CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 020663

Trade Name : MENTAX CREAM 1%

Generic Name: Butenafine HCl Cream

Sponsor : Penederm, Inc.

Approval Date: December 31, 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 020663

APPROVAL LETTER

DEC 31 1996

NDA 20-663

Penederm Incorporated
Attention: John Quigley, Ph.D.
Senior Vice President, Research and Development
320 Lakeside Drive, Suite A
Foster City, CA 94404

Dear Dr. Quigley:

Please refer to your December 22, 1995, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mentax (butenafine hydrochloride cream) Cream, 1%.

We acknowledge receipt of your amendments and correspondence dated December 27, 1995, January 8 and 19, March 1 (two), 27 and 28, October 23, 24 and 25, November 5 and 15, and December 12 and 31, 1996.

This new drug application provides for the treatment of tinea corporis and tinea cruris.

We have completed the review of this application 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. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed revised draft labeling. The enclosed revised draft labeling was stated to be acceptable to you in the facsimile of your letter dated December 31, 1996. Marketing the product with FPL that is not identical to the enclosed revised draft labeling may render the product misbranded and an unapproved new drug.

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 20-663. 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 the 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.

If you have any questions, please contact:

Frank H. Cross, Jr., M.A., LCDR
Project Manager
(301) 827-2020

Sincerely yours,

12/31/96

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and
Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

cc:
Original NDA 20-663
HFD-540/Division File
HFD-105/Weintraub (with draft labeling)
HFD-2/Lumpkin (with draft labeling)
HFD-735 (with draft labeling)
HFD-92 (with draft labeling)
HFD-222
District Office
HF-2/Medwatch (with draft labeling)
HFD-40/(with draft labeling)
HFD-613 (with draft labeling)
HFD-540/MO/O'Connell/12/11/96 w/ labeling
HFD-540/CHEM/Pappas/12/11/96 w/ labeling
HFD-520/MICRO/Dionne w/ labeling
HFD-805/MICRO/Stinavage/12/12/96 w/ labeling
HFD-540/PHARM/Mainigi/12/11/96 (Dr. Jacobs) w/ labeling
HFD-725/BIOSTAT/Thomson/12/11/96 w/ labeling
HFD-880/BIOPHARM/Lee/12/11/96 w/ labeling
HFD-540/PM/Cross w/ labeling

Concurrence:

HFD-540/DEP DIR/Katz/12/12/96
HFD-540/CHEM TL/DeCamp
HFD-540/PHARM TL/Jacobs/12/11/96
HFD-520/MICRO TL/Sheldon/12/11/96
HFD-160/MICRO TL/Cooney/12/12/96
HFD-880/BIOPH TL/Bashaw/12/11/96 (Dr. Lee)
HFD-725/BIOSTAT TL/Srinivasan/12/11/96
HFD-540/PROJ MGT SUPV/Kozma-Fornaro 12/31/96

drafted: fhc/November 22, 1996/n20663a.ap
r/d Initials:
Final:

APPROVAL

PENEDERM INCORPORATED
[illegible] LAKESIDE DRIVE, SUITE A
TER CITY, CA 94404
-358-0100
AX 415-358-0101

PENEDERM

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: _____ Date: 12/20/95

John Quigley, PhD
Vice President
Research and Development

PATENT CERTIFICATION

NDA 20-663

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

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-663 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-540 Trade (generic) name/dosage form: Mentax (butenafine HCl cream) Cream, 1% Action: (AP) AE NA

Applicant Penederm Therapeutic Class 6S

Indication(s) previously approved Tinea pedis

Pediatric labeling of approved indication(s) is adequate X inadequate ___

Indication in this application Tinea corporis/cruris

(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.

___ 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 formation 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.

X 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.

Jonathan Willi 12/30/96

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

cc: Orig NDA/PLA # 20-663
HFD-540 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

NOTE: 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.

5/95

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 020663

MEDICAL OFFICER REVIEW

DEC 3 1996

MEDICAL OFFICER'S REVIEW OF NDA 20-663

NDA: 20-663

Submission date: 12/22/95
Received date: 1/5/96
Review date: 11/18/96

1 General Information

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 tinea cruris and tinea corporis

Dosage Form/Route: 1% cream; topical

NDA Drug Classification: 6/S

Related Drugs:
Terbinafine HCl cream 1%
Naftifine cream

Related Reviews:
Statistical Review
Microbiology Review
Pharmacology Review
Chemistry Review
Biopharm Review

Related Submissions: IND 42,762 (Butenafine HCl cream 1%)
NDA 20-524 (Butenafine HCL cream 1% for the treatment of interdigital tinea pedis; approved 18Oct96)

Formulation:

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

Background

Butenafine HCl, a benzylamine derivative, is closely related in mechanism of action to the new class of allylamine antifungal agents. Butenafine HCl is also similar in structure to the allylamine terbinafine. In vitro studies show butenafine HCl to be highly efficacious against dermatophytes. In this application, Butenafine HCl Cream 1%, is proposed for the treatment of tinea corporis and tinea cruris. This product was Approved by the Agency for tinea pedis on 10/18/96. The product formulation proposed for marketing in the current NDA (PD-010-C-003) is identical to that approved for tinea pedis 10/18/96, and was utilized in the Phase III pivotal clinical trials, as well as in human dermal tolerance and pharmacokinetic studies.

The results of two clinical trials were submitted in support of this NDA. Protocol 010-004 is a randomized, double-blind, vehicle controlled study involving 78 patients with tinea corporis. Tinea cruris was studied in Protocol 010-005 involving 76 patients. Both studies were conducted in the U.S. In addition, the sponsor has submitted a pharmacokinetic study.

2 Table of Contents

3 Material Reviewed

- NDA 20-663 Volumes 1.8-1..18
- Revised combined Package Insert for tinea pedis, corporis, cruris submitted 10/25/96
- Medical Officer's review of NDA 20-524 (tinea pedis)
- Microbiology review NDA 20-524 dated 7/31/95

4 Chemistry/Manufacturing Controls

See Chemist's Review

5 Animal Pharmacology/Toxicology (see Pharm/Tox review for full discussion)

This section of the Application Summary contains information that is essentially the same as that presented in NDA #20-524, in which the indication for Butenafine HCl Cream 1% is tinea pedis. The approved dose for tinea pedis is 1 gram/day for four weeks. For the proposed indications, tinea corporis and tinea cruris, dosage amounts will be different, and the treatment period will be for only two weeks. The estimated average daily dose for the treatment of tinea cruris is 1.5 grams/day, and the dose for tinea corporis will be somewhat lower (approximately 1 gm per day).

Mechanism of Action

Butenafine hydrochloride, a benzylamine derivative, was developed as a result of investigations of the structure-activity relationship of bis (naphthalenemethyl) amine. This compound, with a chemical structure similar to that of the allylamine agents, exhibited more potent antifungal activity than naftifine, a member of the allylamine class.

Studies were subsequently conducted to elucidate the antifungal mechanism of action of butenafine HCl. Using a wild-type strain and several tolciclate-resistant mutant strains of *S. schenckii.,* Hiratani et al. (Kaken Study E-11) demonstrated that butenafine HCl inhibits squalene epoxidase. Other investigators demonstrated the accumulation of squalene in the cell membrane of *C. albicans* treated with butenafine HCl, an observation consistent with inhibition of squalene epoxidase. This is the same mechanism by which thiocarbamates and allylamines act. In contrast, the imidazole antifungal agents inhibit the demethylation of lanosterol in the synthesis of ergosterol.

Pharmacology

A series of studies were performed to characterize the acute toxicity of butenafine HCl when administered by different routes to different species. Since butenafine HCl is only moderately soluble in water, it was dosed at maximum

achievable concentrations as a suspension for oral administration and as a solution for topical, intravenous (IV) and subcutaneous (SC) administration.

Results of the studies indicate that the acute oral toxicity of butenafine HCl is relatively low. The oral LD_{50} of butenafine HCl was estimated to be greater than 4 g/kg for rats, mice and dogs when administered as a [redacted]% solution in [redacted]% aqueous ethanol and [redacted]% aqueous (polyethylene glycol). The acute toxicity profile established via the topical or subcutaneous route was also favorable: doses up to 200 mg/kg subcutaneously and 1000 mg/kg topically did not result in any mortality.

Repