†

* Fisher's Exact Test (2-tailed)

† Wilcoxon rank-sum test

Reviewer's Comment:

1) These results indicate that there was not a statistically significant difference in the number of previous episodes of tinea pedis or the median Total Signs/Symptoms score at baseline between the butenafine and vehicle treatment groups.

2) In contrast to Study #1, the patients in Study #2 had a higher median Total Signs/Symptoms Score for the target lesion at baseline.

3) As with Study #1, although there was not a statistically significant difference between the 2 treatment groups in the median Total Signs/Symptoms Score at baseline, the butenafine treatment group had a lower median score than the vehicle group.

8.1.2.3.2 Efficacy Endpoint Outcomes

The following results are for the modified intent-to-treat (MITT) population with last-observation-carried-forward and the sponsor's per protocol population, as defined under section 8.0 "Statistical Considerations." As with Study #1, the endpoint of the study was week 8. Also, as with Study #1, patients were included in the MITT analysis who had missed the theoretical date of the week 8 visit by as many as 16 days late. Statistical analyses using the original per protocol population (i.e., ± 3 days) were performed by the FDA biostatistician. In addition, where noted, the results were reanalyzed excluding Patients # [REDACTED] (vehicle) because of not meeting the inclusion criteria of a positive culture for a dermatophyte and [REDACTED] (vehicle) because of lack of a dermatophyte at baseline (although positive for *T. rubrum* at week 4).

The primary efficacy variable was considered to be "Overall Cure" as defined by "Mycological Cure" (negative culture and KOH) + Investigator's Global of "Cleared". The results for "Overall Cure" and "Mycological Cure" are shown below in Tables 29, 30, 31, and 32. For week 8, results for each of the statistical populations are presented. In addition, the results were analyzed with the exclusion of Patients # [REDACTED] (vehicle) and [REDACTED] (vehicle).

Table 29 - - Overall Cure ("Mycological Cure" + Investigator's Global of "Cleared"); all evaluable patients (including Patients [REDACTED] and [REDACTED])

	Wk 1	Wk 2	Wk 4	Wk 8		
				MITT	Sponsor's per protocol	Original per protocol
Butenafine	0/40 (0%)	0/40 (0%)	7/40 (18%)	9/40 (23%)	9/38 (24%)	9/32 (28%)
Vehicle	0/40 (0%)	0/40 (0%)	2/40 (5%)	2/40 (5%)	2/36 (5.5%)	2/31 (6.5%)
p value*	1.0	1.0	0.08	0.035	0.056	0.02
95% CI	Not defined	Not defined	-1.1%, 26.1%	2.9%,32.1%	2.7%,33.6%	

* Cochran Mantel Haenszel test

Reviewer's Comment:

1) These results indicate that in all 3 statistical populations, at week 8, there was a statistically significant difference between the butenafine and vehicle treatment groups.

The percent of patients in the butenafine group who exhibited "Overall Cure" was similar to that in Study #1 whereas the percent of patients in the vehicle group who achieved "Overall Cure" was slightly less than that of Study #1. This may account for the slightly more statistically favorable result for the butenafine treatment group seen in Study #2.

2) Analysis of the original per protocol population at week 8 was performed by the FDA biostatistician (see Biostatistics review, p. 15). As shown in Table 29, this analysis confirmed that there was a statistically significant difference between the 2 treatment groups.

3) It should be noted that of the 6 evaluable butenafine patients treated by Dr. Pariser, 3 of them (50%) achieved an "Overall Cure." This is a greater percentage of "Overall Cure" patients in comparison to the other investigators in this study.

Reanalysis of the data by FDA with the exclusion of Patient [REDACTED] (vehicle) using the 3 statistical populations (i.e., MITT, sponsor's per protocol, and original per protocol) is shown in Table 30 for week 8.

Table 30 - - Overall Cure ("Mycological Cure" + Investigator's Global of "Cleared"); Week 8; Exclusion of Patient [REDACTED]

	MITT	Sponsor's per protocol	Original per protocol
Butenafine	9/40 (23%)	9/38 (24%)	9/32 (28%)
Vehicle	2/39 (5.1%)	2/35 (5.7%)	2/30 (6.7%)
p-value*	0.014	0.022	0.029

* Cochran-Mantel-Haenszel test

Reviewer's Comment:

1) These results indicate that with exclusion of [REDACTED] (vehicle), the denominator of the vehicle group was affected. As shown in Table 30, a statistically significant difference between the butenafine and vehicle treatment groups remained in all 3 statistical populations (see Biostatistics addendum #1, p.2).

2) Similarly, when both Patients [REDACTED] (vehicle) and [REDACTED] (vehicle) were excluded, the results remained statistically significant at week 8 in all 3 statistical populations: 23% vs. 5.3%, p=0.014 (MITT); 24% vs. 5.9%, p=0.022 (sponsor's per protocol); 28% vs. 6.9%, p=0.029 (original per protocol) (see Biostatistics addendum #1, p.2)

The number and percent of patients achieving "Mycological Cure" (negative culture and negative KOH) at the indicated timepoints are shown in Table 31 (all patients) and Table 32 (exclusion of Patients [REDACTED]).

Table 31 -- "Mycological Cure" (Negative Culture and KOH); all evaluable patients (including Patients [REDACTED] and [REDACTED])

	Wk 1	Wk 2	Wk 4	Wk 8 MITT	Wk 8 Sponsor's per protocol
Butenafine	16/40 (40%)	28/40 (70%)	35/40 (88%)	35/40 (88%)	33/38 (87%)
Vehicle	8/40 (20%)	15/40 (38%)	18/40 (45%)	13/40 (33%)	13/36 (36%)
p-value*	0.081	0.006	<0.001	<0.001	<0.001
95% CI	-0.4%, 39.6%	11.8%, 53.2%	24%, 61%	37.2%, 72.8%	31.7%, 69.8%

* Cochran Mantel-Haenszel test

Reviewer's Comment:

1) These results indicate that there was a statistically significant difference between the butenafine and vehicle treatment groups at weeks 2, 4, and 8 for all patients.

2) As with Study #1, the percent of vehicle patients showing negative mycology was relatively high (i.e., about 35%).

Reanalysis of the data by FDA excluding Patient [REDACTED] (vehicle) is shown Table 32.

Table 32 -- "Mycological Cure" (Negative culture and KOH); Exclusion of Patient [REDACTED]

	Wk 1	Wk 2	Wk 4	Wk 8 MITT	Wk 8 Sponsor's per protocol
Butenafine	16/40 (40%)	28/40 (70%)	35/40 (88%)	35/40 (88%)	33/38 (87%)
Vehicle	8/39 (21%)	18**/39 (46%)	18/39 (46%)	13/39 (33%)	13/35 (37%)
p-value*	0.08	0.03	<0.001	<0.001	<0.001

* Cochran Mantel-Haenszel test

** Includes 1 patient [REDACTED] with a "sterile" mold, and Patients [REDACTED] and [REDACTED]. See Comments #3 and #4 below

Reviewer's Comment:

1) As shown in Table 32, exclusion of Patient [redacted] affected the denominator of the vehicle treatment arm. The results did not significantly change.

2) Similarly, reanalysis of the data by the FDA biostatistician when both Patients [redacted] (vehicle) and [redacted] (vehicle) are excluded confirmed the above results.

3) The sponsor should be aware that the presence of a "sterile" mold should be considered a negative culture.

4) Examination of the line listings shows that 2 additional vehicle patients ([redacted] and [redacted]) were listed under Mycological Cure as "Not Cured" (vol. 1.21, Listing L-8) and yet had negative KOH and cultures according to the Mycological Examination data (vol. 1.21, Listing L-9). The sponsor was requested to clarify these discrepancies.

The results for "Effective Treatment," defined as "Mycological Cure" + Investigator's Global of "Cleared" or "Excellent" are considered a secondary efficacy variable, and are shown in Table 33.

Table 33 - - Effective Treatment ("Mycological Cure" + Investigator's Global of "Cleared" or "Excellent"); all evaluable patients (including Patients [redacted] and [redacted])

	Wk 1	Wk 2	Wk 4	MITT	Wk 8 Sponsor's per protocol
Butenafine	0/40 (0%)	6/40 (15%)	22/40 (55%)	28/40 (70%)	27/38 (71%)
Vehicle	0/40 (0%)	1/40 (2.5%)	9/40 (23%)	9/40 (23%)	9/36 (25%)
p value*	1.0	0.041	0.001	<0.001	<0.001
95% CI	Not defined	0.4%, 24.6%	12.4%, 52.6%	28.3%, 66.7%	25.9%, 66.3%

* Cochran Mantel Haenszel test

Reviewer's Comment:

1) These results indicate that there was a statistically significant difference between the two treatment groups at weeks 2, 4, and 8.

2) Analysis by FDA at week 8 with exclusion of both Patients [redacted] and [redacted] confirmed the results shown in Table 33.

3) Examination of the results by investigator at week 8 (end of study) shows that all of the investigators had numerical results that favored the butenafine treatment group, although only Drs. Pariser and Tschen were able to demonstrate statistical significance (MITT population).

Efficacy results using the Total Signs/Symptoms score for the target lesion plus negative mycology are shown in Tables 34 and 35 for week 8.

Table 34 - - Patients with "Mycological Cure" + Total Signs/Symptoms Score of 0 (target lesion); week 8; all evaluable patients (including Patients [REDACTED] and [REDACTED])

	MITT	Sponsor's per protocol	Original per protocol
Butenafine	11/40 (28%)	11/38 (28%)	10/32 (31%)
Vehicle	4/40 (10%)	4/36 (11%)	4/31 (13%)
p-value*	0.021	0.035	0.066

* Cochran-Mantel-Haenszel test

Reviewer's Comment:

1) These results indicate that, at week 8, there was a statistically significant difference between the 2 treatment groups in the MITT and sponsor's per protocol analysis. However, as shown in Table 34, analysis of the data by the FDA biostatistician using the original per protocol population gave results which were of only marginal statistical significance ($p=0.066$). This may be because of the small number of patients comprising the original per protocol population in comparison to the MITT and sponsor's per protocol populations.

2) Reanalysis of the data by FDA for week 8 with exclusion of Patient [REDACTED] shows: 28% vs. 10%, $p=0.025$ (MITT); 29% vs. 11%, $p=0.043$ (sponsor's per protocol); 31% vs. 13%, $p=0.081$ (original per protocol) (see Biostatistics addendum #1, p.3). When both Patients [REDACTED] are excluded, the results are almost identical: $p=0.026$ (MITT), $p=0.044$ (sponsor's per protocol), and $p=0.081$ (original per protocol) (see Biostatistics addendum #1, p.3). These results are similar to those found when "all evaluable patients" were included in the analyses. In summary, with or without Patients [REDACTED] there was a statistically significant difference between the 2 treatment groups in the MITT and sponsor's per protocol analyses; however, when the original per protocol population was analyzed, the results were of only marginal statistical significance.

Table 35 - - Patients with "Mycological Cure" + Total Signs/Symptoms Score of 0 or 1 (target lesion); all evaluable patients (including Patients

	Wk 1	Wk 2	Wk 4	Wk 8		
				MITT	Sponsor's per protocol	Original per protocol
Butenafine	0/40 (0%)	3/40 (7.5%)	15/40 (38%)	23/40 (57.5%)	23/38 (58%)	19/32 (59%)
Vehicle	0/40 (0%)	0/40 (10%)	5/40 (13%)	8/40 (20%)	8/36 (22%)	7/31 (23%)
p value*	Not done	0.1	0.004	<0.0001	0.0004	0.001

* Cochran-Mantel-Haenszel test

Reviewer's Comment:

1) *These results indicate that at weeks 4 and 8, there was a statistically significant difference between the butenafine and vehicle treatment groups. As with Study #1, there were fewer patients who met the criteria of a Total Signs/Symptoms score of 0 or 1 than those defined by "Effective Treatment."*

2) *As shown in Table 35, analysis of the data performed by the FDA biostatistician using the original per protocol population showed a statistically significant difference between the 2 treatment groups (p=0.001).*

3) *Analysis of the data by FDA with the exclusion of both Patients for week 8 confirmed the above results (see Biostatistics addendum #1, p. 4).*

The median of the Total Signs/Symptoms Score for the target lesion for the MITT population is shown below for each timepoint.

Table 36 - - Median Total Signs/Symptoms Score for Target Lesion

	Baseline	Wk 1	Wk 2	Wk 4	Wk 8
Butenafine (n = 40)					
Median Range	11	8	4.5	2	1
Vehicle (n = 40)					
Median Range	12	8	6	3	3
p-value*	0.397	0.511	0.073	0.008	0.001

* Wilcoxon rank-sum test

Reviewer's Comment:

These results indicate that a statistically significant difference between the 2 treatment groups in the Total Signs/Symptoms score for the target lesion at weeks 4 and 8 (end of study). As with Study #1, both treatment groups showed marked improvement in comparison to their respective baseline median values.

The distribution of total scores at baseline and week 8 for each treatment group for the MITT population is shown in Table 37. The number of patients with each score is shown. As indicated, the maximum possible score per patient was 18.

Table 37 - - Distribution of Scores for Signs/Symptoms of the Target Lesion

Baseline																			
Score	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
B*							1	1	2	6	2	9	5	7	4	2		1	
V*						1		1	4	3	6	2	5	5	3	3	2	1	4
Week 8																			
Score	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
B*	11	14	6	5		2				1	1								
V*	4	8	7	2	1	3	2	4	2	2		1	1	3					

* B = butenafine cream

* V = vehicle

Reviewer's Comment:

It should be noted that Tables 36 and 37 include Patient [REDACTED] (vehicle) whose baseline Total Signs/Symptoms score was the maximum (i.e., 18) and at week 8 had decreased only to a score of 13.

The Investigator's Global Scores are shown in Table 38 for each timepoint for the MITT population.

Table 38 - - Investigator's Global Scores[†]; all evaluable patients

	Cleared 100% <i>improved</i>	Excellent 80-99% <i>improved</i>	Good 50-79% <i>improved</i>	Fair 25-49% <i>improved</i>	Poor <25% <i>improved</i>	Unchange	Worse	p- value
Week 1								
Butenafine (n = 39)	0 (0%)	1 (3%)	10 (26%)	8 (21%)	13 (33%)	4 (10%)	3(8%)	0.654
Vehicle (n = 39)	0 (0%)	1 (3%)	7 (18%)	12 (31%)	10 (26%)	7 (18%)	2(5%)	
Week 2								
Butenafine (n = 40)	0 (0%)	8 (20%)	12 (30%)	9 (23%)	7 (18%)	3 (8%)	1(3%)	0.173
Vehicle (n = 40)	0 (0%)	3 (8%)	16 (40%)	7 (18%)	8 (20%)	4 (10%)	2(5%)	
Week 4								
Butenafine (n = 40)	8 (20%)	19 (48%)	3 (8%)	6 (15%)	2 (5%)	1 (3%)	1(3%)	0.014
Vehicle (n = 40)	2 (5%)	14 (35%)	9 (23%)	8 (20%)	2 (5%)	4 (10%)	1(3%)	
Week 8								
Butenafine (n = 40)	9 (23%)	22 (55%)	3 (8%)	3 (8%)	2 (5%)	1 (3%)	0(0%)	< .001
Vehicle (n = 40)	2 (5%)	12 (30%)	7 (18%)	8 (20%)	3 (8%)	5 (13%)	3(8%)	

[†] From vol. 1.20, pp.88-89

[†] Cochran-Mantel-Haenszel mean score test

Reviewer's Comment:

As with Study #1, these results indicate that, by weeks 4 and 8, there was a statistically significant difference between the butenafine and vehicle treatment groups.

The "Patient Assessment of Response" at weeks 4 and 8 is shown in Table 39.

Table 39 - - Patient Assessment of Response; all evaluable patients

	Greatly improved	Somewhat Improved	No Change	Somewhat Worse	Much Worse	p-value
Week 4						
Butenafine (n = 40)	25 (63%)	14 (35%)	1 (3%)	0 (0%)	0 (0%)	0.003
Vehicle (n = 40)	16 (40%)	14 (35%)	7 (18%)	2 (5%)	1 (3%)	
Week 8						
Butenafine (n = 40)	30 (75%)	8 (20%)	2 (5%)	0 (0%)	0 (0%)	<0.001
Vehicle (n = 40)	18 (45%)	9 (23%)	8 (20%)	3 (8%)	2 (5%)	

* Cochran-Mantel-Haenszel mean score test

Reviewer's Comment:

These results indicate that there was a statistically significant difference between the butenafine and vehicle treatment groups at weeks 4 and 8.

Those patients who achieved "Overall Cure" in the MITT population and the sponsor's per protocol population are listed in Table 40.

Table 40 -- Patients with "Overall Cure"

Butenafine

<u>Patient #</u>	<u>Investigator</u>	<u>Organism</u>
	Elewski	T. rubrum
	Elewski	T. rubrum
	Pariser	T. rubrum
	Pariser	T. rubrum
	Pariser	T. rubrum
	Tschen	T. rubrum

Vehicle

<u>Patient #</u>	<u>Investigator</u>	<u>Organism</u>
	Elewski	T. rubrum
	Tschen	T. mentagrophytes

Reviewer's Comment:

- 1) All of the patients who achieved an "Overall Cure" were within the window of ± 3 days as specified in the original protocol.*
- 2) All of the butenafine-treated patients who achieved "Overall Cure" had T. rubrum infection. T. rubrum is assumed to be more difficult to cure than the other 2 organisms.*

Subgroup analyses were performed for gender, age, and ethnic group. For males, at week 8, in both the MITT population and the sponsor's per protocol population, there was a statistically significant difference between the butenafine and vehicle treatment groups for all efficacy parameters, including "Overall Cure" ($p=0.025$ [MITT] and $p=0.034$ [sponsor's per protocol]). For females, there was not statistically significant difference between the butenafine and vehicle treatment groups for "Overall Cure"; however, a statistical difference was achieved for "Effective Treatment" and "Mycological Cure" for both the MITT population and the sponsor's per protocol population.

Subgroup analyses by age were performed on age strata of <45 years (31 butenafine patients/27 vehicle patients), 45-65 years (7 butenafine patients/13 vehicle patients), and >65 years (2 butenafine patient/0 vehicle patients). At week 8, for those less than 45 years old, there was a statistically significant difference between the butenafine and vehicle treatment groups for all efficacy parameters, including "Overall Cure," "Effective Treatment," and "Mycological Cure" in both the MITT and sponsor's per protocol population. For those patients between 45 to 65 years of age, at week 8, there was not a statistically significant difference between the 2 treatment groups for any efficacy parameter except "Mycological Cure" ($p=0.007$). There were too few patients over 65 years to statistically analyze.

Analyses stratified by ethnic group showed that for Caucasian patients (21 butenafine/29 vehicle), at week 8, there was a statistically significantly difference between the butenafine and vehicle treatment groups for all of the efficacy parameters, including "Overall Cure," "Effective Treatment," and "Mycological Cure" in both the MITT population and sponsor's per protocol population. For Hispanic patients (10 butenafine/5 vehicle), there was a statistically significant difference between the butenafine and vehicle treatment groups for "Effective Treatment" and "Mycological Cure." The number of Hispanic patients achieving "Overall Cure" (2/10 butenafine patients vs. 1/5 vehicle patients) was not statistically significant. There were too few African-American patients (7 butenafine/3 vehicle) to statistically analyze.

Reviewer's Comment:

In summary, the therapeutic effect of butenafine was more apparent in males, those patients who were less than 45 years old, and in Caucasian and Hispanic patients. However, as with Study #1, it is possible that the lack of statistical therapeutic efficacy seen in African-American patients and in those patients older than 45 years of age may be because there were too few patients in each group per treatment arm which may have resulted in insufficient power to detect a statistical difference.

8.1.2.3.3 Safety Outcomes

Adverse Events

A total of 119 patients were enrolled in this study, with 60 butenafine and 59 vehicle patients having applied at least 1 dose of medication. Of these, 40 butenafine patients and 36 vehicle patients were exposed to the assigned medication for 4 weeks. For laboratory studies, 57 butenafine patients and 56 vehicle patients had at least 1 set of laboratory studies.

There were no serious adverse events reported during the study in either treatment group. One patient (██████████ vehicle) withdrew from the study due to an adverse event consisting of severe burning/stinging and itching of the feet. There were 2 additional patients (██████████ butenafine and ██████████ vehicle) who experienced burning or itching after application of the medication.

All adverse events related to the skin are shown in Table 41. Adverse events unrelated to the skin reported in more than 1% of the patients are also listed in Table 41.

Table 41 - - Adverse Events (expressed as number of patients)

Event	Butenafine n = 60 pts.	Vehicle n = 59 pts.
Hyperbilirubinemia ¹	2 (3%)	0 (0%)
Infection ²	2 (3%)	3 (5%)
Elevated SGOT/SGPT ³	1 (2%)	0 (0%)
Application site reaction ⁴	1 (2%)	1 (2%)
Burning	1	0
Itching	0	1
Rash ⁵	0 (0%)	1 (2%)
Skin disorder ⁶	0 (0%)	1 (2%)
Conjunctivitis	0 (0%)	3 (5%)
Pain ⁷	0 (0%)	2 (3%)
Burning/stinging	0	1
Itching	0	1
Other (unrelated to the skin)	0	1
Headache	0 (0%)	2 (3%)

¹ Includes Patients (See "Laboratory Tests" section below)

² Includes patients with URI and sinusitis

³ Includes Patient (see "Laboratory Tests" section below)

⁴ Includes Patient (butenafine) with mild burning upon application and Patient ██████████ (vehicle) with severe itching after each application of medication

⁵ Includes Patient ██████████ with unspecified "rash" at site of KOH scraping. This patient also had facial irritation.

⁶ Includes Patient ██████████ with "bleeding on the face"

⁷ Includes Patient ██████████ (vehicle) described above with severe burning/stinging and itching of the feet

Laboratory Tests

Patients with elevated laboratory values (see footnote to Table 42 for definition) beyond the baseline visit are listed in Table 42. Those laboratory studies of particular interest were the percent eosinophils, SGPT, SGOT, and total bilirubin. As noted below, 2 patients in the butenafine treatment group developed elevated SGOT/SGPT values. For Patient 1, the abnormal values tended to return to baseline values; for Patient 2 the maximum value was reported at week 4, without additional follow-up blood levels. In addition, Patient 3 had a significantly elevated LDH (1115 IU/L [normal values 100-250]) at week 4 (no subsequent values were reported).

Table 42 - - Selected Abnormal Laboratory Values

Pt. #	Investigator	Treatment Group Butenafine n=57 Vehicle n=56	Test	Result
	Gorsulowsky	Butenafine	SGPT*	55 (baseline) 51 (wk 4)
	Gorsulowsky	Butenafine	SGPT*	34 (baseline) 130 (wk 2) 51 (wk 4) 43 (wk 8)
			SGOT*	19 (baseline) 119 (wk 2) 37 (wk 4) 20 (wk 8)
			LDH*	157 (baseline) 312 (wk 2) 1115 (wk 4) 164 (wk 8)
	Pariser	Butenafine	SGPT*	39 (baseline) 83 (wk 4)
			SGOT*	36 (baseline) 68 (wk 4)
	Gorsulowsky	Butenafine	T. Bili*	1.3 (baseline) 2.2 (wk 2) 1.4 (wk 4)
	Tschen	Butenafine	T. Bili*	1.5 (baseline) 2.7 (wk 2) 0.9 (wk 4)

Pt #	Investigator	Treatment Group Butenafine n = 57 Vehicle n = 56	Test	Result
	Pariser	Vehicle	% Eos ¹	8% (baseline) 5% (wk 2) 4% (wk 4)
	Gorsulowsky	Vehicle	SGPT ²	63 (baseline) 56 (wk 4) 67 (wk 8)
	Gorsulowsky	Vehicle	SGPT ²	60 (baseline) 43 (wk 2) 54 (wk 4)
	Pariser	Vehicle	SGPT ²	105 (baseline) 145 (wk 2)
			SGOT ³	86 (baseline) 119 (wk 2)
	Tschen	Vehicle	SGPT ²	67 (baseline) 75 (wk 2) 70 (wk 4)
	Tschen	Vehicle	SGPT ²	77 (baseline) 56 (wk 1) 56 (wk 2) 93 (wk 4)
			SGOT ³	53 (baseline) 45 (wk 1) 40 (wk 2) 65 (wk 4)
	Gorsulowsky	Vehicle	T. Bili ⁴	2.1 (baseline) 1.6 (wk 2)

¹ Normal limits 0-4%. Values $\geq 7\%$ are listed.

² Normal limits 0-50 IU/mL.

³ Normal limits 0-50 IU/mL.

⁴ Normal limits 0.1-1.2 mg/dL. Values ≥ 1.8 mg/dL are listed.

⁵ Normal limits 100-250 IU/L.

Reviewer's Comment:

1) For Patient [REDACTED] although the maximum SGOT/PT values are only mildly elevated, a relationship between these abnormal values and the medication cannot be excluded, since there were no subsequent determinations after week 4. In addition, Patient [REDACTED] (butenafine) had significant elevations of SGOT, SGPT, and LDH at week 2. By week 4, the SGOT and SGPT had returned toward baseline, although the LDH had increased even more to 1115 IU/L. By week 8, all values had returned to normal limits. For future studies, it is recommended that, for patients with abnormal laboratory results at week 4 (assuming normal baseline values), the sponsor obtain additional follow-up laboratory studies in order to determine if the levels are continuing to rise (even while not using the medication) or whether they are returning to baseline values.

2) It should be noted that for Patient [REDACTED] the week 4 bilirubin value is not in the line listings and was obtained directly from the case report form. For Patient [REDACTED] the week 8 results were not found in the line listings and were obtained directly from the case report form.

3) It should be noted that Patient [REDACTED] (butenafine) is discussed by the sponsor as having an elevated bilirubin at baseline and week 2 (which returned to normal at week 4). This information is not found in the line listings for this patient (see vol. 1.21, p. 0777) and was obtained directly from the case report form.

Pharmacokinetic Sampling

The protocol specified that plasma samples for the analysis of butenafine (KP-363) and its major plasma metabolite, M2, were to be obtained from all patients at Site #23 (Dr. Pariser) at every visit. After the randomization code was broken, only samples from the butenafine group were analyzed. The level of quantitation for the butenafine and M2 plasma assay is 0.1 ng/mL.

There were 7 patients who had results at week 4 (end of treatment). Plasma samples were obtained 15 to 20 hours after the last application of butenafine cream. At week 4, butenafine levels ranged from <0.1ng/mL to 0.19ng/mL; the M2 levels were consistently <0.1ng/mL. The highest butenafine level at any timepoint during the study was 0.30ng/mL. All of the week 8 values (6 patients) for both butenafine and M2 were <0.1ng/mL.

Reviewer's Comment:

1) Without at least one additional timepoint, these values would have to be considered trough levels, and are of limited value.

2) There does not appear to be an accumulation of parent drug or M2 metabolite over 4 weeks of treatment, as measured by serum levels.

8.1.2.4 REVIEWER'S CONCLUSIONS REGARDING EFFICACY DATA

The results presented below are with the exclusion of both Patients [redacted] (vehicle) and [redacted] (vehicle), as a "worst case" scenario. However, as previously shown, the statistical analyses with or without these 2 patients yielded results that were very similar for all parameters.

Summary of p-values, week 8
Exclusion of Patients

	MITT	Sponsor's Per Protocol (-5 to +16 days)	Original Per Protocol (± 3 days)
"Overall Cure" ("Mycological Cure" + Global of "Cleared")	0.014	0.022	0.029
"Mycological Cure" (negative culture and KOH)	< 0.001	< 0.001	< 0.001
"Effective Treatment" ("Mycological Cure" + Global of "Cleared" or "Excellent")	< 0.001	< 0.001	< 0.001
"Mycological Cure" + Total Signs/Symptoms Score of 0 (target lesion)	0.026	0.044	0.081
"Mycological Cure" + Total Signs/Symptoms Score of 0 or 1 (target lesion)	< 0.001	0.001	0.002

With or without exclusion of Patients [redacted] for the primary efficacy variable of "Overall Cure" at week 8 (end of study), there was a statistically significant difference between the butenafine and vehicle treatment groups in all 3 statistical populations. For the parameter of "Mycological Cure + Total Signs/Symptoms Score of 0," there was a statistically significant difference between the butenafine and vehicle treatment groups in the MITT and sponsor's per protocol analyses, but not in the original per protocol population. This may be due to the smaller sample size of the original per protocol population in comparison to the MITT and sponsor's per protocol populations. However, it is of interest, that, in contrast to Study #1, the parameter of "Overall Cure" was more easily achieved than the parameter of "Mycological Cure + Total Signs/Symptoms Score of 0."

There was a statistically significant difference between the 2 treatment groups for the other efficacy variables, including "Mycological Cure," "Mycological Cure + Total Signs/Symptoms Score of 0 or 1," "Median Total Signs/Symptoms Score," "Investigator's Global Score," and "Patient Assessment of Response."

9. OVERVIEW OF EFFICACY

In support of this NDA, the sponsor has performed 2 clinical trials. In my opinion, the issues complicating the interpretation of the results of these studies were: 1) small sample size with resulting lack of statistical power given that the primary efficacy variable was "Overall Cure" in which a relatively low therapeutic effect was evidenced, and 2) extending the "window" of the last evaluation beyond the original protocol window of 3 days.

The results of each study were analyzed using the modified intent-to-treat (MITT) population, the sponsor's per protocol population ("window" of -5 days to +16 days after the scheduled evaluation date), and the original per protocol population ("window" of ± 3 days after the scheduled evaluation date). For the primary efficacy variable of "Overall Cure" (defined as "Mycological Cure + Investigator's Global of Cleared"), in Study #1, at week 8, there was a statistically significant difference between the butenafine and vehicle treatment groups in the MITT population (21% butenafine vs. 8% vehicle). In the sponsor's per protocol population, the results were of marginal significance (22% butenafine vs. 9% vehicle; $p=0.06$); in the original per protocol analysis, butenafine failed to show statistically significant superiority in comparison to the vehicle (22% butenafine vs. 11% vehicle; $p=0.14$). In contrast, Study #2 demonstrated a statistically significant difference between the butenafine and vehicle treatment groups in all 3 statistical populations. The vehicle effect seen in Study #2 (approximately 6%) was slightly less than that in Study #1 which may have contributed to the statistically significant findings found in Study #2. Both studies were relatively small, which may have resulted in marginal statistical power to detect a difference between the 2 treatment groups given the low "Overall Cure" rate achieved in the butenafine group and the relatively high vehicle effect. In both Study #1 and #2, for "Mycological Cure" (defined as negative culture and KOH), at week 8, the butenafine treatment group was clearly statistically superior to the vehicle treatment group (approximately 85% butenafine versus 38% vehicle; $p<0.001$).

The supportive efficacy variable of "Mycological Cure + Total Signs/Symptoms Score of 0" showed that, for Study #1, there was a statistically significant difference between the butenafine and vehicle treatment groups in all 3 statistical populations. In contrast, for Study #2, the results were statistically significant in the MITT population ($p=0.026$) and sponsor's per protocol population ($p=0.044$), but of only marginal statistical significance in the original per protocol population ($p=0.081$).

When the 2 clinical trials are compared, regardless of the statistical population analyzed, in Study #2, "Overall Cure" was more easily achieved than "Mycological Cure + Total Signs/Symptoms Score of 0" whereas in Study #1, the parameter of "Mycological Cure +

Total Signs/Symptoms Score of 0" was more easily achieved than "Overall Cure." Depending on the study, there were patients who were judged as being "Cleared" yet who did not have a "Total Signs/Symptoms Score of 0"; conversely, there were several patients, particularly in Study #1, who had a "Total Signs/Symptoms Score of 0" yet who were not judged as "Cleared." **It is strongly recommended that, for future studies, the sponsor carefully discuss with the investigators the criteria to be used for the Investigator's Global and the Signs/Symptoms Score for each clinical parameter so that perhaps these discrepancies may be avoided.**

When the less clinically stringent parameters of "Effective Treatment" (defined as "Mycological Cure + Investigator's Global of Cleared or Excellent") or "Mycological Cure + Total Signs Symptoms Score of 0 or 1" are used to assess efficacy, in both Study #1 and #2, butenafine was statistically superior to the vehicle. Similarly, for the remaining secondary efficacy variables of "Median Total Signs/Symptoms Score," "Investigator's Global," and "Patient Assessment of Response," butenafine was statistically superior to the vehicle.

10. OVERVIEW OF SAFETY

The total number of patients exposed to at least 1 application of butenafine cream during the clinical trials submitted in support of this NDA for tinea pedis was 136. Of these, 92 patients applied the medication for 4 weeks. Excluding laboratory abnormalities (discussed below), overall, of those adverse events directly related to application of the drug material or classified as worsening of tinea pedis, there were 2 reports in the butenafine group (1.5% [2/136]) and 4 reports (occurring in 3 patients) in the vehicle group (3% [4/132]), as shown below in Table 43. In the 2 studies, 1 patient (██████████ vehicle) withdrew due to an adverse event, which consisted of severe burning/stinging and itching of the feet, and 1 patient (#1201/vehicle) withdrew because of lack of efficacy.

In the **uncontrolled studies** of tinea pedis/manuum submitted by the sponsor (approximately 435 enrolled patients), the most frequently reported adverse events were erythema (1.5%), contact dermatitis (1.5%), irritation (1.5%), and itching (1%).

Table 43 - - Adverse Events (expressed as number of patients)

Event	Butenafine n = 136	Vehicle n = 132
Headache	2 (1.5%)	7 (5%)
Worsening of tinea pedis	1 (0.7%)	0 (0%)
Burning/stinging	1 (0.7%)	1 (0.8%)
Itching	0 (0%)	2 (1.5%)
Unspecified "rash" at site of KOH	0 (0%)	1 (0.8%)

In the 2 clinical trials submitted in support of this NDA, there were several patients with laboratory abnormalities in both the butenafine and vehicle treatment groups. Most of the abnormalities consisted of elevations of bilirubin and/or SGOT/PT. In most instances the elevations of SGOT/PT were not more than twice the upper limit of normal. Patients with laboratory abnormalities 2X normal are presented in Table 44. There did not appear to be an increased number of patients with these abnormalities in comparison to the vehicle-treated group. However, Patient # [REDACTED] had elevated bilirubin levels which remained elevated as of the last determination. This patient was reported as having a familial hyperbilirubinemia disorder, type not specified. The rise in bilirubin for Patient # [REDACTED] (maximum 3.0mg/dL at week 4), in parallel with butenafine administration, with a decrease after discontinuation of the drug, was rather striking. The patient's twin sibling, Patient # [REDACTED] was terminated from the study after week 2 because of a negative baseline culture. The maximum bilirubin for this patient was 2.3mg/dL at week 2, and is not listed in Table 44 below. It is possible that, depending on the type of familial hyperbilirubinemia, these patients may be more likely to exhibit elevated bilirubin levels in response to systemic absorption of butenafine.

Table 44 - - Laboratory Abnormalities (expressed as number of patients)

Test	Butenafine n = 130	Vehicle n = 127
SGOT/PT	2 (1.5%)	2 (1.5%)
Total bilirubin	1 (0.8%)	0 (0%)
LDH	1 (0.8%)	0 (0%)
Eosinophils	2 (1.5%)	1 (0.8%)

* Laboratory values 2X normal are presented

Reviewer's Comment:

Because of the small number of patients exposed to butenafine during the controlled clinical trials, there may have been too few patients to detect relatively infrequently occurring adverse reactions (e.g., 1-2%).

10.1 OTHER SAFETY FINDINGS

10.1.2 Foreign Post-Marketing Surveillance

Butenafine cream has been marketed in Japan since April, 1992, for the indications of tinea pedis, tinea cruris, tinea corporis, and tinea versicolor. Post-marketing surveillance reports from Japan submitted in support of this NDA are dated from January, 1992, to April, 1995, and comprise approximately 3,000 patients. These reports are the result of surveying various medical institutions in Japan. **For all indications**, the most commonly reported adverse events occurring at the site of application were contact dermatitis, erythema, pruritus, and irritation. Each of these occurred at less than 1%. There were no reports of severe adverse events related to the treatment.

10.1.3 Special Studies

Seven studies were conducted to evaluate the irritancy, contact sensitization, phototoxicity, and photoallergy potential of butenafine cream 1%, and are summarized in the table on the following pages:

Human Use Safety Studies

Protocol No. Site	Type of Study	No. of Subjects (Male/Female) Age	Study Drugs	Study Design	Results
Study G-1 Japan	Primary irritation	36 (30M/6F) 20 - 55	Butenafine 0.5%, 1% cream Butenafine cream vehicle Butenafine 0.5%, 1% lotion Butenafine lotion vehicle Econazole 1% cream and lotion Bifonazole 1% cream and lotion Tolciclate 1% cream Blank	20 mg test drug applied to patch and taped to upper dorsal skin. Applied for 48 hrs. Evaluation at 1 hr. and 24 hrs. after removal.	2 subjects with \pm reaction to cream and vehicle at 1 hr. evaluation after removal. 0 subjects with reaction at 24 hr. evaluation.
PDC 010-009	Primary irritation	17 (3M/14F) 18 - > 66	Butenafine cream 1% Butenafine cream vehicle Butenafine gel vehicle	0.2 mL test drug applied to patch under occlusion. Applied for 24 hrs. Evaluation at 30 min. and 24 hrs. after removal.	0 subjects with any reaction at either evaluation.
PDC 010-010	21-day cumulative irritation	24 (5M/19F) 18 - > 66	Butenafine cream 1% Butenafine cream vehicle Butenafine gel 1% Butenafine gel vehicle Saline	0.2 mL applied to patch under occlusion. Each patch in place for 23 \pm 1 hr. for 21 consecutive applications. Evaluations 24 hrs. after each application.	Butenafine cream, gel, gel vehicle, and saline were considered mild irritants. No subject had a single score greater than 2 (definite erythema). The butenafine cream vehicle was significantly more irritating than the other tested materials, with the highest single score being 4 (definite edema).
PDC 010-006	Contact sensitization Repeat Insult Patch Test	204 (39M/165F) 18 - > 66	Butenafine cream 1% Butenafine cream vehicle	0.2 mL applied to patch under occlusion. Induction: 24 hr application of patch followed by a 24 hr "rest" (48 hrs. on weekend) for total of 9 applications over 3-wk period. Challenge: after 10-17 day rest, application of challenge patch for 48 hrs.	See review.

Human Use Safety Studies (cont.)

Protocol No. Site	Type of Study	No. of Subjects (Male/Female) Age	Study Drugs	Study Design	Results
Study G-2 Japan	Phototoxicity	30 pts with dermatitis or photodermatitis (7M/23F) 24 - 76	Butenafine cream 0.5%, 1%, 2% Butenafine lotion 0.5%, 1%, 2% Econazole cream 1% Econazole lotion 1% Bifonazole cream 1% Bifonazole lotion 1% Tolciclate cream 1% Tolciclate lotion 1%	20 mg of test material applied to each set of duplicate patches and applied for 48 hrs. Sites uncovered, and 1 set irradiated with UVA (number of joules/cm ² not stated). Evaluation at 1 hr. and 24 hrs. after irradiation.	No positive reactions.
PDC 010-007	Phototoxicity	27 (5M/22F) 18 - 50	Butenafine cream 1% Butenafine cream vehicle Distilled water	0.2 mL test drug applied to duplicate set of occlusive patches and applied for 24 hrs. Sites uncovered, and 1 set irradiated with UVA (16 J/cm ²). Evaluation at 1, 24, 48, and 72 hrs. after irradiation.	2 subjects with a 1+ reaction at 1 hr. with butenafine cream and vehicle. 9 subjects with a 1+ reaction at 1 hr. with distilled water.
PDC 010-008	Photoallergy Potential	31 (4M/27F) 18 - 50	butenafine cream 1% Butenafine cream vehicle Distilled water	0.2 mL test drug applied to each occlusive patch. <u>Induction:</u> Each patch remained in place for 24 hrs. After removal of patch, sites were irradiated with UVB (2X MED). 6 applications over a 3 wk. period. <u>Challenge:</u> After 2 wk. rest, duplicate set of patches applied for 24 hrs. After removal, 1 set was exposed to UVA (16 J/cm ²). Evaluations 1, 24, 48, and 72 hrs. after removal of patches.	See review.

Contact Sensitization Potential:

Study Title: Human Repeat Insult Test for Butenafine HCl 1% (Study #PDC 010-006)

Investigator: Jerold L. Powers, M.D.
Hill Top Research, Inc.
Scottsdale, AZ

Method: This was a contact sensitization study in 204 subjects in which the following formulations were applied:
Butenafine HCl cream 1% (PD-010-C-003)
Vehicle cream (PD-010-C-004)

A dose of 0.2mL was applied to each occlusive patch (size not stated) and applied to the paraspinal region of the back of each subject. Each patch remained in place for 24 hours, followed by a 24-hour "rest" before the application of the next patch, for a total of 9 applications over a 3-week period. Evaluations were conducted 48 hours after patch application (72 hours for week-ends). After a 10 to 17 day "rest," challenge patches were applied to a naive site and remained in place for 48 hours. Evaluations were conducted 48 and 96 hours after patch application.

Results: Two hundred twenty-five subjects were enrolled in the study. Of these, 204 (39 male/165 female; age range 18- >66 years) were considered evaluable. One adverse event was reported during the study which resulted in early termination: 1 subject had a myocardial infarction and was hospitalized. An additional subject was excluded from the analysis because of receiving a NSAID for back pain that developed during the study. The remaining 19 subjects were excluded for a variety of reasons, such as a mix-up in patch application (1 subject), receiving an excluded medication (4 subjects), absence/lost to follow-up (13 subjects), and illness (1 subject). There were numerous protocol deviations at the time of challenge. These consisted of 36 subjects in whom the patch to which **butenafine cream** had been applied was lost prior to the specified 48-hour contact time. According to the investigator, in 30 subjects, the patches were lost at or after a contact period of 24 hours, but before 48 hours; in 6 subjects, the patch was lost prior to 24 hours of application. For the **vehicle**, there were 86 subjects in whom challenge patch to which the vehicle had been applied was lost prior to the specified 48-hour contact period. In 75 of these subjects, the patches were lost at or after a contact period of 24 hours, but before 48 hours; in 11 subjects, the patch was lost prior to 24 hours of application.

For the butenafine cream, all subjects were graded as 0 during the induction and at the time of challenge. For the vehicle, there was 1 subject with a 1+ during the induction applications. At the time of challenge, all subjects were graded as 0.

Reviewer's Comment:

The lack of even a mild reaction at the time of induction is somewhat surprising, given the results of the previously conducted irritation studies. It is preferred that each induction patch remain in place for 48 hours in order to increase the likelihood of producing a sensitization reaction. In addition, loss of the challenge patches in 11 subjects (6 butenafine cream, 11 vehicle) before the completion of 24 hours of contact with the skin may have resulted in a decreased ability to elicit a sensitization reaction. Even though a study population of 200 subjects may fail to detect a sensitization reaction, as many as 15 of every 1000 of the general population may react (95% confidence) (see Marzulli FN, Maibach HI. Contact allergy: predictive testing in humans in: Marzulli FN and Maibach HI, eds. Dermatotoxicology. New York: Hemisphere Publishing Corporation, 1991:422).

Photoallergy Potential:

Study Title: Evaluation of human photoallergy for butenafine HCl 1% (Study #PDC 010-008)

Investigator: Robert A. Harper, Ph.D.
Hill Top Research, Inc.
Miamiville, OH

Reviewer's Comment:

The sponsor should be aware that investigational studies involving humans must be conducted by or be under the supervision of a licensed physician. The qualifications of this individual should be indicated in the NDA.

Method: This was a photoallergy potential study in 31 subjects in which the following formulations were applied:

- Butenafine cream 1% (PD 010-C-003)
- Vehicle cream (PD-010-C-004)
- Distilled water

An MED using UVB exposures was determined for each subject. The light source was a Xenon arc solar simulator. 0.2 mL of test material was applied to each occlusive patch and applied to the paraspinal area of the back. Each patch remained in place for 24 hours for a total of 6 applications over a 3-week period. After removal of each patch, the site was irradiated with 2X MED. Evaluations were at 24 hours after irradiation (72 hours on the weekends). After a "rest" of 2 weeks, duplicate patches were applied to a naive site. After 24 hours, one of each pair of patches was removed and exposed to 16 J/cm² of UVA. The other duplicate patches were then removed and served as the unirradiated control. Evaluations were at 1, 24, 48, and 72 hours following removal of the patches.

Results: Thirty-two subjects were enrolled of which 31 (4M/27F) were considered evaluable. One patient terminated early because of starting a new job. Of the 31 subjects considered evaluable, 6 had protocol deviations in which the challenge patch for the **butenafine cream** was "lost" before 24 hours of contact with the skin. Of the remaining 25 subjects, 4 subjects had score of 1+ at 1 hour after irradiation. All subjects had a score of 0 at 24, 48, and 72 hours after irradiation. For the vehicle, 2 subjects "lost" their challenge patches before 24 hours of contact with the skin. Of the remaining 29 subjects, 4 subjects had a 1+ score at 1 hour after irradiation. All subjects had a score of 0 at 24, 48, and 72 hours after irradiation.

Reviewer's Comment:

It should be noted that the UV absorption of butenafine is primarily in the UVC (200 to 290 nm) and UVB range (290 to 320 nm). There is minimal absorption in the UVA range (320 to 400 nm), the wavelengths used by the sponsor to test for phototoxicity and photoallergy potential in the submitted studies. Because the proposed indication in this NDA is for the treatment of tinea pedis, an area which is usually protected from sunlight, photosensitivity secondary to the use of butenafine for this indication would have a low probability of occurring. However, for future indications in which butenafine may be used to treat lesions on sun-exposed areas of the body (e.g., some types of tinea corporis), it is recommended that phototoxicity and photoallergy potential be tested using UVB and/or a combination of UVA and UVB light at the time of challenge.

Pages 75-81
deleted
Labeling Review

12. CONCLUSIONS

In the 2 clinical trials submitted in this NDA in support of the indication of interdigital tinea pedis, there was a statistically significant difference between the butenafine and vehicle treatment groups as assessed by the primary efficacy variable "Overall Cure" (Mycological Cure + Investigator's Global of "Cleared") in the modified intent-to-treat (MITT) population at week 8 (4 weeks post-treatment). Although in Study #1, the original per protocol analysis failed to show a statistically significant difference between the butenafine and vehicle groups for "Overall Cure," butenafine cream was superior to vehicle as assessed by the parameter of "Mycological Cure + Total Signs/Symptoms Score of 0" in the original per protocol analysis. It should be noted that the percent of patients achieving "Overall Cure" in the butenafine treatment group was low (approximately 22% in the 2 combined studies), even though statistically significantly different from the vehicle (approximately 7% in the 2 combined studies). Moreover, the number of patients comprising the original per protocol population was much smaller than the MITT population, perhaps accounting for the difficulty of showing a statistically significant difference when the therapeutic effect is relatively small.

As expected, a much greater percent of patients were able to achieve the less clinically stringent secondary efficacy variables of "Effective Treatment" (Mycological Cure + Investigator's Global of "Excellent" or "Cleared") and "Mycological Cure + Total Signs/Symptoms Score of 0 or 1." Based on these efficacy variables, the butenafine treatment group was clearly superior to the vehicle at week 8 as well as week 4. Similarly, for the efficacy variable of "Mycological Cure" (negative culture and KOH), there was a statistically significant difference between the butenafine and vehicle treatment groups at weeks 4 and 8. The remaining secondary efficacy variables, including the "Median Total Signs/Symptoms Score" and the "Patient Assessment of Response" showed a statistically significant difference between the 2 treatment groups at week 8.

There were very few adverse events related to the skin reported during the controlled clinical trials. One patient (vehicle) withdrew due to severe burning/stinging and itching of the feet. There was 1 butenafine patient who reported burning/stinging and 2 vehicle patients who reported itching. However, in the uncontrolled clinical trials and the Japanese post-marketing surveillance, "contact dermatitis" was reported as an adverse event, having occurred in less than 2% of patients. Laboratory abnormalities were usually mild (less than 2X normal) and occurred in patients in both the butenafine and vehicle treatment groups.

The standard human use safety studies did not show evidence of irritation, contact sensitization, or photosensitivity. However, it should be noted that the contact sensitization study was not carried-out under optimum conditions in that each patch remained in place for only 24 hours rather than 48 hours during the induction phase. In addition, many of the challenge patches were "lost" before the full 48-hour application time, thus potentially reducing the likelihood of eliciting a positive response. The phototoxicity and photoallergy potential studies were performed using only UVA at the time of challenge, even though butenafine shows an absorption spectrum in the UVB range. For indications in which butenafine cream may be applied to sun-exposed areas (e.g., tinea corporis), additional information should be provided regarding the photosensitivity potential of butenafine in the UVB range.

13. RECOMMENDATIONS

- 1) NDA 20-524, butenafine cream 1%, is recommended to be clinically approvable for the treatment of interdigital tinea pedis caused by the organisms *Epidermophyton floccosum*, *Trichophyton mentagrophytes*, and *Trichophyton rubrum* with the labeling revisions noted in section 11 of this review.
- 2) The sponsor should provide information regarding any foreign countries not previously reported in the NDA in which butenafine cream 1% is marketed as well as any pending applications. In addition, all safety information from foreign markets not previously reported in this NDA should be submitted.

13.1 Other Recommendations/Comments

- 1) It should be noted that the approximate dose for the treatment of tinea pedis would be 1 gram of butenafine cream 1% per foot per application (total of 2 grams of formulation per day; approximately 0.4mg/kg/day [assuming a 50kg patient] of butenafine HCl).
- 2) The clinical trial protocols stated that butenafine cream was to be applied nightly (see vol. 1.18, p.143 and vol. 1.20, p.144). It was not specified if this was to occur only after bathing. Therefore, it is unclear if the clinical trials were conducted under the conditions of the proposed labeling. If the sponsor desires the medication to remain in place for a certain period of time before being washed off, then it should be stated as such in the directions for use.
- 3) The sponsor should be aware that the "positive fungal culture" used to determine enrollment eligibility at baseline must be **positive for a dermatophyte**, since it is those organisms for which the labeled indication is being sought.
- 4) It is strongly recommended that, for future studies, the sponsor carefully discuss with the investigators the criteria to be used for the Investigator's Global and the Signs/Symptoms Score for each clinical parameter so that perhaps discrepancies may be avoided.
- 5) Reading of the KOH slide by an investigator other than the one performing the clinical evaluation would be preferred in order to reduce investigator bias.
- 6) For the study of contact sensitization, it is preferred that each induction patch remain in place for 48 hours in order to increase the likelihood of producing a sensitization reaction.

- 7) It should be noted that the UV absorption of butenafine is primarily in the UVC (200 to 290 nm) and UVB range (290 to 320 nm). There is minimal absorption in the UVA range (320 to 400 nm), the wavelengths used by the sponsor to test for phototoxicity and photoallergy potential in the submitted studies. Because the proposed indication in this NDA is for the treatment of tinea pedis, an area which is usually protected from sunlight, photosensitivity secondary to the use of butenafine for this indication would have a low probability of occurring. However, for future indications in which butenafine may be used to treat lesions on sun-exposed areas of the body (e.g., some types of tinea corporis), it is recommended that phototoxicity and photoallergy potential be tested using UVB and/or a combination of UVA and UVB light at the time of challenge.
- 8) It is recommended that additional information be provided to substantiate the diagnosis of familial hyperbilirubinemia for Patient [REDACTED] (PDC 010-001). In addition, it is recommended, if possible, that the sponsor consider re-challenging this patient with the topical administration of butenafine cream to determine if there is a reproducible elevation of bilirubin (with determination of direct and indirect fractions).
- 9) For future studies, it is recommended that, for patients with abnormal laboratory results at week 4 (assuming normal baseline values), the sponsor obtain additional follow-up laboratory studies in order to better assess their clinical relevance.
- 10) It is recommended that the results of the Penederm pharmacokinetic study (PDC 010-011) be analyzed by gender.

Nancy Slifman 3/4/96
 Nancy Slifman, M.D.
 Howard W. Katz, M.D.
 3/5/96

cc: orig NDA 20-524
 HFD-340
 HFD-540
 HFD-540/DepDir/LKatz
 HFD-540/MO/NSlifman
 HFD-540/Chem/EPappas
 HFD-540/Pharm/KMainigi
 HFD-520/Micro/PDionne
 HFD-540/Biostat/VFreidlin
 HFD-540/Biopharm/SLee
 HFD-540/CSO/FCross

92 3/12/96

Appendix 1

Patient Evaluability - - Protocol PDC 010-001

Butenafine Treatment Group

Patient #	Difference from date med last used and theoretical date of wk 8 visit	Outcome on Day Eval.	Sponsor's Per Protocol Analysis?	Organism
	+3	Fail	Y	
	+16	Fail	Y	
	+9	Fail	Y	
	+8	Cure	Y	T.rubrum
	+1	Fail	Y	
	+1	Fail	Y	
	+1	Cure	Y	E.floccosum
	0	Fail	Y	
	+3	Fail	Y	
	+2	Cure	Y	T.rubrum
	+1	Cure	Y	T.rubrum
	+1	Cure	Y	T.rubrum
	+1	Cure	Y	T.rubrum
	+2	Fail	Y	
	0	Fail	Y	
	+1	Cure	Y	T.rubrum
	0	Cure	Y	T.rubrum
	+2	Fail	Y	
	+1	Fail	Y	
	<u>No wk 8</u>	<u>Fail</u>	<u>N Terminated wk2. Culture report neg.</u>	
	+1	Fail	Y	
	<u>No wk 8</u>	<u>Fail</u>	<u>N Lost to F/U after wk1</u>	
	+2	Fail	Y	
	+2	Fail	Y	
	+1	Fail	Y	
	+1	Fail	Y	
	+1	Fail	Y	
	0	Fail	Y	
	+1	Cure	Y	T.mentag
	+1	Fail	Y	
	0	Fail	Y	
	+2	Fail	Y	
	+1	Fail	Y	

+4*	Fail	Y	
+1*	Cure	Y	T.mentag
+3*	Fail	Y	
+6	Cure	Y	T.rubrum
+1*	Fail	Y	
+7	Fail	Y	
10*	Fail	N	
+1	Fail	Y	
-4	Fail	Y	
+1	Fail	Y	
+7	Fail	Y	
+7	Fail	Y	
0	Fail	Y	
0	Fail	Y	
+1	Fail	Y	
-2	Fail	Y	
+1	Fail	Y	
0	Fail	Y	
+2	Fail	Y	
-4	Fail	Y	

* These patients were listed as having stopped their medication on the same date as their week 4 visit. For purposes of this review, these patients are considered to have stopped their medication on the evening prior to the date of their week 4 visit.

Vehicle Treatment Group

Patient #	Difference from date med last used and theoretical date of wk 8 visit	Outcome on Day Eval	Sponsor's Per Protocol Analysis?	Organism
	<u>No wk 8</u>	<u>Fail</u>	<u>Y Lack of efficacy. Early termination</u>	
	-7	Fail	N	
	<u>No wk 8</u>	<u>Fail</u>	<u>N Delayed +cult.</u>	
	+1	Fail	Y	
	<u>No wk 8</u>	<u>Fail</u>	<u>N Death in family. Stopped after wk1</u>	
	+1	Fail	Y	
	+1	Fail	Y	
	+1	Fail	Y	
	+1	Fail	Y	

+1	Cure	Y	T.rubrum
-5	Fail	Y	
+5	Fail	Y	
+8	Fail	Y	
+2	Cure	Y	T.rubrum
-1	Fail	Y	
<u>No wk 8</u>	<u>Fail</u>	<u>N Delayed +cult.</u>	
0	Fail	Y	
+1	Fail	Y	
0	Fail	Y	
+1	Cure	Y	T.mentag
+2	Fail	Y	
+2	Cure	Y	T.rubrum
+2	Fail	Y	
+1	Fail	Y	
0	Fail	Y	
+4*	Fail	Y	
+1*	Fail	Y	
0*	Fail	Y	
+2*	Fail	Y	
+1	Fail	Y	
+1*	Fail	Y	
+7*	Fail	Y	
-4*	Fail	Y	
<u>-7*</u>	<u>Fail</u>	<u>N</u>	
0*	Fail	Y	
+2	Fail	Y	
-4	Fail	Y	
+1	Fail	Y	
+2	Fail	Y	
+1	Fail	Y	
<u>-5</u>	<u>Fail</u>	<u>N</u>	
+1	Fail	Y	
+8	Fail	Y	
+1	Fail	Y	
<u>No wk 8</u>	<u>Fail</u>	<u>N Delayed +cult.</u>	
+2	Fail	Y	
+1	Fail	Y	
-5	Fail	Y	

* These patients were listed as having stopped their medication on the same date as their week 4 visit. For purposes of this review, these patients were considered to have stopped their medication on the evening prior to the date of their week 4 visit.

NDA 28-524

2 OF 5

Appendix 2

Patient Evaluability - - Protocol PDC 010-002

Butenafine Treatment Group

Patient #	Difference from date med last used and theoretical date of v.k 8 visit	Outcome on Day Eval.	Sponsor's Per Protocol Analysis?	Organism
	<u>-15</u>	Fail	N	
	<u>-10</u>	Fail	N	
	+1	Fail	Y	
	0	Cure	Y	T.rubrum
	0	Fail	Y	
	+1	Fail	Y	
	+1	Fail	Y	
	+1	Fail	Y	
	0	Fail	Y	
	-2	Cure	Y	T.rubrum
	+1	Fail	Y	
	+5	Fail	Y	
	+1	Fail	Y	
	+8	Fail	Y	
	+2	Fail	Y	
	+1	Fail	Y	
	+10	Fail	Y	
	+1	Fail	Y	
	0	Fail	Y	
	-5	Fail	Y	
	+1	Fail	Y	
	0	Fail	Y	
	+3	Cure	Y	T.rubrum
	+1	Cure	Y	T.rubrum
	-1	Fail	Y	
	+1	Cure	Y	T.rubrum
	+2	Fail	Y	
	0	Fail	Y	
	+1	Cure	Y	T.rubrum
	-2	Fail	Y	
	+1	Cure	Y	T.rubrum
	+11	Fail	Y	
	+2	Fail	Y	

+1	Fail	Y	
+1	Fail	Y	
-5	Fail	Y	
+2	Fail	Y	
+1	Cure	Y	T.rubrum
-3	Fail	Y	
-3	Cure	Y	

Vehicle Treatment Group

Patient #	Difference from date med last used and theoretical date of wk 8 visit	Outcome on Day Eval.	Sponsor's Per Protocol Analysis?	Organism
	+1	Fail	Y	
	+1	Fail	Y	
	+1	Cure	Y	T.rubrum
	+1	Fail	Y	
	+1	Fail	Y	
	-5	Fail	Y	
	+6	Fail	Y	
	+2	Fail	Y	
	+1	Fail	Y	
	+1	Fail	Y	
	+4	Fail	Y	
	<u>+1</u>	<u>Fail</u>	<u>Y</u>	<u>Patient with <i>S. hyalinum</i> at baseline</u>
	+1	Fail	Y	
	+2	Fail	Y	
	+1	Fail	Y	
	+1	Fail	Y	
	+1	Fail	Y	
	-1	Fail	Y	
	+1	Fail	Y	
	+1	Fail	Y	
	+1	Fail	Y	
	<u>No wk 8</u>	<u>Fail</u>	<u>N</u>	<u>Terminated after wk2 due to pregnancy</u>
	+1	Fail	Y	
	+1	Fail	Y	
	<u>No wk 8</u>	<u>Fail</u>	<u>Y</u>	<u>Terminated after 3 days due to AE</u>
	+6	Fail	Y	
	0	Fail	Y	

0	Fail	Y
+2	Fail	Y
<u>No wk 8</u>	<u>Fail</u>	<u>N Terminated after wk2. Lost to follow-up</u>
+1	Fail	Y
+1	Cure	Y T.mentag
0*	Fail	Y
<u>+1</u>	<u>Fail</u>	<u>Y Should be excluded due to negative baseline culture (see review)</u>
+1	Fail	Y
+1	Fail	Y
+6	Fail	Y
+1	Fail	Y
<u>-12</u>	<u>Fail</u>	<u>N</u>
<u>No wk 8</u>	<u>Fail</u>	<u>N Terminated after wk3. Delayed +cult.</u>

* These patients were listed as having stopped their medication on the same date as their week 4 visit. For purposes of this review, these patients were considered to have stopped their medication on the evening prior to the date of their week 4 visit.

SEP 17 1996

MEDICAL OFFICER'S REVIEW OF NDA 20-524

Amendment

NDA 20-524
Amendment
M.O. Review #1

Submission date: 5/8/96
Review date: 7/25/96

DRUG NAME:

Generic Name: **Butenafine hydrochloride**
Proposed Trade Name: Mentax™
Chemical Name: *N*-4-*tert*-butylbenzyl-*N*-methyl-1-naphthalenemethylamine hydrochloride

Sponsor:

Penederm Incorporated
320 Lakeside Drive, Suite A
Foster City, CA 94404
(415) 358-0100

Pharmacologic Category:

Antifungal
Benzylamine

Proposed Indication:

Treatment of interdigital tinea pedis

**Dosage Form and
Route of Administration:**

1% cream; topical

NDA Drug Classification:

1S

Nature of Submission:

Response to approvable letter: revised labeling and safety update

Related Drugs:

Terbinafine HCl cream 1%
Naftifine cream

Related Reviews:

Microbiology Review dated: 5/30/96
Chemistry Review dated: Pending
Biopharm Review dated: Pending

Related Submissions:

IND
NDA 20-663 (Butenafine cream 1% for tinea cruris and tinea corporis)

Pages 2-13

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Labeling Review

Recommendations:

- 1) *It is recommended that the labeling for the package insert be revised in accordance with this review.*
- 2) *For the labeling of the tubes and cartons:*

Nancy Slifman, M.D.

*As above.
JWS/MS
9/6/96*

cc: orig NDA 20-524
HFD-340
HFD-540
HFD-540/MO/NSlifman

JWS 9/12/96

HFD-540/Chem/EPappas
HFD-540/Pharm/KMainigi
HFD-520/Micro/P/Dionne
HFD-540/Biostat/VFreidlin
HFD-540/Biopharm/SLee
HFD-540/CSO/FCross

SEP 17 1996

SUPERVISORY MEDICAL OFFICER'S REVIEW OF NDA 20-524

Amendment

NDA 20-524
Amendment

Submission date: 5/8/96
Review date: 9/12/96

DRUG NAME:

Generic Name: Butenafine hydrochloride
Proposed Trade Name: Mentax™
Chemical Name: N-4-tert-butylbenzyl-N-methyl-1-naphthalenemethylamine hydrochloride

Sponsor: Penederm Incorporated
320 Lakeside Drive, Suite A
Foster City, CA 94404
(415) 358-0100

Pharmacologic Category: Antifungal
Benzylamine

Proposed Indication: Treatment of interdigital tinea pedis

Dosage Form and
Route of Administration: 1% cream; topical

NDA Drug Classification: 1S

Nature of Submission: Response to approvable letter: revised labeling and safety update

Related Drugs: Terbinafine HCl cream 1%
Naftifine cream

Related Reviews: Microbiology Review dated: 5/30/96
Chemistry Review dated: Pending
Biopharm Review dated: Pending

Related Submissions: IND
NDA 20-663 (Butenafine cream 1% for tinea cruris and tinea corporis)

Refer to Medical Officer Review of 7/25/96 for complete labeling and other review comments. This review will concentrate on modifications to that review, which can be located in the Reviewer's Comment section of this review.

REVIEW OF LABELING FOR PACKAGE INSERT

Pages 3-12

Deleted

Labeling Review

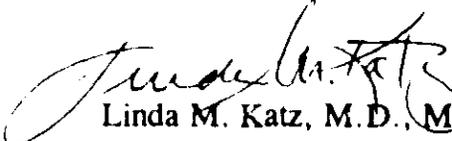
REVIEW OF LABELING FOR TUBES AND CARTONS

Reviewer's Comment:

The comments made by the medical reviewer regarding this section were conveyed to the Chemist. Refer to his review for specifics.

Recommendations:

- 1) *It is recommended that the labeling for the package insert be revised in accordance with this review.*


Linda M. Katz, M.D., M.P.H.

gww 9/17/96

Blank Page

cc: orig NDA 20-524
HFD-340
HFD-540
HFD-540/Div Dir/JWilkin
HFD-540/Dep Dir/LKatz
HFD-540/Chem/EPappas
HFD-540/Pharm/KMainigi
HFD-520/Micro/P/Dionne
HFD-540/Biostat/VFreidlin
HFD-540/Biopharm/SLee
HFD-540/CSO/FCross

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-524 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6 4/3/96

HFD-510 Trade (generic) name/dosage form: Butenafine HCl Cream, 1% Action: AP AE NA

Applicant Pedererm Therapeutic Class 15

Indication(s) previously approved None
Pediatric labeling of approved indication(s) is adequate inadequate

Indication in this application Tinea Pedis
(For supplements, answer the following questions in relation to the proposed indication.)

- 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required. *As revised.*
- 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.
 - a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
 - b. The applicant has committed to doing such studies as will be required.
 - (1) Studies are ongoing,
 - (2) Protocols were submitted and approved.
 - (3) Protocols were submitted and are under review.
 - (4) If no protocol has been submitted, explain the status of discussions on the back of this form.
 - c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
- 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed. *Below age 12 the condition is rare.*
- 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

J.P. Hall PM 3/4/96
Signature of Preparer and Title (PM, CSO, MO, other) Date

cc: Orig NDA/PLA # 20-524
HFD-510 / Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)
Just 2/26, Per MO - Dr. S. L. Fma 3/4/96.

NOTE: A new Pediatric Page must be completed at the time of each action even though one was filed at the time of the last action.

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

AP

OCT 18 1996

NDA/PLA # 20-524

Supplement # _____

Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD 540 Trade (generic) name/dosage form: butenafine HCl Cream, 1%

Action: AP AE NA 10/13/96

Applicant Pearl Derm, Inc.

Therapeutic Class 15

Indication(s) previously approved None

Pediatric labeling of approved indication(s) is adequate inadequate

Indication in this application tinea pedis

(For supplements, answer the following questions in relation to the proposed indication.)

1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

As Revised

2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

a. A new dosing form is needed, and applicant has agreed to provide the appropriate formulation.

b. The applicant has committed to doing such studies as will be required.

(1) Studies are ongoing,

(2) Protocols were submitted and approved.

(3) Protocols were submitted and are under review.

(4) If no protocol has been submitted, explain the status of discussions on the back of this form.

c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed.

Below age 12 the condition is rare

4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

[Signature]

Signature of Preparer and Title (PM, CSO, MO, other)

9/19/96

Date

cc: Orig NDA/PLA # 20-524

HFD-540 /Div File

NDA/PLA Action Package

HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

[Signature] 10/11/96

⚠ A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

Clin. Pharm/
Bio

ADDENDUM TO CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-524 **SUBMISSION DATE:** 10/16/95
PRODUCT: Butenafine HCl Cream 1%
SPONSOR: Penederm Incorporated
320 Lakeside Drive, Suite A
Foster City, CA 94404
TYPE OF SUBMISSION: **REVIEWER:** Sue-Chih Lee, Ph.D.
Original NDA, NME, 1S

I. BACKGROUND:

This review is an addendum to the review dated 9/29/95. In the sponsor's 4/4/95 submission, it was stated that the urine samples for Penederm Study 9425201D (Protocol PDC-010-011) were collected as required in the protocol, but were not analyzed due to technical difficulties associated with the development and validation of the analytical method. After review of that submission, we were not particularly concerned about the safety of the product but a conversation between this reviewer and the Medical Officer, Dr. Nancy Slifman, revealed that the urine samples were later analyzed by another contract laboratory. Therefore, we requested through the CSO, Mr. Frank Cross, that the sponsor submit the urine data for the study. The submission dated 10/16/95 includes the urine data and the revised report for Study 9425201D to reflect the inclusion of the urine sample results.

II. STUDY 9425201D - URINE SAMPLE ANALYSIS:**A. Study Design:**

This is a one-period, multiple application study. Two groups of normal, healthy subjects were included and all subjects completed the study. In one group of 8 subjects (4M/4F), about 6 grams of the formulation were applied once daily for 14 days to the posterior trunk of each individual, an area comprising 3,000 cm². In the second group, which consisted of 12 subjects (6M/6F), about 20 grams of the cream were applied once daily for 14 days to the arms, trunk (including the inframammary area in females) and groin area (including the scrotum in males), an area of approximately 10,000 cm². (The usual dose is approximately 1 g for tinea pedis infections.)

In addition to blood samples, urine samples were collected prior to Day 1 dosing and for the 24-hour intervals beginning on Days 1, 14 and 28.

B. Assay:

Urine samples were analyzed for butenafine and metabolites (M1, M2 and M3) by
To determine butenafine and M2 metabolite, urine samples

were extracted with acetonitrile and the extract was injected onto a LC/MS/MS equipped with a short cation exchange HPLC column using deuterated butenafine as the internal standard. The peak areas measured are m/z 318-141 for butenafine, m/z 334-141 for M2 and m/z 325-148 for the internal standard.

For the analysis of M1 metabolite, urine samples were acidified and extracted with cyclohexane/isopropanol (80:20) solution. To analyze M3 metabolite, urine samples were acidified and extracted with ethylacetate. The organic layer was then analyzed using LC/MS/MS equipped with a normal phase HPLC system. Mefenamic acid was used as the internal standard. The peak areas measured were m/z 171-127 for M1, m/z 228-127 for M3 and m/z 240-196 for the internal standard.

Quantitation was performed using a 1/x weighted linear regression line generated from spiked urine samples. The standards contained all metabolites, M1, M2 and M3. Any concentration determined to be below the lower limit of quantitation was assigned a value of 0.0 ng/ml. The validation results are as follows:

Linearity:	ng/mL, r >	(butenafine);	ng/mL, r >	(M2)
	ng/mL, r >	(M1);	ng/mL, r >	(M3)
Accuracy:	% (butenafine);		% (M2)	
	% (M1);		% (M3)	
Precision:	% (butenafine);		% (M2)	
	% (M1);		% (M3)	
LLOQ:	ng/mL (butenafine);		ng/mL (M2)	
	ng/mL (M1);		ng/mL (M3)	

Specificity: Satisfactory, chromatograms submitted.

C. Results:

Butenafine appeared in the urine of both high and low dose subjects on Days 1 and 14, but was undetectable in all but two samples on Day 28. The metabolite *M2* was the most predominant metabolite detected on Day 14, a time when subjects had presumably reached steady-state plasma levels. This indicates *M2* is the major urinary metabolite in human. Levels of *M2* were substantially reduced by Day 28. *M1* appeared in the urine samples of 4 out of the 20 subjects and *M3* was not detectable in any urine sample. (Note: The detection limit for *M1* and *M3*, 2.0 ng/mL, is higher than those for butenafine and *M2*.)

Mean urinary excretion of butenafine and the three metabolites on Days 1, 14 and 28 are given in Tables 1-4. (For individual data, see Table 5.)

Some observed high values are noted here:

The butenafine value on Day 1 for subject 108 (25.7 ug) is an order of magnitude higher than the next highest value (2.5 ug for subject 102). Because a concomitant increase in metabolites was not seen nor was this high value of butenafine sustained throughout the study, the sponsor concluded that this high level in the urine sample may have been due to contamination. However, this value was included in the calculation of mean butenafine excretion for Day 1.

The amount of M1 in the urine of Subject 102 on Days 14 and 28, and the amount from Subject 204 on Day 28, were an order of magnitude higher than any other M1 values. These values were also included in the calculations of mean values.

III COMMENTS:

1. Some subjects had much higher butenafine or metabolite plasma concentrations, but these subjects had no systemic adverse events that were considered related to the product.
2. The mean total daily urinary excretion (including butenafine and the metabolites) is very small and the highest value is 0.01% of the applied dose. Due to the detection limit of the analytical method, this number may be an underestimate. However, even if this factor is considered, the mean urinary excretion can at most be doubled.
3. M2 is shown to be the major urinary metabolite in human, while M1 and M3 have been found to be the major urine metabolites in rat.
4. Regarding the analytical method:
 - a. Urine sample analysis:

The validation results show that the extraction procedure gives a recovery of 69% for M1 itself and 107% for the internal standard, mefenamic acid. The difference in recovery indicates that mefenamic acid is not an ideal internal standard for M1. Additionally, there may be endogenous compound that interferes with the analysis of M1. (The sponsor did not explain the high M1 values observed with 2 subjects.)

Urine samples appear to have been stored for an extended period of time before analysis. Data on extended stability at the sample storage temperature should be provided.
 - b. Plasma sample analysis:

In the analysis, the standard curve was constructed through linear regression using 1/x weighting. The sponsor did not demonstrate that this weighting is most appropriate.

IV. RECOMMENDATIONS:

See the recommendation in our review dated 9/29/95. Additionally, the sponsor should respond to Comment # 4 given above.

 1/3/96

Sue-Chih Lee, Ph.D.

Pharmacokinetics Evaluation Branch III

RD/FT Initialed by Frank Pelsor, Pharm.D.



Biopharm Day (Date: 9/21/95; Attendees: Drs. Lesko, Malinowski, ML Chen, Fleischer, Hepp, Pelsor and Lee)

cc: NDA 20-524, HFD-540 (2 copies), HFD-880 (Fleischer, Pelsor, Lee), HFD-860 (Malinowski), Chron, Drug, Reviewer, HFD-19(FOI), HFD-340 (Viswanathan)

Table 5: Amount of Butenefine, M-1, M-2 and M-3 Excreted (μg) in 24-Hour Urine Collections.
 (Subjects 20-gram/day Group; Subjects 6-gram/day Group.)

SUBJECT	KP363	KP363	KP363	M1	M1	M1
	DAY 1	DAY 14	DAY 28	DAY 1	DAY 14	DAY 28
	0.404	0.185	0.000	0	0.000	0.000
	2.174	2.523	0.329	0	50.847	71.709
	1.612	0.988	0.000	0	0.000	0.000
	0.321	0.372	0.000	0	0.000	0.000
	1.051	2.435	0.000	0	0.000	0.000
	1.251	0.176	0.000	0	0.000	0.000
	0.760	0.281	0.000	0	0.000	0.000
	25.696	0.324	0.000	0	0.000	1.335
	0.584	0.342	0.000	0	0.000	0.000
	0.318	0.778	0.000	0	0.000	0.000
	0.132	0.252	0.084	0	0.000	0.000
	0.405	0.325	0.000	0	0.000	0.000
	0.000	0.000	0.000	0	0.000	0.000
	0.366	0.120	0.000	0	0.000	0.000
	0.167	0.000	0.000	0	0.000	0.000
	0.068	0.963	0.000	0	0.000	26.052
	0.000	0.000	0.000	0	0.000	0.000
	0.000	0.263	0.000	0	0.000	0.000
	0.000	0.000	0.000	0	0.000	1.673
	0.000	0.000	0.000	0	0.000	0.000

SUBJECT	M2	M2	M2	M3	M3	M3
	DAY 1	DAY 14	DAY 28	DAY 1	DAY 14	DAY 28
	0	10.758	1.444	0	0	0
	0	7.075	3.694	0	0	0
	0	9.154	0.000	0	0	0
	0	12.275	2.008	0	0	0
	0	13.809	0.000	0	0	0
	0	7.463	1.069	0	0	0
	0	0.000	0.000	0	0	0
	0	11.812	0.965	0	0	0
	0	3.390	0.000	0	0	0
	0	4.336	1.192	0	0	0
	0	4.041	0.000	0	0	0
	0	5.325	2.481	0	0	0
	0	0.000	0.000	0	0	0
	0	4.605	0.000	0	0	0
	0	2.682	0.000	0	0	0
	0	1.021	0.000	0	0	0
	0	3.587	0.000	0	0	0
	0	0.000	0.000	0	0	0
	0	4.957	2.244	0	0	0
	0	2.125	0.000	0	0	0

Table 1: 24-Hour Mean Urinary Excretion of Butenafine

Dose		Day 1	Day 14	Day 28
6 g QD	Mean (μg)	0.075	0.056	0.00
	Std.Dev.	0.132	0.095	0.00
	(CV%)	(175)	(170)	(-)
20 g QD	Mean (μg)	2.92	0.665	0.051
	Std.Dev.	7.21	0.699	0.152
	(CV%)	(247)	(105)	(299)

Table 2: 24-Hour Mean Urinary Excretion of M-1

Dose		Day 1	Day 14	Day 28
6 g QD	Mean (μg)	0.00	0.00	3.466
	Std.Dev.	0.00	0.00	9.15
	(CV%)	(-)	(-)	(264)
20 g QD	Mean (μg)	0.00	4.237	6.087
	Std.Dev.	0.00	14.7	20.7
	(CV%)	(-)	(346)	(340)

- * Mean of 20-g QD dosing group for each day did not differ statistically from that of the 6-g QD dosing group when tested by ANOVA at $\alpha=0.05$.

Table 3 : 24-Hour Mean Urinary Excretion of M-2

Dose		Day 1	Day 14	Day 28
6 g QD	Mean (μg)	0.00	2.372	0.281
	Std.Dev.	0.00	1.94	0.794
	(CV%)	(-)	(82)	(283)
20 g QD	Mean (μg)	0.00	7.453	1.071
	Std.Dev.	0.00	4.21	1.19
	(CV%)	(-)	(56)	(111)

Table 4 : 24-Hour Mean Urinary Excretion of M-3

Dose		Day 1	Day 14	Day 28
6 g QD	Mean (μg)	0.00	0.00	0.00
	Std.Dev.	0.00	0.00	0.00
	(CV%)	(-)	(-)	(-)
20 g QD	Mean (μg)	0.00	0.00	0.00
	Std.Dev.	0.00	0.00	0.00
	(CV%)	(-)	(-)	(-)

* Mean of 20-g QD dosing group for each day did not differ statistically from that of the 6-g QD dosing group when tested by ANOVA at $\alpha=0.05$.

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-524	SUBMISSION DATES: 05/08/96
PRODUCT: Butenafine HCl Cream 1% (Mentax™)	06/19/96
SPONSOR: Penederm Incorporated 320 Lakeside Drive, Suite A Foster City, CA 94404	
TYPE OF SUBMISSION: NDA Amendments	REVIEWER: Sue-Chih Lee, Ph.D.

I. BACKGROUND:

Butenafine hydrochloride, a benzylamine derivative, is closely related to allylamine antifungal agents. Its antifungal properties may be related to its ability to impair the synthesis of ergosterol, a component of fungal and yeast cell membranes, which leads to increased membrane permeability and a disorder of cellular organization. The product will be indicated for the treatment of interdigital tinea pedis.

The sponsor was issued an approvable letter dated April 3, 1996. Subsequently, the sponsor submitted two amendments to address the issues cited in the approvable letter. This review is based on these two amendments.

II. SPONSOR'S RESPONSES TO COMMENTS:**Comment #1:**

The sponsor states that M2 is the primary metabolite in human plasma although this was only demonstrated in rats. The sponsor should provide data to support the statement.

Response:

An attempt was made to measure plasma metabolite levels after topical administration of 10 mg butenafine HCl/kg. However, absorption was low and subsequent metabolite levels were not measurable. In Rats, M2 was the major metabolite found in plasma (M1: 14.7%, M2: 42.8%, M3: 0.7%, M4: 10.8% and M5: 0.8%).

In the human pharmacokinetic study at doses of 6 g/day and 24 g/day for 14 days, metabolite M2 was detected in human plasma. (No attempt was made to determine other possible plasma metabolites.) For the 20 urine samples collected at Day 14, M1 was detected in one sample, M2 in most of the samples (17 out of 20), and M3 in none of the samples. This confirms that hydroxylation of the t-butyl group to form M2 is a significant pathway in the human as well as the rat.

A review of literature indicates that the major elimination routes for M1 (1-naphthoic acid) are glycine conjugation to form M3 and renal excretion. Based on the above human urine sample results, it is concluded that the M1 pathway did not occur to an appreciable extent in the human.

Hydroxylation of a terminal t-butyl group resulting in the formation of an alcohol has been identified as a significant metabolic pathway for a number of compounds including bupropion (a nontricyclic antidepressant), and 2-methyl-2-(4-acetaminophenoxy) propane, a phenacetin derivative. For compounds like terbinafine, finasteride and terfenadine, hydroxylation of t-butyl group was also a significant metabolic pathway although the alcohol formed was further metabolized.

Comment: Based on the information in the NDA, this reviewer agrees that formation of M2 is a significant metabolic pathway in the human but the sponsor does not prove that M2 is the primary metabolite in human plasma.

Comment #2:

Regarding the analytical method:

- A. Urine sample analysis:
1. The validation results show that the extraction procedure gives a recovery of 69% for M1 itself and 107% for the internal standard, mefenamic acid. The difference in recovery indicates that mefenamic acid is not an ideal internal standard for M1. Additionally, there may be endogenous compound that interferes with the analysis of M1. An explanation of the high M1 values observed with 2 subjects should be provided.
 2. Urine samples appeared to have been stored for an extended period of time before analysis. Data on extended stability at the sample storage temperature should be provided.
- B. Plasma sample analysis:
1. In the analysis, the standard curve was constructed through linear regression using 1/x weighting. Data to demonstrate that this weighting is appropriate should be submitted.
 2. The mobile phase for the HPLC/MS/MS analysis used in Study 9425201D should be specified.
 3. The assay method and method validations for Study G3 should be provided.

Responses:

A-1: Although the recovery of mefenamic acid, the internal standard, is high compared to the analytes, it is very consistent and, therefore, does not pose any problem during the analysis. The assay validation data demonstrate that this is the case. (OK.)

The following addresses the issue in regard to endogenous compounds in urine that may potentially interfere with the assay of M1. Out of seven different blank urine control samples, four showed no interference, two showed an interference equivalent to 1.0 ng/mL and one had an interference equivalent to the 2.0 ng/mL level. As a result, the LOQ was established at 2.0 ng/mL. Further, baseline study samples from 19 out of 20 subjects in the study showed no interference (< 2.0 ng/mL). One of the subjects had a value of 2.6 ng/mL.

Out of the 60 pooled 24-hour urine samples collected at different time intervals, M1 was present at quantifiable levels in only 5 samples. Also, M1 was present in only one sample on Day 14 of the study. Urine samples from the two subjects with high M1 values were analyzed in duplicate and yielded similar results. Although the possibility of any endogenous compound cannot be completely ruled out, it is unlikely that endogenous compounds could be present in the concentrations observed. These individuals might process the metabolite differently than the other subjects. Alternatively, these subjects might have been exposed to other compounds that were metabolized to M1.

Comment: Many urine samples were determined to have no quantifiable M1 concentrations. The higher LOQ for M1 as compared to that for M2 can underestimate the significance of M1 in urine. However, in view of the M2 levels in urine samples, M2 is still considered the primary metabolite in urine.

A-2:

The urine samples were stored for approximately nine months before analysis. The long-term stability studies (-70°C, 8 months) performed by _____ are provided and the results indicate this storage time did not adversely affect the assay results. (OK.)

B-1:

The use of 1/x weighting was to decrease the deviation at the low concentrations. Comparison of 1/x weighting and no weighting was provided using the new data generated to demonstrate this point. It also showed no compromise at the high end of the concentration range.

Comment: This reviewer raised this question in view of the marginal validation results for this assay. Furthermore, it was also felt that since the purpose of the percutaneous absorption study was for safety evaluation, it might be more appropriate to have equal weighting for all standards so that concentrations at high end could be more accurately determined.

B-2:

The mobile phase for the HPLC/MS/MS analysis used in Study 9425201D is 68:23:9 acetonitrile/tetrahydrofuran/250mM aqueous ammonium acetate. (OK.)

B-3:

The schematic procedures for the GC-MS assay method used in Study G3 are provided but the validation results of the this assay method are not.

Comment: Since this method was not used in the major PK studies, we will not pursue this matter any further.

Comment #3:

It is recommended that the results of PK Study 9425201D be analyzed by gender.

Response:

The results of the by-gender analysis of the PK study are summarized below: (See Tables 1-4.)

Male subjects:

At the dose of 6 g/day (n=4), the mean C_{max} of butenafine HCl on Day 1 was 0.82 ± 0.50 ng/mL at a mean T_{max} of 17.7 ± 6.6 hours with a mean AUC of 9.98 ± 6.10 ng.h/mL; on Day 14 (steady-state), the mean C_{max} was 1.46 ± 0.96 ng/mL at a mean T_{max} of 17.7 ± 6.6 hours with a mean AUC of 27.1 ± 14.8 ng.h/mL. Because few subjects had quantifiable plasma concentrations of the M2 metabolite at this dosing level, the mean results for the metabolite will not be listed here. (See Table 2.)

At the dose of 20 g/day (n=6), the mean C_{max} of butenafine HCl on Day 1 was 2.71 ± 1.52 ng/mL at a mean T_{max} of 15.8 ± 5.9 hours with a mean AUC of 44.5 ± 26.8 ng.h/mL; on Day 14 (steady-state), the mean C_{max} was 5.08 ± 2.72 ng/mL at a mean T_{max} of 5.0 ± 3.5 hours with a mean AUC of 92.5 ± 63.8 ng.h/mL.

The results for the plasma M2 metabolite at the dose of 20 g/day are:

The mean C_{max} on Day 1 was 0.09 ± 0.10 ng/mL at a mean T_{max} of 22.9 ± 0.3 hours with a mean AUC of 0.63 ± 0.85 ng.h/mL; on Day 14 (steady-state), the mean C_{max} was 0.23 ± 0.12 ng/mL at a mean T_{max} of 12.2 ± 9.2 hours with a mean AUC of 4.53 ± 3.07 ng.h/mL.

The urine data indicates that the total urinary excretion (parent drug and all metabolites) on Day 14 was $0.0050 \pm 0.004\%$ of the total dose for the low dose group and $0.004 \pm 0.003\%$ of the total dose for the high dose group.

Female subjects:

At the dose of 6 g/day (n=3), the mean C_{max} of butenafine HCl on Day 1 was 0.46 ± 0.30 ng/mL at a mean T_{max} of 16.8 ± 11.0 hours with a mean AUC of 7.11 ± 5.67 ng.h/mL; on Day 14 (steady-state), the mean C_{max} was 1.38 ± 0.64 ng/mL at a mean T_{max} of 12.5 ± 10.8

hours with a mean AUC of 19.6 ± 3.1 ng.h/mL. Because few subjects had quantifiable plasma concentrations of the M2 metabolite at this dosing level, the mean results for the metabolite will not be listed here. (See Table 2.)

At the dose of 20 g/day (n=6), the mean C_{max} of butenafine HCl on Day 1 was 3.45 ± 1.80 ng/mL at a mean T_{max} of 21.3 ± 4.5 hours with a mean AUC of 44.3 ± 21.9 ng.h/mL; on Day 14 (steady-state), the mean C_{max} was 4.97 ± 1.33 ng/mL at a mean T_{max} of 6.5 ± 8.3 hours with a mean AUC of 83.0 ± 20.0 ng.h/mL.

The results for the plasma M2 metabolite at the dose of 20 g/day are:

The mean C_{max} on Day 1 was 0.04 ± 0.06 ng/mL at a mean T_{max} of 22.8 ± 0.2 hours with a mean AUC of 0.20 ± 0.31 ng.h/mL; on Day 14 (steady-state), the mean C_{max} was 0.17 ± 0.11 ng/mL at a mean T_{max} of 10.8 ± 11.2 hours with a mean AUC of 3.24 ± 2.02 ng.h/mL.

The urine data indicates that the total urinary excretion (parent drug and all metabolites) on Day 14 was $0.0035 \pm 0.0034\%$ of the total dose for the low dose group and $0.013 \pm 0.021\%$ of the total dose for the high dose group.

Statistical analysis:

SAS General Linear Model procedure was used for the by-gender analysis. The PK parameters from the low dose group were adjusted to the high dose (20 g/day) and the combined data were tested for gender by dose interaction. When no significant difference in gender by dose interaction was detected, this interaction term was dropped and the model included only gender and dose. The analysis results for the plasma data are presented in Tables 3 and 4, and the results for the urine data are shown in Table 5. The analysis revealed no significant differences between genders for all PK parameters tested. ✓

Comment: The analysis failed to detect any gender differences in any PK parameters. However, the sponsor did not indicate the power for the gender analysis.

COMMENT #4

Since animal studies suggest deposition of butenafine in stratum corneum, the dose level may be exaggerated through increase in total quantity of formulation applied to the skin as well as the amount applied per unit surface area. The sponsor did not explain why a lower level (2 mg/cm²) was selected.

Response:

The amount of cream formulation used in the PK study (2 mg/cm²) was considered by the sponsor to be near the maximum amount per unit surface area that could be applied to subjects without considerable build-up on the skin. Even at this dose level, there were reports of material flaking off at the dosing site, indicating that the formulation dried out on the skin surface. Therefore, application of 2 mg/cm² was considered the maximum amount per unit surface area that the formulation can be applied onto the skin. This dosing level was also

reflected in a study by Schlagel and Sanborn using Veriderm Cream, which determined the amount of cream applied by patients to be 2.05 g/cm².

It is anticipated that the usual daily dose would be 1 g/day. In two clinical trials conducted in tinea pedis patients, the mean amount of cream applied per patient was 0.77 g/day. However, some patients did apply more than 1 g/day with the maximum amount applied being approximately 2 g/day. In these clinical trials, surface area over which the formulation was applied was not recorded. Therefore, the amount of formulation applied per unit surface area in these patients cannot be accurately determined although it is possible that patients applied over 2 g/cm² on the affected skin. (OK.)

COMMENT #5

The continued development of an in vitro drug release test method and test specifications for the cream as delineated in volume 1.2, pages 2-0289 of the NDA is encouraged.

Response:

The sponsor will continue to develop the method. ✓

III. LABELING COMMENTS:

We consider it necessary to add the information on butenafine metabolite, time to peak plasma concentration (T_{max}), and plasma concentrations found in patients. Therefore, the label should read as follows: ✓

Pharmacokinetics

IV. RECOMMENDATION:

From the biopharmaceutics standpoint, the application is approvable. Labeling comment should be communicated to the sponsor. ✓

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[Handwritten signature] 9/9/96

Sue-Chih Lee, Ph.D.

Division of Pharmaceutical Evaluation III

RD Initialed by Dennis Bashaw, Pharm.D. *[Handwritten initials]* 9/16/96

FT Initialed by Dennis Bashaw, Pharm.D. *[Handwritten initials]* 9/16/96

CC:

NDA 20-524

HFD-540 (2 copies)

HFD-880 (Division File)

HFD-880 (TL - Bashaw)

HFD-880 (Reviewer - Lee)

HFD-340 (Viswanathan)

HFD-205 (FOI)

Drug File (Clarence Bott, HFD-870, Pkln 13B31)

Gender (M/F)

Table

STUDY NO. 9425201D: BUTENAFINE PLASMA RESULTS
Evaluation of G effects

Arithmetic means

< Male >

< Female >

GENDER=M DOSE=6

GENDER=F DOSE=6

(a) Dose = 6g

Variable Label	N	Mean	Std Dev	N	Mean	Std Dev
AUC1	4	9.982500	6.096231	3	7.113000	5.671019
C _{MAX1}	4	0.823000	0.498598	3	0.460000	0.300000
T _{MAX1}	4	17.650000	6.570941	3	16.756667	11.047924
AUC _{SS}	4	27.103750	14.783827	3	19.606000	3.133001
C _{MAX_{SS}}	4	1.460000	0.964814	3	1.383333	0.637364
T _{MAX_{SS}}	4	17.700000	6.570865	3	12.513333	10.759188
C _{SS}	4	1.125000	0.611692	3	0.813333	0.128970
A _{REARAT}	4	2.862500	0.923630	3	4.590000	4.141642
D _{RATE}	4	0.022287	0.009532	3	0.036495	0.018760
D _{HALF}	4	38.987500	25.299124	3	21.496667	8.303965
K _E	0			0		
T _{HALF}	0			0		

(b) Dose = 2.0g

Variable Label	N	Mean	Std Dev	N	Mean	Std Dev
AUC1	6	44.514000	26.818603	6	44.272333	21.933520
C _{MAX1}	6	2.708333	1.524643	6	3.445000	1.804979
T _{MAX1}	6	15.815000	5.895062	6	21.255000	4.545515
AUC _{SS}	6	92.529000	63.776617	6	83.023000	20.005816
C _{MAX_{SS}}	6	5.083333	2.715950	6	4.966667	1.334686
T _{MAX_{SS}}	6	5.003333	1.513475	6	6.539333	0.259081
C _{SS}	6	3.830000	2.633439	6	3.440000	0.832562
A _{REARAT}	6	2.123333	0.545148	6	2.385000	1.462884
D _{RATE}	5	0.020542	0.003275	6	0.033878	0.017507
D _{HALF}	5	34.484000	5.903256	6	39.608333	51.439807
K _E	2	0.001837	0.001558	3	0.002512	0.000482
T _{HALF}	2	589.370000	499.910352	3	283.570000	58.926291

STUDY NO. 94252010: METABOLITE M-2 PLASMA RESULTS
Evaluation of Gender Effects

Arithmetic Means

< Female >

GENDER=F DOSE=6

GENDER=M DOSE=6

(a) Dose = 6 g/day

Variable Label	N	Mean	Std Dev	N	Mean	Std Dev
AUC1	4	0.00000	0.00000	3	0.00000	0.00000
C _{MAX} 1	4	0.00000	0.00000	3	0.00000	0.00000
T _{MAX} 1	0	.	.	0	.	.
AUC _{SS}	4	0.47850	0.95700	3	2.54500	2.687317
C _{MAX} SS	4	0.01000	0.06000	3	0.35000	0.505866
T _{MAX} SS	1	23.50000	.	2	23.46000	0.084853
CSS	4	0.02000	0.04000	3	0.10333	0.110604
AREARAT (AUC _{SS} /AUC1)	0	.	.	0	.	.
DRATE	0	.	.	0	.	.
DHALF	0	.	.	0	.	.
KE	0	.	.	0	.	.
THALF	0	.	.	0	.	.

(b) Dose = 20 g/day

GENDER=F DOSE=20

GENDER=M DOSE=20

Variable Label	N	Mean	Std Dev	N	Mean	Std Dev
AUC1	6	0.634667	0.845561	6	0.197500	0.308509
C _{MAX} 1	6	0.086667	0.101127	6	0.036667	0.057155
T _{MAX} 1	3	22.076667	0.277549	2	22.760000	0.226274
AUC _{SS}	6	4.529333	3.072384	6	3.239667	2.017860
C _{MAX} SS	6	0.231667	0.115658	6	0.170000	0.106019
T _{MAX} SS	6	12.223333	9.236893	5	10.828000	11.231027
CSS	6	0.188333	0.127971	6	0.133333	0.083586
AREARAT (AUC _{SS} /AUC1)	3	6.320000	3.095860	2	7.825000	0.799031
DRATE	5	0.023079	0.019357	2	0.021436	0.023339
DHALF	5	41.800000	18.433514	2	79.375000	86.415520
KE	3	0.014625	0.003752	1	0.037939	.
THALF	3	49.303333	11.226475	1	18.270000	.

Gender Analysis

3
 Table 31: Comparison by Gender of Butenafine in Plasma Pharmacokinetic Parameters.

Parameter	Least Squares Means		P-Value ¹
	Female	Male	
AUC 1 (ng-hr/ml)	34.84	38.47	0.73
C _{max} 1 (ng/ml)	2.67	2.63	0.97
T _{max} 1 (hour)	19.58	16.44	0.32
AUC ss (ng-hr/ml)	75.60	90.73	0.46
C _{max} ss (ng/ml)	4.80	4.97	0.88
T _{max} ss (hour)	10.14	11.05	0.79
C ss (ng/ml)	3.13	3.76	0.46
Area Ratio	3.35	2.56	0.35

¹ P-value for test of equivalence of results for females and males.

Parameters

AUC 1 - Day 1 area under the curve.

C_{max} 1 - Peak concentration on Day 1.

T_{max} 1 - Time of peak concentration on Day 1.

AUC ss - Steady-state area under the curve.

C_{max} ss - Peak concentration during steady-state interval.

T_{max} ss - Time of peak concentration during steady-state interval.

C ss - Average steady-state concentration.

Area Ratio - AUC ss / AUC 1

Gender Analysis

4
 Table S2: Comparison by Gender of Metabolite M-2 in Plasma Pharmacokinetic Parameters.

Parameter	Least Squares Means		P-Value ¹
	Female	Male	
AUC 1 (ng-hr/ml)	0.059	0.337	0.26
Cmax 1 (ng/ml)	0.014	0.046	0.31
Tmax 1 (hour)	22.76	22.88	0.66
AUC ss (ng-hr/ml)	5.12	3.43	0.43
Cmax ss (ng/ml)	0.57	0.22	0.28
Tmax ss (hour)	17.04	18.16	0.83
C ss (ng/ml)	0.21	0.14	0.46
Area Ratio	7.83	6.32	0.57

¹ P-value for test of equivalence of results for females and males.

Parameters

- AUC 1 - Day 1 area under the curve.
- Cmax 1 - Peak concentration on Day 1.
- Tmax 1 - Time of peak concentration on Day 1.
- AUC ss - Steady-state area under the curve.
- Cmax ss - Peak concentration during steady-state interval.
- Tmax ss - Time of peak concentration during steady-state interval.
- C ss - Average steady-state concentration.
- Area Ratio - AUC ss / AUC 1

Gender Analysis

⁵
Table S3: Comparison by Gender of Urinary Excretion of Butenafine Equivalents.

Parameter	Least Squares Means		P-Value ¹
	Female	Male	
Percent (%) Excretion	0.0088	0.0039	0.37

¹ P-value for test of equivalence of results for females and males.

Bio

SEP 29 1995

BIOPHARMACEUTICS REVIEW

NDA: 20-524
PRODUCT: Butenafine HCl Cream 1%
SPONSOR: Penederm Incorporated
320 Lakeside Drive, Suite A
Foster City, CA 94404

SUBMISSION DATE: 04/04/95

TYPE OF SUBMISSION:
Original NDA, NME, 1S

REVIEWER: Sue-Chih Lee, Ph.D.

I. SYNOPSIS:

Provided in the Human Pharmacokinetics section is detailed information regarding a multiple dose study on percutaneous absorption in healthy volunteers (Penederm study 9425201D, Protocol PDC-010-011). Also submitted are final reports of a single and multiple dose study conducted in Japan with normal healthy volunteers (Kaken Study G3) and an in vitro percutaneous absorption study. In addition, a brief summary on plasma butenafine HCl concentrations determined with 11 of the patients participated in a clinical trial (PDC-010-002) was included. The results are as follows:

1. Penederm Study 9425201D: This study used the formulation intended for marketing. At a daily dose of 6 g, the mean (\pm SD) steady state C_{max} values for butenafine and the metabolite M_2 were 1.43 ± 0.78 and 0.17 ± 0.34 ng/ml, respectively. At a daily dose of 20 g, the mean steady state C_{max} values for butenafine and the metabolite M_2 were 5.03 ± 2.04 ng/ml and 0.20 ± 0.11 ng/ml, respectively. (The usual dose for the proposed indication is considered to be 1 g/day.) In the study, all adverse events considered to be possibly due to the medication were local side effects.
2. Kaken Study G3: The formulation used is slightly different from that intended for marketing. In the multiple dose study with a daily dose of 5 g (which was then removed from skin surface 12 hours after application), the mean C_{max} was 4.1 ± 1.7 ng/ml on Day 1 and 4.8 ± 2.3 ng/ml on Day 7.
3. Clinical Study PDC-010-002: In this clinical trial, the formulation intended for marketing was used and plasma butenafine concentrations for patients participating in a designated site were determined. During treatment, there were a total of 25 samples from 11 patients and the mean plasma butenafine concentration was found to be 0.12 ± 0.10 ng/mL, with a range from undetectable levels to 0.30 ng/mL. The metabolite M_2 was below the limit of detection (0.1 ng/ml) at all time points examined. (In Beagle dogs, the threshold of toxicity was determined to be greater than 100 ng/ml for butenafine HCl.)
4. In vitro percutaneous absorption study: This study compares the two formulations used

in Penederm Study 9425201D and Kaken Study G3. The drug in the receptor fluid and in the skin were $0.23 \pm 0.08\%$ and $5.4 \pm 2.9\%$ of the applied dose for the Kaken cream and $0.19 \pm 0.02\%$ and $4.4 \pm 2.7\%$ for the Penederm cream. These results were found not to be significantly different.

II. COMMENTS:

A. General Comments:

1. In the Penederm in vivo percutaneous absorption study, the systemic exposure in terms of percent of dose absorbed was not determined.
2. The sponsor states that M2 is the primary metabolite in human plasma although this was only demonstrated in rats. The sponsor should provide data to support the statement.
3. Percutaneous absorption through the diseased skin may be expected to be greater. However, the plasma butenafine concentrations obtained from patients were low (up to 0.3 ng/ml) at the recommended daily dose.
4. In the study, the mean peak plasma concentration was 4.8 ± 2.3 ng/mL on Day seven after a daily dose of 5 gram. In the Penederm study, the mean peak plasma concentration with a daily dose of 6 g was 1.43 ± 0.78 ng/mL on Day 14. The possible reasons are differences in study population, amount of formulation applied per unit surface area and study design. (In the study, the involved skin surface area was smaller and was covered with gauze. In the Penederm study, the skin surface area was larger and was not covered except for loose clothing.)
5. In the Penederm study, the formulation was applied to the designated surface area to obtain a level of 2 mg of formulation per cm^2 . According to the Medical Officer, Dr. Nancy Slifman, the usual range is approximately 2-5 mg/cm^2 . Therefore, the amount applied per unit surface area used in the Penederm study is considered to be at the low side of the normal range, while that for the study ($10 \text{ mg}/\text{cm}^2$) is above the normal range. Despite of this, exaggerated doses were used in both studies (6 g and 20 g in the Penederm study and 5 g in the study).
6. Since animal studies suggest deposition of butenafine in stratum corneum, the dose level may be exaggerated through increase in total quantity of formulation applied to the skin as well as the amount applied per unit surface area. The sponsor did not explain why a lower level ($2 \text{ mg}/\text{cm}^2$) was selected.
7. The mobile phase for the HPLC/MS/MS analysis used in the Penederm study is not specified and the assay method and method validations for the study are not provided.
8. The sponsor is encouraged to develop an in vitro drug release test method and test specifications for the cream.

B. Labeling Comments:

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

Although 8 healthy subjects were included in the 6-gram dose group of the Penederm study, data from one of the subjects was not available.

The mean plasma butenafine concentration should be given along with the standard deviation.

Therefore, the labeling should read as follows:

Following daily application for 14 days of 6 grams of butenafine HCl 1% cream to the dorsal skin (3,000 cm²) of healthy subjects, the mean (\pm SD) maximum plasma concentration of butenafine HCl from 7 subjects was 1.4 ± 0.8 ng/mL. After daily dosing to the arms, trunk and groin areas (10,000 cm²) of 12 normal subjects for 14 days with 20 grams of butenafine HCl cream, the mean (\pm SD) maximum plasma concentration of butenafine HCl was 5.0 ± 2.0 ng/mL. ✓
OK

III. RECOMMENDATIONS:

The Biopharmaceutics and Pharmacokinetics section of NDA 20-524 is acceptable to the Division of Biopharmaceutics provided that the sponsor revises the labeling as indicated under Labeling Comment and satisfactorily responds to our general comments #2, 6, 7 and 8.

Sue-Chih Lee 9/22/95

Sue-Chih Lee, Ph.D.

Pharmacokinetics Evaluation Branch II

RD/FT Initialed by Frank Pelsor, Pharm.D.

F. Pelsor

Biopharm Day (Date: 9/21/95; Attendees: Drs. Lesko, Malinowski, ML Chen, Fleischer, Hepp, Pelsor and Lee)

cc: NDA 20-524, HFD-540 (2 copies), HFD-427 (ML Chen, Pelsor, Lee), Chron, Drug, Reviewer, HFD-19(FOD), HFD-340 (Viswanathan)

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BACKGROUND:

Butenafine hydrochloride, a benzylamine derivative, is closely related to allylamine antifungal agents. In vitro studies suggest that the antifungal properties of butenafine may be related to its ability to impair the synthesis of ergosterol, a component of fungal and yeast cell membranes, which leads to increased membrane permeability and a disorder of cellular organization. The proposed product is intended for the treatment of interdigital tinea pedis. A 1% cream formulation and a 1% lotion formulation were approved in Japan in 1992.

FORMULATION:

PD-010-C-003 (Penederm Cream) is the formulation intended for marketing. PD-010-C-001 Cream) differs from the Penederm Cream in that it does not contain 0.5% benzyl alcohol.

<u>Ingredient</u>	<u>% w/w</u>	
	<u>PD-010-C-003</u> <u>(Penederm Cream)</u>	<u>PD-010-C-001</u> <u>(Keken Cream)</u>
✓ Butenafine HCl	1.0	1.0
✓ Purified Water USP		
✓ Propylene Glycol Dicaprylate		
✓ Glycerin USP		
✓ Cetyl Alcohol NF		
✓ Glyceryl Monostearate		
✓ White Petrolatum USP		
Stearic Acid NF		
✓ Polyoxyethylene (23) Cetyl Ether		
✓ Benzyl Alcohol NF		
✓ Diethanolamine NF		
✓ Sodium Benzoate NF		

IN VIVO PERCUTANEOUS ABSORPTION STUDIES

- 1) PENEDERM STUDY NO. 9425201D**

Penederm Study No. 9425201D:

A SINGLE-CENTER, OPEN LABEL STUDY TO DETERMINE THE PLASMA LEVEL OF BUTENAFINE FOLLOWING MULTIPLE TOPICAL APPLICATIONS OF BUTENAFINE HCL 1% CREAM TO NORMAL VOLUNTEERS (Protocol PDC-010-011, Vol. 1.13)

INVESTIGATOR AND LOCATION:

Principal investigator:

Sub-Investigators:

OBJECTIVES:

The objective of this study was to measure plasma levels of butenafine and the major plasma metabolite, M2, in subjects with normal skin following daily applications of butenafine cream once a day for 14 days under an exaggerated dosing regimen. In addition, the metabolic pattern of butenafine and key metabolites excreted in the urine was to be determined after multiple topical doses.

FORMULATION: PD-010-C-003 (Penederm Cream)

STUDY DESIGN:

This is a one-period, multiple application study. Two groups of normal, healthy subjects were included and all subjects completed the study. Table 1 shows the demographic data.

In one group of 8 subjects (4M/4F), about 6 grams of the formulation were applied to the posterior trunk of each individual, an area comprising 3,000 cm². In the second group, which consisted of 12 subjects (6M/6F), about 20 grams of the cream were applied to the arms, trunk (including the inframammary area in females) and groin area (including the scrotum in males), an area of approximately 10,000 cm². (The usual dose is approximately 1 g for tinea pedis infections and 2 g for crural infections.)

Sample collections -

Blood samples:

Prior to dosing on Days 1, 2, 5, 6, 9, 12, 13 and 14;

After dosing on Day 1 at 2, 4, 8, 12 and 24 (Day 2) hours;

After dosing on Day 14 at 2, 4, 8, 12, 24 (Day 15), 36 (Day 15), 48 (Day 16), 72 (Day 17), 96 (Day 18), 120 (Day 19), 192 (Day 22) and 336 (Day 28) hours.

Urine samples:

Prior to Day 1 dosing;

For the 24-hour intervals beginning on Days 1, 14 and 28.

ASSAY:

Plasma was analyzed for butenafine and M2 by

The following validation results were obtained from 6 sets of QC samples, each set consists of 4 sample concentrations.

Linearity:	$r \geq$	(range:	ng/mL)
Accuracy:		% (butenafine);	% (M2 metabolite)
Precision (CV with n=6/batch):			
within batch:		% (butenafine);	% (M2 metabolite)
among batches:		% (butenafine);	% (M2 metabolite)
Sensitivity (LOQ):		ng/mL (butenafine);	ng/mL (M2 metabolite)
Specificity:		Satisfactory, chromatograms submitted.	

Comments:

1. The mobile phase for the HPLC/MS/MS analysis is not specified. The precision and accuracy of the assay indicates that the method is not rugged.
2. The urine samples were collected as required in the protocol, but were not analyzed due to technical difficulties associated with the development and validation of the analytical method. This constitutes a deviation from the stated protocol objective. The sponsor stated that because of the low absorption of butenafine observed in this study, the safety of this new drug formulation is adequately demonstrated on the basis of plasma data alone and the characterization of the urinary metabolites is not essential.

DATA ANALYSIS:

The complete plasma data from 19 subjects were analyzed. The data from one of the subjects were not available due to sample loss during the extraction procedure. Pharmacokinetic parameter estimates were calculated using the actual rather than the scheduled times of sample collection. Graphical presentations of individual subject results used the exact times of sample collection. Graphical presentations of mean results used the scheduled times of sample collection.

The apparent first-order elimination rate (K_e) was estimated from the terminal log-linear concentration-time values following the Day 14 dose. An estimate of the effective rate of decline of plasma concentration was calculated based on the log-linear values following the steady-state peak concentration, prior to the slow terminal elimination phase.

Regression analyses for each subject's trough samples collected on Days 3, 6, 9, 12 and 13, and Day 14 at 24 hours were evaluated to determine if steady-state had been attained by the final dose (Day 14). Area under the plasma concentration-time curve from 0 to 24 hours post-dose on Day 1 (AUC₁) and Day 14 (AUC_{ss}) was calculated by the linear trapezoidal method. Average steady-state concentration (C_{ss}) was calculated as steady-state area (AUC_{ss}) divided by the actual length of the measured steady-state interval (approximately 24 hours for each subject).

All statistical analyses were conducted using SAS. For each dosing group, arithmetic means, standard deviations and coefficients of variation were calculated for all pharmacokinetic parameters and the measured concentrations. Means were also calculated on the dose-adjusted (20 gram/dose administered) results and Analyses of Variance (Proc GLM) were conducted to assess the dose proportionality between the 20 gram and 6 gram applications.

RESULTS:

All subjects were considered to be at steady-state by the time of the Day 14 dose, since the slopes of the regression lines of the trough concentrations (determined from samples taken prior to dosing on Days 3, 6, 9, 12, 13 and 14) against time did not differ significantly from zero for either butenafine or its M2 metabolite.

At steady state, the mean C_{max} (\pm SD) were 1.43 ± 0.78 and 5.03 ± 2.04 ng/mL and the mean AUC (\pm SD) were 23.89 ± 11.34 and 87.78 ± 45.33 ng-hr/mL for the 6-gram and the 20-gram doses, respectively (Table 2). No measured plasma concentration from any subject in either group exceeded 10 ng/mL.

The plasma measurements indicate low plasma concentrations of the metabolite M2. For the 6-gram dose group, the mean steady state C_{max,ss} was 0.17 ± 0.34 ng/mL, and the mean steady state AUC_{ss} was 1.36 ± 2.02 ng-hr/mL (Table 3). Similarly low levels were obtained from subjects in the 20 gram group (0.20 ± 0.11 ng/mL for C_{max,ss} and 3.88 ± 2.57 ng-hr/mL for AUC_{ss}).

The low concentrations resulted in many samples, especially those following the initial dose for the 6 gram dosing group and all concentrations for the M-2 metabolite, to be less than the analytical limit of quantitation. As a result, the calculated areas for the Day 1 dose for both parent and metabolite, and the areas at steady-state for the metabolite, are probably underestimations of the true values. This had the effect of inflating the area ratio (steady-state AUC/single-dose AUC).

The extent of butenafine absorption and formation of its M2 metabolite from the 20-gram dose was proportional to that seen with the 6-gram dose.

The time points selected for plasma sampling did not provide sufficient data to obtain precise estimates of the terminal elimination rate and half-life for butenafine. Extremely low levels of butenafine appear to persist for a long time (> 100 hours) following cessation of dosing.

The effective half-life ($T_{1/2, E}$) obtained from the plasma concentrations determined immediately after the steady-state peak appears to be approximately 35 hours, which is a weighted average of the means for the 6-gram group (31 hours) and the 20-gram group (37 hours).

A statistically significant earlier time of butenafine peak at steady-state ($T_{max, ss}$) was observed for the 20-gram group (5.8 hours) than for the 6-gram group (15.5 hours). In order to achieve an exaggeration of the 20-gram dose, additional surface areas had to be used (anterior trunk areas, inframammary and groin/scrotal sites). The sponsor stated that the earlier time of peak for the 20-gram dose may be due to differences in the rates of permeability between these additional sites and the posterior trunk site used for the 6-gram dose. There were no statistically significant differences between the two groups for the other pharmacokinetic parameters measured.

In the high dose group, there were 11 adverse events that were listed by the investigator as mild and possibly related to the use of study medication. All were dermatological in nature, with itching (7 events) reported most frequently. In the low dose group, there was one adverse event, mild itching of the upper back, that was possibly related to the use of the study medication.

Comments:

1. The sponsor did not demonstrate that M2 is the primary metabolite in human plasma although this was demonstrated in rats.
2. The dose was applied to the designated surface area to obtain a level of 2 mg formulation per cm^2 . According to the Medical Officer, Dr. Nancy Slifman, the usual range is approximately 2-5 mg/ cm^2 . Therefore, the dose used in the study is considered to be at the low side.
3. The urine samples were collected as required in the protocol, but were not analyzed due to technical difficulties associated with the development and validation of the analytical method. Therefore, the information regarding the % absorbed and the metabolic pattern of butenafine in humans could not be obtained from the study.
4. The terminal phase shows a very slow decline. This may arise from the redistribution of butenafine from the skin since the drug is highly bound to keratin.

BUTENAFINE STUDY NO. 9425201D

Table 1: Clinical Demographics

Subject No.	Subject Initials	Sex	Age	Race	Height (in)	Weight (lb)	Frame Size	Skin Type *	Skin Surface Area (m ²)
		M	64	Caucasian	75	201	Medium	IV	2.15
		F	65	Caucasian	63	162	Large	III	1.80
		M	47	Caucasian	73	194	Large	III	2.10
		F	37	Caucasian	69	162	Medium	III	1.85
		M	25	African-American	67	156	Medium	VI	1.80
		F	21	African-American	68	118	Medium	V	1.60
		M	29	Caucasian	72	152	Medium	IV	1.85
		F	31	Caucasian	64	146	Medium	III	1.70
		M	34	Asian	72	183	Small	IV	2.00
		F	23	Caucasian	66	112	Medium	III	1.55
		M	23	African-American	69	128	Medium	VI	1.65
		F	21	Caucasian	65	156	Medium	IV	1.80
		M	33	Caucasian	65	155	Medium	II	1.80
		F	37	Caucasian	64	128	Medium	II	1.60
		M	40	Caucasian	66	164	Medium	III	1.85
		F	24	African-American	64	154	Medium	VI	1.75
		M	32	African-American	68	145	Medium	VI	1.75
		F	37	Caucasian	66	151	Medium	III	1.75
		M	44	African-American	70	154	Medium	VI	1.80
		F	20	Caucasian	64	128	Medium	IV	1.60

- * I - Always burns easily; never tans (sensitive)
- II - Always burns easily; tans minimally (sensitive)
- III - Burns moderately; tans gradually (light brown; normal)
- IV - Burns minimally; always tans well (moderately brown; normal)
- V - Rarely burns; tans profusely (dark brown; insensitive)
- VI - Never burns; deeply pigmented (insensitive)

Parameters

- AUC₁: Area under the curve on Day 1.
- AUC_∞: Steady-state area under the curve.
- C_{max1}: Peak concentration on Day 1.
- C_{max∞}: Peak concentration during steady-state interval.
- T_{max1}: Time of peak concentration on Day 1.
- T_{max∞}: Time of peak concentration during steady-state interval.
- T_{½ E}: Effective half-life of plasma concentration decline.
- C_∞: Average steady-state concentration.

Table 2: Summary of butenafine pharmacokinetic data.

Dose		C _{max1} (ng/ml)	T _{max1} (hr)	AUC ₁ (ng-hr/ml)	C _{max∞} (ng/ml)	T _{max∞} (hr)	AUC _∞ (ng-hr/ml)	T _{½ E} (hr)	C _∞ (ng/ml)
6 g QD	Mean	<u>0.67</u>	<u>17.27</u>	<u>8.75</u>	<u>1.43</u>	<u>15.48</u>	<u>23.89</u>	<u>31.49</u>	<u>0.99</u>
	CV%	65.71	45.79	64.28	54.39	53.23	47.47	65.88	47.4
20 g QD	Mean	<u>3.08</u>	<u>18.54</u>	<u>44.39</u>	<u>5.03</u>	<u>5.77</u>	<u>87.78</u>	<u>37.28</u>	<u>3.64</u>
	CV%	53.26	31.11	52.62	40.62	105.77	51.65	98.35	51.53

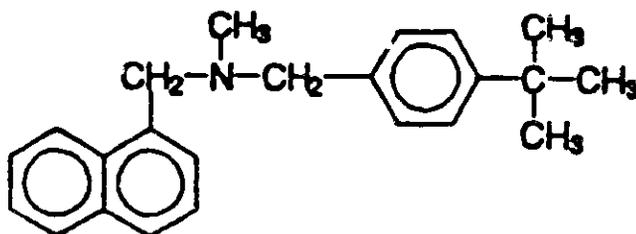
Table 3: Summary of metabolite M-2 pharmacokinetic data.

Dose		C _{max1} (ng/ml)	T _{max1} (hr)	AUC ₁ (ng-hr/ml)	C _{max∞} (ng/ml)	T _{max∞} (hr)	AUC _∞ (ng-hr/ml)	T _{½ E} (hr)	C _∞ (ng/ml)
6 g QD	Mean	0	*	0	<u>0.17</u>	<u>23.47</u>	<u>1.36</u>	*	<u>0.06</u>
	CV%	-	*	-	204.1	-0.27	148.17	*	149
20 g QD	Mean	<u>0.06</u>	<u>22.83</u>	<u>0.416</u>	<u>0.2</u>	<u>11.59</u>	<u>3.88</u>	<u>52.54</u>	<u>0.16</u>
	CV%	133.9	1.03	155.83	55.06	83.5	66.11	80.91	66.5

* Parameters for 6 g dose were not estimable because Day 1 concentrations were all less than assay limit of quantitation.

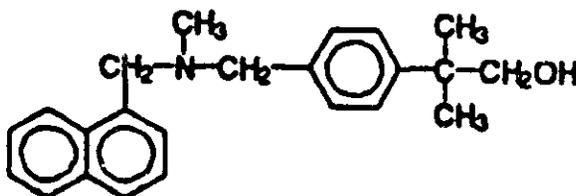
FIGURE 1
CHEMICAL STRUCTURES

KP-363



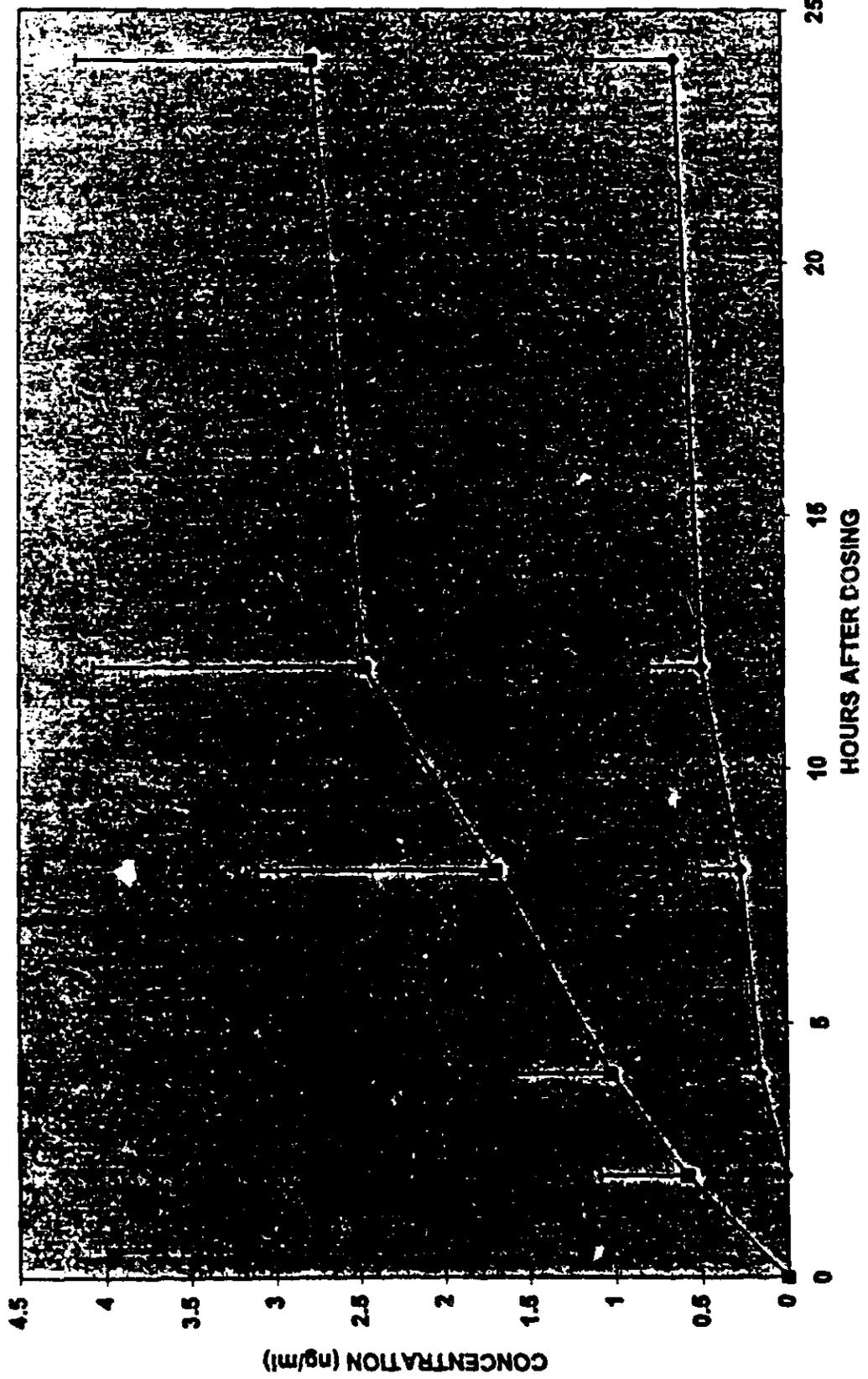
Butenafine; $C_{23}H_{27}N$; Mol. Wt. 317

M2

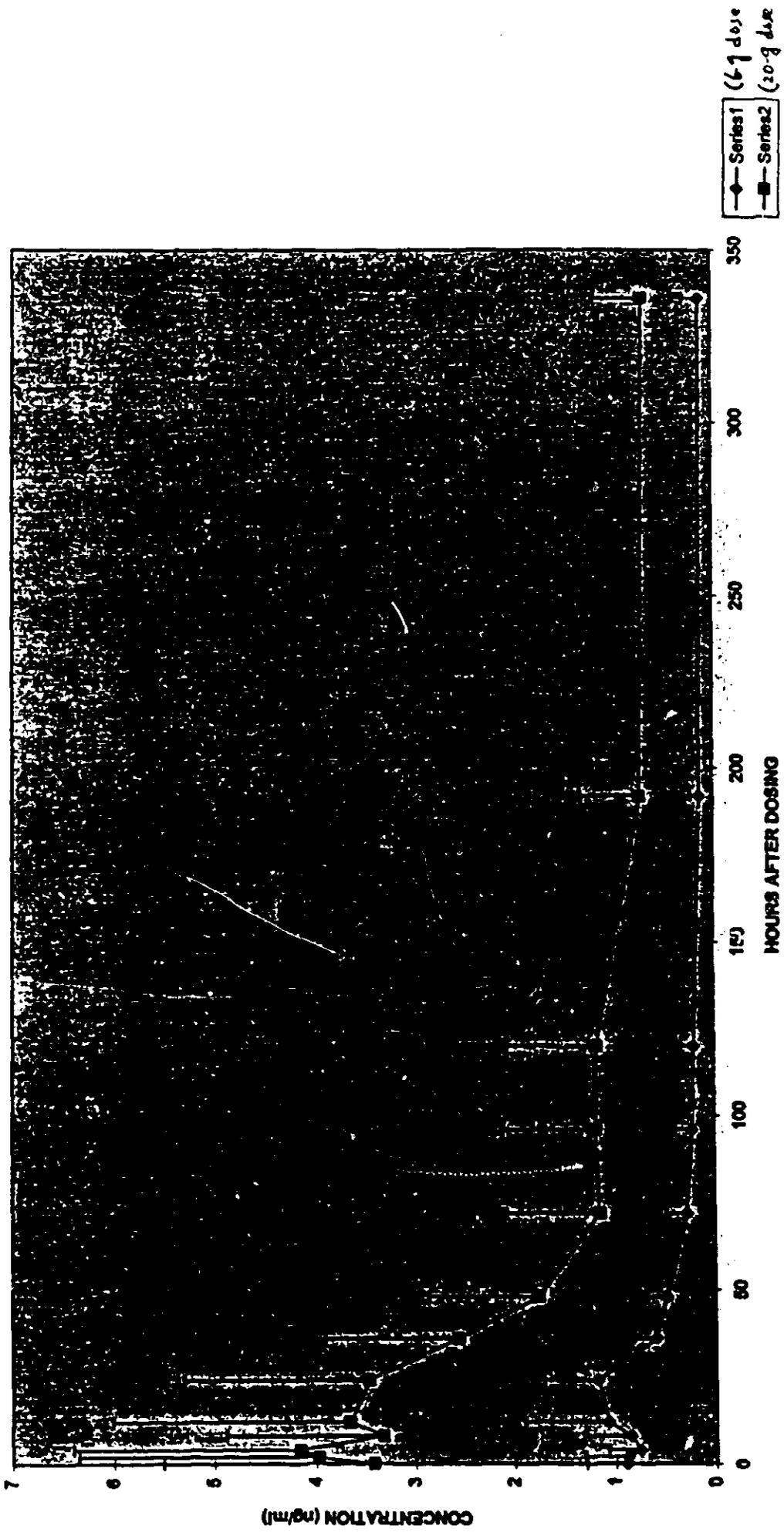


4-(2-hydroxy-1,1-dimethylethyl)benzyl-N-methyl-1-Naphthalenemethyl Amine;
 $C_{23}H_{27}NO$; Mol. Wt. 333

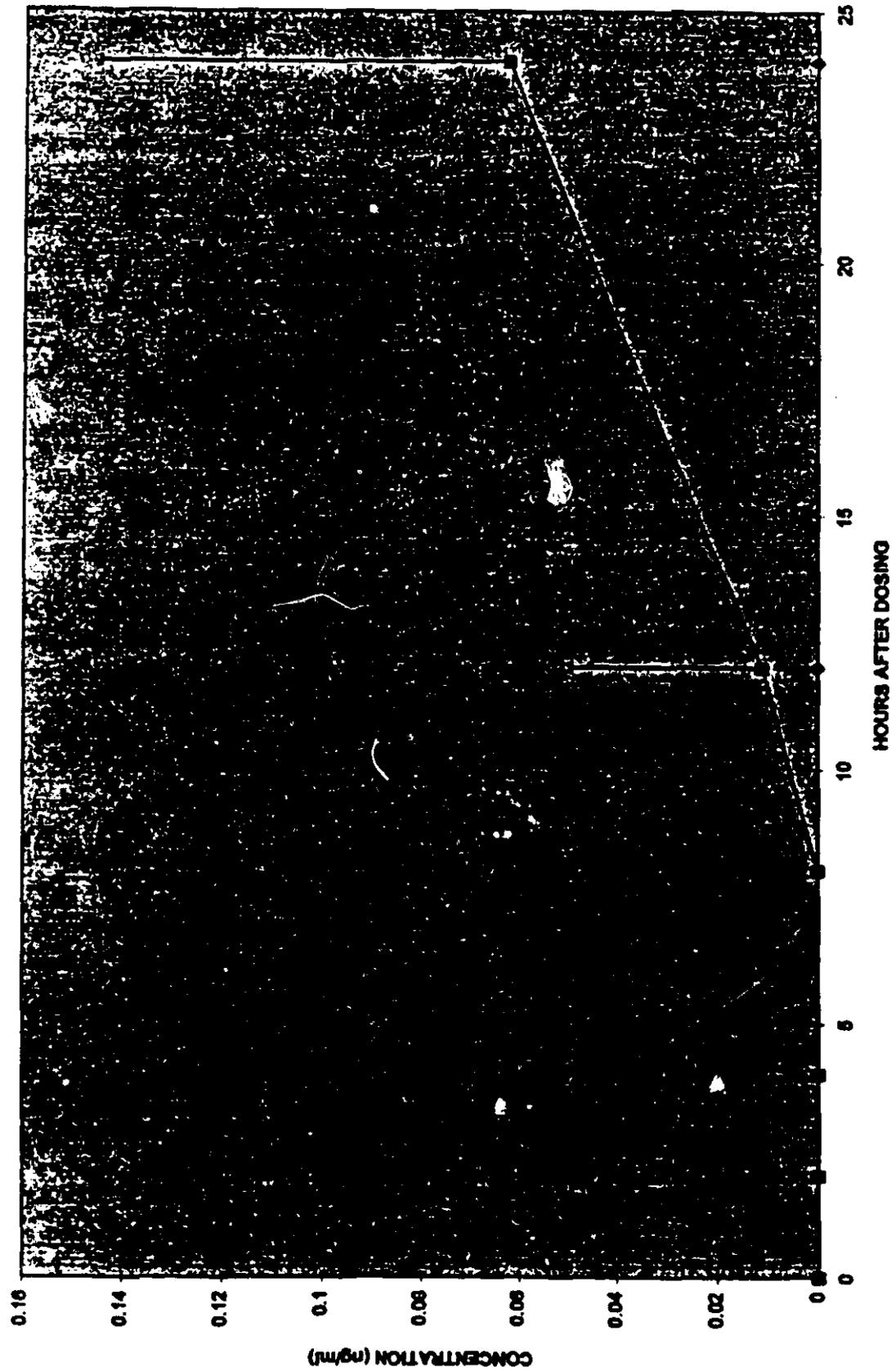
MEAN PLASMA BUTENAFINE HCL CONCENTRATION PROFILE:
DAY 1



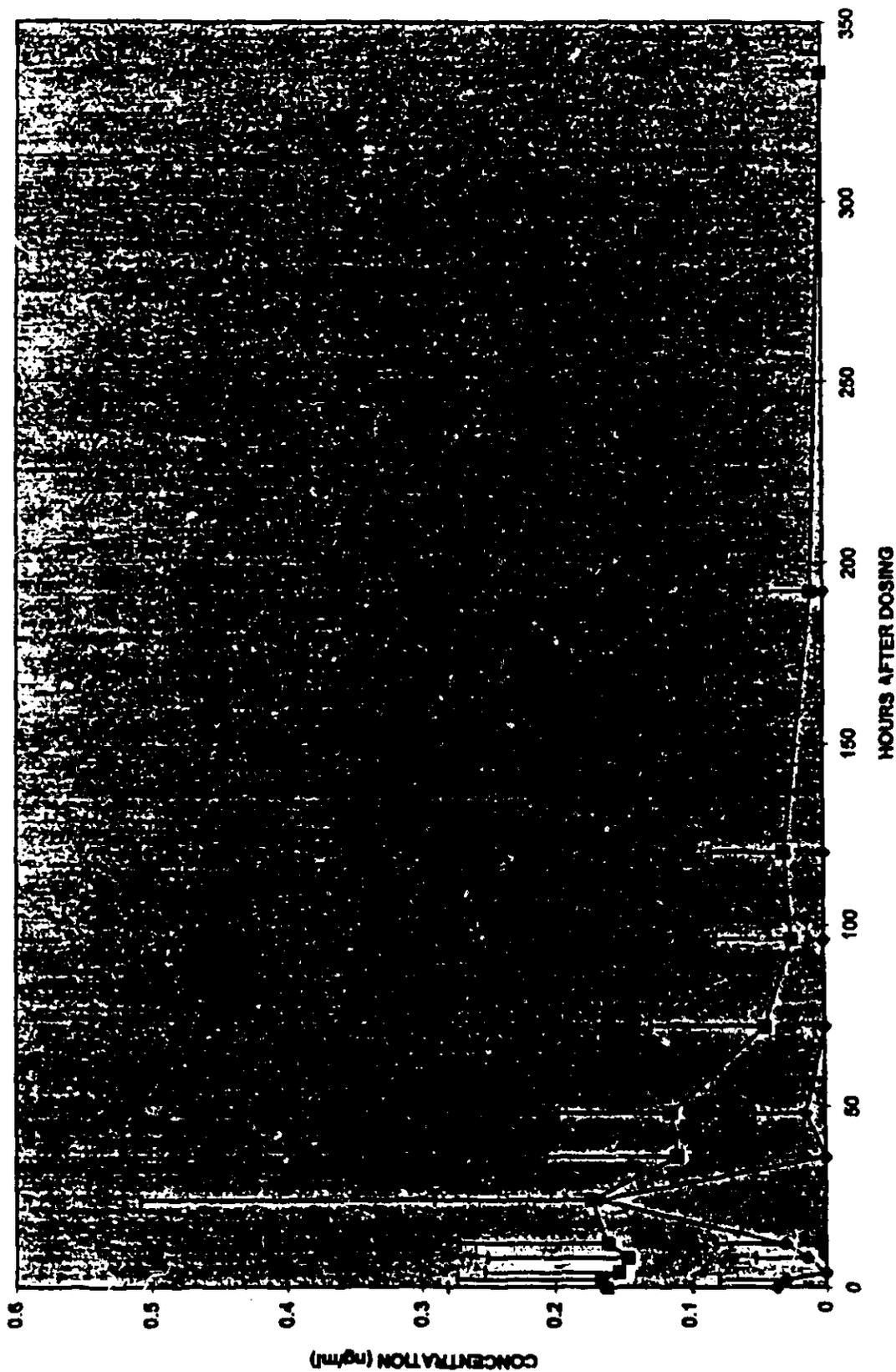
**MEAN PLASMA BUTENAFINE HCL CONCENTRATION PROFILE:
DAY 14**



MEAN PLASMA M2 CONCENTRATION PROFILE: DAY 1



MEAN PLASMA M2 CONCENTRATION PROFILE: DAY 14



IN VIVO PERCUTANEOUS ABSORPTION STUDIES

2) STUDY G3

Study G3:

SINGLE AND MULTIPLE APPLICATION STUDY OF KP-363 (BUTENAFINE HCl), A NEW ANTIFUNGAL AGENT, IN HEALTHY ADULTS

INVESTIGATOR AND LOCATION: This study was performed by

OBJECTIVES:

The study was conducted to assess pharmacokinetic parameters of Butenafine HCl Cream 1% and to examine skin irritating effect, and safety.

FORMULATION: PD-010-C-001 (Cream)

STUDY DESIGN:

Among the ten healthy adult males included in the study, 5 subjects received 5 grams of the formulation as a single dose and another 5 subjects received one 5-gram dose per day for 7 days. Table 1 shows the demographics of the subjects. Cream was applied to the back (500 cm²) as evenly as possible. The application region of each subject was covered with gauze for 12 hours while the formulation was on the skin. At the end of 12 hours, the gauze was removed, and the drug which remained on the skin was removed using a spatula. The dosing region was then wiped 10 times with cotton soaked in lukewarm water. The amount of drug remained on the skin was assessed by measuring the drug recovered from the skin surface, gauze and cotton.

Sample Collection -

i) Single dose study: Blood samples were collected at 0 (pre-dose), 4, 8, 12, 14, 24, 30, 36, 48, 168 (Day 8) and 336 (Day 15) hours and urine samples collected from 0-12, 12-24, 24-36 and 36-48 hours after dosing.

ii) Multiple dose study:

Blood samples -

Day 1: 0 (pre-dose), 4, 8 and 12 hours
Days 2-6: 0 (pre-dose), 12 hours
Day 7: 0 (pre-dose), 4, 8 and 12 hours
After Day 7: 12, 18, 24, 36, 48, 60, 184 hours after removal of drug on Day 7

Urine samples -

Day 1 : every 12 hours
Days 2-6: every 24 hours
Days 7-10: every 12 hours
(A 500 mL aliquot of each sample was stored at -80°C for analysis.)

Hematology and clinical chemistry parameters, skin conditions and physiological parameters (blood pressure, heart rate, respiratory rate and body temperature) were measured at various time points during the course of each study.

ASSAY:

Both plasma and urine samples were analyzed for butenafine using a GC/MS method (limit of detection: 0.5 ng/mL).

Comment:

The assay method and method validation results are not provided.

RESULTS:

A large proportion (72-85%) of the drug formulation was recovered from the skin surface 12 hours after application (Table 2). Assuming a complete recovery of formulation from skin surface, penetration into the stratum corneum represented approximately 20% of the dose.

After a single dose of butenafine, plasma concentrations of unchanged drug increased until the drug was removed from the skin surface twelve hours after dosing, then rapidly decreased within two hours after removal (Figure 1 and Table 3). After that, plasma butenafine concentrations decreased slowly. Plasma $T_{1/2}$ during the later phase was estimated to be 23.4 hours, although this parameter could not be definitively determined. The mean C_{max} was 4.0 ± 1.6 ng/mL.

Plasma butenafine concentrations in the multiple dosing study increased slowly every day until the 12th hour after dosing, when drug was removed. The mean C_{max} was 4.1 ± 1.7 ng/mL on the first day, and ranged from _____ ng/mL on the second to seventh days. The $T_{1/2}$ obtained from the mean plasma concentrations after termination of dosing on the 7th day was 26.0 hours.

Excretion of unchanged butenafine in the urine was less than 0.01% of the dosed amount in both the single and multiple dosing studies.

No patient complained of skin irritation, and there were no effects on any physiology parameter measured. The only changes in clinical chemistry parameters observed was an increase in SGPT on the 8th day for one patient. This change was considered incidental.

Comment:

In this study, the metabolite concentrations in the plasma and urine were not determined and excretion of unchanged butenafine in urine was found to be less than 0.01% of the dosed amount. In animal studies, butenafine was shown to be rapidly metabolized and very little parent drug was recovered in urine and feces.

Table 1 Background of volunteers

Test	No.	Name	Age	Height (cm)	Weight (kg)
Single dosing study	1	K. H.	31	172.0	73.5
	2	O. Y.	30	177.0	76.5
	3	H. M.	32	165.0	64.0
	4	K. H.	20	178.5	63.5
	5	O. Y.	38	175.0	71.0
	Mean ± S. D.			30.2 ± 6.5	173.5 ± 5.3
Multiple dosing study	6	E. K.	25	172.0	58.0
	7	O. M.	21	166.0	50.0
	8	K. Y.	24	160.0	57.0
	9	N. M.	20	173.0	63.0
	10	M. K.	27	163.0	52.0
	Mean ± S. D.			23.4 ± 2.9	166.8 ± 5.6

Table 2 Drug recovery rate in single and multiple dosing study

1) Single dosing study

Case's No.	1	2	3	4	5	Mean ± S. D.
Recovery rate (%)	79.5	79.0	75.5	74.7	80.6	77.9 ± 2.6

2) Multiple dosing study

Case's No.		6	7	8	9	10	Mean ± S. D.
Recovery rate (%)	1st day						85.9 ± 5.6
	2nd day						72.3 ± 5.2
	3rd day						79.7 ± 2.5
	4th day						79.8 ± 4.6
	5th day						79.0 ± 2.3
	6th day						80.2 ± 2.9
	7th day						79.3 ± 2.1

Table 3 Concentration of unchanged KP-363 in plasma after single dosing of 5g of KP-363 cream

Case's No Time (hr)	1	2	3	4	5	Mean ± S. D. **
(Application)	ND	ND	ND	ND	ND	0.0 ± 0.0
	ND	1.8	2.5	0.4	1.7	1.2 ± 1.0
	ND	2.9	3.4	1.0	1.1	1.7 ± 1.4
(Removal)	3.0	4.6	6.5	3.0	2.8	4.0 ± 1.6
	0.6	1.1	4.2	1.7	1.8	1.9 ± 1.4
	1.6	ND	3.2	1.6	1.6	1.6 ± 1.1
	ND	0.1	1.3	1.9	1.8	1.0 ± 0.9
	ND	0.1	0.8	ND	1.8	0.5 ± 0.8
	ND	0.3	1.8	0.2	2.2	0.9 ± 1.0
	ND	ND	0.4	0.1	0.8	0.3 ± 0.3
	ND	0.2	ND	ND	0.5	0.1 ± 0.2

Note) Unit: ng/ml

* : ND shows under the limit of detection.

** : ND is included as 0 ng/ml.

Table 4 Concentration of unchanged KP-363 in plasma after multiple dosing of 5g of KP-363 cream

Case's No Time (hr)	6	7	8	9	10	Mean ± S.D. **
(Application)	ND	ND	ND	ND	ND	0.0 ± 0.0
	3.5	1.2	2.0	1.1	2.3	2.0 ± 1.0
	4.3	0.7	1.0	5.0	0.9	2.4 ± 2.1
(Removal)	5.4	1.1	4.4	5.0	4.6	4.1 ± 1.7
(Application)	1.7	0.4	1.3	4.8	2.4	2.1 ± 1.6
(Removal)	3.9	2.1	4.0	9.2	4.4	4.7 ± 2.7
(Application)	1.6	4.0	1.5	0.5	1.7	1.7 ± 1.3
(Removal)	2.8	6.7	3.8	2.6	7.0	4.6 ± 2.1
(Application)	0.9	1.1	1.2	2.7	2.1	1.8 ± 0.8
(Removal)	4.2	4.2	3.8	6.2	3.8	4.4 ± 1.0
(Application)	2.8	1.7	1.2	1.6	2.2	1.9 ± 0.6
(Removal)	4.2	7.7	2.3	4.4	4.3	4.6 ± 1.9
(Application)	5.5	0.4	0.2	2.1	0.2	1.7 ± 2.3
(Removal)	4.6	5.3	1.2	8.8	1.8	4.3 ± 3.0
(Application)	3.8	1.0	0.1	2.2	2.6	1.9 ± 1.4
	2.5	2.4	3.9	1.6	1.8	2.4 ± 0.9
(Removal)	2.5	3.2	2.6	4.2	3.9	3.3 ± 0.8
	6.4	4.5	3.9	7.8	1.6	4.8 ± 2.3
	3.7	1.6	0.7	3.9	2.1	2.4 ± 1.4
	3.3	ND	-	2.3	3.7	2.3 ± 1.7
	2.2	1.0	1.1	3.0	2.3	1.9 ± 0.9
	1.8	2.7	ND	3.2	2.3	2.1 ± 1.3
	1.6	1.5	2.0	1.5	ND	1.3 ± 0.8
	2.0	0.1	0.7	0.8	ND	0.7 ± 0.8
	1.8	ND	0.1	ND	0.6	0.5 ± 0.8

Note) Unit: ng/ml

* : ND shows under the limit of detection.

** : ND is included as 0 ng/ml.

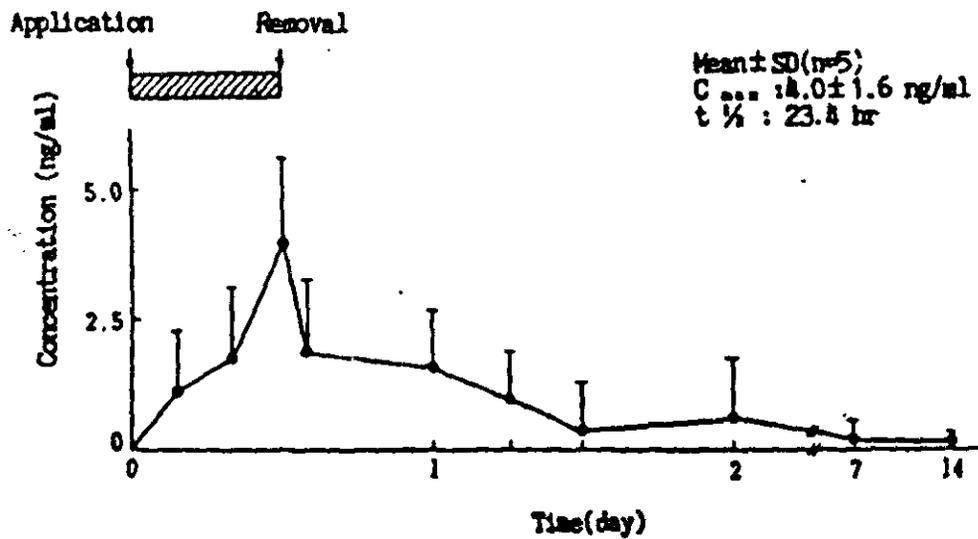


Fig. 1 Time-course of plasma concentration after single dosing of 5g of 1% KP-363 cream

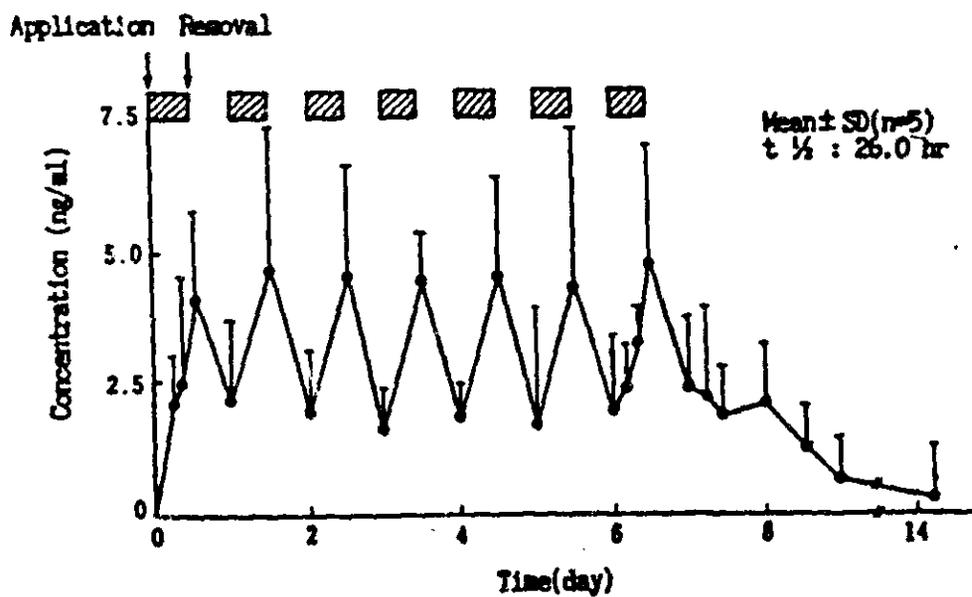


Fig. 2 Time-course of plasma concentration after multiple dosing of 5g of 1% KP-363 cream

IN VIVO PERCUTANEOUS ABSORPTION STUDIES

3) PLASMA BUTENAFINE LEVELS IN PATIENTS

Penederm Clinical Study PDC 010-002:

DOUBLE-BLIND EVALUATION OF BUTENAFINE HCL 1% CREAM AND VEHICLE IN THE TREATMENT OF TINEA PEDIS

INVESTIGATOR AND LOCATION:

OBJECTIVES:

The objective of this Phase III study was to determine the efficacy of the cream when compared to the vehicle. The study protocol specified that plasma samples for the determination of concentrations of butenafine and its major metabolite (M₂) be obtained from all patients at Site #23 at every visit.

FORMULATION: PD-010-C-003 (Penederm Cream)

STUDY DESIGN:

The butenafine and M₂ plasma concentrations during and after treatment with Butenafine HCl Cream 1% were studied in 11 patients participating in one of the pivotal clinical interdigital tinea pedis studies. Butenafine HCl cream was applied by the patient to cover the affected and immediately surrounding skin once daily for 4 weeks.

Sample Collection - Blood samples were obtained 10 to 20 hours after the last dose was applied, at 1, 2 and 4 weeks after treatment was initiated and at four weeks after the cessation of treatment. In addition, a blood sample was obtained before the initiation of treatment.

ASSAY:

Plasma samples from 12 butenafine-treated patients were analyzed by LC/MS/MS for the presence of butenafine and metabolite M₂. This is the same method as that employed in the in vivo percutaneous absorption study (Penederm study 9425201D).

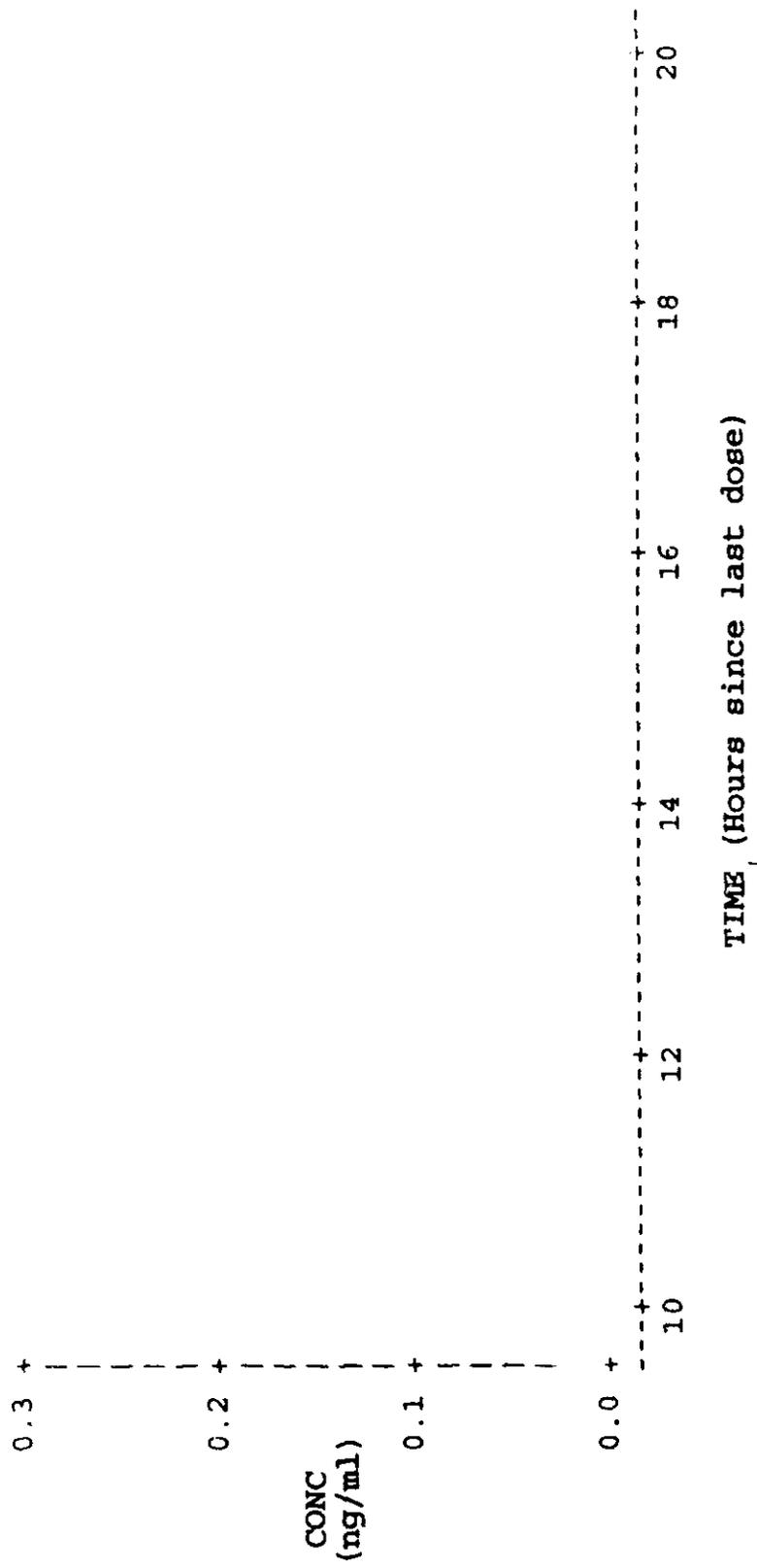
RESULTS:

Of the 11 patients included in the plasma level determinations, 5 patients had full plasma data and 6 patients had partial plasma data with a total of 31 evaluable data points. During treatment (25 samples), the mean plasma butenafine concentration was 0.12 ± 0.10 ng/mL, with a range from undetectable levels to 0.30 ng/mL. At 4 weeks post treatment, all plasma samples had butenafine concentrations below the detection limit. The concentration of metabolite M₂ was below the limit of detection (0.1 ng/mL) at all time points examined. (See Table 1.)

Comment:

In this study, dose was not fixed and the blood sampling time varied from 10 to 20 hours after application of the formulation.

PLASMA BUTENAFINE HCl CONCENTRATIONS IN PATIENTS DURING TREATMENT



NOTE: 1 obs hidden.
Each number or letter represents a subject.

IN VITRO PERCUTANEOUS ABSORPTION STUDY

IN VITRO PERCUTANEOUS ABSORPTION OF BUTENAFINE HYDROCHLORIDE FROM _____ CREAM AND PENEDELM CREAM

Objective:

This study was conducted to characterize the deposition and penetration of butenafine into and through human dermatomed skin from _____ cream (Formulation PD-010-C-001) and Penederm cream (Formulation PD-010-C-003).

Experimental:

Both the _____ cream and Penederm cream were spiked with ^{14}C -butenafine to achieve a radioactivity of about $0.31 \mu\text{Ci}/\text{mg}$ of formulation. The human cadaver skin was mounted on a Bronnough flow-through diffusion cell. Approximately 3.2 mg of formulation was spread over a skin area of 0.64 cm^2 to achieve a level of $5 \text{ mg}/\text{cm}^2$. The flow rate of the receptor fluid, phosphate-buffered saline at pH 7.4 containing 0.01% sodium azide with 1.5% oleth-20, was set at 1 mL/hr at 37°C . The receptor samples were collected at 6-hr intervals for a total of 24 hours. After 24 hours, the skin surface was wiped consecutively with two dry cotton swabs, followed by one tape-strip. The radioactivity due to ^{14}C -butenafine in the skin surface wipes, tape-strip, skin and receptor fluid were determined.

Results:

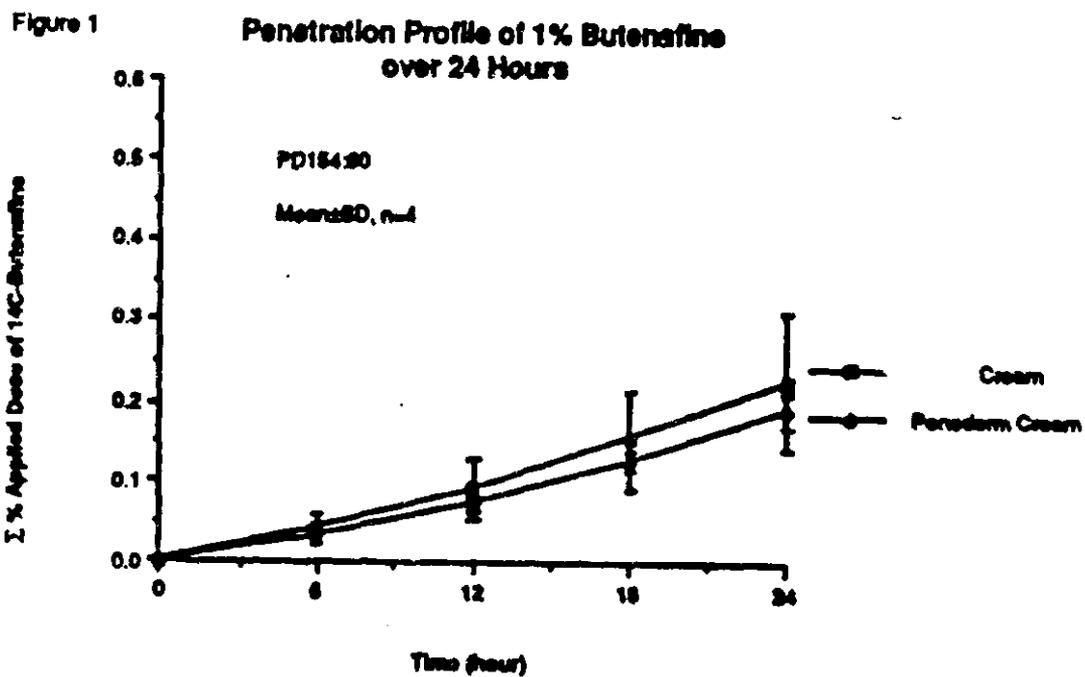
The percentage of radiolabeled butenafine in the receptor fluid, skin, tape strip and skin wipes from both formulations are given in Table 1. The skin content of radiolabeled butenafine delivered from _____ cream ($5.4 \pm 2.9\%$ in the skin and $5.2 \pm 3.2\%$ in tape strip) was similar to that from Penederm cream ($4.4 \pm 2.7\%$ in the skin and $4.8 \pm 3.5\%$ in tape-strip). The graphical representation of the receptor levels of radiolabeled butenafine from both formulations is shown in Figure 1. There is no statistically significant difference ($p > 0.05$) in the penetration of radiolabeled butenafine from the two formulations ($0.23 \pm 0.08\%$ for Kaken cream and $0.19 \pm 0.02\%$ for Penederm cream at 24 hours).

Comment:

In this study, the formulation was applied to achieve a level of $5 \text{ mg}/\text{cm}^2$ while the Penederm in vivo percutaneous absorption study used a level of $2 \text{ mg}/\text{cm}^2$.

Table 1
Penederm Study PD 154:80
***In Vitro* Percutaneous Absorption of Butenafine Cream Formulations**
Percent of Applied Dose (Mean \pm SD, n =4)

Formulation Identification	Receptor	Skin	Tape-Strip	Wipes	Recovered
Cream 1.0% Butenafine PD-010-C-001 Lot # KC-122, D239	0.23 \pm 0.08	5.4 \pm 2.9	5.2 \pm 3.2	84.1 \pm 2.7	95.0 \pm 8.8
Penederm Cream 1.0% Butenafine PD-010-C-003 Lot #4B01	0.19 \pm 0.02	4.4 \pm 2.7	4.8 \pm 3.5	84.6 \pm 7.5	94.0 \pm 5.7



Pharm/
Tox

97

REVIEW AND EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA
Division of Topical Drug Products, HFD-540

NDA 20-524 (Original Submission 04-05-1995)

Drug: Butenafine Hydrochloride Cream 1%

Sponsor: Penederm Incorporated
320 Lakeside Drive, Suite A
Foster City, CA 94404

Contact Person: Barry Calvarese
415-358-0100

Number of Volumes: Twelve (12)

Date CDER Received: 04-05-1995

Date Assigned: 04-11-1995

Date Review Started: 05-22-1995

Date Ist Draft Completed: 08-24-1995

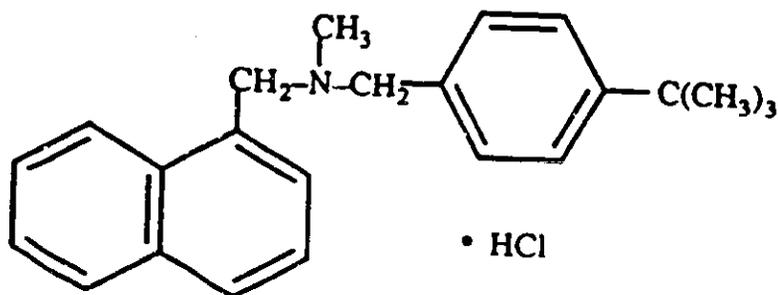
Date Review Accepted by Supervisor:

Dosage and Route of Administration: Topical Cream

Category: Antifungal

Indication: For the treatment of interdigital tinea pedis

Chemical Name: N-4-tert-Butylbenzyl-N-methyl-1-naphthalenemethylamine Hydrochloride
Chemical Structure:



Code Name: KP-363

Composition of Butenafine HCl Cream 1%

Ingredients	% w/w	
	PDC-010-C-003	PDC-010-C-001
1 Purified water USP		
1 Propylene glycol dicaprylate		
1 Glycerine USP		
1 Cetyl alcohol NF		
1 Glyceryl monostearate		
1 White petrolatum USP		
1 Stearic acid NF		
1 Polyoxyethylene cetyl ether		
1 Butenafine HCl		
1 Benzyl alcohol NF		
1 Diethanolamine NF		
1 Sodium benzoate NF		

Note: Non-clinical and clinical studies were conducted with both the formulations. See discussion.

Background: Butenafine, a benzylamine derivative is structurally similar to another antifungal allylamine, terbinafine. Like many other antifungal agents, butenafine inhibits microsomal ergosterol synthesis in the fungi. The proposed mechanism involves inhibition of demethylation of precursor lanosterol. The 14 α -methyl group of lanosterol is axial, protruding from the otherwise planar face. Van der Waals interactions of the sterol underside with the fatty acyl groups in the phospholipid bilayer of the cell membrane are therefore very much less favorable to the stability of the mosaic. This increases the permeability to protons, which eventually makes the membrane burst.

In a 4-week treatment period, once daily application of approximately one gram cream formulation (0.2 mg/kg/day for a 50 kg person) is proposed to treat tinea pedis.

Index of Studies: Except for studies listed below, all other supporting animal studies were reviewed under INDs. The current reviewer decided to re-evaluate the general pharmacology and ADME sections of the submission. These sections have previously been reviewed by Mr. Harold Carlin (appendix I).

Pharmacology:

1. General pharmacology of butenafine HCl.
2. General pharmacology of butenafine metabolites and degradation products.
3. Effect of butenafine HCl on the experimental tinea pedis in guinea pigs.
4. Butenafine HCl: Skin permeability and adsorption to horny materials.
5. Blood hormone levels in rats treated subcutaneously with butenafine HCl.

Acute Toxicity:

6. Oral toxicity of old formulation (PDC-010-C-001) in rats.
7. Oral toxicity of new formulation (PDC-010-C-003) in rats.
8. Intra-peritoneal toxicity of butenafine metabolites in rats.

Primary Irritation:

9. Eye irritation testing with PDC-010-C-003 in rabbits.
10. Skin irritation testing with PDC-010-C-003 in rabbits.
11. Dermal irritation testing with deteriorated drug in rabbits.

Biodisposition:

12. Single dose ADME studies in rats, guinea pigs and dogs.
13. Multiple dose ADME study in rats.
14. Skin penetration of butenafine in guinea pigs.
15. Metabolism of butenafine in rats.

Genotoxicity:

- 16 Rat micronucleus assay.

GLP Compliance: Except for studies # 12-14, all other studies (# 1-5, 8, 15) conducted by

The studies conducted by _____ followed the United States
() and _____
GLP guidelines (CFR Part 58). All GLP studies have included signed Quality Assurance
Statements.

Pharmacology

1. General Pharmacological Studies of Butenafine Hydrochloride (E-14; May 1987 to February 1990).

Study Design/ Procedures / Observations

Test Solutions: Butenafine hydrochloride was dissolved in % for subcutaneous, in % propylene glycol for intravenous, and in % for topical administrations.

Functions Evaluated / Protocols / Observations / Results

Effects on the Circulatory and Respiratory Systems, EEG, and Body Temperature

Animals

Male Wistar rats (174-300 g; 5-6 rats / experiment)

Male and female Mongrel dogs (9-12 kg; 4 dogs / sex / experiment)

Dose(mg/kg) of Butenafine HCl

Subcutaneous: 1, 10, 100 (rats only)

Intravenous: 10, 30 (rats and dogs)

Observations

Blood pressure

Respiration rate

Heart rate

Electrocardiogram

Blood flow

All animals were anesthetized prior to dosing. Following the subcutaneous dose, blood pressure was determined by a pressure transducer passed through a cannula inserted into the femoral artery. After the intravenous dose, heart and respiration rates were determined using tachometers, and the measurements were concurrently recorded on the electrocardiographs. For electroencephalography (EEG) in rats, bipolar electrodes were implanted in the frontal cortex and dorsal hippocampus. EEGs were recorded one week after the surgery following the subcutaneous dose. Body temperature was recorded at 1, 2, 3, and 4 hours after the subcutaneous dose. Each parameter was observed up to 60 minutes after the intravenous dose, and up to 120 minutes after the subcutaneous dose.

Results

In rats, an intravenous dose of 30 mg/kg decreased the heart rate, while a subcutaneous dose of 100 mg/kg reduced the blood pressure. None of the other tested parameters were affected. Only in the high dose dogs, an increase in blood pressure and respiration rate, and a decrease in heart rate as well as in the blood flow were observed.

Effects on the Autonomic Nervous System and Smooth Muscle: Isolated Organs

Animals / Dose

Female Wistar rats (156-195 g)
Subcutaneous dose: 100mg/kg

Observations

The effect of drug on the:

- spontaneous movements in the pregnant (fetus removed) females
- spontaneous movements in the non-pregnant uteri isolated 24 hours after the estradiol treatment
- contractions induced by oxytocin

Animals / Dose

Male guinea pigs (253-398 g)
Dose: Pretreatment with drug (10^{-4} M) 5 minutes before application of an inducer or initiation of a test.

Observations

The effect of drug on the:

- the ileum contraction induced by acetylcholine, serotonin, and nicotine
- the tracheal muscle relaxation induced by isoproterenol
- the contraction of vas deferens induced by norepinephrine
- the spontaneous movement of the atrial muscle

Animals / Dose

Male Japan white rabbits (2.75 3.80 kg)
Dose: Pretreatment with drug (10^{-4} M) 30 minutes before the application of an inducer or initiation of a test.

Observations

The effect of drug on the:

- spontaneous movement of jejunums
- norepinephrine-induced contractions of thoracic aortae.

Results

None of the organ functions were influenced by butenafine treatment in any species.

Effects on CNS, Blood Coagulation, Digestive Tract Transport, and Renal Functions

Animals / Dose

Male Jcl or Slc-ddy mice (18- 26 g; 3-10 mice / experiment)
Subcutaneous Dose: 1, 10, 100 mg butenafine HCl / kg

Observations

Central Nervous System

General signs (Irwin's observation method)

Hexobarbital-induced sleeping time

Muscle relaxation and coordination (traction and rota-rod tests)

Acetic acid-induced writhing

Anti-convulsion effect (penterazol-induced convulsion; maximum electroshock)

Diuretic Effect

Prior to drug administration, mice received 0.5 mL distilled water per 10 g body weight. The volume of urine, its pH and levels of electrolytes were determined.

Digestive Tract Transport Function

Following drug administration to overnight fasting mice, 0.2 mL of 10% gum acacia suspension containing 5% active charcoal was orally administered. Mice were sacrificed 30 minutes after the charcoal treatment, and the dissected small intestine was used to determine the transport ratio (charcoal transport vs the length of the intestine). Atropine (30 mg/kg) was used as a standard reference.

Blood Coagulation

Blood samples collected 3 hours postdose were used to determine the prothrombin (PT) and activated partial thromboplastin (APTT) times.

Results

The drug treatment did not influence the general signs, spontaneous locomotion, sleeping time, and muscle relaxation. No changes in urinary parameters, PT or APTT were observed.

2. General Pharmacology of Metabolites and Degradation Products of KP-363 (E-16; September 1989 to January 1990).

Study Objective / Design

In this study, general pharmacological effects of normal metabolites (M1, M2, M3), a photodegradation product (D1), and two thermal decomposition products (D2, D3) of butenafine were investigated.

Test Substances

D1= 1-naphthalenemethanol

D2= 1-(chloromethyl) naphthalene

D3= N-methyl-bis (1-naphthalenemethyl) amine hydrochloride

M1= 1-naphthoic acid

M2= N-4- (2-hydroxy -1, 1-dimethyl) benzyl-N-methyl-1-naphthalenemethylamine

M3= N-1-naphthoglycine

All substances were dissolved or suspended in 50% or 100% macrogol 400.

Dose levels (mg/kg)

Mice: 100 mg of a test substance

Rats: 10-100 mg of a test substance

Animals

Male Jcl-ICR mice (18-27g; 4-10 mice/group)

Male Wistar rats (214-287g; 5 rats/group)

Male Hartley guinea pigs (304-520g; isolated organs)

Procedures / Observations

Effect on Hexobarbital-induced Sleep Time and Spontaneous Motility in Mice.

The spontaneous motility was determined after 1, 2, 3, 4, and 5 hours of treatment.

Effect on Blood Pressure, Heart Rate, Respiration and ECG in Rats

Anesthetized rats received intravenous doses of test solutions (1mL) by a continuous infusion pump through a cannula inserted into the right femoral vein. Parameters were determined one hour after the treatment.

Effect on Isolated Ileum of Guinea Pig

The individual effects of a test substance on the contraction of ileum induced by acetylcholine, histamine, serotonin, barium chloride, nicotine (at concentrations ranging from $10^{-3}M$ to $10^{-7}M$) were determined.

Results

None of the test substances exhibited any effect on the spontaneous movement, however, M1 prolonged the hexobarbital-induced sleep time in mice. An intravenous dose of M2 (100 mg) produced a transient decrease in blood pressure in rats. The intravenous administrations of M2 (30 mg/kg), M3 (100 mg/kg), and D2 (10 mg/kg) decreased heart rate in rats. At an intravenous dose of 100 mg/kg, both M1 and D2 increased the respiratory rate in rats. Whereas, D1 suppressed the contraction of ileum induced by histamine and serotonin, M2 suppressed the contraction induced by all the agents.

3. Effect of Butenafin HCl, a New Benzylamine Analogue, on Experimental Fungal Pedic in Guinea Pigs— Study of Administration Period and Frequency—(E-6; study period not mentioned).

Study Objective / Design / Procedures

In this study, the effect of drug on the experimental infection was studied by changing the duration and frequency of application. Groups of male Hartley guinea pigs (450-600 g; 5/group) were continuously infected with fungal solution (10^6 spores) for 7 days. Drug was dissolved in a mixture of polyethylene glycol and ethanol (, vol/vol). Treatment started 10 days after the drug application (0.1 mL of 0.25 to 2.0%) once or twice daily for 10, 20, or 40 days.

Guinea pigs were sacrificed two days after the final treatment. About 12 tissue sections from a

plantar were cultured on agar plates for 10 days to detect fungi. Ratios of skin sections using the number of negative and positive cultures were calculated.

Results

A dose dependent therapeutic effect was observed in the range of % . No difference in efficacy between the groups treated with 1 and 2% butenafine was observed. In addition, there was no difference in drug efficacy between once or twice daily drug applications. However, a better therapeutic efficacy was observed with a longer duration of treatment.

4. Activity of Topical Antifungals on Infected Sites--Skin Permeability and Adsorption to Horny Materials (E-7; no dates mentioned).

Study Objectives / Design / Procedures

This study investigated the permeation, retention, and affinity of butenafine (KP-363) to the horny layer where supposedly fungi are lodged.

Percutaneous Absorption

A gauge (2 cm²) laced with 0.2 mL (20 uCi) of 1% [¹⁴C]-KP-363 was attached to each shaved site of male Hartley guinea pigs (number, age, body weights not given) for 6 hours. Animals were sacrificed after either 6 or 24 hours of exposure. Each application site was excised and processed for the determination of radioactivity.

Antifungal Activity

The adsorption of various antifungal agents to horny material was determined by using human hairs. A phosphate-buffered, sterilized suspension of 100 mg powdered human hairs was shaken with KP-363, tolnaftate, clotrimazole, or bifonazole (0.005- 200 ug/100mg powdered-hair/ tube) for 1 hour at 30 °C. Each tube inoculated with *T. mentagrophytes* (2x10⁴ cells) was cultured at 30 °C for 7 days.

In another experiment, after the drug was shaken with a suspension of powdered hairs, unadsorbed compound was removed by multiple washings and centrifugation. As in the first experiment, tubes were inoculated with fungus, and cultured. Presumably, in this situation, the organism grew on the hair as its sole source of nutrition. Microscopic examinations were conducted, and the drug concentration at which no growth was observed was considered as the minimum inhibition drug concentration (MIC).

Results

At 6 hour postapplication, a minimum of 50 ug of butenafine per gram tissue was found in the epidermis including the horny layer. After 24 hours of exposure, 10 ug or more of drug was still present in the horny layer, indicating its strong affinity and retention. All antifungal agents exhibited a strong adsorption onto the human hair. It was inferred that the concentration of KP-363 in the horny layer following the topical application of 1% solution was sufficient to inhibit the fungal growth.

5. Studies of Hormone Levels in Rats Treated Subcutaneously with KP-363 for 6 Weeks (E-15; October 1989 to February 1990).

Study Objectives / Design / procedures

In this study, following the repeated subcutaneous administration of butenafine (1, 5, or 25 mg/kg) to male (151-172 g) and female (118-133 g) Slc:Wistar rats for 6 weeks, drug toxicity and effect on blood hormone levels were investigated. Each test group contained 10 rats per sex. The test substance was dissolved in 50% macrogol 400.

Observations

Clinical signs

Body weight and food consumption

Estrous cycle (diestrus, proestrus, estrus, metestrus)

Blood hormone levels (FSH, LH, ACTH, estradiol, progesterone, testosterone, corticosterone)

Necropsy

Absolute and relative body weights (thymus, adrenals, seminal vesicles, prostate, testis, ovaries, uterus)

Histopathology

Results

A small but statistically significant decrease (5-11%; $p < 0.05$ to 0.01) in gain in body weight was observed in high dose males from day 4 to the end of the treatment period. However, no particular trend in food consumption was observed.

A decrease in estrus frequency due to prolonged diestrus was observed in 3/10 high dose females. In the same group, a significant increase (25%; $p < 0.05$) in blood testosterone level was observed. Hormone levels in all other treatment groups were comparable with controls.

Necropsy examination revealed a slight hypertrophy of the adrenals in the high dose males. It was associated with significantly increased absolute (26-31%; $p < 0.05$) and relative (40-44%; $p < 0.05$) adrenal weights. In addition, a significant ($p < 0.05$) decrease in the absolute (31%)

and relative (27%) thymus weights was observed in the same male group, however, no histopathologic lesions were associated with this change.

Acute Toxicity

6. Acute Oral Toxicity in Rats-Limit Test of: PD 010-C-001 (Tox 010-001; February to May 1993).

7. Acute Oral Toxicity in Rats-Limit Test of: PD-010-C-003 (Tox 010-043; April to June 1994).

Study Objective / Design / Procedures

The old and new formulations were compared for acute toxicity in the same species.

Animals: Sprague Dawley rats (217-280g). Five rats per sex were used in each study.

Test Substance: Butenafine HCl 1% cream.

Route of Administration: Oral (Gavage)

Dose: 5.0 g/ kg

Observations

Following drug administration, all rats were observed for clinical signs of toxicity and change in body weight for 14 days. At study termination, animals were subjected to gross necropsy examinations.

Results

No deaths occurred during the observation period. Except for fecal stains and dirty hair coats, no other gross abnormalities were observed. The oral LD₅₀ value for old and new formulations was found to be greater than 5.0 g/kg in both sexes.

8. Intra-peritoneal Administration Acute Toxicity Studies of Metabolites of Butenafine Hydrochloride in Rats (Tox-010-038; September 1989 to February 1990).

Study Objective / Design / Procedures

In this study, acute toxicity of three major butenafine metabolites (M1, M2, M3) which are excreted in the blood and urine, was investigated.

Animals

Slc: Wistar male (127-167g) and female (102-130g) rats.
10 rats/sex/dose level.

Test Compounds and Dose Levels (mg/kg in 0.1% Polysorbate 80 solution)

Control = Equal volume of water
KP-363 = 500, 1,000, 2,000
M1 = 700, 800, 1,000, 1,500, 2,000
M2 = 500, 700, 1,000, 1,500
M3 = 700, 800, 1,000, 1,500, 2,000

Note: For chemical names of metabolites, refer to study # 2.

Observations

Observation period: 14 days
Clinical signs and mortality
Body weight (days 0, 1, 4, 7, 11, 14)
Necropsy (15 days after dosing)

Results

Clinical Observations and Mortalities

The clinical signs observed following the administration of metabolites were qualitatively similar, and appeared 1 to 3 hours after dosing. The major signs included decreased locomotor activity, staggering gait, asthenia, watery eyes, lacrimation, decreased respiration, hypothermia, and blanching of the body surface. These signs were rarely observed in animals receiving the parent drug.

In case of metabolites, most deaths occurred within 2 days of dosing. After the administration of butenafine, deaths occurred sporadically between days 1 and 5. Among the metabolites, M1 was more lethal (see table below).

Group Distribution of Deaths

Compound	Dose(mg/kg)	MALES (% Mortality)	FEMALES (% Mortality)
Control	0	0	0
KP-363	500	0	0
	1,000	10	10
	2,000	20	10
LD₅₀(mg/kg)		>2,000	>2,000
M1	700	0	20
	800	70	80
	1,000	90	80
	1,500	90	80
	2,000	100	80
LD₅₀		807	748
M2	500	0	0
	700	10	0
LD₅₀	1,000	60	70
	1,500	50	60
		942	1,129
M3	700	0	0
	800	0	70
	1,000	60	80
	1,500	70	100
	2,000	70	90
LD₅₀		1,146	825

Body Weights

In both sexes, body weights decreased one day after the administration of all metabolites, and between days 1 and 4 after the administration of parent drug. However, body weights subsequently increased and tended to return to normal.

Gross Pathology / Histopathology

The major lesions in rats found dead included adhesion between intraperitoneal organs, retention of ascites, and retention of gelosis and congestion of hypermia- or hemorrhage- like changes in the heart. Pathologically, these lesions appeared to be similar for metabolites and butenafine treated rats. Histopathologic examinations revealed congestion or hemorrhage, capsular hypertrophy and adhesion of collagen fiber in various organs.

The gross necropsy examination in the survivors of all treatment groups indicated adhesion between the intraperitoneal organs; histopathologic examinations revealed capsular hypertrophy and adhesion of collagen fiber in various organs.

Primary Irritation

9. Primary Eye Irritation Study in Rabbits of: PD-010-C-003 (Tox 010-044; April to June 1994).

Procedures / Results

Three young NZW rabbits of each sex received 0.1 mL of proposed clinical formulation in one eye of each animal. The untreated eye served as a control. After 24 hours, eyes were examined and lesions were scored according to Draize.

The treated eye of one rabbit exhibited corneal, iritic, or conjunctival changes. There was no evidence for corrosion. The maximum total irritation scores for individual rabbits ranged from 2 to 6 out of a maximum possible score of 110. Therefore, the test material was considered as an ocular nonirritant.

10. Primary Skin Irritation Study in Rabbits of:PD-010-C-003 (Tox 010-045; April 1994).

Procedures / Results

Three young NZW rabbits of each sex received topical application of 0.5 mL of the proposed formulation on one abraded and one nonabraded site under a 1"x 1" gauge on the back of each animal. All sites were scored for dermal lesions according to Draize at 24 and 72 hours postapplication.

Based on erythema and edema, the Primary Irritation Index was found to be 2.5 (on a scale of 0-8) through the 72 hour reading. No necrosis, or changes in skin color or texture were observed. It was concluded that after a single dermal application, the test substance was nonirritant and noncorrosive in rabbits.

11. Primary Dermal Irritation Study of Deteriorated Butenafine Hydrochloride in Rabbits (D-18; January to August 1989).

Study Design / Procedures / Observations

Animals

Approximately 3 months old NZW rabbits (1.88 to 2.20 kg).
Total 22 rabbits; 12 test sites / substance.

Deteriorated Drug Samples

Thermally degraded samples were obtained by placing the packaged formulations in a desiccator containing saturated sodium chloride solution, and the desiccator was stored in a thermostat at 40 °C for six months. To obtain photodegraded samples, the lotion and cream formulations were irradiated with UV light until the residual KP-363 was reduced to 90% (10% degradation).

Dose Groups

1. 1% KP-363 lotion
2. Thermally deteriorated lotion
3. Photodeteriorated lotion
4. Thermally deteriorated lotion vehicle
5. Photodeteriorated lotion vehicle
6. 1% KP-363 cream
7. Thermally deteriorated cream
8. Photodeteriorated cream
9. Thermally deteriorated cream vehicle
10. Photodeteriorated cream vehicle
11. 1% aqueous sodium lauryl sulfate solution (positive control)

Drug Administration and Determination of Primary Irritation Index (PII)

On the shaved dorsal side of each rabbit, six 2.5 cm² sites (3 on each side) were marked. On each animal, 3 sites were abraded by peeling the corneum, other sites were left intact. Each site received application of either 0.5 mL lotion or 0.5g cream formulation. Twelve sites were painted with the positive control.

All occluded sites were exposed to the test substance for 24 hours and then wiped clean with warm water. For the next seven days, sites were examined twice daily and the dermal lesions

were scored according to Draize. The primary irritation indices were calculated from the sum of the scores of abraded and intact sites obtained on days 1 and 3.

Results / Conclusions

A PII of 2.2 (scale 0-8) obtained for the positive control categorized it as a moderately irritating substance. In comparison, the PII for the lotion and cream formulations deteriorated by heat and light were 0.1 and 0.3, respectively, indicating only mild irritating effects which were similar to those observed with the non-deteriorated drug formulations and the corresponding vehicles. It was inferred that the irritation effects of drug did not change even when subjected to deterioration treatments which simulated the aging process. Note: This Japanese study has used a scoring system different from the U. S. study discussed above (# 10).

Biodisposition

12. Biological Fate of Butenafine Hydrochloride (KP-363) - Absorption, Distribution, and Excretion in Rats, Guinea Pigs, and Dogs After Single Administration of ¹⁴C-KP-363- (Non-GLP Study) (F-1; June 1987 to December 1989).

Study Objectives / Design / Procedures

This study investigated the absorption, distribution, and excretion of butenafine hydrochloride after intravenous, subcutaneous, oral, and dermal administration of [¹⁴C]-labeled drug.

Animals

Male (160-280g), female (160-180g), lactating (170-210g), and pregnant (200-260g) Wistar rats.

Male Hartley guinea pigs (550- 650g).

Male beagle dogs (10-13kg).

In each species, 3 animals per experiment were used.

Labeled Drug

Specific activity, 46.1 uCi/mg

Radiochemical purity, > 98.4%

Dose Preparation and Administration

Suspension (0.1%) and solution (0.02%) of radioactive drug were adjusted to a known specific radioactivity using non-radioactive drug and Tween 80.

Rats fasting overnight received radiolabeled drug intravenously (tail vein), subcutaneously (dorsal), and orally. Dogs fasting overnight received similar doses intravenously (forefoot), and dermally (dorsal).

For dermal applications, 1% drug solution prepared using vehicle for clinical formulation was employed. The shaved and occluded dorsal sites received applications of 2 or 10 mg/kg (2 cm²) in rat, 2 mg/kg (4 cm²) in guinea pigs, and 1 mg/kg (16 cm²) in dogs.

Plasma Drug Concentration

To determine the plasma levels, drug was administered through several routes. Rats of both sexes and male dogs received 0.2 mg/kg of radioactive drug intravenously. Subcutaneous and oral doses were administered to male rats at levels of 0.2 or 1 mg/kg, and 0.2 mg/kg, respectively. Male rats were dermally exposed to radiolabeled drug at 2 or 10 mg/kg level for 24 hours under occlusion. Dermal exposure in dogs occurred at 1 mg/kg for 6 hours under occlusion.

Following drug administration, blood samples were drawn from the individual animals at various postdose time points ranging from 5 minutes to 7 days, and the radioactivity was determined by the liquid scintillation method.

Distribution

The drug distribution in the body was determined by whole body radioautography and tissue radioactivity levels following the administration of radiolabeled drug by different routes.

Autradiography

Male rats dermally exposed to 10 mg/kg drug for 24 hours, were subjected to whole body autoradiography at 6 hours, and 1, 3, and 7 days postapplication. Following the subcutaneous administration (2.5 mg/kg) to male and female rats, autoradiograms were taken at 1, 6 hours, and 1 and 7 days. After 1 mg/kg intravenous dose, autoradiograms were prepared at 30 minutes and day 1 postdose.

Absorption and Tissue Concentration

To compare absorption through the intact or damaged skin, male rats received dermal applications of 10 mg/kg drug for 6 hours under occlusion. To compare absorption at different drug concentrations, 0.1 and 0.02% solutions were subcutaneously administered to rats of both sexes at 2.5 mg/kg level. For the determination of tissue drug concentration, male rats received subcutaneous doses of 0.2 mg/kg. The tissue radioactivity was determined at various postdose time intervals ranging from 1 hour to 21 days.

Pregnant rats received 0.2 mg/kg of [¹⁴C]- KP-363 subcutaneously during the organogenic and perinatal periods. The radioactivity in tissues of mother and fetus was determined at 6 hours and day 2 postdose.

Lactating rats were dosed subcutaneously at level of 1 mg/kg. The radioactivity was determined in maternal and neonatal tissues collected at 6 hours and 1, 3, and 7 days postdose.

Maternal plasma and milk samples obtained during the same period were used to determine the amount of radioactivity present.

To determine skin distribution of drug, dorsal sides of guinea pigs were exposed for 6 hours to 2 mg radioactive drug per animal, and skin samples for the determination of radioactivity were collected at 6 hours and day 1 postapplication. The bottom of guinea pig feet were exposed for 24 hours to 2 mg drug per foot. The exposed skin was excised, and processed for microautoradiograms.

Excretion

The excretion of radioactivity in the urine, feces, bile, and exhaled air was determined following drug administration to rats of both sexes by dermal applications (10 mg/kg), and via intravenous, subcutaneous, and oral routes at a level of 0.2 mg/kg. The urine and fecal samples were collected up to 21 and 7 days, respectively. The samples of expired air were collected after the subcutaneous radiolabeled dose. The bile samples were collected up to 1 day following 0.2 mg/kg dose to male rats.

Protein Binding

[¹⁴C]-KP-363 was administered intravenously to male dogs (0.1 mg/kg) and rats of both sexes (0.2 mg/kg), and to male rats subcutaneously (1mg/kg). Blood samples were drawn two hours after the subcutaneous dose and 30 minutes after the intravenous dose. The amount of radioactivity in the filtered (Amicon filter) and centrifuged (1000xg for 10 minutes) serum was used to calculate the protein binding rate.

Results

Plasma Pharmacokinetics

The plasma kinetics of butenafine is summarized in the table adapted from the sponsor (below). Following the topical or subcutaneous dosing at 1.0 to 10.0 mg/kg, the elimination half-lives in rat and dog ranged from 36 to 44 hours. However, following the intravenous dose of 0.2 mg/kg, half-lives differed widely in two species, from 59 hours in dog to 24 hours in rat. In rats, plasma kinetics was similar in both sexes.

Plasma Kinetics of Butenafine After Single Doses

Species	Dose (mg/kg)	Route	C _{max} (ng-eq/mL)	t _{max} (Hour)	AUC (μg-eq-hr/mL)	Elimin. Half-life (Hour)
Rat	0.2	IV	400	—	2.0	24
Dog	0.2	IV	900	—	1.5	59
Rat	0.2	Oral	156	1	1.9	15
Rat	0.2	SC	82	0.5	1.8	27
Rat	1.0	SC	234	0.5	7.9	36
Rat	2.0	Topical	25	24	1.4	38
Rat	10.0	Topical	53	24	3.7	44
Dog	1.0	Topical	3	6-24	0.2	41

The C_{max} in dog following a topical exposure to 1.0 mg/kg only reached a maximum of 3 ng-eq/mL in 24 hours. It was inferred that the low percutaneous absorption following the topical application of butenafine was due to high affinity of drug for keratin and a tendency to localize within the stratum corneum.

Whole Body Autoradiography

Following the dermal application, a high concentration of radioactivity was observed in the dorsal side of rats at 6 to 24 hours postdose. After the intravenous dose, high amounts of radioactivity were present in the intestine, liver, adrenals, pancreas and brown fat; due to a rapid elimination, low amount of radioactivity was found in the blood. The distribution autoradiograph of the subcutaneous dose indicated an organ distribution pattern of radioactivity similar to that observed after the intravenous administration.

In the pregnant rats, the level of radioactivity in the placenta and maternal blood were similar, however, fetus contained less radioactivity.

Tissue and Fluid Distribution of Radioactivity

Six hours after the topical application (10 mg/kg) in rats, 89% (intact) and 79% (abraded) of the applied radioactivity remained on the sites. The tissue concentrations in the intact and abraded skin were 17.8 and 173.0 μg/g, respectively. Four days after the application, the excretion rate in the urine and feces was 4% (intact) and 25% (abraded), respectively. The partitioning into the subcutaneous layer was low in both cases. However, a big difference in maximum plasma concentration was observed, 50-55 ng/mL in the intact versus 245-271 ng/mL in the abraded skin.

A peak blood concentration of radioactivity was achieved at 6 hours after the subcutaneous dose (2.5 mg/kg) in rats. High amounts of radioactivity were found in the intestinal contents, liver, adrenals, pancreas, brown fat, mesenterium and harderian gland. About 90% of the administered radioactivity was eliminated in the excreta after 4 days. Following the 0.2 mg/kg subcutaneous dose, the transfer rate of radioactivity to blood cells was about 7.7%. At 6 hours after the subcutaneous dose (0.2 mg/kg), the transfer of radioactivity to fetus was low (0.01% per embryo) in the organogenic period. In the perinatal period, the amount increased to 0.1% per fetus.

In the lactating rats, the the peak of radioactivity (1320 ng/mL) in the milk was observed at 3 hours after the subcutaneous dose of 1.0 mg/kg. This amount was 6 times higher than the peak maternal plasma concentration. However, the amount of radioactivity in the organs and tissues of neonates consuming milk was about half of its mother after one day.

Dermal Distribution

The topical study in guinea pigs revealed a nonhomogenous distribution of radioactivity, ranging from a high of 50 ug/g in the top 300 um layer including the stratum corneum, to a low of less than 0.5 ug/g in 1000-2500 um depth of the skin. The elimination of drug from the skin was slow, and the stratum corneum contained the highest amount of radioactivity. These data were also supported by the results obtained from the microautoradiography.

Excretion

The total cumulative excretion rate in urine and feces after 6 hours of topical exposure in rats was 4.9 and 5.2% after 7 and 21 days, respectively. Following the intravenous and subcutaneous administrations, the rate of excretion was about 90% in both the sexes, more than 60% of it was excreted in the feces. The urinary excretion rate after the oral dose in rat was little higher than that of other routes. In dogs, following the intravenous dose, the elimination rate in the excreta was about 85%.

Biliary Excretion and Enterohepatic Circulation

About 25% of the administered subcutaneous dose in rats was excreted in the bile after 4 hours, and about 45% after 24 hours.

Protein Binding

After the intravenous and subcutaneous administrations, the drug protein binding rate in serum ranged from 90 to 93%.

13. Biological Fate of Butenafine Hydrochloride (KP-363) - Absorption, Distribution and Excretion in Rats after Repeated Administration- (Non- GLP Study) (F-2; June 1987 to October 1989).

Study Objectives / Design / Procedures

In this study, after the repeated subcutaneous and dermal administrations of butenafine to rats, drug absorption, distribution, metabolism, and excretion were investigated. In addition, drug concentration in the skin and fat was determined after a single topical application.

Animals

Six to ten weeks old male Slc:Wistar rats (body weights not reported).
3-10 rats per dose group per experiment.

Procedures for dose preparation, administration, and determination of radioactivity in the biological samples were essentially similar to study # 12 above. Additionally in this study, the residues of nonradioactive unmetabolized parent compound were chemically extracted from the plasma, skin, and fat, and the drug concentration was determined by the gas chromatography-mass spectrophotometric method (GC-MS).

Protocols

Rats received once daily subcutaneous dose of 0.2 mg/kg of [¹⁴C]-KP-363 for 7 days. Blood samples were drawn at 1 hour and one day after the first 6 doses, and up to 14 days after the last dose.

Radiolabeled drug (2mg/kg) was topically applied to the dorsal skin once daily for 7 days. Blood samples were collected at 6 hours after the first dose, one day after the first 6 doses, and up to 7 days after the last application.

Tissue drug concentrations were determined after the daily subcutaneous (0.2 mg/kg) and topical (2 mg/kg) administrations for 7 days.

In three month long dermal studies using nonradioactive drug (1, 25, 50, 500 mg/kg/day), the concentration of intact drug was determined in the skin, plasma, and fat at the end of dosing and one month recovery period by GC-MS method.

The excretion rate of radioactivity in the urine and feces was determined following the daily subcutaneous administration of drug (0.2 mg/kg) for 7 days.

The effect of KP-363 on the hepatic drug metabolizing enzymes was studied after daily subcutaneous and dermal doses of 10 mg/kg for 7 days.

Results

The plasma concentration of radioactivity following the subcutaneous dosing (0.2 mg/kg) increased gradually and reached a constant value on day 7. After the topical application of 2 mg/kg/day, the concentration in plasma did not increase much during the first 2 days, and then reached a constant value (23.4 ng/mL) until dosing ceased. This plasma concentration and the corresponding half-life of about 32 hours were similar to that obtained after the single dose (C_{max} 25 ng/mL; $T_{1/2}$ 38 hours).

Tissue Distribution and Concentration

The tissue distribution pattern after the multiple subcutaneous dosing (0.2 mg/kg) was essentially similar to that observed after the single exposure in study # 12. However, the amount of radioactivity was several times higher at day 1, and much higher after 7 days. The amounts of radioactivity were found in the following decreasing order: intestinal contents, fat, liver, pancreas, adrenals, and thymus. After the topical applications (2 mg/kg), the residual drug concentration on the skin was much higher than that observed after the single application. Except for the skin and fat, no other tissue had any measurable radioactivity.

In three month dermal study, no clear dose response relationship was observed in the skin concentration of drug. At the end of the one month recovery period (50 mg/kg dose), the drug concentration in the skin was reduced to 1/150 of that recorded on day zero. However, a dose-response relationship was observed in the plasma drug concentration. The concentrations in the plasma and fat were decreased to 1/6 and 1/9, respectively by the end of the recovery period.

14. Penetration in Skin After Dermal Application of Butenafine HCl (Non-GLP Study) (F-3; July to September 1990).

Study Objectives / Design / Procedures

In this study, after repeated dermal applications, penetration and retention of butenafine were studied.

Animals

Male Hartley guinea pigs (350-700g).
3 animals / experiment

Test Compounds:

[^{14}C]- KP-363, specific activity= 44.2 uCi/mg, radiochemical purity= 99%

Radioactive compound was diluted with non-labeled drug and dissolved in the vehicle [macrogol 400:EtOH:H₂O= 30:22:50 (w/w)].

Preshaved, 2x2 cm² dorsal sites of animals received daily dermal applications of 200 uL of 1% test solution (5.5 uCi/ 2 mg) for 7 consecutive days. The application sites in one test group were occluded. At study termination, skin excised (3x3 cm²) from epidermis side of the application sites was cut into slices of various thickness. These slices were processed to determine radioactivity by liquid scintillation method.

Results / Conclusions

In the occluded sites, very high amount of radioactivity (250-500 ug/g equivalent to KP-363 concentration) was found in 50 um thick slices containing stratum corneum. The level reached to a plateau by day 2 and to a constant value by day 7. A fairly high level of radioactivity (70-250 ug/g) was found in the 100- 200 um thick slices containing corium. A low level of radioactivity (1 ug/g) was observed in 1000-2000 um thick slices involving subcutaneous tissue. However, irrespective of a low level of radioactivity, a small peak was observed in 1400 to 1700 um depth. Since a high level of radioactivity was observed in the skin depth of 100-200 um, it was inferred that butenafine exhibited good skin permeability. The appearance of a small radioactive peak after 7 days of occlusive treatment was related to changed skin conditions such as high moisture and swelling.

The pattern of distribution of radioactivity in non-occluded skin was similar to that observed in the occluded skin. In 50 um thickness, the amount of drug ranged from 200 to 1100 ug/g; the level ranged from 60 to 130 ug/g in 100 to 200 um thick slices. An amount less than 1 ug/g was present in depth exceeding 1000 um, and a small peak was observed in depths of 1200 to 1400 um.

15. Metabolism of Butenafine Hydrochloride (F-4; May 1985 to February 1990).

Study Objective / Design / Procedures

In a series of experiments, metabolism of butenafine following its administration through different routes was investigated.

Animals

Seven weeks old Slc:Wistar rats (173-221g; sex of animals not mentioned).
3 rats/ dose/ experiment.

Test Solutions

[¹⁴C]- KP-363 (specific activity 44.3 uCi, radiochemical purity > 98.4%) was diluted with non-labeled drug to prepare the following solutions.

0.3% solution (7.15 uCi/0.17 mg)--oral
0.1% solution (44.3 uCi/mg)-- intravenous and subcutaneous
1% solution (10 uCi/mg)--dermal
0.5% and 3.1% non-labeled KP-363 solutions--oral

Dose Administration and Sampling

Following a 500 mg/kg oral dose (0.5% solution of cold KP-363), excreta samples were collected up to 20 hours postdose.

Following oral dosing of 0.3% solution (115 mg/kg), or 0.1% solution (5 mg/kg) intravenously, urine and bile samples were collected up to 24 hours.

After the subcutaneous administration of 0.1% solution (0.2 mg/kg) to rats with cannulated bile ducts, bile samples were collected after 4 and 24 hours.

Levels of metabolites in the tissues were determined following the dermal application of 1% solution (10 mg/kg) and subcutaneous administration of 0.1% solution (2.5 mg/kg). After the subcutaneous administration, blood samples were drawn at 6 hours and 4 days postdose; liver, kidney and fat were removed.

Reference Standards

The following synthetic compounds were used as reference standards (metabolites) in the chromatographic analyses of tissues and biological fluids.

M1= 1- naphthoic acid
M2= N-4-(2-hydroxy-1, 1-dimethylethyl) benzyl-N-methyl-1-naphthalenemethylamine
M3= N-1-naphthoglycine
M4= N-4-(2-hydroxy-1, 1-dimethylethyl)-1-naphthalenemethylamine
M5= N-tert-butylbenzyl-N-1-naphthalenemethylamine
M6= 4-tert-butyl-benzoic acid
M7= 4-(2-hydroxy-1, 1-dimethylethyl) benzoic acid

Results

GC-MS and HPLC analyses of urine and feces indicated that the biological conversions of butenafine involved N-demethylation (M4, M5), N-dealkylation (M1, M3, M6, M7), hydroxylation of tert-butyl group (M2, M4, M7), hydroxylation of naphthalene ring (M8), and glycine conjugation of 1-naphthoic acid (M3).

Systemically absorbed drug, extensively bound to plasma proteins, was almost completely metabolized by methylation, dealkylation, and hydroxylation into 5 major metabolites. Hardly

any metabolites were detected in the skin after the dermal application, and most of the topically administered drug remained intact.

Subcutaneously administered drug was metabolized rapidly, and only low concentrations of parent drug were found in the plasma and liver. The plasma metabolites (M1, M2, M3) were rapidly excreted in the urine or feces. M2 was present at a much higher concentration in the plasma than M1 or M3, and therefore, was considered a major drug equivalent. M2 was mainly excreted in the bile, with a minimum amount found in the urine. The primary urine metabolites were M1 and M3. Results suggested the presence of conjugates of M1, M2 and M4 in the urine.

Genotoxicity

16. Mutagenicity Test on KP-363 in an In Vivo Rat Micronucleus Assay (Tox-010-046; November 1994).

Study Design / Procedures

Animals: Male (211-256g) and female (163-205g) Sprague- Dawley rats
5 rats / sex / dose / harvest time

Vehicle control: 3% acacia solution, 20 mL/kg

Positive control: Cyclophosphamide 60mg/kg in deionized water

Test dose levels: 1250, 2500, 5000 mg/kg drug suspension in the vehicle

Initially a dose range finding study was conducted in the range of 500 to 5000 mg/kg.

Route of Administration: Single oral (gavage) dose

At 24, 48, and 72 hour harvest times, animals were euthanized and bone marrow smears prepared from samples drawn from both tibiae were analyzed for the formation of micronucleated polychromatic erythrocytes (PCEs).

Results

Butenafine hydrochloride did not induce a statistically significant increase in micronuclei in the bone marrow PCEs under the assay conditions.

Proposed Labeling

The nonclinical portion of the proposed labeling is deficient, and does not fully meet the requirements set under 21 CFR, 201.5.7. For instance, pregnancy category and the nature of studies conducted are not mentioned. This reviewer has partially redrafted the text to be transmitted to the sponsor. In addition, the sponsor should include the human plasma levels in the text for comparison.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies in animals using butenafine hydrochloride were not conducted. Two *in vitro* assays (bacterial reverse mutation test, chromosome aberration test in Chinese hamster lymphocytes) and one *in vivo* study (rat micronucleus bioassay) revealed no mutagenic or clastogenic potential for butenafine hydrochloride. A subcutaneous reproduction study conducted in rats at a dose level 125 times higher than the topical human dose (0.2 mg/kg/day) did not demonstrate any adverse effect on male or female fertility.

Pregnancy

Pregnancy Category B: Subcutaneous doses of butenafine hydrochloride at 25 to 50 mg/kg/day levels (equivalent to 125 to 250 times the maximum potential exposure at the recommended human topical dose) during organogenesis in rats and rabbits were not teratogenic. There are, however, no studies in the pregnant women, and because animal reproduction studies are not always predictive of human response, this drug should be used only if clearly indicated during pregnancy.

Toxicologist's Discussion and Interpretation of Safety Data

The sponsor has extensively tested the safety of butenafine hydrochloride in several animal species (rat, mouse, dog, rabbit). The dose levels used in the animal studies were much higher than the proposed human dose of 0.2 mg/kg/day, and some of these studies were of much longer duration than the suggested human treatment period of 4 weeks. It must be mentioned that most of the nonclinical studies were conducted with the old formulation (PDC-010-001) not containing 0.5% benzyl alcohol as a preservative. The proposed formulation (PDC-010-003) was tested only in a few animal studies, in Phase 3 pivotal clinical trials, and human dermal tolerance and pharmacokinetic studies. However, the sponsor did conduct a few critical studies to compare the animal toxicity profiles of the old and new formulations; no differences were observed in terms of acute oral toxicity in rats, and primary eye and skin irritation in rabbits. This reviewer completely agrees with the sponsor that the presence of benzyl alcohol in the proposed formulation will not change the toxicity profile of butenafine hydrochloride in the animals or humans.

A transient decrease in heart and respiratory rates was observed at high intravenous doses (10-30 mg/kg) in rats. However, an intravenous dose of 100 mg/kg in dogs only caused a slight decrease in the respiration rate. Butenafine hydrochloride at dose levels up to 100 mg/kg did not affect the gastrointestinal, urogenital or endocrine systems or hematologic parameters in rats.

The percutaneous absorption of butenafine in rats following its multiple topical applications (10 mg/kg) was low, and almost 90% of the administered dose was recovered as unmetabolized drug. The percutaneous absorption in guinea pigs also did not exceed 10%.

This limited entry into the systemic circulation is reportedly linked to high affinity of drug for keratin and tendency to localize within the stratum corneum.

After daily applications of 100 mg/kg/day in a 12-month study in dogs, the mean C_{max} drug plasma level reached to 352 ng/mL. However, this high concentration did not produce any systemic toxicity. On the other hand, the mean C_{max} plasma drug level in human reached only to a level of 5.0 ng/mL following a daily application of 20 grams of drug for 14 consecutive days. The human plasma drug level during treatment of tinea pedis with the proposed clinical formulation (1% cream) remained at 0.1 ng/mL level.

More than 90% of the systemically absorbed drug, initially extensively bound to the plasma proteins, was rapidly metabolized by methylation, dealkylation, and hydroxylation into 5 major metabolites, which were readily eliminated in the excreta. In rats and dogs, irrespective of the route of administration and dose level, more than 85% of the administered drug was excreted within 7 days. The elimination half-life in rat and dog after the topical application was about 41 hours.

Acute dermal (LD₅₀) doses of butenafine hydrochloride in rat were several thousand times the recommended human dose. In the subchronic and chronic dermal studies, toxicity observed mainly at high doses (25-500 mg/kg/day) included dose-dependent reversible eczematous symptoms in the skin. No systemic effects were observed at any dose level. The NOEL (systemic) in a 12-month dermal study in dogs was estimated to be 25 mg/kg. The NOEL (systemic, oral) in rat was 15 mg/kg.

The acute toxicity profiles of major metabolites (M1, M2, M3) of butenafine gave much lower LD₅₀ values than obtained for the parent compound. The metabolite M1 (1-naphthoic acid) was most toxic. However, it must be realized that most of the topically applied drug remained intact, a fairly small amount was absorbed through the skin, and the metabolites formed were readily excreted.

According to the sponsor, a short treatment period (4 weeks) exempted the drug from carcinogenicity and photocarcinogenicity testing. In addition, the results of chronic toxicity, phototoxicity, photosensitization, and genotoxicity studies did not warrant testing for potential carcinogenicity and photocarcinogenicity. The sponsor has a valid point. Traditionally in this division, unless some alarming indications were received from other studies or human treatment exceeded 6 weeks, drugs have been exempted from carcinogenicity studies.

A number of short-term studies were conducted to investigate the toxicologic and pharmacologic effects of degradation products of butenafine hydrochloride. Except for sporadic soft stools, no systemic toxicity was observed. The dermal irritation potential of light and heat degraded 1% lotion and cream formulations was also investigated. A mild irritation reaction observed was similar to that observed with the non-deteriorated drug.

The whole body autoradiography in rats indicated high amounts of radioactivity in the intestine, liver, adrenals, pancreas and brown fat. However, because of rapid elimination, a low amount of radioactivity was found in the blood. On the whole, no significant tissue accumulation of drug was observed.

In the subcutaneous and topical reproduction and developmental studies, no changes in the structural, physical, and functional development of offsprings were observed. Reproductive performance and other functions of F₁ generation were similar to the control animals. F₂ generation did not exhibit any changes in the survival rate, postnatal differentiation, and sexual maturity.

Two in vitro and one in vivo genotoxicity tests indicated that butenafine hydrochloride was not mutagenic or clastogenic. Contact allergenicity, phototoxicity, and photocontact allergenicity tests of butenafine also did not reveal any effects.

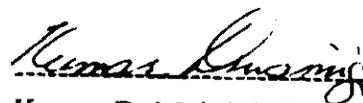
The conduct of a few pharmacokinetic studies is questionable. A number of these were non-GLP studies. In some cases only a small number of animals were used to draw any statistical conclusions from the data. In some critical studies, animals of both sexes were not used, therefore, it was not possible to look for any sex related differences. In one instance, even the sex of the animals used was not mentioned. However, these deficiencies should have been discussed with the sponsor when these studies were first reviewed in 1993 (Appendix I). At this late stage of drug development, it is not proper to raise such issues.

The sponsor has paid a scant attention to the labeling draft; even the pregnancy category has not been mentioned. This draft must be revised by the sponsor to meet the requirements set under 21 CFR 201.57.

In a nutshell, irrespective of a few deficiencies, nonclinical studies have projected a safe and sound toxicity profile for butenafine hydrochloride.

Recommendations

1. From the nonclinical safety point of view, I have no objection to the approval of this new drug application.
2. At an appropriate time, the labeling portion of this review should be transmitted to the sponsor for changes to be made before the approval of this NDA.


Kumar D. Mainigi, Ph.D., DABT
Toxicologist

cc: Original NDA 20-524
HFD-82
HFD-502
HFD-540/Div Dir/Wilkin
MO/ Slifman
~~Chem/ Reppe~~
Pharm/ Mainigi
CSO/ Cross
Spharm/ Jacobs

Concurrence:

J. Wilkin, Director
A. Jacobs, SPharm

JW 9/20/05
11.9. 9/1/05

STAT

STATISTICAL REVIEW AND EVALUATION.

NA#/Drug class: 20-524/1S

Applicant: Penederm Inc.

Name of Drug: Butenafine HCl cream 1%

Documents Reviewed: Volumes 1.1, 1.24-1.27, dated April 4, 1995, and data on disks provided by the sponsor

Type of Report: Clinical.

Indication: Topical treatment of interdigital tinea pedis (athlete's foot) due to Epidermophyton floccosum, Trichophyton mentagrophytes or Trichophyton rubrum

Medical Officer: Nancy Slifman, M.D., HFD-540

I. Introduction

The applicant has submitted two studies (protocols PDC 010-001 and PDC 010-002) as pivotal evidence to support the claim that butenafine HCl cream 1% is safe and effective in the topical treatment of interdigital tinea pedis (athlete's foot). Throughout the review, the terms "Study 001", and "study 002" refer to protocols PDC 010-001 and PDC 010-002, respectively. The treatment name abbreviation butenafine refers to butenafine HCl cream 1%.

Two studies, 001 and 002, were identical in design. The objective of these two studies was to compare the safety and efficacy of butenafine and vehicle when used once daily for 4 weeks to treat interdigital tinea pedis.

II. Study Design, Study Population, and Statistical Methods

Studies 001 and 002 were randomized, parallel group, vehicle-controlled, eight-week trials conducted in the United States. Each study had two treatment arms (butenafine and vehicle). Patients eligible for inclusion in the study were males or females over the age of 12 years with symptomatic interdigital tinea pedis who had positive KOH examination and positive mycological culture for fungus. A patient

was not eligible for inclusion in the study if he/she had a moccasin-type tinea pedis, had clinically significant abnormal laboratory results, received any topical antifungal treatment during the previous two weeks or had some other conditions. For more details on exclusion criteria, please see the RMO report.

Since it can take several weeks for a specimen to be cultured, patients were conditionally enrolled pending their baseline culture and laboratory results. Patients whose baseline tests later revealed either a negative culture or a clinically significant abnormal laboratory test were terminated before completing the study. Patients who conditionally met enrollment requirements were assigned to receive butenafine or its vehicle according to a randomization schedule. Patients were randomized in blocks of four (two active and two vehicle) in order to balance the two treatment arms.

The baseline visit (Week 0) occurred on the same day that study medication started (Visit 1). Patients were scheduled to return at Weeks 1, 2, 4, and 8 (Visits 2-5). At the baseline visit, all patients were instructed on how and when apply their study medication.

At Weeks 0, 1, 2, 4, and 8, a fungal culture was obtained by inoculating two culture tubes with skin scrapings from the patient's target lesion. Week 0 (baseline) cultures were used to confirm study eligibility by demonstrating growth of a fungal pathogen (positive culture). The cultures were held at room temperature for up to 2 weeks. If no growth was observed in either tube at the end of two weeks, the baseline cultures were considered negative and the patient was excluded from the study. Clinical evaluation of the target lesion on the more severely affected foot was measured at each visit and consisted of the following:

- Signs: Cracking/fissures; erythema; scaling; maceration
- Symptoms: pruritus; burning/stinging

The signs and symptoms of the target lesion were scored separately using the following scale:

- 0 = absent (none)
- 1 = mild (barely perceptible)
- 2 = moderate (definitely present)
- 3 = severe (marked, intense)

For entry into the study, patients must have erythema with a score of at least 2 and either scaling or pruritus with a minimum score of 2. Therefore the minimum score for these 3 major signs and symptoms should total at least 4. A Total Signs /Symptoms Score was defined as the sum of the scores and therefore should be at

most 18.

Global Response of the target foot was assessed by the investigator at Weeks 1, 2, 4, and 8. Global Response was defined as 'Cleared' if there was 100% remission of clinical signs and symptoms as compared to baseline.

To be considered evaluable for efficacy, a patient had to meet the eligibility requirements and return for at least one visit after baseline. A delayed positive culture occurs when the baseline culture is negative, but the patient subsequently had a positive Week 1 or Week 2 culture. All patients with delayed cultures were considered evaluable.

For safety evaluation, at each visit during the study, all medical problems occurring since previous visit were recorded. At each visit, after the patient had an opportunity to spontaneously mention any problems, the investigator inquired about adverse events by asking standard questions. Using definitions established in the protocol, the investigator classified the adverse events as related or not related to treatment and also as mild, moderate or severe. To monitor compliance, the dispensed tubes with study medication were weighed at each visit. Four patient populations were considered for statistical analysis:

- Safety population of all patients who used at least one dose of the assigned treatment.
- Per Original Protocol population of all eligible patients who did not violate the protocol, completed four weeks of assigned treatment and attended the Week 8 visit within a window of plus or minus 3 days of a four week period from the date of last study medication use. This was the reviewer's Per Protocol population.
- Per Amended Protocol population of all eligible patients who did not violate the protocol, completed four weeks of assigned treatment and attended the Week 8 visit within an amended window of minus 5 or plus 16 days of a four week period from the date of last study medication use. This was the applicant's Per Protocol population.
- Modified Intent to Treat (MITT) population of all eligible patients who used at least one dose of the assigned treatment and had minimal efficacy data (at least one post-baseline visit and had no noteworthy protocol violations). To be included in the Week 1, Week 2, and Week 4 visits, the visit was required to occur within plus or minus 3 days of the scheduled date. To be included in the Week 8 visit, the visit was required to be within a range of minus 5 to plus 16 days of a four week period from the date of last study medication use. If a visit was missed or out of range, the last available information was carried forward.

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3 OF 5

REVIEWER COMMENT: As a primary efficacy endpoint, this reviewer considered Overall Cure which was defined as both Mycological Cure (negative KOH and negative culture), and investigator's evaluation of Global Response as 'Cleared'. The study hypothesis was as follows: butenafine was superior to vehicle in Overall Cure at Week 8 visit. The null hypothesis was as follows: there was no difference between butenafine and vehicle in Overall Cure at Week 8 visit. The Cochran-Mantel-Haenszel (CMH) test controlling for investigator was used to test the null hypothesis.

Since the applicant changed the original protocol window for the Week 8 visit from plus or minus 3 days to a wider window of minus 5 days or plus 16 days, this reviewer's Per Original Protocol population was different from the Per Amended Protocol population used by the applicant. Efficacy results at Week 8 for the Per Original Protocol population were of primary interest. These results were compared to those for the applicant's Per Amended Protocol population. Week 8 efficacy results for the MITT population are also presented to assess consistency and robustness of the results.

According to protocol, Global Response of the target lesion was defined as 'Cleared' if there was a 100% remission of clinical signs and symptoms as compared to baseline. Therefore, one would expect the patients with Global Response of "Cleared" to have Total Signs/Symptoms Score of 0. However, this reviewer found discrepancies in some patients. The Total Signs/Symptoms Score of 0 is a strong evidence of clinical response, but it is less conservative than the investigators's Global assessment of 'Cleared'. Because of the discrepancies, this reviewer used the endpoint Total Signs/Symptoms Score of 0 plus Mycological Cure as a supportive parameter.

As a secondary efficacy endpoint, this reviewer considered Additional Effective Treatment which was defined as Mycological Cure (negative KOH and negative culture) plus a Total Signs and Symptoms Score of 0 or 1. Analyses of the Additional Effective Treatment rates were performed similarly to the Overall Cure rates.

To check whether the two treatment groups were balanced relative to age and baseline Total Signs and Symptoms Score, the Wilcoxon rank sum test was used. The Chi-square test was employed to test whether the two treatment arms were balanced in sex and race. Contingency tables for baseline pathogens had cells with an expected cell count less than 5. Consequently, an extension of Fisher's exact test for $2 \times k$ tables was used. For the same reason, Fisher's exact test for 2×2 tables was used to compare occurrence rates of adverse events in the two treatment groups. All hypothesis tests were two-sided and used the Type I error $\alpha = 0.05$ to determine statistical significance, except that treatment-by-investigator

interactions were deemed significant at the 0.1 level.

III. Results

A. Study 001

PATIENTS CHARACTERISTICS

One hundred fifty (150) patients were enrolled by six investigators and randomized to treatment (77 to butenafine and 73 to vehicle). Of the 150 enrolled patients, 149 used at least one dose of study medication and were included in the safety analyses. Five patients had delayed positive cultures. Two of them completed the study and three were terminated early. According to protocol, all five patients with delayed positive cultures were considered evaluable.

Of the 150 enrolled patients, 45 (30%) were ruled non-evaluable. Of the 45 non-evaluable patients, 24 (53%) were on butenafine with 22 being ruled non-evaluable due to negative baseline culture, one due to abnormal baseline lab results and one due to moccasin tinea pedis. Twenty one (47%) non-evaluable patients were on vehicle. Of the 21 non-evaluable vehicle patients, 17 were ruled non-evaluable due to negative baseline culture, 2 due to abnormal baseline laboratory results and 2 were lost to follow-up at baseline. CMH test stratifying by investigator showed that there was no significant treatment difference in the proportions of patients ruled non-evaluable ($P=0.7$). There was a consistency in the pattern of patient non-evaluability across investigators ($P=0.4$ in the Breslow-Day test for homogeneity of the odds ratios).

Of the 150 randomized patients, 105 (70%) were considered evaluable and were used in MITT analyses (53 on butenafine and 52 on vehicle). The two treatment groups were not significantly different ($P>0.3$) relative to age, sex, and race (Table 1). Baseline clinical characteristics (Total Signs/Symptoms Score for the target lesion and pathogens) were also balanced in the two treatment groups ($P=0.3$, Table 1).

	Butenafine HCl Cream 1% N = 53	Vehicle N = 52	P-value
Sex			
Male	40 (75%)	37 (71%)	0.6*
Female	13 (25%)	15 (29%)	
Median Age (years)	37	39	0.3†
Race			
Caucasian	20 (38%)	27 (52%)	0.3*
Black	12 (23%)	7 (13%)	
Other	21 (40%)	18 (35%)	
Baseline Median Sign/Symptom Score (Target Lesion)	8	8.5	0.3†
Pathogen			
<i>T. rubrum</i>	42 (79%)	46 (88%)	0.3§
<i>E. floccosum</i>	4 (8%)	1 (2%)	
<i>T. mentagrophytes</i>	7 (13%)	5 (10%)	

* P-value in the Chi-square test.

§ P-value in Fisher's exact test.

† P-value in the Wilcoxon rank-sum test.

Of the 105 evaluable patients in the MITT analysis, 27 (26%) were excluded from the Per Original Protocol analysis. None of the excluded patients could be classified as an 'early failure' (i.e. withdrew due to adverse event or lack of response to the study drug). Of the 27 excluded patients, 6 missed Week 8 visit and 21 patients had the Week 8 visit outside the plus or minus 3 day window. Of the 78 patients in the Per Original Protocol analyses, 41 (53%) were treated with butenafine and 37 (47%) were treated with vehicle.

Of the 105 evaluable patients in the MITT analysis, 10 (10%) were excluded from the Per Amended Protocol analysis. None of the excluded patients could be classified as an 'early failure' (i.e. withdrew due to adverse event or lack of response to the study drug). Of the 10 excluded patients, 6 missed Week 8 visit and for 4 patients the Week 8 visit was outside the amended window of minus 5 or plus 16 days. Consequently, Per Amended Protocol analyses included 95 patients

with 50 (53%) on butenafine and 45 (47%) on vehicle.

REVIEWER COMMENT: According to protocol, Global Response of the target lesion was defined as 'Cleared' if there was a 100% remission of clinical signs and symptoms as compared to baseline. Therefore, one would expect the patients with Global Response of "Cleared" to have Total Signs/Symptoms Score of 0. However, this reviewer found discrepancies in 8 patients. All 8 patients had Total Signs/Symptoms Score of 0 but Global Response of only 'Excellent' (80%-99% improvement of clinical signs and symptoms). Because of the discrepancies, the reviewer will use the endpoint Total Signs/Symptoms Score of 0 plus Mycological Cure as a supportive parameter.

EFFICACY

Since three investigators (Beutner, Shupack, and Weinstein) had fewer than 9 patients per treatment arm, they were combined together. The primary efficacy endpoint assessed at Week 8 was Overall Cure (Mycological Cure plus Investigator's Global Assessment of "Cleared"). Overall Cure rates in Study 001 in the three efficacy populations are shown in Table 2. As can be seen from Table 2, in the Per Original Protocol population, the Overall Cure rates were 22% in the butenafine-treated group and 11% in the vehicle-treated group ($P=0.14$). For comparison, in the applicant's Per Amended Protocol population, the Overall Cure rates were 22% in the butenafine group and 9% in the vehicle group ($P=0.056$). In the MITT analysis, the Overall Cure rates were 21% in the butenafine group and 8% in the vehicle group ($P=0.035$). The treatment by investigator interaction was not significant in all three analyses ($P>0.3$ in the Breslow-Day test for homogeneity of the odds ratios).

Population		Treatment		Total	P-value*
		Butenafine	Vehicle		
Per Original Protocol	Number Cured	9	4	13	0.14
	Number Treated	41	37	78	
	Percent Cured (%)	22%	11%		
Per Amended Protocol	Number Cured	11	4	15	0.056
	Number Treated	50	45	95	
	Percent Cured (%)	22%	9%		
MTT-LOCF	Number Cured	11	4	15	0.035
	Number Treated	53	52	105	
	Percent Cured (%)	21%	8%		

* Cochran-Mantel-Haenszel test, stratifying by investigator

As a supportive efficacy endpoint at Week 8, this reviewer considered Total Signs/Symptoms Score of 0 plus Mycological Cure. The cure rates for the supportive efficacy endpoint in Study 001 in the three efficacy populations are shown in Table 2a. As can be seen from Table 2a, in the Per Original Protocol population, the cure rates were 37% in the butenafine-treated group and 14% in the vehicle-treated group ($P=0.016$). For comparison, in the applicant's Per Amended Protocol population, the cure rates were 34% in the butenafine group and 11% in the vehicle group ($P=0.006$). In the MTT analysis, the cure rates were 32% in the butenafine group and 12% in the vehicle group ($P=0.009$). The treatment by investigator interaction was not significant in all three analyses ($P>0.5$ in the Breslow-Day test for homogeneity of the odds ratios).

Population		Treatment		Total	P-value*
		Butenafine	Vehicle		
Per Original Protocol	Number Cured	15	5	20	0.016
	Number Treated	41	37	78	
	Percent Cured (%)	37%	14%		
Per Amended Protocol	Number Cured	17	5	22	0.006
	Number Treated	50	45	95	
	Percent Cured (%)	34%	11%		
MTT-LOCF	Number Cured	17	6	23	0.009
	Number Treated	53	52	105	
	Percent Cured (%)	32%	12%		

* Cochran-Mantel-Haenszel test, stratifying by investigator

The secondary efficacy endpoint assessed at Week 8 was Additional Effective Treatment (Mycological Cure plus Total Signs and Symptoms Score of 0 or 1). The Additional Effective Treatment rates in Study 001 in the three efficacy populations are shown in Table 3. As can be seen from Table 3, in the Per Original Protocol population, the Additional Effective Treatment rates were 61% in the butenafine-treated group and 22% in the vehicle-treated group ($P < 0.001$). For comparison, in the applicant's Per Amended Protocol population, the Additional Effective Treatment rates were 56% in the butenafine group and 18% in the vehicle group ($P < 0.001$). In the MITT analysis, the Additional Effective Treatment rates were 55% in the butenafine group and 17% in the vehicle group ($P = 0.001$). The treatment by investigator interaction was not significant in all three analyses ($P > 0.4$ in the Breslow-Day test for homogeneity of the odds ratios).

Subgroup analyses were performed for the Additional Effective Treatment rates in the Per Amended Protocol population adjusting for gender, race and age group (below 45 years old, 45-65 years, and over 65 years old). Butenafine was significantly ($P < 0.001$) superior to vehicle when adjusting for gender, race or age

group. The superiority of butenafine was more apparent in males than in females, in Caucasians or Hispanics than in other groups and in patients younger than 45 years old.

Table 3. Additional Effective Treatment Rates at Week 8 in Three Efficacy Populations of Study 001

Population		Treatment		Total	P-value*
		Butenafine	Vehicle		
Per Original Protocol	Number Cured	25	8	33	<0.001
	Number Treated	41	37	78	
	Percent Cured (%)	61%	22%		
Per Amended Protocol	Number Cured	28	8	36	<0.001
	Number Treated	50	45	95	
	Percent Cured (%)	56%	18%		
MTT-LOCF	Number Cured	29	9	38	< 0.001
	Number Treated	53	52	105	
	Percent Cured (%)	55%	17%		

* Cochran-Mantel-Haenszel test, stratifying by investigator

SAFETY

In Study 001, of the 150 patients enrolled, 149 received at least one dose of study medication and thus were included in Safety population, with 76 (51%) receiving butenafine and 73 (49%) receiving vehicle. A total of 52 patients were exposed to butenafine for four weeks while 50 were exposed to vehicle for that period. A total of 48 (32%) patients were dropped from the study before the end of four weeks of treatment.

The number of adverse events possibly, probably or definitely drug-related was very low during the eight weeks of the study. No patient in the butenafine group withdrew from the study due to treatment-related reasons. The number of patients and occurrence rates for most common adverse events are presented in Table 4.

Table 4. Frequencies and Occurrence Rates of Most Common Adverse Events in Study 001, by Treatment Group				
Body System	Treatment Group		Total N = 149	P-value*
	Butenafine N = 76	Vehicle N = 73		
Body/General	7 (9%)	6 (8%)	13 (9%)	1.0
Body/Head	2 (3%)	5 (7%)	7 (5%)	0.3
Skin	4 (5%)	1 (1%)	5 (3%)	0.4
Respiratory	1 (1%)	1 (1%)	2 (1%)	1.0
Metabolic&Nutritional	1 (1%)	1 (1%)	2 (1%)	1.0

* P-value in Fisher's exact test.

As can be seen in Table 4, the butenafine group was comparable to the vehicle group in the occurrence rates of adverse events

REVIEWER CONCLUSIONS: *In the Per Original Protocol population of Study 001, butenafine was not statistically superior to vehicle in the Overall Cure rate ($P=0.14$). However, butenafine was statistically superior to vehicle in the analysis of the supportive efficacy endpoint (Total Signs/Symptoms Score of 0 plus Mycological Cure) with $P=0.016$ and in the analysis of the secondary efficacy endpoint Additional Effective Treatment ($P<0.001$).*

In the applicant's Per Amended Protocol population, the difference between butenafine and vehicle in the Overall Cure rate was very close to being statistically significant ($P=0.056$). The difference between butenafine and vehicle in the analysis of supportive efficacy endpoint (Total Signs/Symptoms Score of 0 plus Mycological Cure) was statistically significant with $P=0.006$. In the analysis of Additional Effective Treatment rate, the difference between butenafine and vehicle was statistically significant with $P<0.001$. Subgroup analyses adjusting for gender, race, or age group supported the results of the efficacy analyses.

Butenafine was comparable to vehicle in occurrence rates of adverse events ($P>0.3$). No patient in the butenafine group withdrew from the study due to treatment-related reasons.

A. Study 002

PATIENTS CHARACTERISTICS

One hundred nineteen (119) patients were enrolled by four investigators and randomized to treatment (60 to butenafine and 59 to vehicle). All 119 patients received study medication and were included in the safety analyses. Two patients had delayed positive cultures. One of them completed 4 weeks of treatment and the other was terminated three weeks into study. According to protocol, both patients with delayed positive cultures were considered evaluable.

Of the 119 enrolled patients, 39 (33%) were ruled non-evaluable. Of the 39 non-evaluable patients, 20 (51%) were on butenafine with 19 being ruled non-evaluable due to negative baseline culture, and one due to ineligible baseline medication. Nineteen (49%) non-evaluable patients were on vehicle. Of the 19 non-evaluable vehicle patients, 17 were ruled non-evaluable due to negative baseline culture, one due to abnormal baseline laboratory results and one patient was lost to follow-up at baseline. The CMH test stratifying by investigator showed that there was no significant treatment difference in the proportions of patients ruled non-evaluable ($P=0.8$). There was a consistency in the pattern of patient non-evaluability across investigators ($P=0.5$ in the Breslow-Day test for homogeneity of the odds ratios).

Of the 119 randomized patients, 80 (67%) were considered evaluable and were used in MITT analyses (40 on butenafine and 40 on vehicle). The two treatment groups were not significantly different ($P>0.1$) in age, sex, and race (Table 5). Baseline clinical characteristics (Total Signs/Symptoms Score for the target lesion and pathogens) were also balanced in the two treatment groups ($P>0.2$, Table 5).

Table 5. Patient Demographic and Clinical Characteristics, MITT Population in Study 002			
	Butenafine HCl Cream 1% N = 40	Vehicle N = 40	P-value
Sex			
Male	26 (65%)	30 (75%)	0.3*
Female	14 (35%)	10 (25%)	
Median Age (years)	34	39	0.1†
Race			
Caucasian	21 (53%)	29 (73%)	0.2*
Black	7 (17%)	3 (7%)	
Other	12 (30%)	8 (20%)	
Baseline Median Sign/Symptom Score (Target Lesion)	11	12	0.4†
Pathogen			
<i>T. rubrum</i>	38 (95%)	35 (88%)	0.2§
<i>E. floccosum</i>	1 (2%)	0 (0%)	
<i>T. mentagrophytes</i>	1 (2%)	3 (8%)	
Other	0 (0%)	2 (5%)	

* P-value in the Chi-square test.

§ P-value in Fisher's exact test.

† P-value in the Wilcoxon rank-sum test.

Of the 80 patients included in the MITT analysis, 17(21%) were excluded from the Per Original Protocol analysis. None of the excluded patients could be classified as an 'early failure' (i.e. withdrew due to adverse event or lack of response to the study drug). Of the 17 excluded patients, for 2 patients Week 8 visit occurred at Week 6, three patients were lost to follow-up and 12 patients had Week 8 visit outside the plus or minus 3 days window. Of the 63 patients in the Per Original Protocol analyses, 32 were treated with butenafine and 31 were treated with vehicle.

Of the 80 evaluable patients in the MITT analysis, 6 (8%) were excluded from the Per Amended Protocol analysis. None of the excluded patients could be classified as an 'early failure' (i.e. withdrew due to adverse event or lack of response to the study drug). Of the 6 excluded patients, for 2 patients Week 8 visit occurred at

Week 6, three patients were lost to follow-up and one patients had Week 8 visit outside the amended window of minus 5 or plus 16 days. Consequently, the Per Amended Protocol population included 74 patients (38 on butenafine and 36 on vehicle).

REVIEWER COMMENT: According to protocol, Global Response of the target lesion was defined as 'Cleared' if there was a 100% remission of clinical signs and symptoms as compared to baseline. Therefore, one would expect the patients with Global Response of "Cleared" to have Total Signs/ Symptoms Score of 0. However, this reviewer found discrepancies in 6 patients. One of the six patients had Total Signs/Symptoms Score of 1 (scaling = 1) but Global Response of 'Cleared'. The other 5 patients had Total Signs/Symptoms Score of 0, but in 3 of them Global Response was 'Excellent' and in two of them Global response was only 'Good' (50%-79% improvement of clinical signs and symptoms). Because of the discrepancies, this reviewer will use the endpoint Total Signs/ Symptoms Score of 0 plus Mycological Cure as a supportive parameter.

EFFICACY

The primary efficacy endpoint assessed at Week 8 was Overall Cure (Mycological Cure and Investigator Global Assessment of "Cleared"). Overall Cure rates are shown in Table 6. As can be seen from Table 6, in the Per Original Protocol population, the Overall Cure rates were 28% in the butenafine-treated group and 6% in the vehicle-treated group ($P=0.02$). For comparison, in the applicant's Per Amended Protocol population, the Overall Cure rates were 24% in the butenafine group and 6% in the vehicle group ($P=0.018$). In the MITT analysis, the Overall Cure rates were 23% in the butenafine group and 5% in the vehicle group ($P=0.012$). The treatment by investigator interaction was not significant in all three analyses ($P>0.4$ in the Breslow-Day test for homogeneity of the odds ratios).

Population		Treatment		Total	P-value *
		Butenafine	Vehicle		
Per Original Protocol	Number Cured	9	2	11	0.02
	Number Treated	32	31	63	
	Percent Cured (%)	28%	6%		
Per Amended Protocol	Number Cured	9	2	11	0.018
	Number Treated	38	36	74	
	Percent Cured (%)	24%	6%		
MITT-LOCF	Number Cured	9	2	11	0.012
	Number Treated	40	40	80	
	Percent Cured (%)	23%	5%		

* Cochran-Mantel-Haenszel test, stratifying by investigator

Subgroup analyses were performed for the Overall Cure rates in the Per Amended Protocol population adjusting for gender, race and age group (below 45 years, 45-65, and over 65 years old). Butenafine was significantly ($P < 0.04$) superior to vehicle when adjusting for gender or race. The superiority of butenafine was more apparent in males than in females, in Caucasians than in other groups and in patients younger than 45 years old.

As a supportive efficacy endpoint at Week 8 this reviewer considered Total Signs/Symptoms Score of 0 plus Mycological Cure. The cure rates for the supportive efficacy endpoint in Study 002 in the three efficacy populations are shown in Table 6a. As can be seen from Table 6a, in the Per Original Protocol population, the cure rates were 31% in the butenafine-treated group and 13% in the vehicle-treated group ($P = 0.066$). For comparison, in the applicant's Per Amended Protocol population, the cure rates were 29% in the butenafine group and 11% in the vehicle group ($P = 0.035$). In the MITT analysis, the cure rates were 28% in the butenafine group and 10% in the vehicle group ($P = 0.021$). The treatment by investigator interaction was not significant in all three analyses ($P > 0.5$ in the Breslow-Day test for homogeneity of the odds ratios).

Table 6a. Cure Rates at Week 8 for the Supportive Efficacy Endpoint (Total Signs/Symptoms Score of 0 plus Mycological Cure) in Three Efficacy Populations, Study 002					
Population		Treatment		Total	P-value *
		Butenafine	Vehicle		
Per Original Protocol	Number Cured	10	4	14	0.066
	Number Treated	32	31	63	
	Percent Cured (%)	31%	13%		
Per Amended Protocol	Number Cured	11	4	15	0.035
	Number Treated	38	36	74	
	Percent Cured (%)	29%	11%		
MTT-LOCF	Number Cured	11	4	15	0.021
	Number Treated	40	40	80	
	Percent Cured (%)	28%	10%		

* Cochran-Mantel-Haenszel test, stratifying by investigator

The secondary efficacy endpoint assessed at Week 8 was Additional Effective Treatment (Mycological Cure plus Total Signs and Symptoms Score of 0 or 1). The Additional Effective Treatment rates in Study 002 in the three efficacy populations are shown in Table 7. As can be seen from Table 7, in the Per Original Protocol population, the Additional Effective Treatment rates were 59% in the butenafine-treated group and 23% in the vehicle-treated group ($P=0.001$). For comparison, in the applicant's Per Amended Protocol population, the Additional Effective Treatment rates were 63% in the butenafine group and 22% in the vehicle group ($P<0.001$). In the MITT analysis, the Additional Effective Treatment rates were 63% in the butenafine group and 20% in the vehicle group ($P<0.001$). The treatment by investigator interaction was not significant ($P>0.7$) for the Per Original and Per Amended Protocol populations in the Breslow-Day test for homogeneity of the odds ratios. For the MITT population, the treatment by investigator interaction was significant ($P=0.07$ in the Breslow-Day Test). This interaction was quantitative: for different investigators, the difference between treatment groups was of different magnitude but in the same direction.

Subgroup analyses were performed for the Additional Effective Treatment rates in

the Per Amended Protocol population adjusting for gender, race and age group (below 45 years, 45-65, and over 65 years old). Butenafine was significantly ($P=0.001$) superior to vehicle when adjusting for gender, race or age group. The superiority of butenafine was more apparent in males than in females, in Hispanics and Caucasians than in other groups, and in patients between 45 and 65 years old.

Table 7. Additional Effective Treatment Rates at Week 8 in Three Efficacy Populations in Study 001					
Population		Treatment		Total	P-value*
		Butenafine	Vehicle		
Per Original Protocol	Number Cured	19	7	26	0.001
	Number Treated	32	31	63	
	Percent Cured (%)	59%	23%		
Per Amended Protocol	Number Cured	24	8	32	<0.001
	Number Treated	38	36	74	
	Percent Cured (%)	63%	22%		
MTT-LOCF	Number Cured	25	8	33	<0.001
	Number Treated	40	40	80	
	Percent Cured (%)	63%	20%		

* Cochran-Mantel-Haenszel test, stratifying by investigator

SAFETY

All 119 patients enrolled in Study 002 received at least one dose of study medication and thus were included in Safety population, with 60 (50%) receiving butenafine and 59 (50%) receiving vehicle. A total of 40 patients were exposed to butenafine for four weeks while 36 were exposed to vehicle for that period. A total of 43 (36%) patients were dropped from the study before the end of four weeks of treatment.

The number of adverse events possibly, probably or definitely drug-related was very low during the eight weeks of the study. No patient in the butenafine group withdrew from the study due to treatment-related reasons. The occurrence rates

for most common adverse events and the corresponding numbers of patients are resented in Table 8.

Body System	Treatment Group		Total N = 119	F-value*
	Butenafine N = 60	Vehicle N = 59		
Body/General	4 (7%)	7 (12%)	11 (9%)	0.4
Body/Head	0 (0%)	2 (3%)	2 (2%)	0.2
Skin	1 (2%)	4 (7%)	5 (4%)	0.2
Metabolic&Nutritional	3 (5%)	2 (3%)	5 (4%)	1:0

* P-value in Fisher's exact test.

As can be seen in Table 8, the butenafine group was comparable to the vehicle group in the occurrence rates of adverse events.

REVIEWER CONCLUSIONS: *In the Per Original Protocol population of Study 002, butenafine was statistically superior to vehicle both in the Overall Cure rate (P=0.02) and in the Additional Effective Treatment rate (P=0.001).*

In the applicant's Per Amended Protocol population, butenafine was statistically superior to vehicle both in the Overall Cure rate (P=0.018) and in the Additional Effective Treatment rate (P<0.001). Subgroup analyses adjusting for gender, race, or age group supported the results of the efficacy analyses.

Butenafine was comparable to vehicle in occurrence rates of adverse events (P>0.2). No patient in the butenafine group withdrew from the study due to treatment-related reasons.

C. Integrated Safety Analysis of Studies 001 and 002

Combined data from 268 patients in Studies 001 and 002 were used to compare butenafine and vehicle with respect to occurrence rates of most common adverse events (Table 9).

Body System	Treatment Group		Total N = 268	P-value*
	Butenafine N = 136	Vehicle N = 132		
Body/General	11 (8%)	13 (10%)	24 (9%)	0.6
Body/Head	2 (1%)	7 (5%)	9 (3%)	0.08
Skin	5 (4%)	5 (4%)	10 (4%)	1.0
Metabolic&Nutritional	4 (3%)	3 (2%)	7 (3%)	0.7

*P-value in the Chi-square test.

As can be seen from Table 9, integrated analysis of adverse events in Studies 001 and 002 showed that the butenafine group was comparable to the vehicle group in the occurrence rates of adverse events.

IV. SUMMARY AND CONCLUSIONS (Which may be conveyed to the Sponsor)

Based on the analyses of the Per Original Protocol population of Study 001, butenafine was not statistically superior to vehicle in the Overall Cure rate ($P=0.14$). However, butenafine was statistically superior to vehicle in the analysis of the supportive efficacy endpoint (Total Signs/Symptoms Score of 0 plus Mycological Cure) with $P=0.016$ and in the analysis of the secondary efficacy endpoint Additional Effective Treatment with $P<0.001$. In the analysis of the MITT population of Study 001, butenafine was statistically superior to vehicle in Overall Cure ($P=0.035$), in Additional Effective Treatment ($P<0.001$) and with respect to the Total Signs/Symptoms Score plus Mycological Cure ($P=0.009$).

Based on the analyses of the Per Original Protocol population of Study 002, butenafine was statistically superior to vehicle both in the Overall Cure rate ($P=0.02$) and in the Additional Effective Treatment rate ($P=0.001$). MITT analyses and subgroup analyses adjusting for gender, race, or age group supported the efficacy of butenafine.

Butenafine was comparable to vehicle in occurrence rates of adverse events ($P>0.08$). No patient treated with butenafine withdrew from the studies due to treatment-related reasons.

Thus, the analyses of the primary efficacy endpoint Overall Cure in the Per Original

Protocol population demonstrated statistical superiority of butenafine to its vehicle only in Study 002 ($P < 0.02$). In the Per Original Protocol population of Study 001, butenafine was not statistically superior ($P = 0.14$) to its vehicle in Overall Cure. However, in the Per Original Protocol population of Study 001, butenafine was statistically superior to its vehicle with respect to the supportive efficacy parameter Total Signs/Symptoms Score of 0 plus Mycological Cure ($P = 0.016$) and with respect to the secondary efficacy endpoint Additional Effective Treatment ($P < 0.001$). MITT analyses and subgroup analyses adjusting for gender, race, or age group supported the efficacy of butenafine. Both Studies 001 and 002 supported the applicant's claim that butenafine had a tolerable safety profile.

This is a matter for the clinical judgement of the reviewing medical division to decide whether these results demonstrated therapeutical superiority of butenafine to its vehicle.

Valeria Freidlin 11.24.95

Valeria Freidlin, Ph.D.
Mathematical Statistician, Biometrics IV

Rajagopalan Srinivasan 11/24/95

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Archival NDA 20-524
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HFD-725/Dr. Freidlin

HFD-701/Dr. Anello

HFD-344/Dr. Pierce

This review contains 21 pages including 11 tables.

WordPerfect 6.1/NDA20524.wpd/11-24-95

STATISTICAL REVIEW AND EVALUATION

JAN 6 1996

ADDENDUM

NDA#/Drug class: 20-524/1S

Applicant: Panederm Inc.

Name of Drug: Butenafine HCl cream 1%

Documents Reviewed: Volumes 1.1, 1.24-1.27, dated April 4, 1995, and data on disks provided by the sponsor

Type of Report: Statistical

Indication: Topical treatment of interdigital tinea pedis (athlete's foot) due to Epidermophyton floccosum, Trichophyton mentagrophytes or Trichophyton rubrum

Medical Officer: Nancy Slifman, M.D., HFD-540

The reviewing medical officer (RMO) differed from the sponsor in determining evaluability of patients and in assessing bacteriological outcomes. The RMO found that patient [REDACTED] (vehicle) in Study 002 had a positive culture for 'yeast' at baseline. No cultures at any time during the study were positive for dermatophytes. The medical reviewer believes that this patient does not meet the inclusion criteria to support the labeling indication (i.e., treatment of interdigital tinea pedis due to E. Floccosum, T. mentagrophytes, or T. rubrum) and should be excluded from the efficacy analyses submitted by the sponsor. Consequently, in this addendum, the efficacy will be re-analyzed excluding patient [REDACTED].

In addition, the reviewing medical officer noted that patient [REDACTED] (vehicle) in Study 002 had a positive culture only for S. hyalinum at baseline and a positive culture for T. rubrum only at week 4. The RMO believes that as a 'worst case' scenario, patient [REDACTED] also should be excluded from the efficacy analyses because of lack of dermatophyte at baseline (although the patient was positive for T. rubrum at week 4). Consequently, in this addendum, the efficacy will also be re-analyzed excluding both patients

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Tables 1 and 1A show the primary efficacy parameter Overall Cure (Negative Mycology + Investigator's Global of 'Cleared') at week 8 in Study 002 excluding patient alone and both patients respectively.

Table 1. Overall Cure (Negative Mycology + Investigator's Global of 'Cleared') at Week 8; Exclusion of Patient

	MITT	Sponsor's per protocol	Original per protocol
Butenafine	9/40 (23%)	9/38 (24%)	9/32 (28%)
Vehicle	2/39 (5.1%)	2/35 (5.7%)	2/30 (6.7%)
P-value*	0.014	0.022	0.029

* Cochran-Mantel-Haenszel test stratifying by investigator.

Reviewer's Comment: These results indicate that with exclusion of patient there was a statistically significant difference ($P < 0.029$) between the butenafine and vehicle treatment groups at week 8 (end of study) in all 3 statistical populations.

Table 1A. Overall Cure (Negative Mycology + Investigator's Global of 'Cleared') at Week 8; Exclusion of Both Patients

	MITT	Sponsor's per protocol	Original per protocol
Butenafine	9/40 (23%)	9/38 (24%)	9/32 (28%)
Vehicle	2/38 (5.3%)	2/34 (5.9%)	2/29 (6.9%)
P-value*	0.014	0.022	0.029

* Cochran-Mantel-Haenszel test stratifying by investigator.

Reviewer's Comment: These results indicate that with exclusion of both patients there was a statistically significant difference ($P < 0.029$) between the butenafine and vehicle treatment groups at week 8 (end of study) in all 3 statistical populations.

Tables 2 and 2A show the cure rates for the Supportive Efficacy Endpoint (Negative Mycology + Total Signs/Symptoms Score of 0 in target lesion) at week 8

in Study 002 excluding patient alone and both patients respectively.

Table 2. Negative Mycology + Total Signs/Symptoms Score of 0 (target lesion) at Week 8; Exclusion of Patient

	MITT	Sponsor's per protocol	Original per protocol
Butenafine	11/40 (28%)	11/38 (29%)	10/32 (31%)
Vehicle	4/39 (10%)	4/35 (11%)	4/30 (13%)
P-value*	0.025	0.043	0.081

* Cochran-Mantel-Haenszel test stratifying by investigator.

Reviewer's Comment: These results indicate that with exclusion of patient there was a statistically significant ($P < 0.043$) difference between the butenafine and vehicle treatment groups at week 8 (end of study) only in MITT and sponsor's per protocol populations. The difference between treatment groups was not significant in the per original protocol population ($P = 0.081$).

Table 2A. Negative Mycology + Total Signs/Symptoms Score of 0 (target lesion) at Week 8; Exclusion of Both Patients

	MITT	Sponsor's per protocol	Original per protocol
Butenafine	11/40 (28%)	11/38 (29%)	10/32 (31%)
Vehicle	4/38 (11%)	4/34 (12%)	4/29 (14%)
P-value*	0.026	0.044	0.081

* Cochran-Mantel-Haenszel test stratifying by investigator.

Reviewer's Comment: These results indicate that with exclusion of both patients there was a statistically significant ($P < 0.044$) difference between the butenafine and vehicle treatment groups at week 8 (end of study) only in MITT and sponsor's per protocol populations. The difference between the two treatment groups was not significant in the per original protocol population ($P = 0.081$).

Tables 3 and 3A show the cure rates for Additional Effective Treatment (Negative Mycology + Total Signs/Symptoms Score of 0 or 1 in target lesion) at week 8 in Study 002 excluding patient alone and both patients respectively.

Table 3. Additional Effective Treatment (Negative Mycology + Total Signs/Symptoms Score of 0 or 1) at Week 8; Exclusion of Patient

	MITT	Sponsor's per protocol	Original per protocol
Butenafine	23/40 (58%)	22/38 (58%)	18/32 (56%)
Vehicle	8/39 (21%)	8/35 (23%)	7/30 (23%)
P-value*	<0.001	0.001	0.002

* Cochran-Mantel-Haenszel test stratifying by investigator.

Reviewer's Comment: These results indicate that with exclusion of patient there was a statistically significant ($P < 0.002$) difference between the butenafine and vehicle treatment groups at week 8 (end of study) was statistically significant in all three populations.

Table 3A. Additional Effective Treatment (Negative Mycology + Total Signs/Symptoms Score of 0 or 1) at Week 8; Exclusion of Both Patients

	MITT	Sponsor's per protocol	Original per protocol
Butenafine	23/40 (58%)	22/38 (58%)	18/32 (56%)
Vehicle	8/38 (21%)	8/34 (24%)	7/29 (24%)
P-value*	<0.001	0.001	0.002

* Cochran-Mantel-Haenszel test stratifying by investigator.

Reviewer's Comment: These results indicate that with exclusion of both patients there was a statistically significant difference ($P < 0.002$) between the butenafine and vehicle treatment groups at week 8 (end of study) in all three populations.

REVIEWER'S CONCLUSIONS REGARDING EFFICACY DATA

The results of the efficacy analyses of Study 002 excluding patient _____ alone are similar to those excluding both patients _____ or including these two patients. Butenafine was statistically superior ($P < 0.029$) to its vehicle with respect to the primary efficacy parameter Overall Cure (Negative Mycology plus Investigator's Global Assessment of 'Cleared') in all three populations (MITT, sponsor's per protocol, and original per protocol). Butenafine was also statistically superior ($P < 0.002$) to its vehicle in all three populations with respect to the secondary efficacy parameter Additional Effective Treatment (Negative Mycology plus Total Signs/Symptoms Score of 0 or 1 in target lesion). This reviewer also considered Supportive Efficacy Endpoint: Negative Mycology plus Total Signs/Symptoms Score of 0 in target lesion. Relative to the Supportive Efficacy Endpoint, butenafine was statistically superior ($P < 0.044$) to its vehicle only in MITT and sponsor's per protocol populations. In the original per protocol population, the difference between butenafine and its vehicle was not significant both including patients _____ or excluding them. This may be explained by the fact that patient _____ (butenafine) had Investigator's Global Assessment of 'Cleared' but Total Signs/Symptoms Score of 1 (because Scaling of target lesion = 1). This discrepancy resulted in a lower success rate for the Supportive Efficacy Endpoint (Negative Mycology plus Total Signs/Symptoms Score of 0) compared to Overall Cure.

Thus the analysis of the primary efficacy parameter Overall Cure in the per original protocol population of Study 002 excluding patient _____ alone or both patients _____ demonstrated statistical superiority of butenafine to its vehicle ($P < 0.029$). The results for the MITT and sponsor's per protocol populations supported this conclusion.

Valeria Freidlin 01.16.96

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Mathematical Statistician, Biometrics IV

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Archival NDA 20-524

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- HFD-540/Dr. Wilkin
- HFD-540/Dr. Chambers
- HFD-540/Dr. Slifman
- HFD-725/Dr. Harkins
- HFD-725/Dr. Srinivasan
- HFD-725/Dr. Freidlin
- HFD-701/Dr. Anello
- HFD-344/Dr. Pierce

This addendum contains 6 pages including 6 tables.
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(ADDENDUM #2)

NDA#/Drug class: 20-524/1S

Applicant: Penederm Inc.

Name of Drug: Butenafine HCl cream 1%

Documents Reviewed: Volumes 1.1, 1.24-1.27, dated April 4, 1995, and data on disks provided by the sponsor

Type of Report: Statistical/Clinical

Indication: Topical treatment of interdigital tinea pedis (athlete's foot) due to Epidermophyton floccosum, Trichophyton mentagrophytes or Trichophyton rubrum

Medical Officer: Nancy Slifman, M.D., HFD-540

I. Introduction

The reviewing medical officer (RMO) decided that the label for butenafine should include a table presenting cure rates for important efficacy parameters using combined data from the two pivotal studies in this application. Therefore, the percent of patients cured in Studies 001 and 002 combined and the corresponding P-values will be shown for the following efficacy parameters:

- Mycological Cure (negative KOH and negative culture)
- Effective Treatment (Mycological Cure and a Physician Global Assessment of 'Cleared' or 'Excellent')
- Overall Cure (Mycological Cure and a Physician Global Assessment of 'Excellent').

The reviewing medical officer (RMO) also differed from the sponsor in determining evaluability of patients and in assessing bacteriological outcomes. The RMO found that patient (vehicle) in Study 002 had a positive culture for 'yeast' at baseline. No cultures at any time during the study were positive for dermatophytes. The medical reviewer believes that this patient does not meet the inclusion criteria to support the labeling indication (i.e., treatment of interdigital tinea pedis due to E. Floccosum, T. mentagrophytes, or T. rubrum) and should be excluded from the efficacy analyses submitted by the sponsor.

In addition, the reviewing medical officer noted that patient (vehicle) in Study 002 had a positive culture only for *S. hyalinum* at baseline and a positive culture for *T. rubrum* only at week 4. The RMO believes that as a 'worst case' scenario, patient also should be excluded from the efficacy analyses because of lack of dermatophyte at baseline (although the patient was positive for *T. rubrum* at week 4). Consequently, in this addendum, the cure rates will be calculated excluding both patients

Three patient populations are considered for statistical analyses:

- Per Original Protocol population of all eligible patients who did not violate the protocol, completed four weeks of assigned treatment and attended the Week 8 visit within a window of plus or minus 3 days of a four week period from the date of last study medication use.

- Sponsor's Per Protocol population of all eligible patients who did not violate the protocol, completed four weeks of assigned treatment and attended the Week 8 visit within an amended window of minus 5 or plus 16 days of a four week period from the date of last study medication use. The definition of the Sponsor's Per Protocol population used an amended protocol.

- Modified Intent to Treat (MITT) population of all eligible patients who used at least one dose of the assigned treatment and had minimal efficacy data (at least one post-baseline visit and had no noteworthy protocol violations). To be included in the Week 1, Week 2, and Week 4 visits, the visit was required to occur within plus or minus 3 days of the scheduled date. To be included in the Week 8 visit, the visit was required to be within a range of minus 5 to plus 16 days of a four week period from the date of last study medication use. If a visit was missed or out of range, the last available information was carried forward.

II. Results

Table 1 shows the cure rates for Mycological Cure (negative KOH and negative culture), Effective Treatment (negative Mycology and Investigator's Global of 'Cleared' or 'Excellent'), and Overall Cure (Negative Mycology + Investigator's Global of 'Cleared') at week 8 in the Per Original Protocol population of the combined data of Studies 001 and 002 excluding patients

Table 1. Mycological Cure, Effective Treatment, and Overall Cure at week 8 for the combined data of Studies 001 and 002 excluding patients

(Per Original Protocol Population)

Patient Outcome Category	Treatment Group		P-value*
	Butenafine	Vehicle	
Mycological Cure	90% (66/73)	38% (25/66)	<0.001
Effective Treatment	74% (54/73)	26% (17/66)	<0.001
Overall Cure	25% (18/73)	9% (6/66)	0.01

* Cochran-Mantel-Haenszel test stratifying by investigator.

Table 2 shows the cure rates for Mycological Cure (negative KOH and negative culture), Effective Treatment (negative Mycology and Investigator's Global of 'Cleared' or 'Excellent'), and Overall Cure (Negative Mycology + Investigator's Global of 'Cleared') at week 8 in the Sponsor's Per Protocol population of the combined data of Studies 001 and 002 excluding patients

Table 2. Mycological Cure, Effective Treatment, and Overall Cure at week 8 for the combined data of Studies 001 and 002 excluding patients

(Sponsor's Per Protocol Population)

Patient Outcome Category	Treatment Group		P-value*
	Butenafine	Vehicle	
Mycological Cure	85% (75/88)	38% (30/79)	<0.001
Effective Treatment	69% (61/88)	25% (20/79)	<0.001
Overall Cure	23% (20/88)	8% (6/79)	0.003

* Cochran-Mantel-Haenszel test stratifying by investigator.

Table 3 shows the cure rates for Mycological Cure (negative KOH and negative culture), Effective Treatment (negative Mycology and Investigator's Global of 'Cleared' or 'Excellent'), and Overall Cure (Negative Mycology + Investigator's Global of 'Cleared') at week 8 in the MITT population of the combined data of Studies 001 and 002 excluding patients

Table 3. Mycological Cure, Effective Treatment, and Overall Cure at week 8 for the combined data of Studies 001 and 002 excluding patients

(MITT population)

Patient Outcome Category	Treatment Group		P-value*
	Butenafine	Vehicle	
Mycological Cure	85% (79/93)	36% (32/90)	<0.001
Effective Treatment	69% (64/93)	23% (21/90)	<0.001
Overall Cure	22% (20/93)	7% (6/90)	0.001

* Cochran-Mantel-Haenszel test stratifying by investigator.

III. SUMMARY AND CONCLUSION

Efficacy results using combined data from Studies 001 and 002 will be presented in the label. One of the three efficacy populations (MITT, Sponsor's Per Protocol, or Per Original Protocol) can be used.

The results for the primary efficacy parameter Overall Cure in the MITT population of the combined data of Studies 001 and 002 are highly significant (P=0.001) due to the increased sample size in the combined data. Presenting these results in the label can be misleading. P-value of 0.001 for the Overall Cure rate can create an impression that butenafine is a very potent treatment which was not the case when analyzing Studies 001 and 002 separately (P-values of 0.035 and 0.012, respectively).

The same is true for the Overall Cure rate in the Sponsor's Per Protocol population of the combined data of Studies 001 and 002 (P=0.003 in the combined data but

P-values of 0.056 and 0.018 in the separate analyses of Studies 001 and 002, respectively).

In the Per Original Protocol population of the combined data of Studies 001 and 002, the P-value for Overall Cure is: $P=0.01$ (in the separate analyses of Overall Cure in the Per Original Protocol populations of Studies 001 and 002, the P-values are 0.14 and 0.02, respectively).

Therefore, it is this reviewer's opinion that the P-values should not be shown in the label. Only success rates in any of the three efficacy populations should be presented in the label (see Tables 1, 2, and 3 on pages 3 and 4). For further details, see Statistical Review and Evaluation (NDA 20-524, November 24, 1995) and Addendum #1 (January 16, 1996).

Valeria Freidlin 02.20.96

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Archival, NDA 20-524 (Addendum #2)

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HFD-725/Dr. Freidlin

HFD-701/Dr. Anello

HFD-344/Dr. Pierce

This addendum contains 6 pages including 3 tables.

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STATISTICAL REVIEW AND EVALUATION.

NDA#/Drug class: 20-524/1S

AUG 7 1996

Applicant: Penederm Inc.

Name of Drug: Butenafine HCl cream 1%

Documents Reviewed: Volumes 1.1, 1.24-1.27, dated April 4, 1995, and data on disks provided by the sponsor

Type of Report: Statistical.

Indication: Topical treatment of interdigital tinea pedis (athlete's foot) due to Epidermophyton floccosum, Trichophyton mentagrophytes or Trichophyton rubrum

Medical Officer: Nancy Slifman, M.D., HFD-540

In reference to NDA 20-524, there are no statistical issues to be resolved. My original recommendations (see Statistical Review and Evaluation dated November 24, 1995, Addendum #1 dated January 18, 1996, and Addendum #2 dated February 20, 1996) did not change.

Valeria Freidlin 08 07 96

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[Signature] 08/07/96.

Concur: Rajagopalan Srinivasan, Ph.D.
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HFD-725/Dr. Freidlin

HFD-344/Dr. Pierce

Chron.

This review contains 2 pages.

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Micro

**Consultative Review for HFD-540
Division of Topical Drug Products
Division of Anti-Infective Drug Products (HFD-520)
Microbiological Clinical Review**

Requestor: Steven Turtill, CSO HFD-540

Date of Request: May 19, 1995

Reason for Request: Microbiological Review of antifungal activity

NDA #: 20-524 **MICRO REVIEW #:** 1 **REVIEW DATE:** 31-JUL-95

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL NDA	04-APR-95	06-APR-95	26-MAY-95

NAME & ADDRESS OF APPLICANT: FENEDERM INCORPORATED
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DRUG PRODUCT NAME

<u>Proprietary:</u>	None
<u>Nonproprietary/USAN:</u>	Butenafine Hydrochloride Cream
<u>Code Names/#'s:</u>	KP-363
<u>Chemical Type/</u>	Allylamine antifungal
<u>Therapeutic Class:</u>	1S

ANDA Suitability Petition/DESI/Patent Status:
Not Applicable

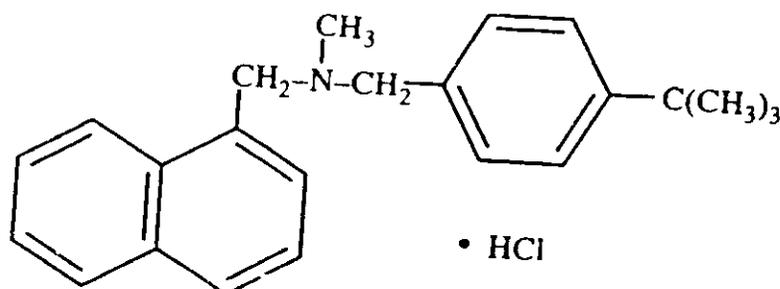
PHARMACOLOGICAL CATEGORY/INDICATION:
Interdigital Tinea pedis

DOSAGE FORM: Cream
STRENGTHS: 1%
ROUTE OF ADMINISTRATION: Topical
DISPENSED: Rx OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOL. WT:**

Chemical Name: N-4-tert-Butylbenzyl-N-methyl-1 naphthalenemethylamine
Hydrochloride

Structural Formula:



$C_{23}H_{27}N \cdot HCl$
M.W. = 353.93

SUPPORTING DOCUMENTS:

DMF
DMF
DMF

DMF
IND

RELATED DOCUMENTS (if applicable): NONE

CONSULTS: HFD-540 consulted the microbiological review of this application to two separate Divisions.

REMARKS/COMMENTS: This microbiological review is concerned with only the clinical aspects of this applications [mechanism of action, *in-vitro* activity, *in-vivo* animal models]. The microbiological aspects of the manufacturing controls for this product are review by a different consulting Division.

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CONCLUSION & RECOMMENDATIONS:

The application is APPROVABLE from the clinical microbiological viewpoint under section 505 of the Act. The sponsor should be notified to revise the MICROBIOLOGY subsection of the package insert as indicated on pages 66-67 of this review.

Microbiological Review

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INTRODUCTION

This NDA is for a product which includes an active ingredient not previously approved by FDA for drug use. The ingredient is butenafine, which belongs to a class of antifungal compounds known as benzylamines. These compounds are chemically related to the allylamines. The drug substance is manufactured by _____ Most of the studies included in this NDA are _____ final reports that have not yet been published. Most drugs currently used against dermatophytes belong to one of five chemical groups: the imidazoles (clotrimazole, miconazole, ketoconazole, and econazole), thiocarbamates (tolnaftate and tolciclate), polyenes (nystatin and amphotericin B), griseofulvin, and the allylamines (naftifine, terbinafine, and butenafine).

PRECLINICAL EFFICACY (*IN VITRO*)

MECHANISM OF ACTION

Morita and Nozawa (1) presented the ergosterol biosynthetic pathway in pathogenic fungi. The typical pathway starts with squalene → 2,3-oxidosqualene → lanosterol → 4,14-Dimethylzymosterol → zymosterol → ergosterol. In some fungi such as *Trichophyton mentagrophytes* lanosterol can be converted to 24-methylene-dihydrolanosterol and then ergosterol.

Two studies included in the NDA (E-10 and E-11), used the yeast phase of the dimorphic fungus, *Sporothrix schenckii*, to study the mechanism of action of butenafine. In these two studies *Sporothrix schenckii* TIMM 0960, which is easily transformable to yeast-phase cells and is highly susceptible to butenafine was used. Cells were subcultured on Sabouraud's dextrose agar and mycelial-form fungi were collected and inoculated into brain-heart infusion broth containing 0.5% yeast extract and 1% dextrose (YG-BHI broth), and the culture was incubated with shaking at 37°C for 24 to 48 hours. The resultant culture, mostly consisting of yeast-phase cells, was filtered to remove hyphae. In study E-10 (2) the nonsaponifiable lipid fraction was extracted from *Sporothrix schenckii* cells after incubation for twenty-four hours in the presence of butenafine at three different concentrations. The extract was analyzed by Gas Liquid Chromatography (GLC) to find out how cellular sterol and precursor compositions changed. Table 1 shows the results of this study.

Table 1
 Composition of Sterols and Precursors after Incubation with Butenafine

Components	Untreated	Treated with Butenafine at:		
		5×10^{-9} M	5×10^{-8} M	5×10^{-7} M
Squalene	1.3 ^a	2.3	51.4	62.3
2,3-Oxidosqualene	5.9	8.5	<0.1	<0.1
Ergosterol	75.3	68.9	46.5	34.5
Lanosterol	8.9	9.1	<0.1	<0.1
24-Methylene-dihydrolanosterol	8.0	11.2	1.7	0.6
Dihydrolanosterol	0.6	<0.1	0.5	2.6
% Growth ^b	100	87.5	23.7	2.0

- a) Percent against the total amount of sterols and their precursors.
 b) Determined on the basis of cellular dry weight of cultures (mg/mL).

The above table shows that most of the sterol in the untreated cells was composed of ergosterol and small peaks of trimethyl sterols such as lanosterol, 24-methylene dihydrolanosterol and dihydrolanosterol. Only a very small amount of squalene, and 2,3-oxidosqualene were detected. More than 75% of the sterol in the cell was ergosterol in the untreated control culture. Most of the rest (about 20%) were trimethyl sterols which were in the preliminary stage of 14- α -demethylation. Squalene and 2,3-oxidosqualene, metabolic precursors of ergosterol were contained in respective ratios of about 1% and 6%. When butenafine was added, a dose dependent change was observed. There was no clear change with butenafine at a concentration of 5×10^{-9} M, which inhibited growth by about 10%, but the ratio of ergosterol was decreased to below 50% in cells treated with drug at a concentration of 5×10^{-8} M (which inhibit growth by over 75%) and the amount of squalene increased to over 50% of the sterols. Intermediate metabolic products such as trimethyl sterol were hardly detected. At a concentration of 5×10^{-7} M (which almost completely inhibited growth), the ratios of ergosterol and squalene reached lower than 35% and over 60%, respectively.

To more directly investigate the effect of butenafine on the sterol synthesis of *Sporothrix schenckii* cells, ¹⁴C labelled acetic acid was used as substrate, and radioactivity incorporated into each sterol during a six hour incubation period in the presence of various concentration of drug was compared. Table 2 gives the results of this testing.

Table 2
 Effect of Butenafine on Incorporation of [¹⁴C] Acetate into Sterols^a

Butenafine concentration (M)	Radioactivity incorporated (%) ^a				
	Squalene	2,3-Oxido-squalene	Trimethyl-sterols	Dimethyl-sterol	Ergosterol
0 (control)	0.4	5.9	5.1	2.9	85.7
5 x 10 ⁻⁹	39.0	4.7	6.0	1.9	47.5
5 x 10 ⁻⁸	86.7	4.3	3.7	0.4	5.8
5 x 10 ⁻⁷	93.9	2.4	1.6	1.6	1.4
5 x 10 ⁻⁶	93.0	2.4	1.6	1.6	1.4
5 x 10 ⁻⁵	90.7	5.3	2.6	0.6	0.9

a) Total radioactivity recovered from all of the sterol and precursors fractions was taken as 100%.

As seen in the above table, in the case of untreated cells, 85% of the total radioactivity was incorporated in ergosterol while incorporation into 14- α -methylated sterol (combining trimethyl and dimethyl sterol) accounted for about 8%, only about 1% was incorporated into squalene. The effect of butenafine starts to appear at concentrations as low as 5 x 10⁻⁹ M. The incorporation into ergosterol was reduced to less than 50% and a drastic increase in the incorporation of radioactivity into squalene to close to 40% was observed. As the concentration of butenafine is increase this trend becomes greater, and the incorporation into ergosterol was almost completely inhibited at the concentration of 5 x 10⁻⁷M, and more than 90% of the radioactivity was found in squalene. These data support the hypothesis that the drug's ability to block the conversion of squalene to 2,3-oxidosqualene (squalene epoxidation) is its primary mode of action. Squalene epoxidase is the enzyme whose function is blocked.

The authors also investigated butenafine's action in direct membrane damaging by measuring the release of K^+ and inorganic phosphate from *Sporothrix schenckii* cells. Samples of growing cells were collected every 2.5 minutes up to 15 minutes after the addition of drug. Samples were immediately filtered to isolate cells from the filtrate. The potassium content was determined by flame photometer and the inorganic phosphate content was determined by colorimetry. The extracellular release was expressed in ratios against the cellular content at zero time which was determined by extracting the cells with 5% ice-cooled trichloroacetic acid. When butenafine was added at concentrations of 1.4×10^{-5} M or more, K^+ release was enhanced within 2.5 minutes of treatment. The amount of K^+ released increased along with the increase in drug concentration, and, at the maximum tested drug concentration of 2.3×10^{-4} M, more than 40% of the cellular K^+ amount was released after 10 minutes. The results of this study are shown in Table 3.

Table 3
 Butenafine induced release of K^+ from *Sporothrix schenckii* cells

Butenafine concentration (M)	% of Total Released			
	2.5 minutes	5 minutes	7.5 minute	10 minute
1.4×10^{-5}				
2.5×10^{-5}				
5.5×10^{-5}				
1.1×10^{-4}				
2.3×10^{-4}				

Table 4 shows the concentration levels and time course of release of inorganic phosphate from the cells under similar conditions. Butenafine causes the release of inorganic phosphate from cells just as it did with K^+ . Higher concentrations caused more release. There also seems to be a greater difference between the two highest doses tested (1.1×10^{-4} M and 2.3×10^{-4} M) than between the other doses tested. The study gives no explanation for this, but it may be that the cell membrane really starts to be destroyed somewhere between these two doses.

Table 4
 Butenafine induced release of inorganic phosphate from *Sporothrix schenckii*

Butenafine concentration (M)	% of Total Released			
	2.5 minutes	5 minutes	7.5 minute	10 minute
1.4×10^{-5}				
2.5×10^{-5}				
5.5×10^{-5}				
1.1×10^{-4}				
2.3×10^{-4}				

As the above two tables show the drug concentration which causes a significant release of cellular components is much higher than that needed to inhibit cell growth. It appears that butenafine's direct damaging of the cell membrane is probably a secondary mode of action and its ability to block the conversion of squalene to 2,3-oxidosqualene (squalene epoxidation) is the drug's primary mode of action. Squalene epoxidase is the enzyme whose function is blocked.

Since it appeared that butenafine acted at the same common action point in sterol synthesis as the allylamine antimycotics such as naftifine and terbinafine and the thiocarbamate antimycotics such as tolnaftate and tolciclate, in Study E-11 (3) [the second part of Study E-10] the authors examined whether the primary action point of butenafine was identical to that of allylamines and thiocarbamates. In this study a wild-type strain of *Sporothrix schenckii*, highly susceptible to butenafine and to the allylamine, naftifine; was studied along with seven tolciclate-resistant mutant strains. Gas liquid chromatography was used to analyze the nonsaponifiable lipid fractions from cells grown in the presence of various levels of drugs for 24 to 48 hours. Table 5 below shows the results of this study.

Table 5
 Sensitivity of butenafine and other antifungal against
 wild-type and tolciolate-resistant mutant strains of *Sporothrix schenckii*
 and their intracellular squalene/ergosterol ratios

Strains	Intracellular squalene/ergosterol ratio ^a	IC ₅₀ (μg/mL) ^b		
		tolciolate	naftifine	butenafine
wild-type	0.047	≤0.3	0.3	0.005
tcr-1	16.9	>20	5	0.16
tcr-2	7.1	>20	10	0.31
tcr-3	8.2	>20	2.5	0.16
tcr-5	2.1	>20	5	0.63
tcr-6	0.047	>20	10	0.31
tcr-8	0.059	>20	>20	0.04
tcr-9	0.048	>20	>20	0.16

- a) Measured on weight basis.
- b) Concentration of drug which gives a 50% reduction in growth measured on the cellular dry weight basis.

As shown in table 5, the content of squalene in the wild-type strain was less than one twentieth the content of ergosterol, which is known to be the major sterol in fungal cells. The resistant strains can be divided into two types by this squalene/ergosterol ratio: one type has a very high ratio of squalene to ergosterol and is represented by ter-1, ter-2, tcr-3, and tcr-5. The other resistant mutants such as tcr-6, tcr-8, and tcr-9 have the same ratio as the wild-type. The first four mutants appeared to be defective in their ability of squalene epoxidation, while the last three mutants were not and must, therefore, be resistant due to

some other unknown mechanism. Naturally, results with tolciclate indicated 70-fold or above lower susceptibilities in all of the tolciclate-resistant strains with IC_{50} values of $20 \mu\text{g/mL}$ or higher. These seven tolciclate-resistant strains showed some cross-resistance to naftifine, to which susceptibility was reduced to one eighth to one seventieth that of the wild-type strain. The results with butenafine also showed cross-resistance. The IC_{50} values against the seven resistant strains rose from eight to 126 fold in comparison to that of the wild-type strain. These results show that cross-resistance exist among butenafine, allylamines and thiocarbamates. This cross-resistance was seen even in the strains that had a normal squalene/ergosterol ratio.

In this same study the authors investigated the release of cellular K^+ in a susceptible wild-type and resistant mutant strain. They used mutant strain tcr-1, which was one of the strains lacking normal sterol synthesis. The results of this study are shown in tables 6 and 7. They observed the release of K^+ from both strains, within 2.5 minutes after exposure to $\geq 5 \mu\text{g/mL}$ doses of butenafine. This K^+ release was similar to that seen in the experiment performed in Study E-10 (2). It appears that at the lower doses K^+ release is higher in the mutant strain than in the wild-type strain. This difference becomes less as the doses increase. Since this resistant strain was one of the four that had a different squalene/ergosterol ratio than the wild-type strain, this may indicate that butenafine's role in blocking ergosterol synthesis may also play a part in the drug's direct membrane damaging ability. This role may be more important at lower doses of the drug. If a high enough dose is used, membrane damaging may take place even if ergosterol synthesis is not blocked.

Table 6
 Butenafine induced release of inorganic phosphate from *Sporothrix schenckii*
 wild-type TIMM 0960 cells

Butenafine concentration ($\mu\text{g/mL}$)	% of Total Released			
	2.5 minutes	5 minutes	7.5 minute	10 minute
5				
10				
20				
40				
80				

Table 7
 Butenafine induced release of inorganic phosphate from *Sporothrix schenckii*
 tolclate-resistant *tcr-1* cells

Butenafine concentration ($\mu\text{g/mL}$)	% of Total Released			
	2.5 minutes	5 minutes	7.5 minute	10 minute
5				
10				
20				
40				
80				

In Study E-12 (4) the authors studied the mechanisms of antifungal action of butenafine against *Candida albicans*. *Candida albicans* strain KC-36, a clinical isolate from culture collection was grown in yeast extract-polypeptone-dextrose broth (Y.P.G.; 3% glucose, 1% polypeptone, 1% yeast extract) under aerobic conditions at 37°C for 16 hours. The effects of butenafine,

tolnaftate, and naftifine on ergosterol biosynthesis were investigated by incorporation of radiolabeled [¹⁴C]-acetate as a substrate. Radioactivities incorporated into cellular sterols and their precursor, squalene, were measured when cells were incubated for two hours in the presence of various concentrations of each drug. After saponification, radiolabeled non-saponifiable lipids were fractionated by TLC and ergosterol, 4- α -methylsterol, 4,4-dimethylsterol, and squalene fractions corresponding to known standard compounds were identified. Radioactivity incorporated into each fraction was measured using a liquid scintillation counter and expressed as a percentage of the total radioactivity recovered from all fractions. Tables 9, 10, and 11 below show the results of this experiment.

Table 9
Effect of Butenafine on Incorporation of [¹⁴C]Acetate
into Sterols and Squalene in *Candida albicans* cells

Drug concentration (μ g/mL)	Incorporation of radioactivity (% of total)			
	Ergosterol	4- α -methylsterol	4,4-dimethylsterol	Squalene
0	81.8	8	7.1	3.1
0.001	77	9	9	5
0.01	64	5.5	5.5	25
0.1	32	7.5	5.5	55
1.0	5.8	6.5	2.2	85.5
10.0	3.2	8.5	3.3	85

Table 10
 Effect of Tolnaftate on Incorporation of [¹⁴C]Acetate
 into Sterols and Squalene in *Candida albicans* cells

Drug concentration (μg/mL)	Incorporation of radioactivity (% of total)			
	Ergosterol	4-α-methylsterol	4,4-dimethylsterol	Squalene
0	81.8	8	7.1	3.1
0.001	83	7.4	7.6	2
0.01	77	7.8	7.7	7.5
0.1	46.5	7.7	7.8	38
1.0	18.1	8.7	5.6	67.6
10.0	10	10.3	5.5	74.2

Table 11
 Effect of Naftifine on Incorporation of [¹⁴C]Acetate
 into Sterols and Squalene in *Candida albicans* cells

Drug concentration (μg/mL)	Incorporation of radioactivity (% of total)			
	Ergosterol	4-α-methylsterol	4,4-dimethylsterol	Squalene
0	81.8	8	7.1	3.1
0.001	82	8	8	2
0.01	78	8.1	9.3	4.6
0.1	55	6.2	7	31.8
1.0	23.4	10	8.2	58.4
10.0	8.2	10	2.5	79.3

These tables show that all three drugs remarkably inhibit incorporation of radioactivity into ergosterol in a drug concentration dependent manner between 0.001 $\mu\text{g/mL}$ and 1.0 $\mu\text{g/mL}$. At the same time radioactivity is markedly accumulated into squalene in a drug concentration dependent manner. The incorporation of radioactivity into 4,4-dimethylsterol and 4- α -methylsterol indicated a tendency to decrease slightly and showed no remarkable change, respectively from control cells.

Table 12 shows a comparison between the inhibitory potencies of the three drugs on ergosterol biosynthesis. This table shows the concentration of each drug needed to cause a 50%, 85%, and 95% inhibition of ergosterol biosynthesis compared to that in control cells. This table shows that butenafine inhibited ergosterol biosynthesis at a lower concentration than tolnaftate and naftifine. The 50% inhibitory concentration of butenafine was 2.9 times and 5.7 times more potent than that of tolnaftate and naftifine, respectively. The 85% inhibitory concentration of butenafine was 9.3 times and 10.6 times more potent than that of tolnaftate and naftifine, respectively.

Table 12
 Inhibitory Concentrations of Butenafine, Tolnaftate, and Naftifine
 on Ergosterol Biosynthesis in *Candida albicans* Cells

Compounds	Concentration ($\mu\text{g/mL}$)		
	50%	85%	95%
Butenafine	0.058	0.59	6.1
Tolnaftate	0.17	5.50	>10
Naftifine	0.33	6.25	>10

The release of cellular components from *Candida albicans* by a direct cell membrane damaging effect was investigated by measuring the amount of inorganic phosphate released from the cells after exposure to butenafine. Tolnaftate and the imidazole antimycotics, bifonazole and miconazole were used as control drugs. A cell suspension was prepared at a concentration of about 10^7 cells/mL in distilled water. 9.9 mL of this suspension was placed in a test tube and pre-incubated for 10 minutes at 37°C. The reaction was initiated by adding 100 μL of drug solution at various concentrations. Samples were withdrawn at certain time intervals and filtered to separate the filtrate from the

cells. The inorganic phosphate released from the cells into the filtrate was determined by colorimetry with a spectrophotometer. The amount of inorganic phosphate extracted from the cells with 5% trichloroacetic acid when no drug was added was regarded as the total amount of cellular phosphate. Tables 13-15 show the results of this experiment. There was no release of inorganic phosphate with tolnaftate even at a concentration of 100 μ g/mL.

Table 13
 Effect of Butenafine on Leakage of Inorganic Phosphate
 out of *Candida albicans* cells

Butenafine concentration (μ g/mL)	% of Total Released			
	10 minutes	30 minutes	60 minutes	120 minutes
12.5				
25				
50				
100				

Table 14
 Effect of Bifonazole on Leakage of Inorganic Phosphate
 out of *Candida albicans* cells

Bifonazole concentration (μ g/mL)	% of Total Released			
	10 minutes	30 minutes	60 minutes	120 minutes
12.5				
25				
50				
100				

Table 15
 Effect of Miconazole on Leakage of Inorganic Phosphate
 out of *Candida albicans* cells

Miconazole concentration ($\mu\text{g/mL}$)	% of Total Released			
	10 minutes	30 minutes	60 minutes	120 minutes
12.5				
25				
50				
100				

The above tables show that the release of inorganic phosphate was incubation time and drug concentration dependent when butenafine was used. There was very slow release and the total release was low at the two lowest drug concentrations. At drug concentrations of 50 and 100 $\mu\text{g/mL}$, inorganic phosphate release was more rapid and % of the total amount was released in 120 minutes. Tolnaftate showed no effect on the cell membrane (inorganic phosphate release) even at 100 $\mu\text{g/mL}$. When bifonazole was used the release of inorganic phosphate was dose dependent between 12.5 and 50 $\mu\text{g/mL}$. In comparison with butenafine the release by bifonazole after 120 minutes was the same of slightly less at concentrations of $\mu\text{g/mL}$ and about greater at 25 $\mu\text{g/mL}$. When miconazole was used, the release of inorganic phosphate was much faster than with the other drugs and reached 100% at concentrations of $\mu\text{g/mL}$. This experiment shows that butenafine has a direct damaging effect on the cell membrane of *Candida albicans* similar to that of bifonazole, but less than that of miconazole. Tolnaftate does not have any direct damaging effect on these cells, its only mode of action is its ability to block ergosterol biosynthesis.

The investigators performed one final experiment. In this experiment *Candida albicans* cells were pretreated with either 0.2 $\mu\text{g/mL}$ or 10 $\mu\text{g/mL}$ of tolinaftate. These concentrations inhibited ergosterol biosynthesis by 50% or 95%, respectively. These cells were then exposed to 25 $\mu\text{g/mL}$ or 50 $\mu\text{g/mL}$ of butenafine and the amount of inorganic phosphate released was measured.

Table 16 shows the results of this experiment.

Table 16
 Accelerating Effect of Butenafine on Leakage of Inorganic Phosphate
 out of *Candida albicans* Cells Pretreated with Tolnaftate

Butenafine concentration ($\mu\text{g/mL}$)	Tolnaftate concentration ($\mu\text{g/mL}$)	% of Total Released		
		5 minutes	10 minutes	20 minutes
25	0			
	0.2			
	10			
50	0			
	0.2			
	10			

The above table shows that there was no difference in the releasing effect between cells pretreated with 0.2 $\mu\text{g/mL}$ of tolnaftate and the non-pretreated control cells when tested with 25 $\mu\text{g/mL}$ of butenafine. In the 10 $\mu\text{g/mL}$ tolnaftate-pretreated cells, the releasing effect was enhanced rapidly and the amount of inorganic phosphate released was about 4 times more than in the non-pretreated cells after 20 minutes. About 100% of the inorganic phosphate was released from both sets of tolnaftate-pretreated cells by treatment with 50 $\mu\text{g/mL}$ of butenafine. This experiment shows that at butenafine concentrations of 25 $\mu\text{g/mL}$ or lower, the direct membrane-damaging effect of butenafine is enhanced by the inhibition of squalene epoxidase (which is the only effect of tolnaftate). On the other hand, the damaging effect of butenafine at a concentration of 50 $\mu\text{g/mL}$ or higher is accelerated in a short time with only a limited alteration in the membrane by inhibition of ergosterol biosynthesis.

Together these three studies indicate that butenafine probably has two mechanisms of action. One is identical with that of thiocarbamates (tolnaftate and tolciclate) and allylamines (naftifine, terbinafine); which is the specific inhibition of the conversion of squalene into 2,3-oxidosqualene catalyzed by squalene epoxidase. The other is similar to that of imidazoles: which is a direct damaging

effect on the cell membrane of the fungus by physical destruction. Ryder (5) has indicated that certain fungi have an inherent adaptability to resist changes in sterol composition in their cell membranes. *Saccharomyces cerevisiae* and other fermentative yeast have been shown to survive despite low ergosterol and high squalene cell content (6). It has been suggested that *Candida albicans* may also have this ability and that the direct membrane damaging effect of butenafine may be its major mode of action in this species. This fact may explain why the inhibitory activity against squalene epoxidase for *Candida albicans* is much lower than the growth inhibitory activity (MIC) for this species. In other species such as dermatophytes (*Trichophyton mentagrophytes*, *Trichophyton rubrum*) the enzyme inhibition and MIC values are about the same and the mode of action is primarily the inhibition of ergosterol synthesis.

ANTIMICROBIAL SPECTRUM OF ACTIVITY

In Study E-1 (7) the *in vitro* activity of butenafine against pathogenic fungi was compared to that of naftifine, tolnaftate and clotrimazole. The drug substances were dissolved in DMSO and an agar dilution method was employed using Sabouraud's Dextrose Agar (SDA) with drug concentrations of $\mu\text{g/mL}$. The plates were inoculated with 10^4 cells and incubated at 37°C for two days for yeast, or at 27°C for seven days for dermatophytes and molds. The minimum inhibitory concentration (MIC) was defined as the highest dilution at which there was no growth on the plates at the completion of the incubation period. There is no standardized NCCLS method for the testing of fungi other than yeast that cause invasive fungal infections (*Candida* species, *Torulopsis glabrata*, and *Cryptococcus neoformans*). This method is a macrobroth dilution method using RPMI 1640 broth and an inoculum of about 2×10^3 cells/mL. There is no reference method for other fungi since the standardization of the inoculum for filamentous fungi would be almost impossible to do. Sabouraud's Dextrose agar is often used to grow fungi. Most susceptibility testing has not been correlated with clinical outcome. Penederm Study CR010-A (9) uses a modified NCCLS method to test strains of the fungi relating to tinea pedis. Table 17-21 below show the results of testing in Study E-1.

Table 17
In Vitro Activity of Butenafine, Naftifine, Tolnaftate
 and Clotrimazole Against Dermatophytes

Microorganism	Number of Strains	Drug	Geometric mean MIC ($\mu\text{g/mL}$) ^a	Range ($\mu\text{g/mL}$)
<i>Trichophyton mentagrophytes</i>	22	Butenafine	0.012	
		Naftifine	0.035	
		Tolnaftate	0.133	
		Clotrimazole	0.255	
<i>Trichophyton rubrum</i>	41	Butenafine	0.007	
		Naftifine	0.031	
		Tolnaftate	0.061	
		Clotrimazole	0.267	
<i>Microsporum canis</i>	14	Butenafine	0.024	
		Naftifine	0.100	
		Tolnaftate	0.181	
		Clotrimazole	0.266	
<i>Microsporum gypseum</i>	7	Butenafine	0.014	
		Naftifine	0.055	
		Tolnaftate	0.110	
		Clotrimazole	0.640	
<i>Epidermophyton floccosum</i>	3	Butenafine	0.016	
		Naftifine	0.025	
		Tolnaftate	0.079	
		Clotrimazole	0.312	

a) Determined on Sabouraud's dextrose agar medium; incubation at 27°C for 7 days.

Table 18
In Vitro Activity of Butenafine, Naftifine, Tolnaftate
 and Clotrimazole Against Aspergilli

Microorganism	Number of Strains	Drug	MIC ($\mu\text{g/mL}$) ^a
<i>Aspergillus fumigatus</i>	3	Butenafine	0.39, 0.78, 0.78
		Naftifine	6.25, 6.25, 6.25
		Tolnaftate	>100, >100, >100
		Clotrimazole	1.56, 1.56, 1.56
<i>Aspergillus flavus</i>	5	Butenafine	0.025, 0.05, 0.1, 0.1, 0.1
		Naftifine	0.78, 0.78, 0.78, 0.78, 0.78
		Tolnaftate	>100, >100, >100, >100, >100
		Clotrimazole	0.78, 0.78, 1.56, 1.56, 1.56
<i>Aspergillus niger</i>	4	Butenafine	0.5, 0.1, 0.2, 0.39
		Naftifine	0.39, 1.56, 3.13, 3.13
		Tolnaftate	0.1, 0.1, 0.39, 0.39
		Clotrimazole	3.13, 3.13, 3.13, 6.25
<i>Aspergillus terreus</i>	2	Butenafine	0.2, 0.2
		Naftifine	0.78, 3.13
		Tolnaftate	3.13, 3.13
		Clotrimazole	1.56, 3.13
<i>Aspergillus nidulans</i>	1	Butenafine	0.2
		Naftifine	3.13
		Tolnaftate	>100
		Clotrimazole	0.78

a) Determined on Sabouraud's dextrose agar medium, incubation at 27°C for 2 days.

Table 19
In Vitro Activity of Butenafine, Naftifine, Tolnaftate
 and Clotrimazole Against Yeast

Microorganism	Number of Strains	Drug	Geometric Mean or Individual MIC ($\mu\text{g/mL}$) ^a
<i>Candida albicans</i>	57	Butenafine	>100
		Naftifine	>100
		Tolnaftate	>100
		Clotrimazole	6.405 (range 0.78-25)
<i>Candida tropicalis</i>	4	Butenafine	6.25, >100, >100, >100
		Naftifine	12.5, >100, >100, >100
		Tolnaftate	>100, >100, >100, >100
		Clotrimazole	0.39, 0.78, 1.56, 3.13
<i>Candida krusei</i>	2	Butenafine	25, >100
		Naftifine	>100, >100
		Tolnaftate	>100, >100
		Clotrimazole	0.1, 0.39
<i>Candida parapsilosis</i>	2	Butenafine	3.13, 6.25
		Naftifine	12.5, 12.5
		Tolnaftate	>100, >100
		Clotrimazole	0.1, 0.39
<i>Candida guilliermondii</i>	1	Butenafine	6.25
		Naftifine	25
		Tolnaftate	>100
		Clotrimazole	0.2

a) Determined on Sabouraud's dextrose agar medium; incubation at 37°C for 2 days.

Table 19 (continued)
In Vitro Activity of Butenafine, Naftifine, Tolnaftate
 and Clotrimazole Against Yeast

Microorganism	Number of Strains	Drug	Geometric Mean or Individual MIC ($\mu\text{g/mL}$) ^a
<i>Candida stellatoidea</i>	1	Butenafine	6.25
		Naftifine	12.5
		Tolnaftate	>100
		Clotrimazole	0.2
<i>Cryptococcus neoformans</i>	4	Butenafine	0.78, 0.78, 1.56, 1.56
		Naftifine	6.25, 12.5, 12.5, 50
		Tolnaftate	>100, >100, >100, >100
		Clotrimazole	0.39, 0.2, 0.39, 0.1
<i>Geotrichum candidum</i>	1	Butenafine	>100
		Naftifine	>100
		Tolnaftate	>100
		Clotrimazole	3.13

a) Determined on Sabouraud's dextrose agar medium, incubation at 37°C for 2 days.

Table 20
In Vitro Activity of Butenafine, Naftifine, Tolnaftate
 and Clotrimazole Against Other Fungi

Microorganism	Number of Strains	Drug	MIC ($\mu\text{g/mL}$) ^a
<i>Sporothrix schenckii</i>	1	Butenafine	0.78
		Naftifine	6.25
		Tolnaftate	>100
		Clotrimazole	25
<i>Exophiala dermatitidis</i>	2	Butenafine	0.2, 0.78
		Naftifine	3.13, 6.25
		Tolnaftate	>100, >100
		Clotrimazole	3.13, 25
<i>Fonsecaea pedrosoi</i>	1	Butenafine	0.78
		Naftifine	3.13
		Tolnaftate	>100
		Clotrimazole	25
<i>Nocardia asteroides</i>	1	Butenafine	>100
		Naftifine	>100
		Tolnaftate	>100
		Clotrimazole	1.56
<i>Actinomyces madurae</i>	1	Butenafine	6.25
		Naftifine	12.5
		Tolnaftate	>100
		Clotrimazole	1.56

a) Determined on Sabouraud's dextrose agar medium; incubation at 27°C for 2 days

Table 20 (continued)
In Vitro Activity of Butenafine, Naftifine, Tolnaftate
 and Clotrimazole Against Other Fungi

Microorganism	Number of Strains	Drug	Geometric Mean or Individual MIC ($\mu\text{g/mL}$) ^a
<i>Cladosporium carrionii</i>	1	Butenafine	0.39
		Naftifine	1.56
		Tolnaftate	>100
		Clotrimazole	6.25
<i>Acrotheca aquaspersa</i>	1	Butenafine	0.39
		Naftifine	6.25
		Tolnaftate	>100
		Clotrimazole	12.5

a) Determined on Sabouraud's dextrose agar medium; incubation at 27°C for 2 days.

These tables show that butenafine has good *in vitro* activity against dermatophytes including *Trichophyton mentagrophytes* (22 strains MIC range $\mu\text{g/mL}$), *Trichophyton rubrum* (41 strains MIC range $\mu\text{g/mL}$), *Microsporum canis* (21 strains MIC range $\mu\text{g/mL}$), *Microsporum gypseum* (7 strains MIC range $\mu\text{g/mL}$) and *Epidermophyton floccosum* (3 strains MIC range $\mu\text{g/mL}$). Butenafine had 2-40 times the activity of naftifine, tolnaftate and clotrimazole against these organisms.

Butenafine also exhibited better activity against *Aspergillus* (15 strains MIC range $\mu\text{g/mL}$) than the control drugs. Butenafine was inactive against *Candida albicans* and *Geotrichum candidum*. It showed some activity against the other yeasts tested. Butenafine's activity against yeast is usually 2- to 4- fold better than naftifine's, but inferior to that of clotrimazole. Tolnaftate was inactive against the yeast strains tested. Against other fungi, butenafine usually showed the best activity while tolnaftate was usually inactive.

Since this drug product is being proposed for an indication against tinea pedis (athlete's foot) its activity against dermatophytes is the important information in these *in vitro* studies. To be included in the labeling for this product an organism must be a potential pathogen in this disease.

Since the above study was performed using fungal strains from Japan, a study using American Type Culture Collection (ATCC) strains was performed by to confirm the MIC results.

In this study (8) three ATCC strains each of *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Microsporium canis*, *Epidermophyton floccosum*, and *Candida albicans* were tested to determine MIC levels of butenafine as compared to clotrimazole. In order to try and keep most variables constant, the agar dilution method using Sabouraud's dextrose agar used in Study E-1 (7) was employed. The results of this study can be seen in table 21.

Table 21
In Vitro Activity of Butenafine and Clotrimazole Against
 ATCC Strains (USA study)

Microorganism	ATCC Number of Strain	Drug	MIC ($\mu\text{g/mL}$)
<i>Candida albicans</i> range Study E-1 Butenafine >100 Clotrimazole 0.78-25	ATCC 18804	Butenafine	>100
		Clotrimazole	1.56
	ATCC 24433	Butenafine	>100
		Clotrimazole	0.781
	ATCC 36232	Butenafine	100*
		Clotrimazole	0.0488*
<i>Epidermophyton floccosum</i> range Study E-1 Butenafine 0.006-0.025 Clotrimazole 0.2-0.39	ATCC 38486	Butenafine	0.0244
		Clotrimazole	0.390
	ATCC 52061	Butenafine	0.0244
		Clotrimazole	0.390
	ATCC 52066	Butenafine	0.0122
		Clotrimazole	0.195

Table 21 (continued)
In Vitro Activity of Butenafine and Clotrimazole Against
 ATCC Strains (USA study)

Microorganism	ATCC Number of Strain	Drug	MIC ($\mu\text{g/mL}$) *
<i>Trichophyton mentagrophytes</i> range Study E-1 Butenafine 0.006-0.025 Clotrimazole 0.2-0.78	ATCC 9128	Butenafine	0.0244
		Clotrimazole	0.39
	ATCC 18748	Butenafine	0.0122
		Clotrimazole	0.781
	ATCC 28185	Butenafine	0.0122
		Clotrimazole	0.39
<i>Trichophyton rubrum</i> range Study E-1 Butenafine 0.0015-0.025 Clotrimazole 0.1-0.75	ATCC 10218	Butenafine	0.006
		Clotrimazole	0.39
	ATCC 28188	Butenafine	0.003
		Clotrimazole	0.39
	ATCC 28089	Butenafine	0.006
		Clotrimazole	0.195
<i>Microsporum canis</i> range Study E-1 Butenafine 0.0125-0.05 Clotrimazole 0.1-0.78	ATCC 11622	Butenafine	0.0976**
		Clotrimazole	1.56**
	ATCC 36299	Butenafine	0.0060*
		Clotrimazole	0.0976
	ATCC 42559	Butenafine	0.0488
		Clotrimazole	0.039

- a) Determined on Sabouraud's dextrose agar medium;
 * Results below the range in Study E-1
 ** Results above the range in Study E-1

The results obtained in this Bioscreen study compared well with those obtained in Japan in the Study E-1. In only a few cases were the results outside the range of the study and most of these differences were only one dilution outside of the range.

Another study, Penederm Study CR-010-A (9), was conducted at the

in which the MIC/MLC of butenafine and terbinafine were compared when tested against recent fungal isolates from clinical trials. A broth macrodilution method similar to the NCCLS standard method for the susceptibility testing of yeast was employed. RPMI-1640 broth containing L-glutamine but not sodium bicarbonate buffered with MOPS buffer to pH 7.0 (pH 5.0 for *Candida albicans*) and an inoculum of $1-2.5 \times 10^4$ cells/tube was used. Two strains each of *T. rubrum*, *T. mentagrophytes*, *E. floccosum*, *M. canis*, *T. tonsurans*, and *C. albicans* were tested. MIC (minimum inhibitory concentration) values were determined to be the lowest concentration to inhibit visible growth. MLC (minimum lethal concentration) values were determined by plating 100 μ L from the MIC tube and each concentration above the MIC to a Sabouraud's dextrose agar plate. The MLC was defined as the lowest concentration resulting in growth of five colonies or less. MIC/MLC reading times were determined as soon as growth was observed in the drug-free control tube. This occurred at 48 to 72 hours for all tested isolates except for *Trichophyton tonsurans* and *Epidermophyton floccosum* which were read at 72 to 96 hours. The results of this study are in Table 22.

Table 22
In Vitro Activity of Butenafine and Terbinafine Against
 USA Clinical Isolates

ISOLATE	BUTENAFINE				TERBINAFINE			
	MIC 48	MIC 72	MLC 48	MLC 72	MIC 48	MIC 72	MLC 48	MLC 72
TR 001	0.015	0.015	0.015	0.015	0.003	0.007	0.007	0.007
TR 002	0.007	0.015	0.015	0.125	0.007	0.015	0.015	0.125
TM 001	0.007	0.015	0.015	0.5	≤ 0.00	0.003	0.015	0.5
TM 002	0.007	0.007	0.015	0.5	0.007	0.007	0.015	0.25
MC 001	0.03	0.03	0.03	0.125	0.015	0.015	0.03	0.06
MC 002	0.03	0.03	0.03	0.25	0.015	0.015	0.03	0.125
CA 001	>1.0	>1.0	>1.0	>1.0	>1.0	>1.0	>1.0	>1.0
CA 002	>1.0	>1.0	>1.0	>1.0	>1.0	>1.0	>1.0	>1.0
	MIC 72	MIC 96	MLC 72	MLC 96	MIC 72	MIC 96	MLC 72	MLC 96
TT 001	0.007	0.06	0.06	0.06	0.007	0.03	0.03	0.03
TT 002	0.06	0.06	0.06	0.06	0.03	0.03	0.03	0.06
EF 001	0.015	0.03	0.03	0.03	0.015	0.015	0.015	0.015
EF 002	0.015	0.03	0.03	0.06	0.015	0.015	0.015	0.03

TR 001, TR 002: *Trichophyton rubrum* isolate #1 and #2, respectively
 TM 001, TM 002: *Trichophyton mentagrophytes* isolate #1 and #2, respectively
 MC 001, MC 002: *Microsporium canis* isolate #1 and #2, respectively
 CA 001, CA 002: *Candida albicans* isolate #1 and #2, respectively
 TT 001, TT 002: *Trichophyton tonsurans* isolate #1 and #2, respectively
 EF 001, EF 002: *Epidermophyton floccosum* isolate #1 and #2, respectively
 Units: μg/mL

This study shows that MIC values against clinical isolates in the United States compared well to those obtained in other studies. The study also demonstrates that a macrodilution method modified from the NCCLS standard method used for yeast gives comparable results to an agar dilution method performed with Sabouraud's dextrose agar.

Table 23 below gives a summary of butenafine's *in vitro* activity against dermatophytes and *Candida albicans*. Geometric means and the means in this table can not really be compared, but the table does give a good idea of the *in vitro* activity of butenafine in the various studies.

Table 23
 Summary of Butenafine's *In vitro* Activity Against Dermatophytes
 and *Candida albicans*

Fungus tested	Study E-1 (Geometric Mean)	Bioscreen (Mean)	Fungus Testing Lab (Mean)
<i>Candida albicans</i>	>100	>100	—
<i>Candida albicans</i> at pH 5.0	27.07	—	>1
<i>Trichophyton</i> <i>mentagrophytes</i>	0.012	0.016	0.011
<i>Trichophyton</i> <i>rubrum</i>	0.007	0.005	0.03
<i>Microsporum canis</i>	0.024	0.050	0.015
<i>Epidermophyton</i> <i>floccosum</i>	0.016	0.020	0.03

ORGANISMS ALLOWED IN THE LABEL

Although the only study submitted in which more than two or three isolates were tested is Study E-1 which was performed in Japan, the other two studies confirm these results in isolates from the United States. Since the MIC values for *Candida albicans* were very high and this organism is not associated with tinea pedis it should be deleted from the labeling. *Trichophyton mentagrophytes* and *Trichophyton rubrum* are the major pathogens associated with tinea pedis and the data support their inclusion in the labeling. There also is enough data to include *Microsporum canis* in the package insert. This organism may be more often associated with other dermatophytic infection, but it may be useful for the prescriber to have information on this organism. The primary habitat for *Microsporum canis* is dogs and cats, but it can be transferred to humans and cause tinea capitis. Weitzman and Summerbell (10) state in their paper that the predominant agents of tinea capitis in North America are *T. tonsurans* and *Microsporum canis*. There were only a total of eight isolates of *Epidermophyton floccosum* tested in the submitted studies, and even though the MIC values were low in all studies there is not enough tested isolates to allow inclusion in the package insert, unless the Medical Officer allows this organism in the Indications and Usage Section. *Trichophyton tonsurans* (only one study with two isolates) and *Microsporum gypseum* (one study with 7 isolates) should be deleted from the package insert since not enough isolates were tested and testing was performed in only one study.

FUNGICIDAL ACTIVITY

Fungicidal activity is usually defined as a 99.9% reduction in cell number (3 log reduction). The fungicidal activity of butenafine was tested in Study E-1 (7). Sabouraud's dextrose broth was inoculated with $2-5 \times 10^3$ cells/mL of *Trichophyton mentagrophytes*, *Microsporum canis*, *Sporothrix schenckii*, *Candida albicans*, *Candida parapsilosis* or *Cryptococcus neoformans*. Butenafine was added at twice the MIC against the test fungi and the tubes were incubated without shaking at 30°C for five days. Samples were collected at 0, 1, 2, 3, 4, and 5 days after the start of the incubation and the samples were incubated on Sabouraud's dextrose agar plates to count the number of fungi. Table 24 gives the results of this study.

Table 24
 Fungicidal Activity of Butenafine

Organism	Butenafine Concentration ($\mu\text{g/mL}$)	Viable Cells (CFU/mL)					
		Initial	Day 1	Day 2	Day 3	Day 4	Day 5
<i>T. mentagrophytes</i>	0.025	3×10^3	9×10^2	1×10^2	8×10^2	0	--
<i>M. canis</i>	0.05	4×10^3	1×10^3	2×10^2	3×10	0	--
<i>S. schenckii</i>	1.56	5×10^3	3×10^3	2.5×10^3	6×10^2	3×10^2	3×10
<i>C. albicans</i>	100	3×10^3	3×10^6	5×10^6	1.5×10^6	1×10^6	1.5×10^6
<i>C. parapsilosis</i>	12.5	3.5×10^3	2×10^2	1×10^2	7×10	2×10	0
<i>C. neoformans</i>	3.13	4×10^3	9×10^2	0	--	--	--

This table shows that butenafine is fungicidal for the dermatophytes, *Trichophyton mentagrophytes* and *Microsporum canis* at 2 x MIC within four days. The drug was fungicidal against *Cryptococcus neoformans* within 2 days at twice the MIC. The drug was fungicidal against *Candida parapsilosis* at 2 x MIC within five days. The drug was not fungicidal against *Candida albicans* and the cell number increased significantly. Butenafine was also not fungicidal at 2 x MIC for *Sporothrix schenckii* within the five days of testing, although the cell number did decrease significantly.

In Study E-10 (2) the fungicidal effect of butenafine was studied using the yeast form of *Sporothrix schenckii* cells. Yeast-form cells at a concentration of approximately 10^8 cells/mL in brain-heart infusion broth containing 0.5% yeast extract and 1% dextrose (YG-BHI broth) were prepared and 10 mL placed in a test tube containing 0.1 mL of drug solution at concentrations of $\mu\text{g/mL}$. The tubes were incubated with shaking at 37°C and samples taken at 0, 6, 24 and 48 hours after the start of incubation. Each sample was immediately diluted with saline and plated on YPG agar plates containing 5 grams of yeast extract, 10 grams of peptone, 20 grams of dextrose and 15 grams of agar per liter. The number of colonies were counted after incubation for four days. The viable cell count was then calculated. Table 25 shows the results of this study.

Table 25
 Fungicidal Activity of Butenafine Against *Sporothrix schenckii*

Butenafine Concentration ($\mu\text{g/mL}$)	Viable Cells (% of inoculum)			
	Initial	6 hrs	24 hrs	48 hrs
0	100			
0.04	100			
0.16	100			
0.63	100			
2.5	100			
10	100			
40	100			

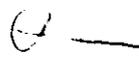
This experiment showed that butenafine was fungicidal in 48 hours at concentration of 0.63 $\mu\text{g/mL}$ or greater against *Sporothrix schenckii*. There was a major reduction in the cell count in 24 hours, but the reduction was not 99.9% or greater (fungicidal definition). This experiment seems to contradict Study E-1 in which 2 X MIC (1.56 $\mu\text{g/mL}$) was not fungicidal against *Sporothrix schenckii* even after five days. The two studies were performed in different media, at different temperatures, and with a different number of starting cells. This experiment was also performed with shaking during the incubation period and Study E-1 was not shaken. All of these differences may have played a part in the

contradicting results. When the same experiment was repeated in Study E-11 (3) with a tolcicalate-resistant mutant strain (tcr-1) it was found that a higher concentration of 40 $\mu\text{g}/\text{mL}$ was needed for fungicidal activity. This resistant strain need 0.16 $\mu\text{g}/\text{mL}$ to inhibit 50% of growth while the wild-type strain only needed 0.005 $\mu\text{g}/\text{mL}$. This indicates that the fungicidal concentration is related to the inhibitory concentration.

In Penederm Study CR-010-A (9) the authors found that the minimal lethal concentration was usually the same or one 2-fold dilution higher than the MIC for *Trichophyton mentagrophytes*, *Trichophyton rubrum*, and *Microsporum canis* at 48 hours. *Trichophyton tonsurans* and *Epidermophyton floccosum* which were read at 72 and 96 hours, usually had MLC values that were the same or only one dilution higher than MIC values [see table 24]. This indicates that butenafine has fungicidal activity against these species.

The important species are the dermatophytes. Most of the work performed by the sponsor involved *Sporothrix schenckii* cells and not the dermatophytic species that will be in the labelling for this product. The only experiment in which a time kill study was performed on these species was Study E-1 which showed that butenafine was fungicidal against a strain of *T. mentagrophytes* in four days at a concentration of 0.025 $\mu\text{g}/\text{mL}$ and a strain of *M. canis* after 4 days at a concentration of 0.05 $\mu\text{g}/\text{mL}$. The Penederm study in which MICs and MLCs were compared also indicates that butenafine has fungicidal activity.

The sponsor performed a study (Penederm Study PD188:39) to measure the concentration of butenafine in both the epidermal and dermal layers of human skin 24 hours after application of butenafine HCl Cream 1%. Radiolabeled drug was applied to human skin at a dose of 5 mg/cm^2 , and after 24 hours of exposure, the skin was given a mild detergent wash (simulating actual use conditions at the trough level) prior to measuring drug concentrations. The concentration of butenafine in the epidermis was $\mu\text{g}/\text{mL}$ and the concentration in the dermis was $\mu\text{g}/\text{mL}$. Since the *in vitro* studies showed butenafine MIC values for the common dermatophytes ranging between $\mu\text{g}/\text{mL}$ and MLC levels only slightly higher than these values, it appears that the drug is present in the epidermis at a minimum of approximately 500 times the MIC levels and in the dermis at a minimum of approximately 15 times the MIC levels. These levels are above the fungicidal level for these organisms. It appears that when dosed as indicated in the NDA that butenafine HCl is fungicidal for most dermatophytes.

The sponsor has included the statement "Depending on the concentration of the drug and the fungal species tested, the antifungal allylamines are not only fungistatic, but also fungicidal." This statement is appropriate for the labeling. 

FACTORS INFLUENCING *IN VITRO* ACTIVITY

Study E-8 (11) studied the *in vitro* activity of butenafine against *Candida albicans* at various pHs. In this experiment *Candida albicans*: MTU 12021 and *Candida albicans* KC-36 were inoculated into Sabouraud's dextrose broth to a final fungal concentration of 1×10^3 /mL and the pH of the media was adjusted from 5.0 to 8.0. Serial two-fold dilutions of butenafine were prepared and added to the above media. The lowest concentration at which no fungal growth was observed was taken as the MIC. The results of this experiment are shown in Table 26.

Table 26
In Vitro Anti-*C. albicans* Activity of Butenafine in Sabouraud's Dextrose Broth with Different pH Values

Organism	MIC (μ g/mL) in medium with pH values of:				
	5.0	5.9	6.0	7.0	8.0
<i>C. albicans</i> MTU 12021	25	>100	>100	>100	>100
<i>C. albicans</i> KC-36	25	>100	>100	>100	>100

In the same study the activity of butenafine was determined against 47 clinical isolates of *Candida albicans* in non-adjusted Sabouraud's dextrose broth (pH 5.9) and in broth adjusted to pH 5.0. The results are seen in table 27.

Table 27
In Vitro Activity of Butenafine Against Clinical Isolates of *C. albicans* in Sabouraud's Dextrose Broth with Two Different pH Values

Organism	Number of strains	Medium pH value	Cumulative % of strains inhibited at drug concentration (μ g/mL)							Geometric mean value
			3.13	6.25	12.5	25	50	100	>100	
<i>C. albicans</i>	57	5.9						7	100	>100
		5.0	4	7	11	63	100			27

Both of these experiments show that the pH of the media can affect the activity of butenafine against *Candida albicans*. At pH 5.0 the mean geometric mean is 27 $\mu\text{g}/\text{mL}$ and 100% of the 57 clinical isolates have MIC values of 50 $\mu\text{g}/\text{mL}$ or below. At pH values of 5.9 or above the MIC values for most isolates is >100 $\mu\text{g}/\text{mL}$. This decreased potency at higher pH may be related to the solubility of the drug. The solubility of butenafine in 0.1M acetic acid buffer solution is 303 $\mu\text{g}/\text{mL}$ at pH 4.4, 69.8 $\mu\text{g}/\text{mL}$ at pH 5.0, and 18.1 $\mu\text{g}/\text{mL}$ at pH 6.22. Decreased solubility in the media may account for higher MIC values in media at pH values of 5.9 or above. Various pH values have been reported for human skin ranging from 3.0-5.0; 4.2-5.6; and 5.2-6.4. These studies indicate that the pH of skin is usually around 5.0, which is the pH at which butenafine showed the best activity at least against *C. albicans*.

In Study E-9 (12) the authors tested the anti-*Candida* activity of butenafine, naftifine, tolnaftate, and clotrimazole in Sabouraud's dextrose agar (pH 5.9) and in this same medium adjusted to pH 5, 6, 7, and 8. They also determined MICs of various *Candida* species in malt extract broth at pH 4.9. The results of these studies can be seen in tables 28 and 29.

Table 28
 Effect of Butenafine on Anti-Candida Activity in
 Sabouraud Dextrose Agar with Different pH Values

Organism	pH	MIC (µg/mL)			
		Butenafine	Naftifine	Tolnaftate	Clotrimazole
<i>C. albicans</i> ATCC 10259	No Correction	100	100	>100	3.13
	5	25	>100	>100	6.25
	6	>100	100	>100	1.56
	7	>100	>100	>100	1.56
	8	>100	>100	>100	0.78
<i>C. albicans</i> ATCC 10261	No Correction	>100	>100	>100	3.13
	5	25	>100	>100	6.25
	6	>100	>100	>100	3.13
	7	>100	>100	>100	1.56
	8	>100	>100	>100	1.56
<i>C. tropicalis</i> N 17495	No Correction	3.13	6.25	>100	0.1
	5	3.13	25	>100	0.2
	6	3.13	6.25	>100	0.1
	7	6.25	1.56	>100	0.1
	8	6.25	0.78	>100	0.5
<i>C. tropicalis</i> KC-103	No Correction	>100	>100	>100	1.56
	5	25	>100	>100	3.13
	6	>100	>100	>100	1.56
	7	>100	>100	>100	0.78
	8	>100	>100	>100	0.39
<i>C. krusei</i> KC-106	No Correction	25	>100	>100	0.2
	5	12.5	>100	>100	0.2
	6	25	>100	>100	0.2
	7	>100	>100	>100	0.1
	8	>100	>100	>100	0.2
<i>C. parapsilosis</i> KC-108	No Correction	3.13	12.5	>100	0.1
	5	3.13	25	>100	0.1
	6	6.25	12.5	>100	0.1
	7	50	12.5	>100	0.1
	8	>100	12.5	>100	0.05
<i>C. guilliermondii</i> KC-112	No Correction	1.56	25	>100	0.05
	5	56	50	>100	0.1
	6	1.56	25	>100	0.05
	7	6.25	25	>100	0.05
	8	>100	25	>100	0.05
<i>C. stellatokeles</i> KC-113	No Correction	6.25	12.5	>100	0.1
	5	6.25	50	>100	0.2
	6	12.5	6.25	>100	0.1
	7	25.5	3.25	>100	0.1
	8	50	1.56	>100	0.05

No Correction = pH 5.9

Table 29
 MICs Against Yeast Determined by Broth Dilution
 Employing Malt Extract Broth Medium (pH 4.9)

Organism	Number of Isolates	Compounds	MIC (μ g/mL)
<i>Candida albicans</i>	57	Butenafine	19.5* (1.56-50)**
		Clotrimazole	3.7 (0.1-12.5)
		Bifonazole	12.8 (3.13-25)
		Miconazole	3.9 (0.1-12.5)
<i>Candida parapsilosis</i>	2	Butenafine	0.78, 3.13
		Clotrimazole	0.2, 0.39
		Bifonazole	12.5, 12.5
		Miconazole	0.39, 1.56
<i>Candida tropicalis</i>	4	Butenafine	6.25, 6.25, 25, 25
		Clotrimazole	0.78, 1.56, 6.25, 6.25
		Bifonazole	6.25, 12.5, 25, 25
		Miconazole	0.39, 3.13, 3.13, 6.25
<i>Candida Krusei</i>	2	Butenafine	6.25, 12.5
		Clotrimazole	0.39, 1.56
		Bifonazole	12.5, 12.5
		Miconazole	1.56, 3.13
<i>Candida guilliermondii</i>	1	Butenafine	3.13
		Clotrimazole	0.2
		Bifonazole	12.5
		Miconazole	0.39
<i>Candida stellatoidea</i>	1	Butenafine	6.25
		Clotrimazole	0.39
		Bifonazole	6.25
		Miconazole	0.39
<i>Cryptococcus neoformans</i>	4	Butenafine	1.56, 1.56, 3.13, 3.13
		Clotrimazole	0.2, 0.39, 0.39, 0.39
		Bifonazole	1.56, 3.13, 3.13, 3.13
		Miconazole	0.2, 0.2, 0.2, 0.2

* Geometric Mean
 ** (Minimum-Maximum MIC)

This study once again showed that the activity of butenafine decreased with increasing pH when tested against *Candida*. Of the four compounds tested using Sabouraud's dextrose agar, clotrimazole was the only compound that showed good activity. Tolnaftate was inactive at all pH values and for all the tested organisms. Unlike the activity of butenafine, the activities of naftifine and clotrimazole tended to increase with higher pH values. When tested using a broth dilution method and malt extract broth the MIC values for butenafine were close to

those observed using Sabouraud's dextrose agar at a pH of 5. Studies E-8 and E-9 both tested 57 isolates of *Candida albicans*, and although the studies do not state that the same isolates were tested the geometric mean MIC using Sabouraud's dextrose agar (adjusted to pH 5.0) in Study E-8 was 27 μ g/mL and the geometric mean using malt extract agar (pH 4.9) in Study E-9 was 19.5 μ g/mL. In both studies when single species were tested the MIC in Sabouraud's at pH 5 was 25 to 50 μ g/mL. These studies indicate that at least for *Candida* the potency of butenafine is greatest around pH 5 (lower pHs were not tested). The type of media and method used (agar dilution vs broth dilution) also are less important than the pH value of the media. This pH value is close to the pH of skin, which is where the drug will be used.

No studies were conducted with dermatophytes (yeast are easier to work with) which would have been the better organisms to study since this product has better activity against dermatophytes and will be used against them.

ACTIVITY OF DEGRADATION PRODUCTS

In Study E-13 (13) the authors investigated the *in vitro* activities of butenafine with regard to its photo-decomposition (D1), thermal-degradation products (D2, D3), and metabolites (M1, M2, M3). Of all these compounds only M2 demonstrated any activity. The MICs for M2 were 0.78-6.25 μ g/mL for dermatophytes and 1.56-100 μ g/mL against *Aspergillus* species. Against yeast-form fungi the MIC was >100 μ g/mL. The potency of M2 was usually less than 1/32 that of butenafine. Table 30 shows the results of this study. Figure 1 shows the chemical structure of butenafine and its decomposition products and metabolites.

Table 30

Table 30 Antifungal activities of decompositions and metabolites of KP-363 against pathogenic fungi

Organism	MIC ($\mu\text{g/ml}$)								
	D1	D2	D3	M1	M2	M3	KP-363	CTZ	BF
<i>T. mentagrophytes</i> KD-01	>100	>100	>100	>100	0.78	>100	0.0125	0.39	1.56
<i>T. mentagrophytes</i> KD-04	>100	>100	>100	>100	1.56	>100	0.025	0.39	0.2
<i>T. mentagrophytes</i> KD-16	>100	>100	>100	>100	3.13	>100	0.0125	0.39	1.56
<i>T. rubrum</i> KC-101	>100	>100	>100	>100	0.78	>100	0.0125	0.39	0.78
<i>T. rubrum</i> KC-109	100	>100	>100	>100	0.78	>100	0.006	0.2	0.78
<i>T. rubrum</i> KC-114	>100	>100	>100	>100	0.78	>100	0.0125	0.39	1.56
<i>T. rubrum</i> KC-124	>100	100	>100	>100	0.78	>100	0.0125	0.39	1.56
<i>T. rubrum</i> KC-133	>100	>100	>100	>100	0.78	>100	0.006	0.39	0.78
<i>M. canis</i> KD-305	>100	>100	100	>100	3.13	>100	0.025	0.39	3.13
<i>M. cookei</i> KD-322	>100	>100	>100	>100	3.13	>100	0.025	1.56	6.25
<i>M. ferruginea</i> KD-324	>100	>100	>100	>100	3.13	>100	0.0125	0.39	1.56
<i>M. gypseum</i> KD-326	>100	100	>100	>100	0.78	>100	0.0125	0.78	3.13
<i>M. gypseum</i> KD-327	>100	>100	>100	>100	1.56	>100	0.025	0.78	6.25
<i>E. floccosum</i> KD-401	>100	>100	>100	>100	1.56	>100	0.0125	0.39	0.1
<i>E. floccosum</i> KD-402	>100	>100	>100	>100	6.25	>100	0.025	0.39	0.1
<i>C. albicans</i> YU-1200	>100	>100	>100	>100	>100	>100	>100	6.25	12.5
<i>C. albicans</i> MTU-12021	>100	>100	>100	>100	>100	>100	>100	6.25	12.5
<i>C. tropicalis</i> NI-7495	>100	>100	>100	>100	>100	>100	3.13	0.39	1.56
<i>C. Kursei</i> NI-7492	>100	>100	>100	>100	>100	>100	6.25	0.39	6.25
<i>C. parapsilosis</i> NI-7493	>100	>100	>100	>100	>100	>100	3.13	0.2	12.5
<i>C. guilliermondii</i> CBS-2082	>100	>100	>100	>100	>100	>100	3.13	0.39	12.5
<i>C. stellatoidea</i> ATCC-10264	>100	>100	>100	>100	>100	>100	6.25	0.39	6.25
<i>C. utilis</i> IPCR	>100	>100	>100	>100	>100	>100	3.13	0.78	6.25
<i>C. neoformans</i> NI-7496	>100	>100	>100	>100	>100	>100	0.78	0.39	1.56
<i>C. neoformans</i> NUDO-83264	>100	>100	>100	>100	>100	>100	0.2	0.78	0.78
<i>A. fumigatus</i> NI-5561	>100	>100	>100	>100	100	>100	0.2	1.56	1.56
<i>A. fumigatus</i> NUDO-7632	>100	>100	>100	>100	100	>100	0.2	1.56	1.56
<i>A. flavus</i> ATCC-9643	>100	>100	>100	>100	1.56	>100	<0.1	0.39	0.39
<i>A. flavus</i> NUD-4501	>100	>100	>100	>100	6.25	>100	<0.1	1.56	6.25
<i>A. niger</i> NUD-3235	>100	>100	>100	>100	25	>100	0.2	6.25	25
<i>A. niger</i> NUD-4861	>100	>100	>100	>100	12.5	>100	0.2	3.13	3.13
<i>A. terreus</i> NUD-3265	>100	>100	>100	>100	6.25	>100	0.2	3.13	1.56
<i>A. terreus</i> NUD-7634	>100	>100	>100	>100	6.25	>100	0.2	1.56	0.78
<i>A. nidulans</i> NUDO-7633	>100	>100	>100	>100	25	>100	0.1	0.39	3.13
<i>S. schenckii</i> KD-504	>100	>100	>100	>100	25	>100	0.39	12.5	12.5
<i>E. dermatitidis</i> KD-505	>100	>100	>100	>100	>100	>100	0.39	3.13	0.78
<i>F. pedrosoi</i> KD-507	>100	>100	>100	>100	>100	>100	0.78	12.5	1.56
<i>N. asteroides</i> KD-509	>100	>100	>100	>100	>100	>100	>100	3.13	6.25

Note) CTZ: clotrimazole, BF: bifonazole

Figure 1

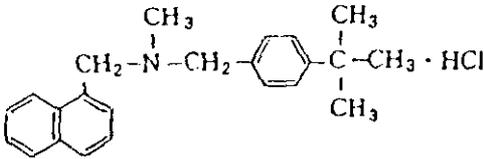
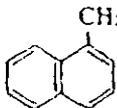
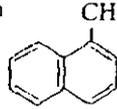
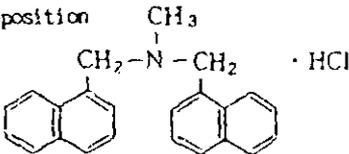
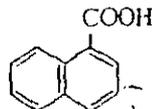
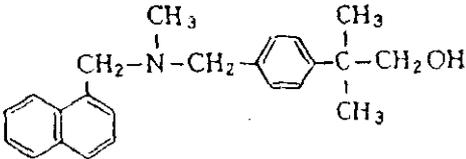
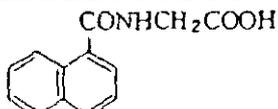
Abbreviations		Chemical structure and chemical name
KP - 363		 <p><i>N</i>-4-<i>tert</i>-butylbenzyl-<i>N</i>-methyl-1-naphthalenemethylamine hydrochloride</p>
Decompositions	D 1	<p>Photodecomposition</p>  <p>1-naphthalenemethanol</p>
	D 2	<p>Thermal decomposition</p>  <p>1-(chloromethyl)naphthalene</p>
	D 3	<p>Thermal decomposition</p>  <p><i>N</i>-methyl-bis(1-naphthalenemethyl)amine hydrochloride</p>
Metabolites	M 1	 <p>1-naphthoic acid</p>
	M 2	 <p><i>N</i>-4-(2-hydroxy-1,1-dimethylethyl)benzyl-<i>N</i>-methyl-1-naphthalenemethylamine</p>
	M 3	 <p><i>N</i>-1-naphthoylethylglycine</p>

Fig. 1. Chemical structure of KP 363 decompositions and metabolites

From NDA 20-524

ASSESSMENT OF RESISTANCE STUDIES

Study E-4 (14) investigated the acquisition of resistance to butenafine by *Trichophyton mentagrophytes* and *Cryptococcus neoformans*. An agar dilution method employing serial doubling dilutions of drug in Sabouraud's dextrose agar was used. MICs for the two organisms were determined and the procedure was repeated 10 times, each time using cells that had grown at the highest drug concentration to prepare fresh inoculum for testing the next generation. An inoculum of 10^6 cells/plate was used. Incubation was at 27°C for 7 days in the case of *T. mentagrophytes* and at 30°C for 3 days in the case of *C. neoformans*.

When butenafine was tested the MIC value for *T. mentagrophytes* increased from $\mu\text{g/mL}$ to $\mu\text{g/mL}$ (one dilution) at the fifth generation and remained at this concentration through the rest of the testing. The MIC for *C. neoformans* increased from $\mu\text{g/mL}$ to $\mu\text{g/mL}$ (one dilution) at the sixth generation time point and remained at this concentration. When clotrimazole was tested the MIC for *T. mentagrophytes* increased from $\mu\text{g/mL}$ to $\mu\text{g/mL}$ (one dilution) at the fifth generation and remained at this concentration through the rest of the testing. The MIC for *C. neoformans* increased from $\mu\text{g/mL}$ to $\mu\text{g/mL}$ (one dilution) at the second generation time point, to $\mu\text{g/mL}$ at the fourth generation and increased to $\mu\text{g/mL}$ at the fifth generation. This is an eight-fold increase for clotrimazole, which has been used against fungi for many years without a major problem. The 2-fold increase shown when butenafine was tested indicates that it is unlikely for these fungi to acquire resistance to this drug.

Study E-11 (3) in which tolclolate-resistant strains of *Sporothrix schenckii* were tested showed that the tolclolate-resistant strains needed a slightly higher concentration of butenafine to give a 50% reduction in growth, but that these concentrations were still very low ($\mu\text{g/mL}$) and these strains would probably still be susceptible to butenafine in clinical use [see Table 5].

No further studies evaluating the mechanism of any resistance that might develop were submitted. No studies involving mutations in the squalene epoxidase gene were performed. No studies looking for permeability mutations that would block the drug from entering the cell were performed, but this may not be important since the drug itself has a direct membrane-damaging effect which is augmented by its ability to inhibit squalene epoxidase. As seen in Study E-1, the antifungal spectrum appears to be similar to that of naftifine, another allylamine drug with the same mechanism of action. The activity of butenafine against the dermatophytes is 2-16 times as strong as that of naftifine, however, so even strains resistant to naftifine may still be susceptible to butenafine although butenafine's MIC may be elevated. Since a different point in the synthesis of ergosterol is blocked by butenafine and the azoles, strains resistant to the azoles, may still be susceptible to butenafine.

PRECLINICAL EFFICACY (IN VIVO)

PHARMACOKINETICS/BIOAVAILABILITY

The information in this section is taken from the studies submitted in the NDA and have not been evaluated by a Biopharmaceutical Reviewer at the present time.

Results from two clinical pharmacokinetic studies and a Phase 3 clinical trial indicate that under conditions of therapeutic dosing for the treatment of tinea pedis or exaggerated dosing in normal subjects there is low absorption of butenafine from the drug formulation.

In the first pharmacokinetic study, subjects that were dosed for 14 consecutive days at 20 times the intended daily clinical dose had average maximal butenafine plasma concentrations of 5 ng/mL. When subjects were dosed at six times the intended clinical dose, maximal plasma levels were approximately 1.4 ng/mL.

In the other pharmacokinetic study, after single clinical doses of butenafine, plasma levels of unchanged drug increased slowly until the drug was removed from the skin surface twelve hours after dosing. After the drug was removed, plasma levels decreased slowly. Plasma $T_{1/2}$ during the later phase was 23.4 hours, but could not be definitively determined due to low plasma levels and differences between subjects. Average C_{max} was 4.0 ng/mL. When dosed once a day for 7 days, plasma levels increased slowly every day until the 12th hour after dosing, when the drug was removed. Average C_{max} on the first day was 4.1 ng/mL, and average C_{max} of the second to seventh days ranged from 4.1 ng/mL. Excretion of unchanged butenafine in the urine was less than 0.01% of the dosed amount in both the single and multiple dosing studies. About 72-86% of the drug formulation was recovered from the surface of the skin when the drug was removed 12 hours after application. Penetration into the stratum corneum was about 20% of the dose.

In the Phase 3 study butenafine and M2 plasma levels were studied in 12 patients. Butenafine was applied by the patient once daily for 4 weeks. Blood plasma samples were obtained 11 to 19 hours after the last dose was applied at 1, 2, and 4 weeks after treatment was started and four weeks after cessation of treatment. The average plasma level of butenafine was 0.11 ng/mL, with a range from undetectable to 0.30 ng/mL. The concentration of M2, in plasma was below the level of detection (0.1 ng/mL).

These studies indicate that absorption is minimal and that most of the drug remains on the skin.

The sponsor performed a study (Penederm Study PD188:39) to measure the concentration of butenafine in both the epidermal and dermal layers of human skin 24 hours after application of butenafine HCl Cream 1%. Radiolabeled drug was applied to human skin at a dose of 5 mg/cm², and after 24 hours of exposure, the skin was given a mild detergent wash (simulating actual use conditions at the trough level) prior to measuring drug concentrations. The concentration of butenafine in the epidermis was _____ μg/mL and the concentration in the dermis was _____ μg/mL. Since the *in vitro* studies showed butenafine MIC values for the common dermatophytes ranging between _____ μg/mL and MLC levels only slightly higher than these values, it appears that the drug is present in the epidermis at a minimum of approximately 500 times the MIC levels and in the dermis at a minimum of approximately 15 times the MIC levels. These levels are above the fungicidal level for these organisms. It appears that when dosed as indicated in the NDA that butenafine HCl is fungicidal for most dermatophytes.

ANIMAL PROPHYLACTIC AND THERAPEUTIC STUDIES

The NDA contains five studies in guinea pigs showing the *in vivo* activity of the topical application of butenafine cream.

Arika et al (15) investigated butenafine for its activity against guinea pig dermatophytosis caused by *Trichophyton mentagrophytes* KD-04 or *Microsporum canis* KD-305 in comparison with the activity of naftifine, tolnaftate, clotrimazole, and bifonazole. The MIC values of butenafine was 0.012 μ g/mL for *T. mentagrophytes* and 0.025 μ g/mL for *M. canis*. The MIC values for naftifine, tolnaftate, clotrimazole and bifonazole were 0.05, 0.20, 0.39, and 0.78 μ g/mL, respectively, for *T. mentagrophytes*. The MIC values for naftifine, tolnaftate, clotrimazole and bifonazole were 0.10, 0.39, 0.78, and 1.56 μ g/mL, respectively, for *M. canis*. Hair was plucked by hand from a 3 x 3 cm area on the backs of the guinea pigs to make a hairless square. On the following day, the skin was lightly abraded with sandpaper, and 50 μ l of inoculum (10^6 cells) were applied with a glass rod. Each animal was topically treated with 0.2 mL of a 0.01%, 0.1% or 1.0 % solution of the test drug. Treatment was started on day 2, 3 or 4 postinfection and was continued for 4 or 10 days. Two days after the last treatment, all animals were sacrificed and 10 skin sections were obtained from each treated site. Each section was implanted onto a Sabouraud dextrose agar plate and all plates were incubated at 27°C for 10 days. The treatment was assessed as effective if no fungal growth was seen. To test the prophylactic effect of the drugs a hairless area was produced on the back of the animals and the following day the skin was treated with 0.2 mL of a 1% solution of butenafine or bifonazole. At 24, 48, or 72 hours after drug application, 50 μ l (10^6 cells) of *T. mentagrophytes* was rubbed onto the pretreated area. Before infection the unabsorbed drug was wiped off with a cotton swab. All infected sites were visually examined daily throughout the experimental period. On day 17 postinfection, culture studies as described above were performed.

The results of the first experiment, in which once daily topical treatment with 0.01, 0.1, and 1.0% solutions of butenafine and the reference drugs was started on day 2 postinfection and continued for 4 or 10 days are shown in Table 31.

Table 31
 Efficiencies of butenafine and reference drugs against
T. mentagrophytes infection after once daily application
 for 4 to 10 days starting on day 2 after infection

Treatment	Duration of Treatment	No. (%) of skin sections with negative cultures (n=50)
0.01% Butenafine	10	30 (60)
0.1% Butenafine	10	47 (94)
1.0% Butenafine	10	50 (100)
0.01% Naftifine	10	2 (4)
0.1% Naftifine	10	29 (58)
1.0 % Naftifine	10	50 (100)
0.01% Tolnaftate	10	5 (10)
0.1% Tolnaftate	10	20 (40)
1.0% Tolnaftate	10	50 (100)
1.0% Clotrimazole	10	14 (28)
Placebo (PEG-ethanol)	10	0 (0)
Placebo (PEG-acetone)	10	0(0)
NONE	10	0(0)
1% Butenafine	4	50 (100)
1% Naftifine	4	41 (82)
1% Tolnaftate	4	32 (64)
NONE	4	0(0)

Table 31 shows that a 1.0% solution of butenafine, naftifine, or tolnaftate was satisfactory with a complete eradication of fungi from the infective site, while clotrimazole at the same concentration only led to 28% negative cultures. The negative rate with 0.1 and 0.01% solutions of butenafine were 94 and 60%, respectively. Comparable concentrations of naftifine and tolnaftate were less effective. When treated for only 4 days instead of 10 days, a 1% solution of butenafine completely cured the *T. mentagrophytes* infection, while the cure rates with naftifine and tolnaftate were 82 and 64%, respectively.

When once daily treatment was started on day 3 or 4 after infection and was continued for 4 or 10 days, butenafine was again effective against *T. mentagrophytes* infection, but 10 days was needed to eradicate fungi from the lesions [Table 32].

Table 32
 Efficiencies of butenafine and naftifine against
T. mentagrophytes infection after once daily application
 for 4 to 10 days starting on day 3 or 4 after infection

Treatment	Treatment period (days)	No. (%) of skin sections with negative cultures (n=50)
1.0% Butenafine	3-6	39 (78)
1.0% Naftifine	3-6	8 (16)
NONE		0 (0)
1.0% Butenafine	3-12	50 (100)
1.0% Naftifine	3-12	45 (90)
NONE		0 (0)
1.0% Butenafine	4-7	19 (38)
1.0% Naftifine	4-7	8 (16)
NONE		0 (0)
1.0% Butenafine	4-13	50 (100)
1.0% Naftifine	4-13	26 (52)
NONE		0 (0)

In a third experiment the therapeutic efficacies of two different butenafine treatment regimens were compared. Once or twice daily treatments with 0.125, 0.25, 0.5, and 1.0% solutions of butenafine was started on day 4 postinfection and was continued for 10 days. Table 33 shows the results of this experiment.

Table 33
 Efficiencies of butenafine against *T. mentagrophytes*
 infection after once or twice daily application
 for 10 days starting on 4 after infection

Treatment	No. (%) of skin sections with negative cultures (n=50)
0.125% Butenafine	
Once daily	25 (50)
Twice daily	36 (72)
0.25% Butenafine	
Once daily	30 (60)
Twice daily	40 (80)
0.5% Butenafine	
Once daily	48 (96)
Twice daily	50 (100)
1.0% Butenafine	
Once daily	50 (100)
Twice daily	50 (100)

As seen in the above table the therapeutic efficacy of twice daily treatment with a 0.125 or 0.25% solution was better than that of once daily treatment. However, once daily treatments with 0.5 or 1% solutions of butenafine gave a 100% cure.

The activity of the drugs against *M. canis* was also evaluated. Only daily topical treatment with a 0.1 or 1.0% solution of butenafine or the reference drugs was started on day 2 or 4 postinfection and was continued for 10 days. Table 34 shows the results of this experiment. As the table shows the results are similar to those seen for *T. mentagrophytes*.

Table 34
 Efficiencies of butenafine and reference drugs against
M. canis infection after once daily application
 for 10 days starting on day 2 or 4 after infection

Treatment	Treatment Period (days)	No. (%) of skin sections with negative cultures (n=50)
0.1% Butenafine	2-11	47 (94)
1.0% Butenafine	2-11	50 (100)
0.1% Naftifine	2-11	21 (42)
1.0% Naftifine	2-11	50 (100)
0.1% Tolnaftate	2-11	8 (16)
1.0 % Tolnaftate	2-11	42 (84)
1.0% Clotrimazole	2-11	30 (60)
Placebo (PEG-ethanol)	2-11	0 (0)
Placebo (PEG-acetone)	2-11	0(0)
NONE	2-11	0(0)
1% Butenafine	4-13	49 (98)
1% Naftifine	4-13	39 (78)
1% Tolnaftate	4-13	24 (48)
NONE	4-13	0(0)

When guinea pigs were pretreated with 0.2 mL of a 1% solution of the drugs at 24, 48, or 72 hours before infection with *T. mentagrophytes*, lesions in the untreated group were the most intense. In the group treated with bifonazole 24

hours before infection, lesions developed in four of five animals on day 17 after infection. When a 1% solution of butenafine was used once at 24 or 48 hours before infection, no lesions developed. In the group pretreated with a 1% of butenafine 72 hours before infection, lesions developed in two of five animals. The concentration of butenafine in the skin of five guinea pigs was measured at 24, 48, and 72 hours after application of 0.2 mL of a 1% solution. The concentration of butenafine in the skin at 24 hours was $\mu\text{g/g}$ of tissue, and it gradually decreased to $\mu\text{g/g}$ at 48 hours and to $\mu\text{g/g}$ at 72 hours.

The experiments in this study show that butenafine 1% exhibits good therapeutic efficacy against *T. mentagrophytes* and *M. canis* infections when applied once daily for 10 days. Its effect is superior to that of naftifine, tolnaftate, and clotrimazole. Butenafine exerted prophylactic efficacy when applied even 48 hours before infection, but not up to 72 hours before. When the amount of drug in the skin was determined, the amount at 72 hours was still 730 times higher than the MIC or MFC (fungicidal) concentration. The explanation may be that the drug is bound to horny materials in the epidermis and the potency of the drug is reduced.

The dermatophytosis model tested in the above study (15) may not be as prolonged as it is in human dermatophytosis, such as tinea pedis. In Arika et al (16) the authors tested a new model of tinea pedis by inoculating *T. mentagrophytes* into the planta of guinea pigs. The infection lasts for more than six months without spontaneous healing and histopathologically and symptomatically mimics human infections. In this study male Hartley strain guinea pigs were divided into groups of 8 to 10 animals. Skin infection was induced by applying a paper disk with 50 μl (10^7 cells) of a suspension onto the planta with a form pad and fixing the pad in place with an adhesive elastic tape. The disk was removed on day 7 postinfection. Each animal was treated with 0.1 mL of the test compound as a solution or cream. The treatment with butenafine or reference drugs was started on day 10 postinfection (3 days after disk removal). On day 2 after the last treatment, all animals were sacrificed and the infected sites rinsed. Twelve skin sections were made from all parts of the infected planta. Each section was implanted onto a Sabouraud dextrose agar plate and cultured at 27 °C for 10 days. The treatment was assessed as effective if no growth was seen.

In the first experiment, once daily treatment with 0.2, 0.5, and 1.0% solutions of butenafine was started on day 10 postinfection and was continued for 20 days. The results of the culture studies performed with tissue specimens excised from the planta on day 31 postinfection are given in table 35.

Table 35
Efficacy of Butenafine Solution in Guinea
Pig Tinea Pedis once daily application for 20 days

Treatment	No. (%) of skin sections with negative cultures (n=240)	No. of feet with negative cultures (n=20)
0.2% Butenafine	152 (63.3)	0
0.5% Butenafine	179 (74.6)	4
1.0% Butenafine	219 (91.3)	10
Placebo (PEG-ethanol)	18 (7.5)	0
None	12 (5.0)	0

This table shows a dose-related therapeutic efficacy, with mycological eradication noted in 91.8% of skin sections treated with a 1% solution of butenafine.

In a second experiment, a 1% butenafine solution was compared to a 1% naftifine, 2% tolnaftate, and a 1% clotrimazole solution. In another study 1% creams were tested and compared. The results of these two experiments are shown in Table 36

Table 36
 Efficacy of Butenafine and Reference Drugs in Guinea
 Pig Tinea Pedis once daily application for 20 days

Treatment	No. of skin sections with negative cultures/total no. of skin sections from infected sites (%)	No. of feet with negative cultures/total no.
1% Butenafine Solution	214/240 (89.2)	9/20
1% Naftifine Solution	209/240 (87.1)	6/20
2% Tolnaftate Solution	153/240 (63.8)	4/20
1% Clotrimazole Solution	95/240 (39.6)	0/20
NONE	40/240 (16.7)	0/20
1% Butenafine Cream	170/192 (88.5)	9/16
1% Bifonazole Cream	60/192 (31.3)	0/16
1% Clotrimazole Cream	52/192 (27.1)	0/16
NONE	18/192 (9.4)	0/16

This table shows that butenafine was superior to tolnaftate and clotrimazole. Naftifine exhibited activity that was almost the same as that of butenafine. Butenafine and clotrimazole creams exhibited activities that were about the same as their solutions. Butenafine cream was superior to bifonazole and clotrimazole creams. The product of this NDA is a butenafine 1% cream so this experiment represents the same type of product and the same type of infection.

When compared to the study of conventional dermatophytosis models (14), in which 0.01 to 1.0% solutions of butenafine showed excellent efficacy when applied topically for 10 days, this model of tinea pedis needed a longer duration of treatment. There is a difference in the thickness of the horny layer between the dorsal skin and the planta in guinea pigs and this difference may play a part in the efficacies of antifungal agents. Tinea pedis usually responds to chemotherapy to a lesser extent than does tinea corporis or tinea cruris. The tinea pedis model in guinea pigs is probably the most appropriate model for prediction of activity of antifungal agents against tinea pedis in humans. The results of both papers indicate that butenafine may be promising for the treatment of all types of dermatophytosis, including tinea pedis.

In Study E-6 (17), the effect of butenafine on experimental tinea pedis in guinea pigs was studied using the same testing method as in the study above. In this study the duration and frequency of administration was changed. Butenafine solution of 0.25% to 2.0% was topically applied once or twice daily for 10 to 40 days. The therapeutic effect was evaluated by the cultured skin specimens from infected sites. Five animals were used in each group. Twelve skin tissue sections were cut from the whole infected plantar. Treatment with butenafine was started on day 10 of infection (3 days after removal of the disk), the same as in the previous study. Butenafine was applied at a concentration of 0.25%, 0.5%, 1.0% or 2.0% once or twice daily for 20 days. Culture of skin specimens were conducted two days after the final treatment (day 31 of infection). Table 37 shows the results of this experiment.

Table 37
 Efficacy of Butenafine Solutions in Guinea
 Pig Tinea Pedis Once or Twice Daily for 20 Days

Treatment	No. (%) of skin sections with negative cultures (n-120)
0.25% Butenafine Solution Once daily	80 (66.7)
0.25% Butenafine Solution Twice daily	85 (70.8)
0.5% Butenafine Solution Once daily	86 (71.7)
0.5% Butenafine Solution Twice daily	97 (80.8)
1.0% Butenafine Solution Once daily	108 (90.0)
1.0% Butenafine Solution Twice daily	110 (91.7)
2.0% Butenafine Solution Once daily	110 (91.7)
2.0% Butenafine Solution Twice daily	112 (93.3)
NO Treatment	11 (9.2)

The above table shows a dose dependent effect between 0.25% and 1.0% butenafine. There was no difference in efficacy between the group treated with 1% and 2% butenafine. There was also only a slight difference between the once daily and twice daily treatments. The difference between the once daily and twice daily dosing was not significant ($p < 0.05$). The results of this study are almost identical to Arika et al (16) in which the same method was used. A comparison of table 35 from that study and the above table 37 can be made. In table 35 a 0.2%

solution of butenafine produced 63.3% of skin sections with negative cultures and in table 37 a 0.25% solution produced 66.7%. A 0.5 % solution produced 74.6% negative cultures in table 35 and 71.7% in table 37; a 1.0% solution produced 91.3% negative cultures in table 35 and 90.0% in table 37. Both these experiments also show that a 1% solution dosed once a day gives excellent results. A 2% solution or twice daily application is no better than a 1% solution dosed once daily.

In this same study another experiment was performed to study the relation between the duration of treatment and its effect. Treatment was started on day 10 of infection as usual. The 1% solution was applied once daily for 10, 20, or 40 days. The results are shown in Table 38.

Table 38
 Efficacy of 1% Butenafine Solution in Guinea
 Pig Tinea Pedis Once Daily for 10, 20 or 40 days

Treatment	Duration of Treatment (days)	No. (%) of skin sections with negative cultures (n=120)	No. of feet with negative cultures (n=20)
1% Butenafine	10	85 (70.8)	2
No Treatment		32 (26.7)	0
1% Butenafine	20	108 (90.0)	5
No Treatment		15 (12.5)	0
1% Butenafine	40	113 (94.2)	8
No Treatment		1 (0.8)	0

The above table shows that the longer the treatment duration, the better the efficacy. The product in the NDA is dosed once daily for 4 weeks (28 days), which is between the two longest periods in the above study. It appears that the increase in efficacy between the two longest dosing periods may not be as great, especially when looking at the number of negative cultures from skin section, between these two dosing schedules as between dosing for 10 days versus 20 days. Dosing for 4 weeks should give good results and may help patients comply with the dosing schedule.

In Study E-7 (18) the authors studied the permeability and retentivity of butenafine on the skin layers of guinea pigs following percutaneous application. Two-tenths of a milliliter of a 1% ¹⁴C-butenafine solution on gauze was applied for six hours to shaven areas of the dorsal skin of guinea pigs. The gauze was sealed

to the site with Parafilm. Using cotton and ethanol the unabsorbed drug was removed six hours after attachment. The animals were killed either six or 24 hours after attachment, and the skin was cut to prepare 50 μm frozen sections in parallel to the skin surface. Using liquid scintillation counting the radioactivity in each section was determined. The curve for the six hour and 24 hour after applications removal were similar, although the six hour curve gave slightly higher radioactive counts for each depth. High concentrations of the drug (radioactive counts of about dpm (disintegrations per minute) were seen between μm of the epidermis. These high counts indicated drug concentrations above 50 $\mu\text{g/g}$ of skin. The curves decrease rapidly from about dpm to about dpm ($\mu\text{g/g}$) at a depth of about 1000 μm . The curves then decreased at a slower rate until no drug (radioactivity) was detected below about 2300 μm of skin depth. There were several peaks seen in the 1,000 to 2,000 μm range which may indicate adsorption into hair follicles. This experiment indicates that butenafine is present in the epidermis including the horny layer where dermatophytes hang out at concentrations of over 10 $\mu\text{g/g}$.

In this same study the authors investigated the antifungal action of drug adsorbed to hair. Powdered hair was put into a test tube with dipotassium phosphate, magnesium sulfate, and calcium chloride. Serially two-fold dilutions of butenafine or a reference drug (tolnaftate, clotrimazole, or bifonazole) was added. This solution was shaken at 30°C for one hour to adsorb drug to the hair. A suspension of 2×10^4 cells/tube of *T. mentagrophytes* was inoculated into the tubes and cultured at 30°C for 7 days. In another experiment drug and hair were shaken for one hour and then the unadsorbed drug was removed and then the above chemical solution and organism was incubated. Minimum inhibition concentrations were observed and compared to MIC values in Sabouraud dextrose broth. The results of these experiments are shown in Table 39.

Table 39
 Effect of Powdered Human Hair on anti-*Trichophyton mentagrophytes* Activity of Butenafine and Reference Drugs

Compound	MIC ($\mu\text{g/g}$ hair)		MIC ($\mu\text{g/mL}$)
	Non-absorbed drug NOT removed	Non-absorbed drug removed	Sabouraud Dextrose Broth
Butenafine	4.0	4.0	0.0125
Tolnaftate	15.6	15.6	0.05
Clotrimazole	62.5	62.5	0.39
Bifonazole	62.5	62.5	0.39

The above table shows that the MIC values for butenafine and the reference drugs all increase when hair is the sole nutritious source, compared with the MIC values obtained in Sabouraud medium. The MIC of butenafine increased 320 times. The table also shows that adsorption to hair is intense, since removal of non-absorbed drug did not alter the MIC values. Butenafine was the most potent drug in all situations tested.

The fungi that cause tinea pedis are usually lodged very close to the surface of the skin and restricted to the horny layer and part of the follicles. This is where butenafine has its highest concentration after topical application. Since the concentration of drug in this layer appears to be greater than $10\mu\text{g/g}$, there should be enough drug present even for the higher MIC value observed when hair alone was the nutrient source.

In Study E-8 (11) the *in vivo* activity of butenafine against *Candida albicans* was studied. The dorsal hair of guinea pigs was shaved in one or two places per animal and 0.05 mL of fungal suspension containing 10^5 *Candida albicans* cells was applied to each shaved site. The infected sites were covered with parafilm and self-adhering foam pads. The sites were fixed with an adhesive bandage for 20 hours. Treatment with drugs started 24 hours after infection. Treatment was conducted by topically applying 0.2 mL of the drug twice a day for 7 days. The animals were killed the day following the final treatment. The infected skin was cleaned and cut out. Ten skin sections each measuring about 5 x 5 mm were cut out. These sections were incubated for 10 days at 37°C in *Candida* GS media. The ratio of skin sections with negative cultures against the total number of skin sections from the infected sites was calculated and the

therapeutic effect of the drug was evaluated. Table 40 shows the results of this experiment.

Table 40
Effect of Butenafine and Reference Drugs on Experimental Cutaneous
C. albicans infection in Guinea Pigs Applied Twice Daily for 7 days

Treatment	Number of animals	No. of skin sections with negative cultures/total number of skin sections from infected sites (%)
None	6	1/60 (1.7)
Placebo (PEG-ethanol)	6	19/60 (31.6)
1.0% Butenafine	6	36/60 (60.0)
1.0% Bifonazole	6	39/60 (65.0)
1.0% Miconazole	6	60/60 (100.0)

The MIC values of butenafine, bifonazole and miconazole against this challenged strain in Sabouraud dextrose broth (pH 5.0) was 25, 12.5 and 3.13 μ g/mL, respectively.

This table shows that the *in vivo* effect is related to the MIC of the drug. Once again it can be seen that butenafine is not a very good drug for infections caused by *Candida albicans*. The efficacy of butenafine in this experiment in which the skin infection was caused by *C. albicans* was only about 30%, while the efficacy in a similar experiment in which the infection was caused by *T. mentagrophytes* and butenafine was applied once daily for 10 days starting on day 2 postinfection was 100.0% [Table 31].

Together these five studies show that butenafine dosed topically once daily as a 1% solution of cream has good *in vivo* activity against dermatophytosis in guinea pigs caused by *T. mentagrophytes*. The efficacy is not as good, but is still very good when a guinea pig model of tinea pedis is used. The *in vivo* activity is not very good against *Candida albicans* infections.

CLINICAL EFFICACY

CLINICAL MICROBIOLOGY

Isolates/Relevance to Approved Indications

Two pivotal clinical studies were conducted in the United States, protocols PDC 010-001 and PDC 010-002. PDC 010-001 had six investigators and PDC 010-002 had four investigators. Both studies were double-blind, randomized, parallel, vehicle controlled studies. Drug was dosed once daily for 4 weeks in both studies and follow-up was at 8 weeks in both studies. In PDC 010-001 there were 53 butenafine and 52 vehicle patients who completed the study. In PDC 010-002 there were 40 butenafine and 40 vehicle patients who completed the study. Both KOH and culture results had to be negative at the eight week time point for a mycological cure.

There were three organisms that were considered to cause tinea pedis. These organisms were *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum*. Shown below are the results by investigator for each study. Only patients that had the organism present at baseline and had an 8-week follow-up visit are listed. In order to be cured (mycologically) both a negative KOH and culture had to be present at the 8-week time point.

STUDY PDC 010-001

Investigator: Karl R. Beutner, M.D.

<u>Pathogen</u>	<u>Treatment</u>	
	<u>Butenafine (cured/total)</u>	<u>Vehicle (cured/total)</u>
T. rubrum	1/1	---
T. mentagrophytes	---	---
E. floccosum	---	---

Investigator: Stanley I. Cullen, M.D.

T. rubrum	7/9	4/13
T. mentagrophytes	1/2	---
E. floccosum	1/1	---

Investigator: Blas A. Reyes, M.D.

T. rubrum	12/12	5/8
T. mentagrophytes	3/3	2/4
E. floccosum	---	0/1

Investigator: Theodore Rosen, M.D.

T. rubrum	5/7	3/9
T. mentagrophytes	1/1	---
E. floccosum	1/2	---

Investigator: Jerome L. Shupack, M.D.

T. rubrum	6/8	3/6
T. mentagrophytes	---	1/1
E. floccosum	1/1	---

Investigator: Mark B. Weinstein, M.D.

T. rubrum	4/4	3/6
T. mentagrophytes	---	---
E. floccosum	---	---

Totals Study PDC 010-001

T. rubrum	35/41 (85.4%)	18/42 (42.9%)
T. mentagrophytes	5/6 (83.3%)	3/5 (60.0%)
E. floccosum	3/4 (75.0%)	0/1 (0%)
Butenafine 43/51 (84.3% cured)		Vehicle 21/48 (43.8% cured)

STUDY PDC 010-002

Investigator: Boni E. Elewski

<u>Pathogen</u>	<u>Treatment</u>	
	<u>Butenafine (cured/total)</u>	<u>Vehicle (cured/total)</u>
T. rubrum	9/11	4/10
T. mentagrophytes	---	---
E. floccosum	---	---

Investigator: David C. Gorsulowsky, M.D.

T. rubrum	3/10	2/6
T. mentagrophytes	1/1	0/1
E. floccosum	---	---

Investigator: David M. Pariser, M.D.

T. rubrum	6/6	3/7
T. mentagrophytes	---	---
E. floccosum	---	---

Investigator: Eduardo Tschen, M.D.

T. rubrum	10/11	1/8
T. mentagrophytes	---	2/2
E. floccosum	1/1	---

Totals Study PDC 010-002

T. rubrum	33/38 (86.8%)	10/31 (32.3%)
T. mentagrophytes	1/1 (100%)	2/3 (66.6%)
E. floccosum	1/1 (100%)	0/0 (0%)

Butenafine 35/40 (87.5% cured)

Vehicle 12/34 (35.3% cured)

Total both studies:

T. rubrum	68/79 (86.1%)	28/73 (38.4%)
T. mentagrophytes	6/7 (85.7%)	5/8 (62.5%)
E. floccosum	4/5 (80.0%)	0/1 (0%)

Butenafine 78/91 (85.7% cured)

Vehicle 33/82 (40.2%)

Cure rates were about the same in both studies. Overall butenafine gave about an 85% mycological cure rate as opposed to a 40% mycological cure rate with the vehicle cream. Butenafine is mycologically effective in treating tinea pedis caused by *Trichophyton rubrum*, *Trichophyton mentagrophytes*, or *Epidermophyton floccosum*.

INTERPRETATIVE CRITERIA

Since the product in this application is a topical anti-fungal for dermatophytes there is no established *in vitro* susceptibility method and no correlation between *in vitro* testing (MICs or zone diameter) and clinical outcome has been established. No susceptibility breakpoints or quality control strains are established for this type of product.

PACKAGE INSERT

The MICROBIOLOGY subsection of the package insert should be rewritten as follows:

Page 63

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NDA 28-524

4 OF 5

**NDA 20-524
PENEDERM INC.
BUTENAFINE HCL CREAM 1%**

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The following information should be relayed to the sponsor:

The MICROBIOLOGY subsection of the package insert should be revised to read as follows:

NDA 20-524
PENEDERM INC.
BUTENAFINE HCL CREAM 1%

PAGE 67 OF 67

Peter A. Dionne

Peter A. Dionne
Review Microbiologist

cc: Orig. NDA 20-524
HFD-540/Division File
HFD-520/Micro/Dionne
HFD-540/MO/Slifman
HFD-540/Pharm/Mainigi
HFD-540/Chem/Pappas
HFD-540/CSO/Turtill

66 8/23/95

Concurrence Only:
HFD-540/Dir/JWilkin
HFD-520/SMicro/ATSheldon
RD init 8/9/95 Fin 8/16/95

8116195

MAR 5 1996

Consultative Review for HFD-540
Division of Topical Drug Products
Division of Anti-Infective Drug Products (HFD-520)
Microbiological Review

Requestor: Frank Cross, CSO HFD-540

Date of Request: February 29, 1996

Reason for Request: Microbiological Review fungicidal vs fungistatic issues

NDA #: 20-J24 MICRO REVIEW #: 2 REVIEW DATE: 05-MAR-96

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
CONSULT	29-FEB-96	----	05-MAR-96

NAME & ADDRESS OF APPLICANT: PENEDERM INCORPORATED
320 Lakeside Drive, Suite A
Foster City, CA 94404

CONTACT PERSON: Barry Calvarese, MS
Phone Number: (415) 358-0100
Fax Number: (415) 358-0101

DRUG PRODUCT NAME

<u>Proprietary:</u>	None
<u>Nonproprietary/USAN:</u>	Butenafine Hydrochloride Cream
<u>Code Names/#'s:</u>	KP-363
<u>Chemical Type/</u>	Antifungal
<u>Therapeutic Class:</u>	1 S

ANDA Suitability Petition/DESI/Patent Status:

Note Applicable

PHARMACOLOGICAL CATEGORY/INDICATION:

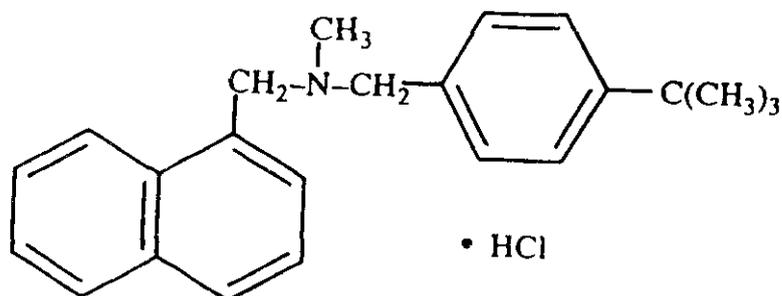
Antifungal/Interdigital Tinea pedis

<u>DOSAGE FORM:</u>	Cream
<u>STRENGTHS:</u>	1%
<u>ROUTE OF ADMINISTRATION:</u>	Topical
<u>DISPENSED:</u>	<input checked="" type="checkbox"/> Rx <input type="checkbox"/> OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOL. WT:**

Chemical Name: N-4-tert-Butylbenzyl-N-methyl-1-naphthalenemethylamine
Hydrochloride

Structural Formula:



$C_{23}H_{27}N \cdot HCl$
M.W. = 353.93

SUPPORTING DOCUMENTS:

DMF
DMF
DMF

DMF
IND

RELATED DOCUMENTS (if applicable): NONE

CONSULTS: HFD-540 has presented reviews of NDA 20-524 (butenafine Cream 1%); NDA 20-192 (Lamisil Cream) and an MO review for fungicidal vs fungistatic issues for NDA 210-510 (Sporanox--itraconazole capsules).

REMARKS/COMMENTS: Dr. Albert T. Sheldon, Group Leader of the Microbiologist in HFD-520 asked all the microbiologist to provide him with their opinions of how they define the terms fungistatic and fungicidal. Their answers, in the form of e-mail responses, have been included with this review.

Their answers suggested that the use of kill curves and a result of 99.9% ($3 \log_{10}$) reduction in the initial inoculum would be considered as bactericidal (fungicidal). Since there are no standard methods for testing the susceptibility of filamentous fungi, this becomes more difficult to define. The inhibitory or cidal concentrations determined may not correlate with clinically relevant levels of activity.

From the reviews provided, it can be seen that kill curves were performed for butenafine and a $3 \log_{10}$ reduction was achieved for certain organisms, including *Trichophyton mentagrophytes* one of the organisms involved in tinea pedis.

The microbiology review of Lamisil (terbinafine hydrochloride) states that terbinafine was fungicidal against *Candida parapsilosis*, *Epidermophyton floccosum*, *Microsporum canis*, *Trichophyton mentagrophytes*, and *Trichophyton rubrum* within 3 to 5 days at a concentration similar to the MIC level.

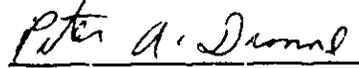
The mechanism of action for both butenafine and terbinafine is the same. Both compounds block the conversion of squalene into squalene epoxide by inhibiting squalene epoxidase. This leads to the accumulation of squalene in the cell. It appears that both these drugs are fungicidal for the dermatophytes.

Itraconazole is an azole and its mechanism of action is different from the above two compounds. The azoles block a later step in ergosterol synthesis. There was no microbiological review of this compound included so it can not be determined whether or not kill curves were performed to determine fungicidal activity.

CONCLUSION & RECOMMENDATIONS:

It appears from *in vitro* studies, that both butenafine and terbinafine are fungicidal for the organisms that cause tinea pedis. A conclusion can not be made about itraconazole since data on *in vitro* testing has not been given.

None of these data indicate, however, that this fungicidal activity will be clinically relevant.



Peter A. Dionne
Microbiologist, HFD-520

cc: Orig. NDA 20-524
HFD-540/Division File
HFD-520/Micro/Dionne
HFD-540/MO/Slifman
HFD-540/Pharm/Mainigi
HFD-540/Chem/Pappas
HFD-540/CSO/Cross

Concurrence Only:
HFD-520/DepDir/LGavrilovich
HFD-520/GLMicro/ATSheldon

TE 28,5776
llb 3/5/06

7
570

**Consultative Review for HFD-540
Division of Topical Drug Products
Division of Anti-Infective Drug Products (HFD-520)
Microbiological Clinical Review #2**

F 6

Requestor: Frank Cross, CSO HFD-540

Date of Request: May 14, 1996

Reason for Request: Microbiological Review of response to approvable letter

NDA #: 20-524 **MICRO REVIEW #:** 2 **REVIEW DATE:** 30-MAY-96

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
Major Amendment	08-MAY-96	10-MAY-96	24-MAY-96

NAME & ADDRESS OF APPLICANT: PENERDERM INCORPORATED
320 Lakeside Drive, Suite A
Foster City, CA 94404

CONTACT PERSON: Barry Calvarese, MS
Phone Number: (415) 358-0100
Fax Number: (415) 358-0101

DRUG PRODUCT NAME

<u>Proprietary:</u>	MENTAX™
<u>Nonproprietary/USAN:</u>	Butenafine Hydrochloride Cream
<u>Code Names/#'s:</u>	KP-363
<u>Chemical Type/</u>	Allylamine antifungal
<u>Therapeutic Class:</u>	1S

ANDA Suitability Petition/DESI/Patent Status:
Not Applicable

PHARMACOLOGICAL CATEGORY/INDICATION:
Interdigital Tinea pedis

DOSE FORM: Cream
STRENGTHS: 1%
ROUTE OF ADMINISTRATION: Topical
DISPENSED: Rx OTC

Shinavage

SEP 8 1995

Consultative Review to HFD-540
DIVISION OF MEDICAL IMAGING, SURGICAL,
and DENTAL DRUG PRODUCTS; HFD-160

PC
9/14

Microbiologist's Review #1
7 September 1995

A. 1. NDA 20-524

APPLICANT: Penederm Incorporated
320 Lakeside Drive
Foster City, CA 94404

2. PRODUCT NAMES: Butenafine HCl Cream 1%

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
Topical cream for application to affected areas of the feet.

4. METHODS OF STERILIZATION:
The product is a topical and as such is not a sterile preparation, but, conforms to microbial limit specifications.

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product is used for treatment of interdigital tinea pedis.

B. 1. DATE OF INITIAL SUBMISSION: 4 April 1995

2. DATE OF AMENDMENT: (none)

3. RELATED DOCUMENTS: Table 1. Documents referenced in this NDA.

Document	Subject/ Document Holder
IND	IND
DMF	
DMF	
DMF	
DMF	

4. ASSIGNED FOR REVIEW: 17 August 1995

C. REMARKS: The application is for a new topical formulation used in the treatment of athlete's foot. As a

product intended for topical application it is not produced as a sterile product, but should conform to microbiological specifications. These specifications are reviewed here.

D. CONCLUSIONS: The submission is recommended for approval on the basis of microbial integrity and preservative effectiveness.


Paul Stinavage, Ph.D. 7 Sep 1995

cc: Original NDA 20-524
HFD-160/Stinavage/Consulc File
HFD-540/Div File/E. Pappas
Drafted by: P. Stinavage
R/D initialed by P. Cooney

Jtc 9/8/95

Chem

241 CROSS

DIVISION OF DERMATOLOGIC AND OPHTHALMOLOGIC DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-524 CHEM. REVIEW #: 1 REVIEW DATE: 9/11/95

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	4/4/95	4/6/95	4/13/95
AMENDMENT/BC	11/16/95	11/17/95	11/20/95

NAME & ADDRESS OF APPLICANT:

Penederm, Incorporated
320 Lakeside Drive
Suite #A
Foster City, California 94404

DRUG PRODUCT NAME

Proprietary:
Nonproprietary/USAN: Butenafine
Hydrochloride
Code Names/#'s: KP-363

Chem. Type/Ther. Class: 1 S

PHARMACOL. CATEGORY/INDICATION: Antifungal;
Tinea Pedis (Interdigital); Tinea Corporis

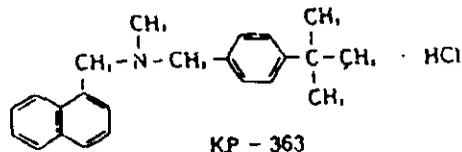
DOSAGE FORM: Cream

STRENGTHS: 1%

ROUTE OF ADMINISTRATION: Topical

DISPENSED: X Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOL. WT:



SUPPORTING DOCUMENTS:

DMF
DMF

DMF

DMF

RELATED DOCUMENTS: IND

CONSULTS: See EA consult dated 1/22/96
See Trade Name consult dated 1/5/96

REMARKS/COMMENTS:

The applicant has submitted a New Drug Application for Butenafine Hydrochloride Cream 1% for the topical treatment of Tinea Pedis; Tinea Corporis. Butenafine hydrochloride Cream, 1% was approved for marketing in Japan, April 1992. This NDA contains a 1S classification. In support of this NDA, the applicant has provided comprehensive information on the chemistry, manufacturing and controls of this drug product. The application also contains draft labeling.

The applicant cross-referenced IND _____ whereby manufacturing and controls information were submitted in support of the subject NDA. It is the same information as was submitted for the NDA with the exception that the applicant incorporated changes as requested during a Pre-NDA meeting with them on 2/13/95 (see chemist IND review dated 3/10/95).

However, even though the CMC information was very comprehensive, deficiencies still remain in the areas of Manufacturing and Packaging, Drug Product Specifications and Methods, and Stability. The labeling was reviewed and found acceptable from a technical standpoint one exception

During the product specific inspection on October 10-16, 1995 at _____ the applicant was requested to make additional CMC revisions to the NDA. In this regard, amendment dated 11/16/95 contained these revisions

CONCLUSIONS & RECOMMENDATIONS:

The NDA is in an approvable state from a manufacturing standpoint. However, minor deficiencies remained with CMC and EA. These deficiencies were communicated to the applicant by telecon on 1/30/96; the applicant agreed to correct these deficiencies by 2/20/96

Methods validation is pending; will be sent to the laboratories upon completion of this review. The labeling is approvable from a technical stand point with exception that it fails to list the storage statement on the

NDA 20-524
Penederm Inc.
Butenafine HCl Cream 1%

Page 3

package insert. Trade Name consult is pending from the
Labeling and Nomenclature Committee.

Ernest G Pappas 1/26/96

Ernest G. Pappas
Review Chemist

cc: Orig. NDA 20-524
HFD-540/Division File
HFD-540/Pappas
HFD-540/Slifman
HFD-540/Mainigi
HFD-160/Cooney
HFD-540/Cross
HFD-540/DeCamp *WD 1/26/96*

92 2/2/96

MAR 13 1996

NDA 20-524
Penederm Inc.
Butenafine HCL Cream 1%

Addendum to Chemist Review #1 dated 9/11/96 for
Butenafine HCl Cream 1%

This addendum was written to correct minor mistakes in
Chemist Review #1 as follows:

1. Page 10

A typographical error was made in the manufacturer's address
for the bulk drug substance as follows:

Instead of indicating that Butenafine Hydrochloride is
manufactured for _____ by:

The Chemist Review should indicate that Butenafine
Hydrochloride is manufactured by _____ in
their facility at:

2. Page 13

The Chemist Review did not indicate the results found for
the elemental analysis for Butenafine HCl drug substance as
compared to the theoretical values. In this regard, the
following values were reported for the elemental analysis of
Butenafine HCl:

	<u>Elements</u>			
	<u>C</u>	<u>H</u>	<u>Cl</u>	<u>N</u>
Theoretical Value:	78.05	7.97	10.02	3.96
Measured Value:	78.29	7.96	10.17	3.94

Ernest G. Pappas 3/13/96

Ernest G. Pappas

- cc: Orig. NDA 20-524
- HFD-540/Division File
- HFD-540/Slifman
- HFD-160/Cooney
- HFD-540/DeCamp
- HFD-540/Pappas
- HFD-540/Mainigi
- HFD-540/Cross

WJ 3/11/96 *722 3/13/96*

MAR - 1

DIVISION OF DERMATOLOGIC AND OPHTHALMOLOGIC DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-524 CDER REVIEW #: 2' REVIEW DATE: 2/20/96

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	4/4/95	4/6/95	4/13/95
AMENDMENT/BC	11/16/95	11/17/95	11/20/95
	2/15/96	2/16/96	2/16/96

NAME & ADDRESS OF APPLICANT:

Peneuerm, Incorporated
320 Lakeside Drive
Suite #A
Foster City, California 94404

DRUG PRODUCT NAME

Proprietary:
Nonproprietary/USAN: Butenafine
Hydrochloride
Code Names/#'s: KP-363

Chem. Type/Ther. Class: 1 S

PHARMACOL. CATEGORY/INDICATION: Antifungal;
Tinea Pedis (Interdigital); Tinea Corporis

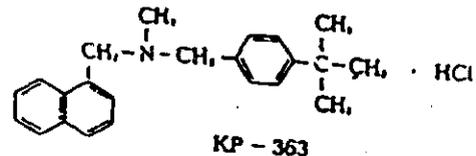
DOSAGE FORM: Cream

STRENGTHS: 1%

ROUTE OF ADMINISTRATION: Topical

DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOL. WT:



SUPPORTING DOCUMENTS:

DMF
DMF

DMF

DMF

RELATED DOCUMENTS: IND

CONSULTS: See EA consult #1 dated 1/22/96
See EA consult #2 dated 2/20/96
See Trade Name consult dated 1/4/96

REMARKS/COMMENTS:

The applicant responded on 2/15/96 to the Chemistry and Environmental Assessment (EA deficiencies found in the original application. These deficiencies were communicated to the applicant via telecon on 1/30/96. In this regard, the chemistry deficiencies were reviewed and found acceptable (see Chemist Review Notes; pg. 4). The new EA information is currently under review by HFD-357.

EER (ID # 8085) for the facilities remain acceptable

EER (ID # 9027) for outside contract laboratories (microbial analysis) are still pending. This EER was initiated on 10/24/95 after the chemist returned from the product specific inspection of facilities on 10/16-20/95. It was during this inspection that the applicant revealed that there were other contract laboratories performing micro testing only in case of emergencies; thus resulting in a another EER (ID # 9027) to be initiated.

Methods validation is pending; to be requested.

The labeling is approvable from a technical stand point with exception that it fails to list the storage statement on the package insert. The applicant made the commitment in the 2/15/96 amendment that the storage statement will be added with FPL. ✓

Trade Name consult was received from the Labeling and Nomenclature Committee on 2/21/96. The committee found the tradename "Lotriphine" unacceptable (see memo dated 2/21/96). ✓

CONCLUSIONS & RECOMMENDATIONS:

The NDA is approvable from a manufacturing standpoint, pending an acceptable EA report from HFD-357 and acceptable EER report (ID # 9027) from HFD-324. CSO should convey the following phase IV commitments to the applicant

The labeling is approvable ✓

Methods Vaidation is pending.

Ernest G. Pappas 2/23/96

Ernest G. Pappas
Review Chemist

cc: Orig. NDA 20-524
HFD-540/Division File
HFD-540/Pappas
HFD-540/Slifman
HFD-540/Mainigi
HFD#160/Cooney
HFD-540/Cross
HFD-540/DeCamp
HFD-830/Sheinin

WJ 2/23/96

JW 3/1/96

NDA 20-524
Penederm Inc.
Butenafine HCl Cream 1%

Addendum to Chemist Review #2 dated 2/20/96 for
Butenafine HCl Cream 1%

This addendum was written to summarize the inspection report (EER # 9027) for the following contract laboratories:

LABORATORY	FUNCTION
	Microbial Analysis
	Microbial Analysis
	Microbial Analysis
	Testing of Raw Materials

The Office of Compliance (HFD 324) found the laboratories listed above acceptable for CGMPs with exception of

Since _____ did not have a profile on it, an evaluation of this facility could not be performed by HFD 324 at this time.

It should be noted that the San Francisco DO had planned to inspect this facility on 2/28/96; however, this inspection was not scheduled to date. Therefore, since the action package for Butenafine HCl Cream had to be out from the division no later than Friday (3/8/96), an acceptable EER (#9027) had to be received by 3/7/96.

NDA 20-524
Penederm Inc.
Butenafine HCl 1%

Page 2

This prompted a request by this reviewer to Penederm Inc. to delete

from the original application (vol.1.2; 2 0198);

The chemist

indicated to Penederm that this facility could be supplemented post approval.

Ernest G. Pappas

3/8/96

Ernest G. Pappas
Review Chemist

cc: Orig. NDA 20-524
HFD-540/Division File
HFD-540/Pappas
HFD-540/Slifman
HFD-540/Mainigi
HFD-160/Cooney
HFD-540/Cross
HFD-540/DeCamp *WB 3/8/96*

AUG 18 1996

DIVISION OF DERMATOLOGIC AND OPHTHALMOLOGIC DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-524 CHEM.REVIEW #: 3 REVIEW DATE: 8/1/96

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	04/04/95	04/06/95	04/13/95 (CR1)
AMENDMENT/BC	11/16/95	11/17/95	11/20/95 (CR1)
	02/15/96	02/16/96	02/16/96 (CR2)
	03/01/96	03/04/96	03/07/96 (CR3)
	05/08/96	05/10/96	05/14/96 (CR3)
	fax	08/05/96	08/05/96 (CR3)

NAME & ADDRESS OF APPLICANT:

Penederm, Incorporated
320 Lakeside Drive
Suite #A
Foster City, California 94404

DRUG PRODUCT NAME

Proprietary:
Nonproprietary/USAN: Butenafine
Hydrochloride
Code Names/#'s: KP-363
Chem. Type/Ther. Class: 1 S

PHARMACOL. CATEGORY/INDICATION: Antifungal;
Tinea Pedis (Interdigital); Tinea Corporis

DOSAGE FORM: Cream

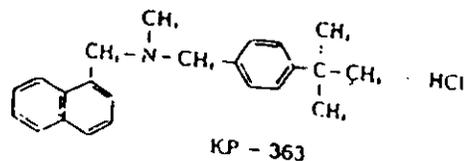
STRENGTHS: 1%

ROUTE OF ADMINISTRATION: Topical

DISPENSED:

X Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOL. WT:



SUPPORTING DOCUMENTS:

DMF

DMF

DMF

DMF

RELATED DOCUMENTS: IND

CONSULTS: See EA consult #1 dated 1/22/96
See EA consult #2 dated 2/20/96
See Trade Name consult dated 1/4/96
See Trade Name consult dated 3/8/96
See EA consult #3 dated 7/31/96

REMARKS/COMMENTS:

The applicant responded on 5/8/96 to FDA's approvable letter of 4/3/96 regarding Phase 4 requests on CMC and EA issues, whereby a commitment was given to report additional X-ray data and to clarify the question regarding SA with the analytical methods. This commitment was found unacceptable because it did not adequately address the question on the analytical methods for SA. Therefore, this prompted a telecon to the applicant, requesting further clarification (see telecon memo dated 8/2/96 from F. Cross, CSO). In this regard, the applicant submitted additional information on 8/12/96 (fax) regarding the SA impurity and the analytical methods

New Environmental Assessment (EA) data were submitted in support of the original application. This EA information is currently under review by HFD-357.

EER (ID # 8085) for the facilities remain acceptable

EER (ID # 9027) for outside contract laboratories found acceptable

Methods validation was requested on 7/30/96 from DDA and San Juan, PR.; status pending.

Labeling: Trade name consult was received from the Labeling and Nomenclature Committee on 2/21/96. The committee found the trade name "LOTRIPHINE" unacceptable (see memo dated 2/21/96). New trade name was proposed by the applicant on 3/1/96 as "MENTAX" and was found acceptable by the committee

CONCLUSIONS & RECOMMENDATIONS:

The NDA should be approved from a manufacturing standpoint.

EA report is pending from HFD-357.

EER reports (ID # 8085 & ID # 9027) were found acceptable by the Office of Compliance (HFD-324) on dated 10/25/95 and 3/6/96, respectively. Note: Collectively, these EERs are good up to 10/25/96. Therefore the action package should be approved by 10/25/96.

The labeling should be approved from a technical standpoint.

Methods Validation is pending.

Ernest G. Pappas 8/7/96

Ernest G. Pappas
Review Chemist

cc: Orig. NDA 20-524
HFD-540/Division File
HFD-540/Pappas
HFD-540/Slifman
HFD-540/Mainigi
HFD-160/Cooney
HFD-540/Cross
HFD-540/DeCamp
HFD-830/Sheinin

WLS 8/9/96

9-2 8/18/96

SEP 17 1996

DIVISION OF DERMATOLOGIC AND OPHTHALMOLOGIC DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-524 CHEM.REVIEW #: 4 REVIEW DATE: 9/10/96

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	04/04/95	01/06/95	04/13/95 (CR1)
AMENDMENT/BC	11/16/95	11/17/95	11/20/95 (CR1)
	02/15/96	02/16/96	02/16/96 (CR2)
	03/01/96	03/04/96	03/07/96 (CR3)
	05/08/96	05/10/96	05/14/96 (CR3)
	08/29/96 ✓	08/30/96	09/06/96 (CR4)

NAME & ADDRESS OF APPLICANT:

Penederm, Incorporated
320 Lakeside Drive
Suite #A
Foster City, California 94404

DRUG PRODUCT NAME

Proprietary:
Nonproprietary/USAN: Butenafine
Hydrochloride
Code Names/#'s: KP-363

Chem.Type/Ther.Class: 1 S

PHARMACOL.CATEGORY/INDICATION: Antifungal;
Tinea Pedis (Interdigital); Tinea Corporis

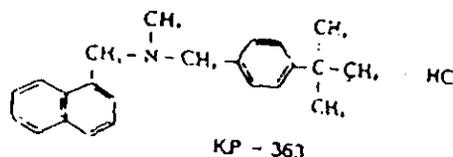
DOSAGE FORM: Cream

STRENGTHS: 1%

ROUTE OF ADMINISTRATION: Topical

DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOL.WT:



SUPPORTING DOCUMENTS:

DMF
DMF

DMF

DMF

RELATED DOCUMENTS: IND

CONSULTS: See EA consult #1 dated 1/22/96
See EA consult #2 dated 2/20/96
See Trade Name consult dated 1/4/96
See Trade Name consult dated 3/8/96
See EA consult #3 dated 7/31/96

REMARKS/COMMENTS:

The applicant submitted an amendment on 5/8/96 in response to FDA's approvable letter of 4/3/96 regarding phase 4 requests on CMC and EA issues. In this regard, new EA information was forwarded to HFD-357 for review. The EA information was reviewed and found acceptable (see FONSI prepared by Nancy Sager dated 8/27/96).

However, the 5/8/96 amendment did not include the remaining CMC requests; e.g., powder X-ray diffraction data, revision of analytical methods (PDM 51 & PDM 52) for adequate resolution of SA and D2 impurities. Therefore, a commitment was given to submit this information (Comment #8) by September 30, 1996, which is the subject of the 8/29/96 amendment

Please note that the response to Comment #8B was provided to Agency by fax on 8/5/96, following a telecon with the applicant.

EER (ID # 8085) for the facilities remain acceptable; see memo dated 10/25/95 from the Office of Compliance (HFD-324).

EER (ID # 9027) for outside contract laboratories found acceptable

Methods validation was requested on 7/30/96 from DDA and San Juan, PR.; status pending.

Labeling: Trade name consult was received from the Labeling and Nomenclature Committee on 2/21/96. The committee found the trade name "LOTRIPHINE" unacceptable ✓

New trade name was proposed by the applicant on 3/1/96 as "MENTAX" and was found acceptable by the committee ✓

CONCLUSIONS & RECOMMENDATIONS:

The NDA should be approved from a manufacturing standpoint.

EER reports (ID # 8085 & ID # 9027) were found acceptable by the Office of Compliance (HFD-324) on dated 10/25/95 and 3/6/96, respectively. Note: Collectively, these EERs are good up to 10/25/96. Therefore the action package should be approved by 10/25/96. ✓

The labeling should be approved from a technical standpoint. ✓

Methods Validation is pending. ✓

Ernest G. Pappas 9/10/96

Ernest G. Pappas
Review Chemist

cc: Orig. NDA 20-524
HFD-540/Division File
HFD-540/Pappas
HFD-540/Slifman
HFD-540/Mainigi
HFD-160/Cooney
HFD-540/Cross
HFD-540/DeCamp
HFD-830/Sheinin

WS 9/10/96

JW 9/17/96

DIVISION OF DERMATOLOGIC AND OPHTHALMOLOGIC DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-524 CHEM.REVIEW #: 5 REVIEW DATE: 10/17/96

<u>SUBMISSION/TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	04/04/95	04/06/95	04/13/95 (CR1)
AMENDMENT/BC	11/16/95	11/17/95	11/20/95 (CR1)
	02/15/96	02/16/96	02/16/96 (CR2)
	03/01/96	03/04/96	03/07/96 (CR3)
	05/08/96	05/10/96	05/14/96 (CR3)
	08/29/96	08/30/96	09/06/96 (CR4)
Methods Val.	04/30/96	05/02/96	05/7/96 (CR5)
(two)	10/16/96	10/17/96	10/16/96 (CR5)

NAME & ADDRESS OF APPLICANT:

Penederm, Incorporated
320 Lakeside Drive
Suite #A
Foster City, California 94404

DRUG PRODUCT NAME

Proprietary: Mentax
Nonproprietary/USAN: Butenafine Hydrochloride
Code Names/#'s: KP-363

Chem.Type/Ther.Class: 1 S

PHARMACOL.CATEGORY/INDICATION: Antifungal;
Tinea Pedis (Interdigital); Tinea Corporis

DOSAGE FORM: Cream

STRENGTHS: 1%

ROUTE OF ADMINISTRATION: Topical

DISPENSED: Rx OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOL.WT:

see review #1

SUPPORTING DOCUMENTS:

DMF
DMF

DMF

DMF

RELATED DOCUMENTS: IND

CONSULTS: See EA consult #1 dated 1/22/96
See EA consult #2 dated 2/20/96
See Trade Name consult dated 1/4/96
See Trade Name consult dated 2/8/96
See EA consult #3 dated 7/31/96

REMARKS/COMMENTS:

The applicant amended their NDA on 10/16/96 (by fax) with additional stability data in response to FDA's request (see telecon of 10/16/96). In this regard the applicant submitted updated stability data on the original three lots (HCGG, HIED, and IAP) as follows:

* 24 months and 6 months stability data were submitted for room temperature (27°C) and accelerated conditions (40°C) for lot HCGG. These studies reflect freeze/thaw conditions of 4°C/40°C (2wks) and 4°C (24 months).

* 18 months and 6 months stability data were submitted for room temperature (27°C) and accelerated conditions (40°C) for lots HIED and IAP. The studies reflect freeze/thaw conditions of 4°C/40°C (7 days) and 4°C (12 months).

Note: It should be noted that lots HCGG, HIED, and IAP were each divided into three sublots to study the finished product in tubes of 2 g, 15 g and 30 g sizes. This was the original protocol.

These data were reviewed and found to fall within the proposed specifications.

It was reported in the applicant's 10/16/96 submission that a change in the lower limit specification for benzyl alcohol (preservative) was proposed as 0.25%. This change varies from that originally proposed for benzyl alcohol [Finished Product Specifications (Vol. 1.2, pg 2 0264): 0.45-0.575%; Stability Product Specifications (Vol. 1.2, pg 2 0266): 0.0375-0.575%]. Microbiologist, Paul Stinavage, Ph.D., approved the original specifications and preservative system (see Micro Review dated 9/7/96).

When advised of this discrepancy, the applicant withdrew the proposed lower limit of 0.25% for benzyl alcohol and

therefore reinstated the current specification of
%

CONCLUSIONS & RECOMMENDATIONS:

The NDA remains approved from a manufacturing standpoint. The additional stability data as submitted will not support the approval of the proposed 24 month expiration date because the benzyl alcohol content fails stability at 24 months. However, we will accept an expiration date of 18 months. Storage conditions remain between 5 and 30°C, as concluded in review #1.

Therefore, the applicant should be advised that the product is approved with an 18 month expiration date instead of a 24 month. CSO should indicate this in the approval letter.

Ernest G. Pappas 10/18/96
Ernest G. Pappas
Review Chemist

cc: Orig. NDA 20-524
HFD-540/Division File
HFD-540/Pappas
HFD-540/Katz
HFD-540/Mainigi
HFD-160/Cooney
HFD-540/Cross
HFD-540/DeCamp *WD 10/18/96*
HFD-830/Sheinin

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Mr. Dan Boring, Chair, (HFD-530)

From: Division of Topical Drug Products (HFD-540)
Attention: Ernie Pappas Phone: 827-2066

Date: 3/8/96

Subject: Request for Assessment of a Trademark for a
Proposed Drug Product

Proposed Trademark: Mentax NDA # 20-524
Company Name: Penederm, Incorporated.

Established name, including dosage form: Butenafine HCl
Cream, 1%

Other trademarks by the same firm for companion products:
N.A.

Indications for Use (may be a summary if proposed statement
is lengthy): Treatment of Interdigital Tinea Pedis

Initial comments from the submitter (concerns, observations,
etc.): Since the proposed trade name, Lotriphine, was found
unacceptable by the Labeling and Nomenclature Committee, the
applicant submitted another name, MENTEX, for acceptance by
the Committee.

NOTE: Meetings of the Committee are scheduled for the
4th Tuesday of the month. Please submit this form
at least one week ahead of the meeting. Responses
will be as timely as possible.

Rev Mar.96

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529

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Mr. Dan Boring, Chair, (HFD-530)

From: Division of Topical Drug Products (HFD-540)
Attention: Ernie Palpas ^{EGP} _{1/4/96} Phone: 827-2066 _{1/4/96}

Date: 1/4/96

Subject: Request for Assessment of a Trademark for a
Proposed Drug Product

Proposed Trademark: LOTRIPHINE NDA # 20-52
Company Name: Penederm, Incorporated.

Established name, including dosage form: Butenafine HCl
Cream, 1%

Other trademarks by the same firm for companion products:
N.A.

Indications for Use (may be a summary if proposed statement
is lengthy): Treatment of Interdigital Tinea Pedis

Initial comments from the submitter (concerns, observations,
etc.): The proposed trade name, Lotriphine, may be too close
to the spelling and pronunciation of the marketed product,
Lotrimin Cream 1%.

NOTE: Meetings of the Committee are scheduled for the
4th Tuesday of the month. Please submit this form
at least one week ahead of the meeting. Responses
will be as timely as possible.

Rev Jan.96

Log-out
1/5/96
AMC

Consult #583

MENTAX

butenafine HCl cr. 1%

The Committee found no look alike/sound alike names conflicting with the proposed trademark nor were there any misleading aspects noted. The Committee did note that the proposed established name is an International Non-proprietary Name and does not appear to have been adopted by USAN as yet.

The Committee has no reason to find the proposed trademark unacceptable but does recommend that the reviewing Division consult with the sponsor regarding the status of the USAN name.

CDER Labeling and Nomenclature Committee

W. Berling 4/1/96, Chair

Consult #529 (HFD-540)

Lotriphine

butenafine HCl cream

A review by the Committee revealed one look-alike/sound-alike name: Lotrimin. Lotrimin is an antifungal used for tinea infection like the proposed product. The Committee feels that the proposed name is too close to Lotrimin and is likely to cause consumer mix-ups with the two products.

The Committee finds the proposed trademark to be unacceptable.

CDER Labeling and Nomenclature Committee

D. H. Boring 2/21/96, Chair

FDA ADDENDUM

In a separate communication to CDER, the applicant stated that the signed compliance statements could be included in the non-confidential EA.

CERTIFICATE

It is hereby certified that _____ is subject to the supervision of _____ and has adequately carried out the measures against environmental pollution in accordance with the agreement related to environmental pollution control that was concluded with _____ on September 2, 1976.

Name of Manufacturing Plant :

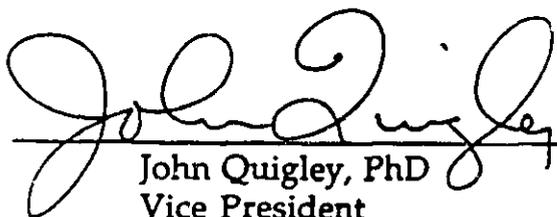
Address :

Agreement : Based on the following Laws;
The Basic Environmental Law
Water Pollution Control Law
Air Pollution Control Law
Noise Regulation Law
Offensive Odor Control Law
Waste Disposal and Public Cleaning Law
Factory Location Law

Date : September 19, 1995

COMPLIANCE STATEMENT

Penederm Incorporated states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the storage, handling and disposition of Butenafine HCl Cream 1% at its facilities in Foster City, California as well as emission requirements set forth in applicable federal, state, and local statutes and regulations applicable to the production of Butenafine HCl Cream 1% at its facilities in Foster City, California.



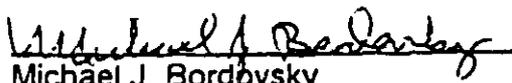
John Quigley, PhD
Vice President
Research and Development

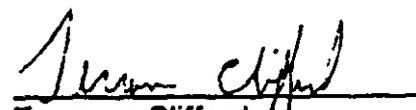
3/28/95
Date

September 20, 1994

GENERAL COMPLIANCE STATEMENT

states that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees and administrative orders applicable to the production of BUTENAFINE CREAM at its facilities at as well as emission requirements set forth in applicable federal, state and local statutes and regulations applicable to the production of BUTENAFINE CREAM at its facilities located at


Michael J. Bordovsky
Vice President
Manufacturing Operations


Terrance Clifford
Manufacturing Manager

E A T.
Fonsi.

AUG 27 1990

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

NDA 20-524

butenafine hydrochloride cream - 1%

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF DENTAL AND DERMATOLOGIC
DRUG PRODUCTS (HFD-540)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-524

butenafine hydrochloride cream - 1%

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for butenafine hydrochloride cream, Penederm Incorporated has prepared an abbreviated environmental assessment in accordance with 21 CFR 25.31a(b)(3) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Butenafine hydrochloride is a synthetic drug intended for topical application in the treatment of interdigital tinea-pedis (athlete's foot). The drug substance will be manufactured at
The drug product will be manufactured at
The product will be used primarily by patients in their homes.

Disposal may result from production waste such as out of specification lots, returned goods and user disposal of empty or partly used product and packaging. Pharmaceutical waste in the United States will be disposed of at licensed facilities. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, although minimal quantities of unused drug may be disposed of in the sewer system.

Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

8/27/96
DATE

Nancy B. Sager

PREPARED BY
Nancy B. Sager
Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

8/27/96
DATE

Charles P. Hoiberg

CONCURRED
Charles P. Hoiberg
Division Director
Office of New Drug Chemistry-Division 1
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

c.c. original to NDA 20-524 through FCross/HFD-540
HFD-357/EA File NDA #20-524
HFD-357/Docket File
HFD-205/FOI COPY

ENVIRONMENTAL ASSESSMENT
ABBREVIATED FORMAT 25.31a(b)(3)
BUTENAFINE HCl CREAM 1%

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ENVIRONMENTAL ASSESSMENT
ABBREVIATED FORMAT 25.31a(b)(3)
BUTENAFINE HCl CREAM 1%

1. DATE

Current submission: May 6, 1996
Second submission: February 15, 1996
Original submission: March 20, 1995

2. NAME OF APPLICANT

Penederm Incorporated

3. ADDRESS

320 Lakeside Drive
Suite A
Foster City, CA 94404

4. DESCRIPTION OF PROPOSED ACTION

A. REQUESTED APPROVAL

The proposed action encompasses the manufacture of the new drug substance, butenafine hydrochloride, and the finished product manufacturing, testing, packaging, and use of the topical product designated as Butenafine HCl Cream 1% (Mentax™).

The product is packaged in 2-gram, 15-gram, and 30-gram epoxy/phenolic-lined aluminum tubes with a blinded end and a polypropylene screw cap. All tubes are then packaged in cartons.

B. NEED FOR THE ACTION

Butenafine is an antifungal agent that is safe and effective for the treatment of interdigital tinea pedis (athlete's foot). According to 25.31a(b)(3), the following information is arranged in the required abbreviated format.

C. LOCATION OF PRODUCTION

The drug substance, butenafine HCl, is supplied to Penederm by:

The drug substance is manufactured at:

No proprietary intermediates are used in the manufacture of the drug substance.

Complete manufacturing, processing, and packaging of the drug product, Butenafine HCl Cream 1%, is done by:

D. LOCATION OF USE AND DISPOSAL OF DRUG PRODUCT

The dosage form is intended for nationwide distribution. Other than trace metabolites resulting from topical application, it is anticipated that the small amount of material remaining unused by the patient will be disposed of nationally as solid wastes and handled in accordance with local conventions (landfill, incineration).

The companies/facilities responsible for disposal are listed in Attachments 1 and 2 and discussed in Section 4.E, which also identifies the materials disposed of by these companies/facilities and the method of disposal. Attachments 1 and 2 include information on the license and permit numbers, the issuing authorities' identification numbers, the expiration dates, and the issuing agent.

E. ENVIRONMENTAL SETTING OF DPT LABORATORIES

is located approximately two miles from the center of the City of San Antonio in a light manufacturing/industrial area at _____ has been at this location since 1953 and has conscientiously observed all environmental considerations for this type of manufacturing facility.

is bordered on the north and east perimeters by an Interstate Highway (I.H. 37) and by the San Antonio River on the west. An elementary school is located approximately two blocks west of the facility on _____. A major city park (Brackenridge Park) occupies approximately 600 acres immediately north and northwest of the manufacturing facility and is the location of a municipal golf course, driving range, city zoo, and other recreational facilities.

is registered with the EPA and the local Emergency Planning Commission regarding the storage of chemicals located at this site. location is listed as: Latitude 20°, 26 minutes, 45 seconds; Longitude 98°, 28 minutes, 43 seconds.

Due to proper controls which are utilized in the receipt, storage, and use of these substances, probable impact on the environment will be minimal. Controls exercised in the handling of these substances are as follows:

- Covered loading dock for receipt of substances.
- Environmentally-controlled and covered warehouse storage areas.
- Localized dust collection units for the sampling, weighing, and dispersion of ingredients.
- Handling of ingredients is conducted in appropriately controlled manufacturing areas.
- Preparation of batch is conducted in environmentally-controlled and GMP-controlled areas.

Waste generated from the production of Butenafine HCl Cream 1% will be disposed of in accordance with local, state, and federal requirements. _____ utilizes the resources of licensed, bonded, and certified waste disposal firms for both hazardous and nonhazardous disposal.

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Rejected, returned, or expired drug product, rejected raw materials, and scrap from packaging lines will be disposed of by incineration by the hazardous waste disposal contractor identified in Attachment 1.

General nonhazardous plant refuse including waste paper and corrugated will be disposed of by landfill by the nonhazardous waste disposal contractor identified in Attachment 1.

Water for cleaning and cooling used in the manufacturing of the drug product are discharged into the sewage treatment system. The permits for this purpose are identified in Attachment 2.

It is anticipated that preparation of Butenafine HCl Cream 1% will have no significant impact on any existing waste streams. Please refer to Attachment 2 for a list of environmental permits of

Wastewater Permit: The San Antonio Water System (Wastewater Quality Division) is responsible for assuring that complies with EPA and state requirements for wastewater discharge, storm water runoff, and other applicable functions. They conduct quarterly, random wastewater sampling to monitor plant discharge as well as semi-annual inspections of the facility for compliance. In order to continue to discharge into the wastewater system, the agency also requires self-monitoring, semi-annual tests to assure that effluent meets requirements.

Texas Natural Resource Conservation Commission (TNRCC): This agency is responsible for enforcing EPA regulations, both state and federal, regarding the generation, storage, and disposition of both nonhazardous and hazardous waste. Under the regulation of this authority, DPT generates, stores, and disposes of various categories of liquid and solid waste, manifests shipments when required, and submits annual summary reports on waste generated.

EPA and RCRA ID Number: This particular identification number is issued in conjunction with the TNRCC and is used in all pertinent state and federal reporting activities regarding various generation, storage, and disposition of both hazardous and nonhazardous waste.

Air Quality: has been exempted from requiring an Air Pollution License by the City of San Antonio, San Antonio Metropolitan Health District. This agency is charged with maintaining air quality standards in the city limits of San Antonio. This exemption will be in effect as long as continues at their current low level of emissions.

NON-CONFIDENTIAL

Safety: Operating procedures are safely established to minimize exposure to chemicals. Health and environmental monitoring is performed as required. Manufacturing employees participate in group and individual health and safety training programs. Training regarding the proper operation of both the manufacturing equipment and material handling equipment is conducted. Monthly reviews of employee safety records are conducted and reported in a formalized report. Routine blood profile monitoring is conducted for manufacturing, technical, and other personnel who might come in contact with products manufactured at the facility. Annual blood profiles are compared to baselines previously established by qualified medical personnel.

Appropriate particulate monitoring of environmental air is conducted by in-house personnel for evaluation of bioburden and by contract industrial hygienist for determination of airborne exposure levels. Additionally, determination of decibel ratings of different pieces of manufacturing facility's equipment are made to identify any potential areas where hearing protection is required.

Employees routinely receive documented training in the safe and proper handling of all chemicals used in the department and have Material Safety Data Sheets available for timely reference. Prior to the manufacturing of Butenafine HCl Cream 1%, compounders review the safety precautions outlined in the section provided in the Compounding Module.

Personal safety protection equipment available includes surgical latex gloves when handling chemical components of the drug product; safety glasses/goggles worn during the entire manufacturing process; personal respirators when handling chemicals which are prone to generation of dust and/or exposure to organic vapors. Tyvek disposal coveralls, shoe coverings, and head protection are also available when required. is currently operating in compliance with all applicable emission requirement (including operational) at local, state, and federal levels.

The additional production of Butenafine HCl Cream 1% should not have any appreciable effect on their ability to continue to comply with environmental emission/discharge requirements.

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Emergency Response Plan: In the event of a minor release, the Emergency Response Team is activated, and the area is evacuated. Plant personnel who are trained in emergency response will re-enter the area wearing proper protective clothing and respiratory protection to take remedial action. Emergency equipment immediately available includes: Hazmat carts, spill control kits, personal protective equipment, respirators, rescue and escape air, and first aid supplies.

In the event of a serious release or an escalation of an existing situation, the external emergency plan will take effect with plant evacuation and mobilization of the Regional Hazmat Team, Fire Department, and Hospital/Emergency Services.

All material generated during a cleanup will be treated as hazardous and dealt with according to federal, state, and local regulations.

The finished product stability program and testing will be conducted by:

Penederm Incorporated
320 Lakeside Drive
Suite A
Foster City, CA 94404

Penederm may perform raw material and finished product release testing as needed. Penederm is located on flat terrain in an urban area.

5. LIST OF CHEMICAL SUBSTANCES THAT ARE SUBJECT TO THE PROPOSED ACTION

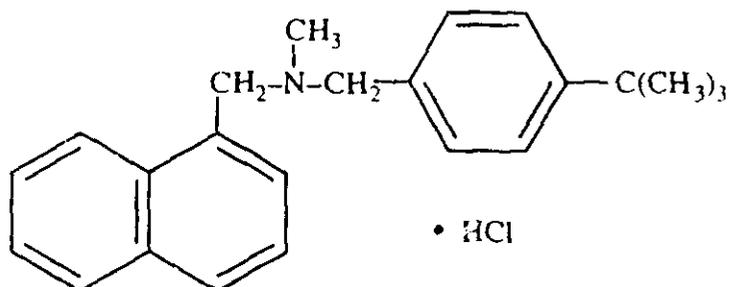
All relevant chemical information on the new drug substance, butenafine HCl, is summarized below. This compound will be manufactured and supplied by

Chemical characterization of the active was also performed. No impurities at levels greater than 1% are present in the butenafine HCl drug substance, hence none are identified by name or Chemical Abstracts Service (CAS) registry number. The MSDS for butenafine hydrochloride is provided in Attachment 3.

DRUG SUBSTANCE

Proper Name: Butenafine HCl
 Chemical Name: N-4-tert-Butylbenzyl-N-methyl-1-naphthalenemethylamine Hydrochloride

Structural Formula:



Code Name: KP-363
 CAS Registry Number: 101828-21-1
 Molecular Formula: $C_{23}H_{27}N \cdot HCl$
 Molecular Weight: 353.93
 Description: White crystals or crystalline powder, odorless or with a faint characteristic odor
 Melting Point: 210° to 217° C

A list of the other ingredients used in this dosage form (cream) are provided below. These ingredients are commonly used in the pharmaceutical and/or the cosmetic industry.

LIST OF OTHER INGREDIENTS IN THE FORMULATION

Purified water USP
 Propylene glycol dicaprylate
 Glycerin USP
 Cetyl alcohol NF
 Glyceryl monostearate, self emulsifying type
 White petrolatum USP
 Stearic acid NF
 Polyoxyethylene (23) cetyl ether
 Benzyl alcohol NF
 Diethanolamine NF
 Sodium benzoate NF

6. INTRODUCTION OF THE SUBSTANCES TO THE ENVIRONMENT

A. MANUFACTURING

Butenafine HCl drug substance is manufactured in the facilities in full compliance with all environmental regulations in Japan.

The drug product is manufactured at as indicated earlier. The waste consists of the amount delivered into the sewage treatment system as a result of cleaning the equipment. The maximum possible amounts obtained from these sources and the resultant concentrations in the wastewater are shown in Attachment 4. As can be seen the concentrations are much lower than almost all of the reported minimum inhibitory concentrations for this compound.

Solid production wastes or lots that are rejected will be disposed of in compliance with local, state, and federal environmental requirements (incineration, landfill), as discussed in detail in Section 4.E above.

B. PATIENT DISPOSAL

The maximum amount of drug that could enter the wastewater system is shown in Attachment 5. This calculation is a gross overestimate that is based on the assumption that the entire product manufactured in the year will enter the wastewater system throughout the United States in a single day. The concentrations of the active, in this case also, are negligible.

C. COMPLIANCE STATEMENTS

The drug substance manufacturer, drug product manufacturer, and Penederm Incorporated have provided the appropriate documents indicating their compliance to emission requirements, namely, a compliance certificate for the drug substance manufacturer, and compliance statements from the drug product manufacturer and Penederm Incorporated.

7. FATE OF EMITTED SUBSTANCES

These items are ordinarily not required according to 25.31a(b)(3). However, expert summaries of the toxicologic and pharmacologic properties of the drug substance are provided in Attachment 6 as additional information. This information indicates that the amount entering the environment is considerably lower than the amount required to elicit adverse effects in microorganisms or any other species.

*8. ENVIRONMENTAL EFFECTS OF RELEASED SUBSTANCES

*9. USE OF RESOURCES AND ENERGY

*10. MITIGATION MEASURES

*11. ALTERNATIVES TO THE PROPOSED ACTION

12. LIST OF PREPARERS

This document was prepared by:

Sui Yuen Eddie Hou, PhD
Research Scientist, Formulations/Product Development

Bhaskar Chaudhuri, PhD
Executive Director, Pharmaceutical Sciences

Lester Gibbs, PhD
Toxicologist, Pharmacology/Toxicology

Barry Calvarese, MS
Executive Director, Clinical/Regulatory Affairs

- * These items are ordinarily not required according to 25.31a(b)(3), as indicated in the "Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements," CDER, November 1995, CMC 6, pages 7 and A-1.

13. CERTIFICATION

The undersigned official certifies that the information presented is true, accurate, and complete to the best of his knowledge.

Jerry Gutshall

Jerry Gutshall
Vice President, Operations

5/7/96

Date

14. REFERENCES

- Berg D., Plempel M. Inhibitors of fungal sterol synthesis: squalene epoxidation and ¹⁴C demethylation. J Enzyme Inhibition 3:1-11, 1989.
- Hiratani E. *et al.* Studies on antifungal mechanism of action of butenafine hydrochloride. Kaken Study E-11.
- Iwatani W., Arika T., Yamaguchi H. Mechanisms of antifungal action of butenafine hydrochloride against *Candida albicans*. Kaken Study E-12. (NOTE: This is the Arika reference)
- Ryder N.S. Mechanisms of action of the allyamine antimycotics. In: Evaluation of Antifungal agents, 1987, JR Prous Science Publishers SA 451-459.
- Solley, W.B., Pierce, R.R., Perlman, H.A. Estimated Use of Water in the United States in 1990. U.S. Geological Survey Circular 1081.

PENEDERM INCORPORATED
720 LAKESIDE DRIVE, SUITE A
OSTER CITY, CA 94404
415-358-0100
FAX 415-358-0101

ATTACHMENT 3

NON-CONFIDENTIAL



PENEDERM

MATERIAL SAFETY DATA SHEET

Butenafine Hydrochloride

Section I. IDENTIFICATION

PRODUCT NAME: Butenafine Hydrochloride (KP-363)

CHEMICAL FAMILY: Benzylamine Antifungal

FORMULA: $C_{23}H_{27}N.HCl$ MOLECULAR WEIGHT: 353.93

CHEMICAL NAME: N-4-tert-Butylbenzyl-N-methyl-1-naphthalenemethylamine Hydrochloride

CAS # 101828-21-1

CAS NAME: N-((4-(1,1-dimethylethyl)phenyl)methyl)-N-methyl-1-naphthalenemethanamine hydrochloride

Section II. INGREDIENTS

<u>MATERIAL</u>	<u>%</u>	<u>TLV (Units)</u>	<u>HAZARD</u>
Butenafine Hydrochloride	100	None established	See Section V

Section III. PHYSICAL DATA (Determined on typical material)

BOILING POINT: N/A MELTING POINT: 210 - 217 °C (decomposes)

SPECIFIC GRAVITY (H₂O = 1): N/A VAPOR PRESSURE AT 20°C: N/A

VISCOSITY (35°C): N/A SOLUBILITY IN WATER: Slightly soluble

EVAPORATION RATE (Butyl Acetate = 1): N/A APPEARANCE AND ODOR: White crystals or crystalline powder. Odorless or has a faint characteristic odor

ATTACHMENT 3

PRODUCT NAME: Butenafine Hydrochloride (KP-363)

PAGE 2

IV. FIRE AND EXPLOSION HAZARD DATA

FLASH POINT: N/A

FLAMMABLE LIMITS IN AIR,
% by volume: N/AEXTINGUISHING MEDIA: Apply alcohol-type or all-purpose-type foams by manufacturer's recommended techniques for large fires. Use CO₂ or dry chemical media for small fires.

SPECIAL FIRE FIGHTING PROCEDURES: Firefighters should use self-contained breathing equipment and protective clothing

UNUSUAL FIRE AND EXPLOSION HAZARDS: Assume combustible. As with all powder, grounding is advised. At decomposition point, toxic fumes are released.

V. HEALTH HAZARD DATA

TLV AND SOURCE: N/A

ORAL LD50 > 4 gm/kg for rats, mice and dogs

MUTAGENICITY: NONE IDENTIFIED NTP: NO IARC: NO OSHA REG: NO

REPRODUCTIVE EFFECTS: NONE IDENTIFIED

MEDICAL CONDITIONS AGGRAVATED BY OVEREXPOSURE: N/A

EMERGENCY AND FIRST AID PROCEDURES:

SWALLOWING: Induce vomiting if the patient is conscious.

SKIN: Wash skin with soap and water.

ATTACHMENT 3

PRODUCT NAME: Butenafine Hydrochloride (KP-363)

PAGE 3

INHALATION: Remove to fresh air.

EYES: Flush eyes with water thoroughly and continuously for 15 minutes.

NOTES TO PHYSICIAN: There is no specific antidote. Treatment of overexposure should be directed at the control of symptoms and the clinical condition.

VI. REACTIVITY DATA

STABILITY: Stable

CONDITIONS TO AVOID: Heating in the presence of air (oxygen) to temperatures above 212°C will result in decomposition.

INCOMPATIBILITY (materials to avoid): None

HAZARDOUS COMBUSTION OR DECOMPOSITION PRODUCTS: Burning can produce oxides of carbon and nitrogen.

HAZARDOUS POLYMERIZATION: Will Not Occur

CONDITIONS TO AVOID: None

VII. SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED: Vacuum or sweep up spill. Wash down area.

WASTE DISPOSAL METHOD: Dispose of waste in accordance with appropriate Federal, State and local regulations.

VIII. SPECIAL PROTECTION INFORMATION

RESPIRATORY PROTECTION (specify type): NIOSH/OSHA approved respirator.

VENTILATION: General mechanical room ventilation is satisfactory for normal handling and storage operations.

ATTACHMENT 3

PRODUCT NAME: Butenafine Hydrochloride (KP-363)

PAGE 4

PROTECTIVE GLOVES: PVC-coated

EYE PROTECTION: Safety glasses

OTHER PROTECTIVE EQUIPMENT:
Eye bath and safety shower

NOTE ----

The opinions expressed herein are those of qualified experts within Penederm Incorporated. We believe that the information contained herein is current as of the date of this Material Safety Data Sheet. Since the use of this information and of these opinions and the conditions of the use of the product are not within the control of Penederm Incorporated, it is the user's obligation to determine the conditions of safe use of the product.

Memo

MEMORANDUM OF TELEPHONE CONFERENCE

NDA 214-124

DATE: 8/1/95

FROM: Frank Cross, Jr., Project Manager, Mary Jean Kozma-Fornaro, Project Manager, Ralph Harkins, Supervisor Biostatistics, R. Srinivasan, Biostatistician, Nancy Slifman, Medical Officer, (301) 594-4877

TO: Barry Calvarese, Penederm Incorporated, Foster City, CA, M. Noursalehi and Barbara Brennen, (415) 378-6479

SUBJECT: Butenafine Hydrochloride Cream, 1%

SPONSOR: Penederm Incorporated

The purpose of the teleconference was to discuss and request the results, analyzed by investigator, for both pivotal studies.

Applicant's Position:

According to Mr. Calvarese and Dr. Noursalehi, the applicant will provide analyses for all parameters. They stated that they would also recreate all tables for all data and would use the CMH test, Breslow Day test and provide the full SAS data output as well as raw data in SAS or similar computer ready format for the two pivotal studies. Further, they stated that they would provide a table for each time point and each variable. The output would be provided at the bottom of the table.

Mr. Calvarese stated that they were providing additional efficacy analyses using a total score of 0 or 1 plus negative mycology (negative KOH and culture). FDA emphasized that this analysis might be considered only supportive of efficacy. As previously discussed with the applicant, the primary efficacy variable is "Overall Cure." A score of 0 plus negative mycology should support the definition of "Overall Cure" (i.e., "Cleared" plus negative mycology).

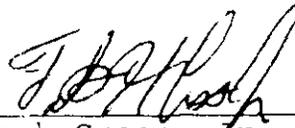
Other items mentioned during the discussion were:

1. Need for safety update for post-marketing surveillance from
2. Need clarification of "other" dermatophytes listed: vol. 1.18, p6-1834 and vol. 1.20, p6-2072.
3. A tradename should be submitted as soon as possible.

4. Need for clarification regarding the presence of benzyl alcohol in the formulations used in all clinical trials, and in the formulation to be marketed. Also, specify why benzyl alcohol is used in the formulation. Please present, in tabular form:
 - a. Each different compositional formulation used, including the one intended to be marketed.
 - b. All clinical studies performed, and an indication as to which formulation was used in each study.
5. A letter from the Japanese government certifying compliance with environmental laws.

Mr. Calvarese said that he would be sending in all of the information in the next few weeks. He also said that he would submit all information requested as official submissions to the NDA.

The meeting ended amicably.



Frank Cross, Jr., MA, LCDR
Project Manager

cc: Orig NDA 20-524
HFD-540
HFD-540/DIR/Wilkin
HFD-540/DEP DIR/Katz
HFD-540/SCHEM/DeCamp
HFD-540/SPharm/Jacobs
HFD-426/SBiopharm/Pelsor
HFD-713/SBiostat/Harkins
HFD-520/SMicro/Sheldon
HFD-540/SPM/Cook
HFD-540/MO/Slifman
HFD-540/Chem/Pappas
HFD-540/Pharm/Mainigi
HFD-426/Biopharm/Lee
HFD-713/Biostat/Srinivasan
HFD-713/Biostat/Freidlin
HFD-520/Micro/Dionne
HFD-540/PM/Cross

TELEPHONE MEMO

MEMORANDUM OF TELEPHONE CONFERENCE

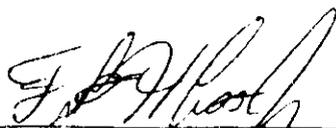
NDA: 20-524 DATE: 8/9/95
FROM: Frank Cross, Jr., Project Manager and Maria Rossana R. Cook, M.B.A.,
Supervisor Project Management Staff, HFD-540, (301) 594-4877
TO: Barry Calvarese, Penederm Incorporated, Foster City, CA (415) 378-6479
SUBJECT: Butenafine Hydrochloride Cream, 1%
SPONSOR: Penederm Incorporated

Barry Calvarese was informed that NDA 20-524 was fileable, but that the following deficiencies needed to be addressed:

1. Need for safety update for post-marketing surveillance from
2. Need results (cure rate analysis), by investigator for both pivotal studies and analysis of investigators by treatment interaction. Mr. Calvarese said that he would be calling Dr. Srinivasan for further clarification.
3. Need clarification of "other" dermatophytes listed: vol. 1.18, p6-1034 and vol. 1.20, p6-2072
4. Regarding Protocol PDC 010-002 (Phase III efficacy trial), plasma samples were drawn at 11 and 19 hours after dose. The sponsor indicates that these samples represent trough levels of butenafine. It is unclear why the sponsor prefers to determine the trough levels (It appears that the sponsor is trying to monitor the efficacy from the trough levels). Mr. Calvarese will be calling Dr. Lee for further clarification.
5. A tradename should be submitted as soon as possible.
6. Need for clarification regarding the presence of benzyl alcohol in the formulations used in all clinical trials, and in the formulation to be marketed. Also, specify why benzyl alcohol is used in the formulation. Please present, in tabular form:
 - a. Each different compositional formulation used, including the one intended to be marketed.
 - b. All clinical studies performed, and an indication as to which formulation was used in each study.
7. A letter from the Japanese government certifying compliance with environmental laws. Mr. Calvarese was advised that he could call Christina Good of HFD-004 for further clarification.

Mr. Calvarese said that he would be sending in the information in the next two weeks, with the exception of the post-marketing surveillance from [REDACTED] Japan. Regarding this information, Mr. Calvarese said that he would be checking the data received to date from Japan and would submit it early, if necessary. If Mr. Calvarese determined that there was no new safety data to report, then he was going to wait until all of the data was in before formally submitting it to the NDA. Mr. Calvarese said that he would submit all information requested as an official submission to the NDA.

The meeting ended amicably.


Frank Cross, Jr., MA, LCDR
Project Manager

cc: Orig NDA 20-524
HFD-540
HFD-540/DIR/Wilkin
HFD-540/DEP DIR/Katz
HFD-540/SCHEM/DeCamp
HFD-540/SPharm/Jacobs
HFD-426/SBiopharm/Pelsor
HFD-713/SBiostat/Harkins
HFD-520/SMicro/Sheldon
HFD-540/SPM/Cook

HFD-540/MO/Slifman
HFD-540/Chem/Pappas
HFD-540/Pharm/Mainigi
HFD-426/Biopharm/Lee
HFD-713/Biostat/Srinivasan
HFD-520/Micro/Dionne
HFD-540/PM/Cross

TELEPHONE MEMO

MEMORANDUM OF TELEPHONE CONFERENCE

NDA 20-524

DATE: 10/20/95

FROM: Frank Cross, Jr., Project Manager, Maria Rossana R. Cook, M.B.A.,
Supervisor Project Management Staff, (301) 594-4877

TO: Barry Calvarese, Penederm Incorporated, Foster City, CA,
(415) 378-6479

SUBJECT: Butenafine Hydrochloride Cream, 1%

SPONSOR: Penederm Incorporated

The purpose of the teleconference was to clarify the definition of mycological cure, and request SAS data sets and case report forms.

FDA's Position:

The agency restated to the applicant that the primary efficacy parameter for NDA 20-524, Butenafine HCL is "mycological cure plus an Investigator's Global score of "Cleared," and is termed "Overall Cure." In the applicant's submission the use of mycological cure plus a signs/symptoms score of less than 2 is not an "additional definition of cure" and would only be supportive of efficacy.

The agency requested the submission of additional SAS data files, which include the baseline pathogen for each patient, in an uncompressed format.

The agency requested copies of additional case report forms from Study 001 - Patient

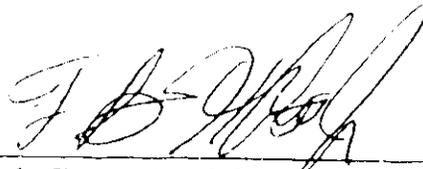
The agency asked if the applicant had previously submitted a SAS file that would allow the SAS data sets already received to be uncompressed.

Applicant's Position:

Mr. Calvarese agreed with the agency's definition of "Overall Cure."

Mr. Calvarese said that the other requested items would be submitted next week and that the SAS data files would be sent in an uncompressed format. The additional file to uncompress the SAS data sets had been submitted earlier in the week.

The meeting ended amicably.



Frank Cross, Jr., MA, LCDR
Project Manager

cc:

Orig NDA 20-524

HFD-540

HFD-540/DIR/Wilkin/8.5.96

HFD-540/DEP DIR/Katz

HFD-540/SChem/DeCamp

HFD-540/SPharm/Jacobs

HFD-426/SBiopharm/Pelsor

HFD-713/SBiostat/Harkins

HFD-520/SMicro/Sheldon

HFD-540/SPM/Cook/8.5.96

HFD-540/MO/Slifman/8.5.96

HFD-540/Chem/Pappas

HFD-540/Pharm/Mainigi

HFD-426/Biopharm/Lee

HFD-713/Biostat/Srinivasan

HFD-713/Biostat/Freidlin

HFD-520/Micro/Dionne

HFD-540/PM/Cross

TELEPHONE MEMO

Co. Corres.

PENEDERM INCORPORATED
20 LAKESIDE DRIVE, SUITE A
DOSTER CITY, CA 94404
415-358-0100
FAX 415-358-0101



March 1, 1996

Jonathan Wilkin, MD
Director
Division of Dental and Dermatological Drug products
Document Mail Room
Office of Drug Evaluation II
Center for Drug Evaluation And research
Food and Drug Administration
Bldg. 2
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-663, Butenafine HCl Cream 1%
For the treatment of Tinea Corporis and Tinea Cruris

Dear Dr. Wilkin:

Enclosed is the patent information and certification requested by Frank Cross on March 1, 1996. Please contact us if you have any further questions regarding this NDA application.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

PATENT CERTIFICATION

NDA 20-524

In the opinion of Penederm Incorporated and to the best of our knowledge, the following is an accurate account of all patents containing the listed drug substance, butenafine, for which Patent Certification in accordance with 21 U.S.C. 355 (b) (1) must be provided.

Patent No.	5,021,458	Expiration Date	June 4, 2008
Patent No.	5,106,866	Expiration Date	April 21, 2009

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
-358-0100
(415-358-0101



DEBARMENT STATEMENT

Penederm Incorporated herewith certifies that the services of any persons debarred under Section 306 (a) or (b) were not and will not be used in any capacity in conjunction with this application.

Signed: John Quigley
John Quigley, PhD
Vice President
Research and Development

Date: 4/3/95

PENEDERM INCORPORATED
320 LAMESIDE DRIVE, SUITE A
FOSTER CITY, CA 9404
TEL 415-358-0100
FAX 415-358-0101

DESK COPY



May 8, 1996

Jonathan Wilkin, MD, Director
Division of Dental and Dermatologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA #20-524, Butenafine HCl Cream 1% (Mentax™)
Response to FDA Approvable Letter dated April 3, 1996

Dear Dr. Wilkin:

Pursuant to Section 505(b) of the Federal Food, Drug and Cosmetic Act Penederm Incorporated herewith submits responses to the issues cited in your approvable letter dated April 3, 1996. Eight copies of this one-volume response are provided.

A disk containing the Mentax™ Package Insert in DOS WordPerfect® 5.1 format is also included in the Archive and Clinical copies.

Your prompt review of this document is appreciated. Please contact Barry M. Calvarese, Executive Director, Regulatory/Clinical Affairs for further information regarding this application.

Please be advised that the material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under the applicable provisions of 18 USC, Section 331(j) and/or 21 CFR 312.130.

Sincerely,



Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

COMMENT 2

2. All safety information you now have regarding your new drug, in accordance with the requirements of 21 CFR 314.50(d)(5)(vi)(b). Please provide updated information as listed below:
 - a. Retabulate all safety data, including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.
 - b. Retabulate drop-outs with new drop-outs identified. Provide discussion where appropriate.
 - c. Submit case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.
 - d. Provide details of any significant changes or findings, if any.
 - e. Summarize worldwide experience on the safety of this drug.

RESPONSE TO COMMENT 2

Safety data has been compiled from the Penederm-sponsored clinical studies of butenafine HCl listed in Table 2.

Table 2
Clinical Studies of Butenafine HCl

Study Number	Title
PDC 010-001	A Double-Blind Evaluation of Butenafine HCl Cream 1% and Vehicle in the Treatment of Tinea Pedis
PDC 010-002	A Double-Blind Evaluation of Butenafine HCl Cream 1% and Vehicle in the Treatment of Tinea Pedis
PDC 010-003	A Double-Blind Evaluation of Butenafine HCl 1% (KP-363) Gel and Vehicle in the Treatment of Onychomycosis
PDC 010-004	A Multicenter, Double-Blind Study to Evaluate Butenafine HCl Cream 1% and Vehicle in the Treatment of Tinea Corporis
PDC 010-005	A Multicenter, Double-Blind Study to Evaluate Butenafine HCl Cream 1% and Vehicle in the Treatment of Tinea Cruris
PDC 010-006	Human Repeated Insult Patch Test for Butenafine HCl 1%
PDC 010-007	Evaluation of Human Phototoxicity for butenafine HCl 1%
PDC 010-008	Evaluation of Human Photoallergy for Butenafine HCl 1%
PDC 010-009	Evaluation of Primary Irritation for Butenafine HCl 1% Cream and Vehicle
PDC 010-010	Evaluation of Cumulative Irritation for Butenafine HCl 1%
PDC 010-011	A Single Center, Open Label Study to Determine the Plasma Level of Butenafine Following Multiple Topical Applications of Butenafine HCl Cream 1% to Normal Volunteers
PDC 010-012	A Comparison of the Safety and Efficacy of Butenafine HCl with Vehicle in the Treatment of Distal Subungual Onychomycosis of the Fingernails
PDC 010-014	A Multicenter, Double-Blind Study to Evaluate Butenafine HCl Cream 1% and Vehicle in the One-Week Treatment of Tinea Pedis
PDC 010-015	A Multicenter, Double-Blind Study to Evaluate Butenafine HCl Cream 1% and Vehicle in the One-Week Treatment of Tinea Pedis

A. RETABULATION OF SAFETY DATA

A total of 1,042 subjects received at least one dose of Butenafine HCl 1% Cream or Gel in the Penederm-sponsored clinical studies listed above. Twenty patients treated with Butenafine HCl Cream 1% and five patients treated with Butenafine HCl Gel 1% experienced adverse events that were considered at least possibly treatment-related. The rate of occurrence of adverse events for all patients treated with butenafine HCl, including those patients treated with an exaggerated dose in Clinical Study PDC 010-011, was <2%.

Table 3
Treatment-Related Adverse Events

Study Number	Butenafine		Vehicle	
	# of Patients	# of AEs	# of Patients	# of AEs
PDC 010-001	1	1	1	1
PDC 010-002	1	1	4	6
PDC 010-003	5	7	3	3
PDC 010-004	0	0	0	0
PDC 010-005	1	1	0	0
PDC 010-006	0	0	N/A	N/A
PDC 010-007	0	0	N/A	N/A
PDC 010-008	0	0	N/A	N/A
PDC 010-009	0	0	N/A	N/A
PDC 010-010	0	0	N/A	N/A
PDC 010-011	7	13	N/A	N/A
PDC 010-012	0	0	1	1
PDC 010-014	4	6	7	7
PDC 010-015	1	1	4	5

The following is a summary of Adverse Experience information for Penederm clinical studies of butenafine HCl.

PDC 010-001:

A total of 45 adverse events were reported during the study, 18 in the butenafine group and 27 in the vehicle group. The body system accounting for the most adverse events in either treatment group was Body/General. Six adverse events were reported in this category from the vehicle group and seven from the butenafine group. The category with the second highest incidence of reported adverse events was Body/Head with five adverse events reported from the vehicle group and two from the butenafine group. One adverse event in each treatment group was characterized by the investigator as possibly treatment-related: the development of moccasin-type tinea pedis in one patient randomized to butenafine, and a headache in one patient randomized to vehicle. One patient in the butenafine group was diagnosed with basal cell carcinoma of the face during enrollment, an event considered serious but unrelated to treatment. No patient in either group withdrew because of an adverse event.

PDC 010-002:

A total of 42 adverse events were reported during the study, 14 in the butenafine group and 28 in the vehicle group. The body system accounting for the most adverse events in either treatment group was Body/General. Six adverse events were reported in this category from the vehicle group and four from the butenafine group. The category with the second highest incidence of reported adverse events was Body/Head with four adverse events reported from the vehicle group and none from the butenafine group. One adverse event in the butenafine group (mild burning at the application site) was characterized by the investigator as related to treatment, six adverse events in the vehicle group were thought to be possibly, probably, or definitely related to treatment. There were no serious, unexpected adverse events reported. One patient in the vehicle group withdrew from the study because of treatment-related adverse events; burning, stinging, itching of both feet. No patients in the butenafine group withdrew because of adverse events.

PDC 010-003:

Adverse events (probably related, possibly related, or related to treatment) were reported in 33% (5/15) and 19% (3/16) of patients treated with butenafine and vehicle, respectively. Adverse events in the butenafine group consisted of avulsion of the large toenail, cellulitis of the knee, malodor of the toes, purulent drainage from the large toe, rash on ankles, skin peeling, and burning/stinging in the large toenail. Adverse events in the vehicle group consisted of bruising of the large toe, interdigital erythema/scaling, and white mottling of the toenails. No patient withdrew from the study because of an adverse event.

PDC 010-004:

A total of three adverse events were reported in the butenafine group and seven in the vehicle group. There were no adverse events assessed by the investigators as possibly, probably, or definitely treatment-related. The body system accounting for the most adverse events in either treatment group was Respiratory. One adverse event was reported in this category from the butenafine group and four from the vehicle group. There were no serious, unexpected adverse events reported. No patient in either group withdrew because of an adverse event.

PDC 010-005:

A total of 10 adverse events were reported in the butenafine group and nine in the vehicle group. The body system accounting for the most adverse events in either treatment group was Body as a Whole, with six adverse events in this category in each treatment group. One patient in the butenafine group experienced an adverse event thought to be treatment related; burning upon application of study medication. There were no serious, unexpected adverse events reported. No patient in either group withdrew because of an adverse event.

PDC 010-006:

Three adverse events were observed during exposure to the test materials. One patient had a myocardial infarction and was dropped from the study. One patient had a concomitant illness and withdrew after the second application. One patient had a back injury and medicated with excluded medication. The patient completed the study but the data was dropped from the final tabulations.

PDC 010-007:

There were no adverse events during the study.

PDC 010-008:

There were no adverse events during the study.

PDC 010-009:

There were no adverse events during the study.

PDC 010-010:

There were no adverse events during the study.

PDC 010-011:

During this study of butenafine HCl use under exaggerated dosing conditions, there were 29 adverse events reported. The most frequently reported adverse events were dermatological in nature, with 13 reported. All dermatological adverse events were considered mild, and itching was the most frequent adverse event reported. There were no serious adverse events reported. No patient withdrew because of an adverse event.

PDC 010-012:

A total of 35 adverse events were reported during the study, 24 in the butenafine group and 11 in the vehicle group. One adverse event in the vehicle group (Patient [redacted]) was categorized by the Investigator as at least possibly treatment-related. Patient [redacted] developed paronychia of the target fingernail and withdrew from the study. All other adverse events were considered unrelated to treatment. There were three serious adverse events reported during the study by patients in the butenafine group. Patient [redacted] was hospitalized for a prostatectomy, Patient [redacted] was hospitalized for an appendectomy, and Patient [redacted] was hospitalized for diverticulitis. All three patients completed the study.

PDC 010-014:

A total of 145 adverse events were reported during the study, 63 in the butenafine group and 82 in the vehicle group. The body system accounting for the most adverse events in either treatment group was Body as a Whole. A total of 37 events were reported in this category, 16 from the butenafine group and 21 from the vehicle group. The category with the second highest incidence of reported adverse events was Urogenital with 28 adverse events reported, seven in the butenafine group and 21 in the vehicle group. A total of 13 adverse events were categorized by the Investigators as at least possibly treatment-related. Six of the treatment-related adverse events occurred in the butenafine group and seven occurred in the vehicle group. There were four serious adverse events (SAEs) reported during the study, one in the butenafine group (Patient [redacted] was hospitalized for an enlarged heart) and three in the vehicle group (Patient [redacted] automobile accident; Patient [redacted] phlebitis; and Patient [redacted] hysterectomy). All of the SAEs were considered unrelated to treatment. Three patients in the vehicle group withdrew from the study because of an adverse event.

PDC 010-015:

A total of 86 adverse events were reported during the study, 36 in the butenafine group and 50 in the vehicle group. The body system accounting for the most adverse events in either treatment group was Body as a Whole. A total of 27 adverse events were reported in this category, 10 from the butenafine group and 17 from the vehicle group. The category with the second highest incidence of reported adverse events was Urogenital System, with a total of 19 adverse events reported, eight in the butenafine group and 11 in the vehicle group. A total of six adverse events were categorized by the Investigators as at least possibly treatment-related. One of the treatment-related adverse events occurred in the butenafine group and five occurred in the vehicle group. There was one serious adverse event reported in the vehicle group, an ankle fracture that required hospitalization of the patient. No patient withdrew from the study due to an adverse event.

B. RETABULATION OF DROP-OUTS FROM BUTENAFINE HCl CLINICAL STUDIES

**Table 4
Number of Subjects Dropped From Butenafine HCl Studies**

Study Number	Number Entered	Number Completed	Number Dropped for any Reason					
			DNQ	Protocol Violation	AE	Lost To Follow-up	Personal Reasons	Treatment Failure
PDC 010-001	150	105	43			2		
PDC 010-002	119	80	38		1	1		
PDC 010-003	31	31						
PDC 010-004	91	78	11				2	
PDC 010-005	93	76	14	1		2		
PDC 010-006	225	204	5	1	2	8	5	
PDC 010-007	27	27						
PDC 010-008	32	31	1					
PDC 010-009	17	17						
PDC 010-010	30	24						
PDC 010-011	20	20						
PDC 010-012	34	29			1	3		1
PDC 010-014	451	259	180	1	3	6	4	4
PDC 010-015	402	268	114			11	1	8

C. PATIENTS WHO DID NOT COMPLETE A STUDY BECAUSE OF AN ADVERSE EVENT

The following is a list of Adverse Event-associated Subject withdrawals. Copies of the Case Report Forms for these patients are provided at the end of this section. There have been no reported deaths of patients enrolled in Penederm-sponsored clinical studies of butenafine HCl 1%.

Table 5
Case Report Forms of Adverse Events

Study Number	Patient Number	Treatment	Adverse Event
PDC 010-002		Vehicle	Stinging, Burning, Itching
PDC 010-006		Butenafine Butenafine	Concomitant Illness Myocardial Infarction
PDC 010-012		Vehicle	Paronychia
PDC 010-014		Vehicle Vehicle Vehicle	Application Site Reaction Viral Infection Vein Inflammation

D. SIGNIFICANT CHANGES

There are no significant changes or findings since the NDA was submitted.

E. WORLDWIDE EXPERIENCE ON SAFETY OF BUTENAFINE HCL

Well over 4,000 patients have been assessed for the safety of butenafine HCl Cream 1% in Japan, Europe, and the United States. Butenafine HCl Cream 1% is well tolerated with very few local adverse events attributed to drug treatment. The results of pre- and post-marketing surveillance program indicate that approximately 0.99% to 2.76% of patients experienced a local adverse event. Table 6 on the following page summarizes surveillance data.

Table 6

Post-Marketing Surveillance Data
Side Effects Of Mentax Cream

	Before Approval	PMS* 1-21-92 to 1-20-93	PMS* 1-21-93 to 1-20-94	PMS* 4-01-94 to 3-31-95
1. Number of Institutes Surveyed	39	37	140	178
2. Number of Cases Surveyed	907	357	1376	1317
3. Number of Cases with Side Effects	25	8	22	13
4. Number of Instances	36	12	36	18
5. Incidence of Side Effects [(3 ÷ 2) x 100]	2.76	2.24	1.60	0.99
6. Volumes of Shipment (g)	---	261,323	367,084	---
Item	Number of Symptoms (%)			
Symptoms at Application Sites (Cases)	25 (2.76)	8 (2.24)	22 (1.60)	13 (0.99)
Pruritus	5 (0.55)	2 (0.56)	8 (0.58)	3 (0.23)
Papule	2 (0.02)		2 (0.15)	
Irritation	7 (0.77)	2 (0.56)	1 (0.07)	3 (0.23)
Vesicle or Blister	3 (0.33)	1 (0.28)	2 (0.15)	1 (0.08)
Maceration	1 (0.11)			
Contact Dermatitis	5 (0.88)	2 (0.56)	10 (0.73)	5 (0.38)
Redness	8 (0.88)	2 (0.56)	8 (0.58)	4 (0.30)
Expansion of Rash	1 (0.11)			
Edema		1 (0.28)		
Scale	1 (0.11)		3 (0.22)	1 (0.08)
Keratinization and Rhagades		1 (0.28)		
Pustule		1 (0.28)		
Exudative Erythema				1 (0.08)
Subtotal	36 (3.97)	12 (3.36)	36 (2.62)	18 (1.38)
Others (Cases)	0	0	0	0
Total (Cases)	25 (2.76)	8 (2.24)	22 (1.60)	13 (0.99)

* = Post-Marketing Surveillance

NC

RM INCORPORATED
SIDE DRIVE, SUITE A
STER CITY, CA 94404
358-0100
415-358-0101



PENEDERM



October 16, 1996

Frank Cross
Project Manager
Division of Dermatological and Dental Drug products
Document Mail Room
Office of Drug Evaluation II
Center for Drug Evaluation And Research
Food and Drug Administration
Bldg. 2
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20,524, Mentax™ (butenafine HCl cream) Cream, 1%
Package Insert

Dear Mr. Cross:

Thank you for your telefax communication dated October 16, 1996 regarding the final Mentax™ Package Insert labeling recommendation from the Division of Dermatological and Dental Drug products (reference telefax 10/16/96, number 106). We have reviewed this Package Insert language and find it acceptable.

At this time, we withdraw our proposal to change the specification for benzyl alcohol as mentioned in our letter dated 10/16/96. The current specification stands at wt. %.

Based on our recent conversation of 10/16/96, it is our understanding that this version of the Package Insert is the final version and that no further changes are required. As we intend to print this version of the Package Insert in the very near future, please confirm that our understanding is correct. Please call me if you have any further comments or questions regarding the Package Insert.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

EDLKM INCORPORATED
LAKESIDE DRIVE, SUITE A
FARMER CITY, CA 94404
358-0100
415-358-0101



BC
NDA 010 AMENDMENT

October 16, 1996

Jonathan Wilkin, MD, Director
Division of Dental and Dermatologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850



Re: NDA #20-524, Mentax™ Cream (butenafine HCl) 1%
Stability Data

Dear Dr. Wilkin:

Reference is made to our teleconference with Frank Cross and Dr. Tony DeCamp regarding stability data to support a shelf-life claim of two years. Additional stability data is enclosed that supports the two-year expiration dating. The updated stability tables for the three lots (HCGG, HIED, and IAP) of Butenafine HCl Cream 1% (Mentax) provide the latest available data for the packaged sizes of 2-gram, 15-gram, and 30-gram aluminum tubes.

All the data provided remain within the proposed specifications. Please note that the specification for benzyl alcohol is being revised. The proposed lower limit for benzyl alcohol, used as a preservative, is % w/w. The formulation passes the USP Preservative Challenge Test even when benzyl alcohol is present at concentrations of % w/w. This data was submitted as part of the Product Development Report (pages 6, and 7, copy attached) during the PAI at . The data indicates that the product is well preserved with the benzyl alcohol at the current specification.

Please contact us if you have any further questions.

Sincerely,

Barry M. Calvarese

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

REVISIONS COMPLETED	
OSD ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> REC'D
OSD INITIALS	DATE

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
DOSTER CITY, CA 94404
358-0100
FAX 415-358-0101



March 6, 1996

Jonathan Wilkin, MD, Director
Division of Dental and Dermatologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850



Re: NDA #20-524, Butenafine HCl Cream 1%
for the treatment of Interdigital Tinea Pedis

Dear Dr. Wilkin:

Reference is made to our March 6, 1996 teleconference with Frank Cross and Ernie Pappas regarding a facility for microbiological testing for the above-referenced NDA. Because there are two other facilities qualified for microbiological testing cited in NDA #20-524, we have decided to remove this facility from this NDA. Penederm herewith removes
cited in Volume 1.2, page 20-198 of NDA 20-524.

Sincerely,

A handwritten signature in cursive script, appearing to read 'Barry M. Calvarese'.

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

PENEDERM INCORPORATED
LAKEVIEW DRIVE, SUITE A
ROCKVILLE, CA 94404
415-358-0100
FAX 415-358-0101



January 3, 1996

Frank Cross
Project Manager
Division of Dermatologic and Ophthalmic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 2, Room N229
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-524 Butenafine HCl cream 1%, Interdigital Tinea pedis
Request for Tradename

Dear Mr. Cross:

During our August 9, 1995 teleconference you requested that Penederm Incorporated submit a tradename for butenafine cream as soon as possible. The tradename LOTRIPHINE™ has been selected for butenafine cream. We look forward to the approval of this name by the CDER Naming Committee and encourage you to contact us if you have any further questions regarding this NDA application.

Your time and efforts are greatly appreciated

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
358-0100
358-0101



PENEDERM



March 1, 1996

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA 20-524 Butenafine HCl Cream 1%
For the Treatment of Interdigital Tinea Pedis
Request for Backup Trade Name

Dear Dr. Wilkin:

Penederm Incorporated submitted a trade name for Butenafine HCl Cream 1%, LOTRIPHINE™, on January 3, 1996. Because of potential trademark concerns, we would like to submit an additional name, MENTAX™, for review and approval by the CDER Naming Committee.

If both names are approved, we assume that we have the option of choosing either name once this drug product is considered to be approvable. We encourage you to contact us if you have any questions regarding this request.

Your time and efforts are greatly appreciated.

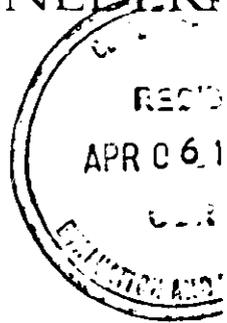
Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

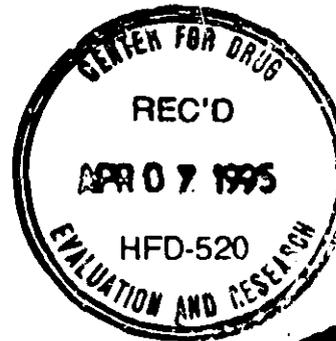
DERM INCORPORATED
LAKEVIEW DRIVE, SUITE A
ROCKVILLE CITY, CA 94404
58-0100
415-358-0101



PENEDERM



4 April 1995



Jonathan Wilkin, MD
Director, Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-540, Room 17B-45
5600 Fishers Lane
Rockville, MD 20857



Subject: New Drug Application #20-524
Butenafine HCl Cream 1%
For the Treatment of Interdigital Tinea Pedis

Dear Dr. Wilkin:

Pursuant to Section 505(b) of the Federal Food, Drug and Cosmetic Act and in accordance with Title 21 of the Code of Federal Regulations, Section 314.50, Penederm Incorporated herewith submits an original New Drug Application (NDA) for Butenafine HCl Cream 1%.

The new drug product contains the active drug substance, butenafine hydrochloride, at a concentration of 1% in a cream vehicle. Previous information concerning this formulation has been submitted to the Agency under Investigational New Drug Application (IND)

We consider all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of all enclosed information is provided for under 18 USC, Section 1905 and/or 21 USC, Section 331j.

Jonathan Wilkin, MD
Director, Division of Topical Drug Products
4 April 1995
Page 2 of 4

The complete NDA is submitted in the following volumes:

Section	Archival Copy Volume Number(s)	Review Copy Volume Number(s)
Application Summary	1.1	(Provided for Each Section)
Chemistry, Manufacturing and Controls	1.2 to 1.5	1.1 and 1.2 to 1.5 1.3* (3 Additional Copies)
Nonclinical Pharmacology and Toxicology	1.6 to 1.12	1.1 and 1.6 to 1.12
Human Pharmacokinetics and Bioavailability	1.13 to 1.14	1.1 and 1.13 to 1.14
Microbiology	1.15	1.1 and 1.15
Clinical Data	1.16 to 1.23	1.1 and 1.16 to 1.23
Statistical Data	1.24 to 1.27	1.1 and 1.24 to 1.27
Sample and Labeling	1.28	N/A
Total Number of Volumes	28	32

* Three additional copies of the Methods Validation Package (Volume 1.3) are included with the Review copy of the CMC Section.

In addition, four desk copies of Section I. (Application Summary), Volume 1.1, are included at the request of the Agency.

Penederm Incorporated and
approval inspection by July 1, 1995.

will be prepared for a pre-

- All clinical trials submitted in this new drug application were conducted in accordance with 21 CFR, Part 56 for Institutional Review Boards or the Declaration of Helsinki provisions of the CFR.
- All pharmacology/toxicology studies conducted in support of NDA #20-524 have been performed using acceptable, state-of-the-art protocols reflective of agency animal welfare concern. The protocols are designed to support the safety and have been used for these types of studies to allow the data to be compared to that of other compounds.

Jonathan Wilkin, MD
Director, Division of Topical Drug Products
4 April 1995
Page 3 of 4

- The studies compiled with all applicable sections of the Final Rules of the Animal Welfare Act regulations (9 CFR) and the Public Health Service Policy on Humane Care and Use of Laboratory Animals (OPRR, NIH, 1986). Wherever possible, procedures used in the studies were designed to avoid or minimize discomfort, distress and pain to the animals. All methods were described in the study protocols, or in written laboratory standard operating procedures. All procedures were based on the most currently available technologies concerning proper laboratory animal use and management.
- The integrated summary of safety for this new drug application includes all known safety data for the drug product from all domestic and foreign sources, to the greatest extent possible.
- The cut-off date for clinical data inclusion and preparation of the integrated summary of safety in this new drug application is March 31, 1995.
- Reference is made to the pre-IND meeting that occurred on January 21, 1993, and the pre-NDA meeting held February 13, 1995 [meeting minutes dated 3/03/95 (IND
- All nonclinical toxicology studies performed by in Japan (series D studies) were conducted in accordance with the Good Laboratory Practice (GLP) standards of the Japanese Ministry of Health and Welfare. All nonclinical toxicology studies performed by Penederm Inc. in the U.S. were conducted in accordance with Part 58 of the CFR.

Enclosed with this NDA in the Statistical Section and Archive copies are two (2) complete sets of five disks each containing the following:

- 1 diskette with SAS datasets for both U.S. pivotal studies in SAS transport format. Each file includes a README file of instructions
- 2 diskettes with tables and data listings for pivotal clinical study PDC 010-001 in DOS WordPerfect® format

Jonathan Wilkin, MD
Director, Division of Topical Drug Products
4 April 1995
Page 4 of 4

- 2 diskettes with tables and data listings for pivotal clinical study PDC 010-002 in DOS WordPerfect® format

All pivotal trial statistical calculations were performed on PC compatible computers containing Intel 486DX chips. Software development and some of the data listing tasks were performed on a computer which had previously contained a [redacted] which was replaced with a chip certified by the computer's manufacturer [redacted] to be free of the floating point error present in earlier versions of the [redacted] chip.

Sincerely,



Barry Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE
OR AN ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, 314)

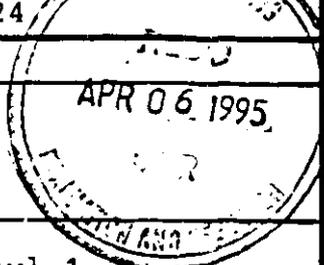
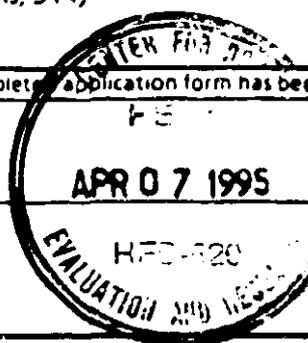
Form Approved: GMB No. 0910-0001.
Expiration Date: April 30, 1994.
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED 5 Apr 95	DATE FILED
DIVISION ASSIGNED 540	NDA/ANDA NO. ASS. 20524

NOTE: No application may be filed unless a complete application form has been received (21 CFR Part 314).

NAME OF APPLICANT Penederm Incorporated	DATE OF SUBMISSION 3 April 1995
ADDRESS (Number, Street, City, State and Zip Code) 320 Lakeside Drive, Suite A Foster City, CA 94404	TELEPHONE NO. (Include Area Code) 415-358-0100
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (if previously issued) 20-524



DRUG PRODUCT

ESTABLISHED NAME (e.g., USPIUSAN) Butenafine Hydrochloride Cream 1%	PROPRIETARY NAME (if any)
--	---------------------------

CODE NAME (if any) KP-363	CHEMICAL NAME N-4-tert-Butylbenzyl-N-methyl-1-naphthalenemethylamine Hydrochloride
------------------------------	---

DOSAGE FORM Cream	ROUTE OF ADMINISTRATION Topical	STRENGTH(S) 1%
----------------------	------------------------------------	-------------------

PROPOSED INDICATIONS FOR USE

Indicated for topical application in the treatment of interdigital tinea pedis.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (21 CFR 314.420) REFERRED TO IN THIS APPLICATION:

- IND
- DMF
- DMF

- DMF
- DMF

INFORMATION ON APPLICATION

TYPE OF APPLICATION (Check one)

THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION
--------------	--------------------------------

TYPE SUBMISSION (Check one)

- | | | |
|--|--|---|
| <input type="checkbox"/> PRESUBMISSION | <input type="checkbox"/> AN AMENDMENT TO A PENDING APPLICATION | <input type="checkbox"/> SUPPLEMENTAL APPLICATION |
| <input checked="" type="checkbox"/> ORIGINAL APPLICATION | <input type="checkbox"/> RESUBMISSION | |

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70(b)(2)(iv))

PROPOSED MARKETING STATUS (Check one)

APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (R0028) APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

CONTENTS OF APPLICATION

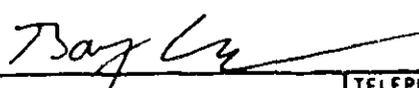
his application contains the following items. (Check all that apply)

X	1. Index
X	2. Summary (21 CFR 314.50 (c))
	3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1))
	4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request)
X	b. Methods Validation Package (21 CFR 314.50 (e) (2) (i))
	c. Labeling (21 CFR 314.50 (e) (2) (ii))
X	i. draft labeling (4 copies)
	ii. final printed labeling (12 copies)
X	5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2))
X	6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3))
X	7. Microbiology section (21 CFR 314.50 (d) (4))
X	8. Clinical data section (21 CFR 314.50 (d) (5))
	9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b))
X	10. Statistical section (21 CFR 314.50 (d) (6))
	11. Case report tabulations (21 CFR 314.50 (f) (1))
X	12. Case reports forms (21 CFR 314.50 (f) (1))
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. OTHER (Specify)

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

NAME OF RESPONSIBLE OFFICIAL OR AGENT Barry Calvarese, MS Penederm Incorporated	SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	DATE 4/03/95
ADDRESS (Street, City, State, Zip Code) 320 Lakeside Drive, Suite A, Foster City, CA 94404	TELEPHONE NO. (Include Area Code) 415-358-0100	

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

PENEDERM INCORPORATED
LAKESIDE DRIVE, SUITE A
FARMER CITY, CA 94404
58-0100
415-358-0101



April 12, 1995

Jonathan Wilkin, MD, Director
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
HFD-540, Room 17B-45
Rockville, MD 20857

RE: NDA #20-524
Butenafine HCl Cream 1%

Dear Dr. Wilkin:

NDA 20-524 was submitted to the Topical Drug Product Division on April 4, 1995. The User Fee Cover Sheet (volume 1.1, page 1 0030) indicated that the application was submitted under 505(b)(2). This is a mistake and a new User Fee Cover Sheet is enclosed to replace the one originally submitted.

Please call me if you have any additional questions.

Sincerely,

A handwritten signature in cursive script, appearing to read "Barry M. Calvarese".

Barry M. Calvarese, M.S.
Executive Director
Clinical/Regulatory Affairs



DERM INCORPORATED
LAKE SIDE DRIVE, SUITE A
BERKELEY CITY, CA 94404
415-358-0100
415-358-0101



Confidential

May 18, 1995

Jonathan Wilkin, M.D., Director
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
HFD-540, Room 17B-45
Rockville, MD 20857

RE: NDA #20-524, Butenafine HCl Cream 1%

Dear Dr. Wilkin:

On April 28, 1995, Penederm Incorporated submitted to the FDA, electronic copies (WordPerfect® 5.1 DOS files) of the individual sections of the NDA (Application Summary, CMC, Nonclinical Pharmacology and Toxicology, Human Pharmacokinetics, Microbiology, Clinical and Statistical).

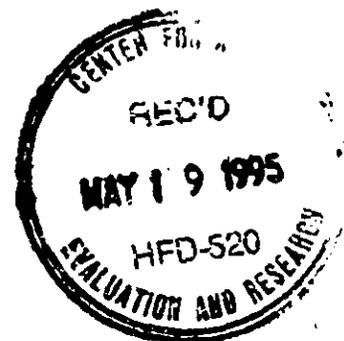
The wording of the electronic copies is identical to the hard copy of NDA #20-524 which was submitted to you on April 4, 1995.

Please call me at 415-378-6479 if you have questions.

Sincerely,

A handwritten signature in cursive script that reads 'Barry M. Calvarese'.

Barry M. Calvarese, M.S.
Executive Director
Chief/Regulatory Affairs



PENEDERM INCORPORATED
LAKEVIEW DRIVE SUITE A
SANTA MONICA, CA 90404
Tel: 310-358-0100
Fax: 310-358-0101



PENEDERM

~~CONFIDENTIAL~~

NC

June 21, 1995

Steven Turtill
Project Manager
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
HFD-540, Room 17B-45
Rockville, MD 20857

RE: NDA 20-524
Butenafine Cream 1% tinea pedis

Dear Mr. Turtill:

It was a pleasure talking to you the other day regarding the additional information requested for the Biopharmaceutic section of NDA 20-524. I am sending you two 3.5" diskettes each containing a WordPerfect® 5.1 file of the pharmacokinetic study report and the raw pharmacokinetic data in ASCII format. Please call me if you have any further questions.

Your time and efforts are greatly appreciated.

Sincerely,

Barry M. Calvarese, M.S.
Executive Director
Clinical/Regulatory Affairs



PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
DUBLIN, CALIFORNIA 94568
DUBLIN, CA 94568
TEL: (415) 358-0100
FAX: (415) 358-0101



PENEDERM

July 2, 1995

QA # 95-488

Lieutenant Commander Frank Cross
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-540, Room 17B-45
5600 Fishers Lane
Rockville, MD 20857

Reference: Butenafine HCl Cream 1%, NDA # 20-524
Volume 1.1 (Application Summary)

Dear Mr. Cross:

We have enclosed two copies of the following per your request:

1. NDA # 20-524; Butenafine HCl Cream 1% (Submitted 4 April 1995- Application Summary, Volume 1.1).

Please give me a call at 415-638-3019 if you have any questions or need additional information.

Sincerely,

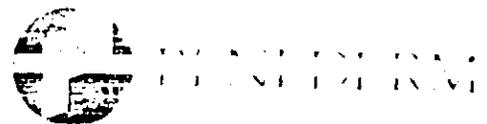
Subru Y. Bhat, M. S., R. Ph.
Senior Group Leader, Quality Assurance
and Regulatory Compliance
(415)-638-3019
Fax (415)-358-0101

Attachments.

Sent By FedEx

CC: Barry Calvarese

PENEDERM INCORPORATED
20 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
TEL: 415-358-0100
FAX: 415-358-0101



August 15, 1995

Frank Cross
Project Manager
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
HFD-540, Room 17B-45
Rockville, MD 20857

RE: NDA 20-524 Butenafine HCl cream 1%, Interdigital Tinea pedis

Dear Mr. Cross:

Reference is made to our teleconference of August 9, 1995, when you requested a statistical analysis of investigational site and treatment outcome interaction. I am requesting a teleconference to discuss how this analysis will be conducted. I recommend that Dr. Nancy Slifman, Dr. Srinivasan and Dr. Ralph Harkins participate in this teleconference. Our consultant biostatistician and I will represent Penederm.

I look forward to scheduling this teleconference in the near future.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs



PENEDERM INCORPORATED
LAKESIDE DRIVE, SUITE A
FITCH CITY, CA 94404
318-0100
415-358-0101



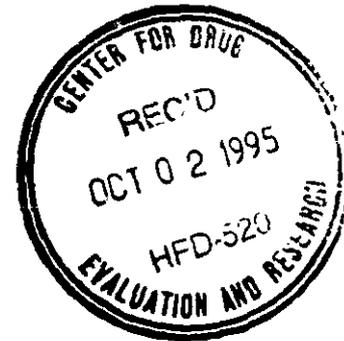
PENEDERM

ORIGINAL

AM

September 29, 1995

Jonathan Wilkin, MD, Director
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Document Control, HFD-540
5600 Fishers Lane
HFD-540, Room 17B-45
Rockville, MD 20857



Re: NDA #20-524 for Butenafine HCl Cream 1%
Response to Questions from Rosemary Cook and Frank Cross

Dear Dr. Wilkin:

On August 9, 1995, Rosemary Cook and Frank Cross of the Topical Drug Product Division called me to discuss seven questions regarding the above referenced NDA. We have compiled the answers to these questions in a separate attachment to this letter. A copy of my teleconference report is attached as well.

Please call me if you have any additional questions regarding this NDA.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs



PENEDERM

FDA TELEPHONE CONFERENCE REPORT

DATE: August 9, 1995 2:10 pm PDT

CONTACT: Barry Calvarese, Executive Director, Clinical/Regulatory, Penederm

CALLER: Rosemary Cook and Frank Cross, CDER, TOPICAL DRUG PRODUCT DIVISION

SUBJECT: Butenafine HCl cream 1% NDA 20-524

Rosemary and Frank called to summarize several questions regarding this NDA. Steve Turtill, who was the CSO responsible for this NDA, recently left CDER and has been replaced by Frank Cross.

Seven questions were presented:

1. Provide the PMS report.
2. Provide cure rate results for both pivotal studies by investigator and provide investigator by treatment interaction. If there are any questions call the reviewing biostatistician Sri Vasam 301 4434594.
3. Clarify other dermatophytes in volume 1.18 page 6-1034 and volume 1 page 6-2072.
4. Regarding protocol PDC 010-002. Plasma levels of butenafine were determined 11 to 19 hours after dosing which the sponsor considers to be trough levels. Was this performed to monitor efficacy. Questions call Sue Lee 310 4431640.
5. Provide tradename as soon as possible.
6. Clarify why benzyl alcohol is in formulation and not version. Provide a table showing which clinical studies used each formulation.
7. Provide a copy of a letter from the Japanese government that states that is in compliance with Japanese environmental laws. Questions call Christina Good at 301 5945721.

PENEDERM INCORPORATED
LAKESIDE DRIVE, SUITE A
STER CITY, CA 94404
58-0100
15-358-0101



*Out
BM*

October 16, 1995

Jonathan Wilkin, MD, Director
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
HFD-540, Room 17B-45
Rockville, MD 20857

RE: NDA #20-524
Butenafine HCl Cream 1%
Clinical Study PDC 010-011, "A Single Center, Open Label Study to Determine the Plasma Level of Butenafine Following Multiple Topical Applications of Butenafine HCL 1% Cream to Normal Subjects"

Dear Dr. Wilkin:

Clinical Study PDC 010-011 was designed to measure the levels of butenafine and its major metabolites in the plasma and urine of normal volunteers. When NDA 20-524 was submitted on April 4, 1995, the urine data was not included in the final report because the analytical methods were not completed at that time. Enclosed are three copies of the amended report for Study PDC 010-011 which now include the urine data.

The results of Study PDC 010-011 indicate very low exposure of subjects to butenafine, even at doses which were significantly exaggerated over the 1-gram per day projected tinea pedis clinical dose. These findings are consistent with low plasma levels of butenafine and M-2 which were seen in the same subjects. The amount of butenafine and its metabolites (M-1, M-2, M-3) excreted in the urine on Day 14 (steady-state) was very low. A 20-gram per day dose of the clinical formulation (Butenafine HCl Cream 1%) resulted in urinary excretion of butenafine and metabolites equal to 0.008% of the administered dose; a 6-gram per day dose resulted in 0.004% of the administered dose excreted as butenafine and metabolites.

Please call me if you have any additional questions regarding this NDA.

Sincerely,

A handwritten signature in black ink, appearing to read 'Barry M. Calvarese'.

Barry M. Calvarese, M.S.
Executive Director
Clinical/Regulatory Affairs



NEW YORK, NY 10017

October 19, 1995

Jonathan Wilkin, MD, Director
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
HFD-540, Room 17B-45
Rockville, MD 20857

RE: NDA #20-524
Butenafine HCl Cream 1%
SAS data sets for clinical studies PDC 010-001 and PDC 010-002

Dear Dr. Wilkin:

Recently, Dr. Valeria Freidlin, reviewing biostatistician for NDA 20-524, requested the SAS data sets for a strict per-protocol population for clinical studies PDC 010-001 and PDC 010-002. Additionally, she requested the SAS programming steps that generated tables 2.A, 2.B, 5.1D, 5.2D and 6 for clinical studies PDC 010-001 and PDC 010-002. This information is provided on two separate disks containing the following: 1) Disk one contains the original data set used to create the strict per-protocol population in a SAS transport file, a self extracting file of the SAS programming steps used to create the strict per-protocol population and the SAS programming steps used to generate the cure rate tables; 2) the second disk contains the SAS programming steps used to generate tables 2.A, 2.B, 5.1D, 5.2D and 6 for clinical studies PDC 010-001 and PDC 010-002.

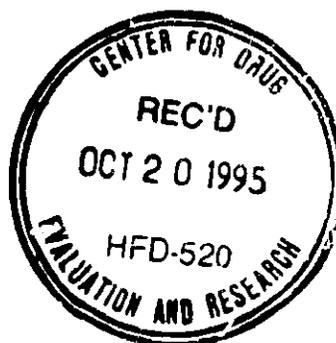
A total of four (4) disks are enclosed, two copies of disk one and two copies of disk two. Disk one contains macros which specify what directories contain the datasets. The macros can easily be replaced by LIBNAME statements in the programs, which will allow them to be run on any system. Each executable file should be expanded into its own directory, since the program names are analogous for each study.

Please call me if you have any additional questions regarding this NDA.

Sincerely,



Barry M. Calvarese, M.S.
Executive Director
Clinical/Regulatory Affairs



NDA 28-524

5 OF 5

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
DUBLIN, CALIFORNIA 94568
TELEPHONE 415-358-0100
FAX 415-358-0101



November 3, 1995

Frank Cross
Project Manager
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
HFD-540, Room 17B-45
Rockville, MD 20857

RE: NDA 20-663 Butenafine HCl cream 1%, Tinea Cruris, Tinea Corporis

Dear Mr. Cross:

As you know, Penederm Incorporated plans to submit a line extension type NDA in December 1995 for the above referenced indications. This NDA will be comprised of clinical data only and will cross-reference all other sections of NDA 20-524 (Butenafine HCl cream 1%, Tinea Pedis indication), which is currently under review. We will submit an updated version of the Package Insert and tube/carton labeling that will reflect the addition of the tinea cruris/corporis indications.

During our recent telecon with Rosemary Cook, we discussed the cross-reference approach but did not agree to a definitive format. Therefore, I would like to schedule a teleconference with you to discuss a mutually agreed upon approach to cross referencing NDA 20-524 in NDA 20-663.

I look forward to scheduling this teleconference in the near future.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs



PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
358 0100
415-358 0101



November 6, 1995

Frank Cross
Project Manager
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
HFD-540, Room 17B-45
Rockville, MD 20857

RE: NDA 20-524 Butenafine HCl cream 1%, Interdigital Tinea pedis
Lab Normal Values

Dear Mr. Cross:

I am enclosing the Lab Normal Values for clinical studies PDC 010-001 and PDC 010-002, which you requested on November 6, 1995.

This information is being submitted in duplicate to the Document Room.

Your time and efforts are greatly appreciated

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

ORIGINAL

DERM INCORPORATED
LAKEVIEW DRIVE, SUITE A
BERKELEY, CA 94404
415-841-0100
415-358-0101



PENEDERM

November 13, 1995

Bm
NDA ORIG AMENDMENT

Jonathan Wilkin, MD, Director
Division of Topical Drug Products
Office of Drug Evaluation
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
HFD-540, Room 17B-45
Rockville, MD 20857

RE: NDA #20-524
Butenafine HCl Cream 1%
Case Report Forms, Patient

Dear Dr. Wilkin:

Recently, Dr. Nancy Slifman, medical reviewer for NDA 20-524, requested copies of case report forms for one patient in clinical study PDC 010-001. Copies of the case report forms are provided in triplicate in this submission.

Please call me if you have any additional questions regarding this NDA.

Sincerely,

Barry M. Calvarese, M.S.
Executive Director
Clinical/Regulatory Affairs



PENEDERM INCORPORATED
LAKESIDE DRIVE, SUITE A
SAN FRANCISCO, CA 94404
415-358-0100
415-358-0101

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ORIGINAL

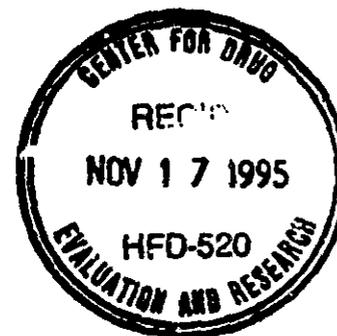


01/17/95
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indij
PENEDERM

November 16, 1995

BC
NDA ORIG AMENDMENT

Jonathan Wilkin, MD,
Director, Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
HFD-540, Room 17B-45
Rockville, MD 20857



Re: NDA #20-524
Butenafine HCl Cream 1% - CMC Update

Dear Dr. Wilkin:

During the recent Pre-Approval Inspection at Ernie Pappas, CMC reviewer for NDA #20-524, requested additional for the above-referenced NDA. The following information is submitted in triplicate:

Mr.

1. Updated stability data to substantiate the shelf life request of two years for all package sizes.
2. Revised version of the analytical method used for quantitating butenafine hydrochloride in the product. This was reviewed by the investigators during the PAI. The Analytical Method Validation Report for is also provided, along with the revised method for the drug substance.
3. Representative Certificates of Analysis for the drug product that have been modified to include test results for pH and viscosity.
4. Revised Stability Specification for the Drug Product which states that homogeneity (top, middle, and crimp of the tubes) is tested during the stability studies.
5. Modified Flow Chart for Drug Product Manufacturing of the 200-kg batch size which includes mixing speeds and mixing times.
6. Analytical Methods (Apparent pH of Formulations) and (Viscosity of Formulations) that were inadvertently omitted from the original NDA submission.

Please call me at 415-378-6479 if you have any additional questions regarding this NDA.

Sincerely,

Barry Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

ORIGINAL

ERM INCORPORATED
ESIDE DRIVE, SUITE A
STER CITY, CA 94404
358-0100
415-358-0101



PENEDERM

November 22, 1995

NEW CORRESPONDENCE

Jonathan Wilkin, MD, Director
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
HFD-540, Room 17B-45
Rockville, MD 20857

RE: NDA #20-524
Butenafine HCl Cream 1%
Case Report Forms, patient

Dear Dr. Wilkin:

On November 13, 1995 the case report forms for the above referenced patient were submitted to NDA 20-524. A data clarification form was inadvertently omitted from the set of case report forms for patient [REDACTED]. I am enclosing, in triplicate, copies of the amended case report form for patient [REDACTED].

Please call me if you have any additional questions regarding this NDA.

Sincerely,

Barry M. Calvarese, M.S.
Executive Director
Clinical/Regulatory Affairs



PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
ROCKFORD CITY, CA 94404
58-0100
TEL 415-358-0101



12/4/95
noted
N. Slifman
PENEDERM

December 4, 1995

Jonathan Wilkin, MD
Director, Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 12B-30
HFD-540
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-524 Butenafine HCl cream 1%, Interdigital Tinea pedis
Physician Package Insert

Dear Dr. Wilkin:

I am enclosing an electronic version, identical to the written version, of the Physician Package Insert which Dr. Nancy Slifman requested on December 4, 1995. This electronic document is being provided in a WordPerfect 5.1 DOS format.

This information is being submitted in duplicate.

Your time and efforts are greatly appreciated.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

M INCORPORATED
SIDE DRIVE, SUITE A
LA 94404

358-0101



ORIGINAL
NEW COMBESP
PENEDERM

December 7, 1995

Jonathan Wilkin, MD
Director, Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 12B-30
HFD-540
5600 Fishers Lane
Rockville, MD 20857

E: NDA 20-524 Butenafine HCl cream 1%, Interdigital Tinea pedis
butenafine 1994 Post-marketing Surveillance Report

Dear Dr. Wilkin:

I am enclosing the butenafine 1994 Post-marketing Surveillance
Report which Dr. Nancy Slifman requested.

This information is being submitted in duplicate.

Your time and efforts are greatly appreciated.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs



EDERM INCORPORATED
LAKESIDE DRIVE, SUITE A
FARMER CITY, CA 94404
358-0100
415-358-0101



PENEDERM

NEW CORRESPONDENCE

December 12, 1995

Frank Cross
Project Manager
Division of Dermatologic and Ophthalmic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 7, Room N229
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-524 Butenafine HCl cream 1%, Interdigital Tinea pedis
butenafine 1994 Post-marketing Surveillance Report

Dear Mr. Cross:

I am enclosing the butenafine 1994 Post-marketing Surveillance
Report which Dr. Nancy Slifman requested.

Your time and efforts are greatly appreciated.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

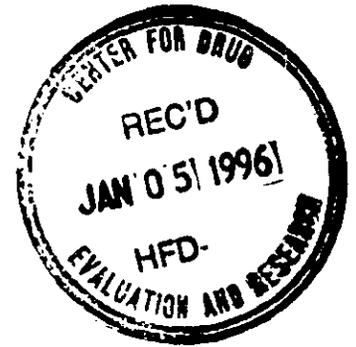


ORIGINAL

DERM INCORPORATED
AKESIDE DRIVE, SUITE A
ER CITY, CA 94404
58-0100
15-358-0101



PENEDERM



NEW CORRESPONDENCE

January 3, 1996

Jonathan Wilkin, MD
Director
Division of Dermatologic and Ophthalmic Drug Products
Document Mail Room
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 2
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-524 Butenafine HCl cream 1%, Interdigital Tinea pedis
Request for Tradename

Dear Dr. Wilkin:

During an August 9, 1995 teleconference Mr. Frank Cross requested that Penederm Incorporated submit a tradename for butenafine cream as soon as possible. The tradename LOTRIPHINE™ has been selected for butenafine cream. We look forward to the approval of this name by the CDER Naming Committee and encourage you to contact us if you have any further questions regarding this NDA application.

Your time and efforts are greatly appreciated.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

AKESIDE DRIVE, SUITE A
BERKELEY, CA 94404
58-0100
415-358-0101



January 8, 1996

Jonathan Wilkin, MD, Director
Division of Dermatologic and Ophthalmic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850



Re: NDA #20-524, Butenafine HCl Cream 1%
Case Report Forms for Patients

Dear Dr. Wilkin:

Recently, Dr. Nancy Slifman, medical reviewer for NDA #20-524, requested
copies of the case report forms for patients in
Clinical Study PDC 010-002.

Copies of the requested case report forms are provided in triplicate in this
submission. Please call me at 415-378-6479 if you have any additional questions
regarding this NDA.

Sincerely,

A handwritten signature in cursive script, appearing to read 'Barry Calvarese'.

Barry Calvarese, MS
Executive Director, Clinical/Regulatory Affairs

NEDERM INCORPORATED
1 LAKESIDE DRIVE, SUITE A
STEER CITY, CA 94404
t-358-0100
X 415-358-0101



January 8, 1996

NEW CORRESPONDENCE

Jonathan Wilkin, MD, Director
Division of Dermatologic and Ophthalmic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA #20-524, Butenafine HCl Cream 1%
for the treatment of Interdigital Tinea Pedis

Dear Dr. Wilkin:

Penederm has been asked to clarify the foreign approval status of the above referenced drug product. Butenafine cream and lotion 1% are approved in Japan for the treatment of tinea pedis, tinea cruris, tinea corporis, tinea versicolor, and candidal skin infections. Penederm Incorporated has submitted an NDS application to the Canadian Health Protection Branch for Butenafine HCl Cream 1% for the treatment of interdigital tinea pedis. Penederm Incorporated is not aware of any other pending or approved applications for this drug product in other foreign countries.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs





February 15, 1996

Jonathan Wilkin, MD, Director
Division of Dermatologic and Ophthalmic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA #20-524, Butenafine HCl Cream 1%
for the treatment of Interdigital Tinea Pedis
Response to FDA Questions During 1/30/96 Teleconference

Dear Dr. Wilkin:

This response includes the information addressing your queries, based on our teleconference of January 30, 1996. The information has been divided into two parts as follows:

- Issues specific to Chemistry, Manufacturing, and Controls
- Issues pertaining to the Environmental Assessment Report

This response is submitted in triplicate.

Should you have any questions regarding this NDA or require additional information, please call me at 415-378-6479.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs



PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
358-0100
X 415-358-0101



PENEDERM



March 1, 1996

Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA 20-524 Butenafine HCl Cream 1%
For the Treatment of Interdigital Tinea Pedis
Request for Backup Trade Name

Dear Dr. Wilkin:

Penederm Incorporated submitted a trade name for Butenafine HCl Cream 1%, LOTRIPHINE™, on January 3, 1996. Because of potential trademark concerns, we would like to submit an additional name, MENTAX™, for review and approval by the CDER Naming Committee.

If both names are approved, we assume that we have the option of choosing either name once this drug product is considered to be approvable. We encourage you to contact us if you have any questions regarding this request.

Your time and efforts are greatly appreciated.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

N229

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FERRIS CITY, CA 94404
Tel: 415-358-0100
FAX 415-358-0101



PENEDERM

March 27, 1996

Jonathan Wilkin, MD, Director
Division of Dental and Dermatologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA #20-524, Butenafine HCl Cream 1%
for the treatment of Interdigital Tinea Pedis

Dear Dr. Wilkin:

In response to Mr. Frank Cross' request of March 20th, I have enclosed two tables which provide the amount of drug used for Clinical Studies PDC 010-004 and PDC 010-005.

Please call me at 415-378-6479 if you have any questions or require additional information.

Sincerely,

Barry Calvarese, MS
Executive Director
Clinical/Regulatory Affairs



ORIGINAL
NEW CORRESP

NC

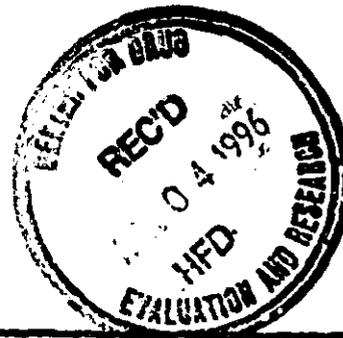
PENEDERM INCORPORATED
10 LAKESIDE DRIVE, SUITE A
ROCKVILLE CITY, CA 94404
1-358-0100
FAX 415-358-0101



PENEDERM

April 2, 1996

Jonathan Wilkin, MD
Director
Division of Dental and Dermatological Drug products
Document Mail Room
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 2
9201 Corporate Blvd.
Rockville, MD 20850



REVIEWS COMPLETED	
CSO ACTION:	
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CSO INITIALS	DATE

RE: Butenafine HCl Cream 1%
NDA 20-524, For the Treatment of Interdigital Tinea Pedis

Dear Dr. Wilkin:

It was a pleasure meeting with you and your colleagues on April 1, 1996 regarding the end-of-Phase II requirements for butenafine gel 1%. During our discussions, you indicated that there are still unresolved issues regarding the studies on phototoxicity and photoallergy of butenafine. Penederm was surprised that this issue is considered to be still outstanding and that we were informed of this concern at such a late date in the butenafine cream 1% NDA review process.

The phototoxicity and photoallergy issue was raised by FDA during our February 13, 1995 butenafine cream pre-NDA meeting. Penederm was asked to determine how much UVB exposure was used in the animal and human phototoxicity and photoallergy studies. Penederm responded to FDA in the minutes of that meeting and in NDA 20-524 with a description of the UVB exposure and with a justification of the existing methods. Our understanding from the discussion at the February 13 meeting was that no additional testing to further examine the phototoxic or photoallergenic potential of butenafine was required. Furthermore, it was stated that in lieu of any further testing, a statement might have to be added to the precaution section of the physician package insert that relates to minimizing exposure to sunlight during treatment with butenafine cream. It was clearly acknowledged by the agency that the risk of phototoxicity or photoallergy is very low, considering that the interdigital spaces of the foot are rarely exposed to direct sunlight. This is also summarized in the minutes of this meeting, which we forwarded to the

During our meeting yesterday (April 1, 1996) you invited us to collaborate with you to resolve the outstanding issues related to the methods for evaluating photoallergy of butenafine. Although Penederm feels that the studies have adequately addressed these issues, we plan to immediately solicit your input in modifying the design of the new phototoxicity/photoallergy studies that are proposed for the butenafine 1% skin gel. We will, therefore, initiate a dialog with you and your colleagues to work out the details of such a study.

In summary, Penederm will work with the Agency to address the concerns which you raised in yesterday's meeting. We continue to believe that the testing which has been conducted to date adequately establish that butenafine is neither phototoxic or photoallergenic. However, as suggested at the pre-NDA meeting, a statement could be included in the precaution section of the physician package insert which instructs the patient to refrain from excessive exposure to sunlight.

Sincerely,



Barry Calvarese, MS
Executive Director,
Clinical & Regulatory Affairs

Attachments:

Letter from Dr. R. Sayre dated 8/10/95
Curriculum Vitae of Dr. R. Sayre
Letter to Dr. J. Wilkin, dated 3/3/95

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
5-358-0100
FX 415-358-0101

1A2



PENEDERM

NEW CORRESPONDENCE



April 4, 1996

Jonathan Wilkin, MD, Director
Division of Dental and Dermatologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA #20-524, Butenafine HCl Cream 1%
for the treatment of Interdigital Tinea Pedis

Dear Dr. Wilkin:

Penederm Incorporated acknowledges the receipt of your April 3, 1996
approvable letter regarding the above-referenced drug product. Pursuant to
21 CFR 314.20, we are providing notification of our intent to file an
amendment.

We consider all the information contained in this letter proprietary and
confidential.

Your time and efforts are greatly appreciated.

Sincerely,

Barry Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

REVIEWS COMPLETED
COORDINATION
<input type="checkbox"/> LETTER <input type="checkbox"/> FINAL <input type="checkbox"/> REVIEW

DUPLICATE

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
T-358-0100
FAX 415-358-0101



NEW CORRESPONDENCE

April 8, 1996

Jonathan Wilkin, MD, Director
Division of Dermatologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re. NDA #20-524, Butenafine HCl Cream 1%
for the treatment of Interdigital Tinea Pedis

Dear Dr. Wilkin:

On March 27, 1996, Penederm Incorporated responded to a request from Frank Cross to provide the amount of drug used in Clinical Studies PDC 010-004 and PDC 010-005. This response was inadvertently submitted to NDA #20-524 on March 27, 1996. These clinical studies pertain to NDA #20-663 and this information was submitted to the appropriate NDA on March 28, 1996.

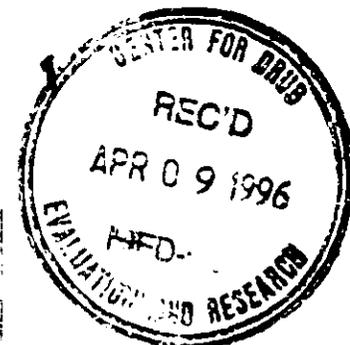
Please disregard the information submitted to NDA #20-524 dated March 27, 1996.

Please call me at 415-378-6479 if you have any questions or require additional information.

Sincerely,

Barry Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

REVIEWS COMPLETED
DISPOSITION:
<input type="checkbox"/> APPROVE <input type="checkbox"/> REJECT <input type="checkbox"/> INFO
DISC. INITIALS



ORIGINAL

EDERM INCORPORATED
LAKESIDE DRIVE, SUITE A
FERRIS CITY, CA 94404
8-0100
415-358-0101



PENEDERM

April 30, 1996

BC
NDA ORIG AMENDMENT



Jonathan Wilkin, MD, Director
Division of Dermatologic and Ophthalmic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850

Re: NDA #20-524, Butenafine HCl Cream 1% (Mentax™)

Dear Dr. Wilkin:

In response to Dr. Ernie Pappas' comments (received via fax on March 5, 1996) regarding the Methods Validation Package for the above NDA, we have provided this response. It is divided into two sections: A. Response to FDA Comments, and B. Revised Methods Validation Package. This information is provided in triplicate.

Should you have any questions or require additional information, please call me at 415-378-6479.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

REVIEWS COMPLETED
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PENEDERM INCORPORATED
LAKESIDE DRIVE, SUITE A
FARMER CITY, CA 94404
8-0100
15-358-0101

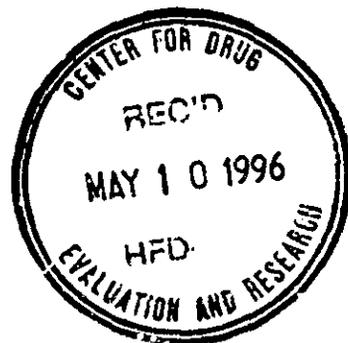
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PENEDERM

May 8, 1996

Jonathan Wilkin, MD, Director
Division of Dental and Dermatologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850



Re: NDA #20-524, Butenafine HCl Cream 1% (Mentax™)
Response to FDA Approvable Letter dated April 3, 1996

Dear Dr. Wilkin:

Pursuant to Section 505(b) of the Federal Food, Drug and Cosmetic Act Penederm Incorporated herewith submits responses to the issues cited in your approvable letter dated April 3, 1996. Eight copies of this one-volume response are provided.

A disk containing the Mentax™ Package Insert in DOS WordPerfect® 5.1 format is also included in the Archive and Clinical copies.

Your prompt review of this document is appreciated. Please contact Barry M. Calvarese, Executive Director, Regulatory/Clinical Affairs for further information regarding this application.

Please be advised that the material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under the applicable provisions of 18 USC, Section 331(j) and/or 21 CFR 312.130.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION	
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ORIGINAL

PENEDERM INCORPORATED
LAKESIDE DRIVE, SUITE A
PETER CITY, CA 94404
358-0100
415-358-0101



May 30, 1996

RECEIVED
MAY 31 1996

Jonathan Wilkin, MD, Director
Division of Dental and Dermatologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850



Re: NDA #20-524, Butenafine HCl Cream 1% (Mentax™)
Response to FDA Approvable Letter Submitted 5/08/96

Dear Dr. Wilkin:

With regard to the above-referenced submission of May 8, 1996, we are providing the following information at the request of Dr. Nancy Slifman.

1. Table 5 (page 228 of the above-referenced Response) provides a list of clinical studies and the total number of adverse events for each study. Dr. Slifman requested that Penederm indicate the type of study in addition to its reference number. This information is provided below.

Study Number	Study Title
PDC 010-001	Double-Blind Evaluation of Butenafine HCl Cream 1% and Vehicle in the Treatment of Tinea Pedis
PDC 010-002	Double-Blind Evaluation of Butenafine HCl Cream 1% and Vehicle in the Treatment of Tinea Pedis
PDC 010-004	A Multicenter, Double-Blind Study to Evaluate Butenafine HCl Cream 1% and Vehicle in the Treatment of Tinea Corporis
PDC 010-005	A Multicenter, Double-Blind Study to Evaluate Butenafine HCl Cream 1% and Vehicle in the Treatment of Tinea Cruris
PDC 010-006	Human Repeat Insult Patch Test for Butenafine HCl 1%
PDC 010-007	Evaluation of Human Phototoxicity for Butenafine HCl 1%
PDC 010-008	Evaluation of Human Photoallergy for Butenafine HCl 1%
PDC 010-009	Evaluation of Primary Irritation for Butenafine HCl Cream 1% and Vehicle
PDC 010-010	Evaluation of Cumulative Irritation for Butenafine HCl 1%
PDC 010-011	A Single Center, Open Label Study to Determine the Plasma Level of Butenafine Following Multiple Topical Applications of Butenafine HCl Cream 1% to Normal Volunteers
PDC 010-014	A Multicenter, Double-Blind Study to Evaluate Butenafine HCl Cream 1% and Vehicle in the One-Week Treatment of Tinea Pedis
PDC 010-015	A Multicenter, Double-Blind Study to Evaluate Butenafine HCl Cream 1% and Vehicle in the One-Week Treatment of Tinea Pedis

Jonathan Wilkin, MD, Director
May 30, 1996
Page 2 of 2 -

2. Penederm stated that a New Drug Submission (NDS) for Butenafine HCl Cream 1% was submitted to the Health Protection Branch in Canada in June 1994 (page 229 of the Response). Dr. Slifman requested the status of this application.

The NDS for Butenafine HCl Cream 1% is currently under active review by the Health Protection Branch.

Please call me at 415-378-6479 if you have any questions or require additional information.

Sincerely,



Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

REVIEWS COMPLETED	
GSO ACTION	
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GSO INITIALS	DATE

LAKESIDE DRIVE, SUITE A
FARMER CITY, CA 94404
58-0100
415-358-0101



August 29, 1996

BC
NDA ORIG AMENDMENT

Jonathan Wilkin, MD, Director
Division of Dental and Dermatologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Document Mail Room #N115
9201 Corporate Blvd., HFD-540
Rockville, MD 20850



Re: NDA #20-524, Butenafine HCl Cream 1% (Mentax™)
Response to Comment #8
(FDA Approvable Letter dated April 3, 1996)

Dear Dr. Wilkin:

Penederm Incorporated submitted an NDA amendment on May 8, 1996 in response to your April 4, 1996 approvable letter for the above-referenced application. Penederm committed to responding to Comment #8 by September 30, 1996, and is now submitting this response to NDA #20-524. Please note that the Response to Comment #8.B was also provided to Mr. E. Pappas, Review Chemist, by fax on August 5, 1996, following a phone conversation between him and Dr. Bhaskar Chaudhuri.

Nine copies of this response are provided. Please be advised that the material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under the applicable provisions of 18 USC, Section 331(j) and/or 21 CFR 312.130.

If you need additional information regarding this application, please call me at 415-378-6479.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

REVISIONS COMPLETED	
ACTION	
LETTER <input type="checkbox"/>	MAIL <input type="checkbox"/>
MEMO <input type="checkbox"/>	
CSO INITIALS	DATE

PENEDERM INCORPORATED
220 LAKESIDE DRIVE, SUITE A
DUBLIN, CA 94568
5-358-0100
FAX 415-358-0101



BL
NDA ORIG AMENDMENT

October 3, 1996

Frank Cross
Project Manager
Division of Dermatological and Dental Drug products
Document Mail Room
Office of Drug Evaluation II
Center for Drug Evaluation And Research
Food and Drug Administration
Bldg. 2
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-524, Mentax™ (butenafine HCl cream) Cream, 1%
Package Insert

Dear Mr. Cross:

Upon more extensive review of the Mentax™ Package Insert labeling sent to you on October 2, 1996 we have made the following changes to the Pregnancy and Carcinogenesis sections:

Carcinogenesis, Mutagenesis, Impairment of Fertility

In this section, FDA has requested that the dose used in the fertility study (rat Segment I) be presented as mg/kg/day. The high dose used in this study was 25 mg/kg (Study D-10). Based on our calculations, this is a dose of approximately 150 $\mu\text{g}/\text{m}^2/\text{day}$. It appears that the dose of _____ cited in your version dated 10/2/96 may be a typographic error and the zero was dropped. The dose has been changed to _____ $\text{mg}/\text{m}^2/\text{day}$.

Pregnancy

Two Segment II (teratology) studies were performed with butenafine: one via the subcutaneous route in rats (maximum dose of 25 mg/kg) and one via the topical (percutaneous) route in rabbits (maximum dose of 50 mg/kg). The reference to the topical route of application should be inserted into the first sentence of the Pregnancy section ("Subcutaneous or topical doses of butenafine . . .").

We look forward to your response to these changes and encourage you to call if you have any questions or comments.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs



REVIEWS COMPLETED
REACTION
LETTER <input type="checkbox"/> N.A. <input type="checkbox"/> MEMO
REVISIONS INITIALS
DATE

ORIGINAL

PENEDERM INCORPORATED
LAKEVIEW DRIVE, SUITE A
ROCKVILLE, CA 94404

9 0130
-358-0101



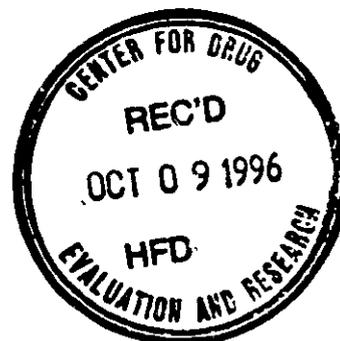
PENEDERM

Safety Update Contents

October 8, 1996

SU
NDA ORIG AMENDMENT

Lt. Cmdr. Frank Cross
Regulatory Program Manager
Division of Dental and Dermatologic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Building 2, Room N229
9201 Corporate Blvd.
Rockville, MD 20850



Re: NDA #20-524, Mentax™ (Butenafine HCl) Cream 1%
Package Insert

Dear Mr. Cross:

Thank you for your fax dated October 8, 1996 regarding the final Mentax™
Package Insert labeling recommendation from the Division of Dermatological
and Dental Drug products (reference telefax 10/08/96, #040). We have
reviewed this Package Insert language and find it acceptable.

The most recent safety update is enclosed which is nearly identical to the one
submitted in the approvable letter response dated May 8, 1996. The only new
safety information provided is the updated Postmarketing Surveillance (PMS)
Summary (Table 5) from This table
summarizes the Japanese PMS experience through January 20, 1996. The
PMS summary table provided in the May 8, 1996 submission covered
the period ending March 31, 1995.

Based on our conversation of 10/08/96, it is Penederm's understanding that
this version of the Package Insert is final and no further changes are required.
As we intend to print this version of the Package Insert in the very near future,
please confirm that our understanding is correct. Please call me if you have
any further comments or questions regarding the Package Insert.

Sincerely,

Barry Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

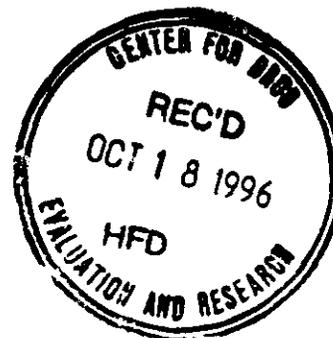
REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

Approved for Release

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
5-358-0100
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PENEDERM



October 17, 1996

Jonathan Wilkin, MD
Director, Division of Dermatological and Dental Drug products
Document Mail Room
Office of Drug Evaluation II
Center for Drug Evaluation And Research
Food and Drug Administration
Bldg. 2
9201 Corporate Blvd.
Rockville, MD 20850

RE: NDA 20-524, Mentax™ (butenafine HCl cream) Cream, 1%
Package Insert

Dear Dr. Wilkin:

Thank you for your telefax communication dated October 17, 1996 regarding the final Mentax™ Package Insert labeling recommendation from the Division of Dermatological and Dental Drug products (reference telefax 10/17/96, number 54). We have reviewed this Package Insert language and find it acceptable.

Based on our recent conversation of 10/17/96 with Mr. Frank Cross, it is our understanding that this version of the Package Insert is the final version and that no further changes are required. As we intend to print this version of the Package Insert in the very near future, please confirm that our understanding is correct. Please call me if you have any further comments or questions regarding the Package Insert.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

DERM INCORPORATED
LAKE DRIVE, SUITE A
CITY, CA 94404
58-0100
415-358-0101

ORIGINAL
NEW COPY
ORIGINAL



NC
PENEDERM

October 18, 1996

Jonathan Wilkin, MD
Director, Division of Dermatological and Dental Drug products
Document Mail Room
Office of Drug Evaluation II
Center for Drug Evaluation And Research
Food and Drug Administration
Bldg. 2
9201 Corporate Blvd.
Rockville, MD 20850



RE: NDA 20-524, Mentax™ (butenafine HCl cream) Cream, 1%
Package Insert

Dear Dr. Wilkin:

Thank you for your telefax communication dated October 18, 1996 regarding the final Mentax™ Package Insert labeling recommendation from the Division of Dermatological and Dental Drug products (reference telefax 10/18/96, number 108). We have reviewed this Package Insert language and find it acceptable.

Based on our recent conversation of 10/18/96 with Mr. Frank Cross, it is our understanding that this version of the Package Insert is the final version and that no further changes are required. As we intend to print this version of the Package Insert in the very near future, please confirm that our understanding is correct. Please call me if you have any further comments or questions regarding the Package Insert.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs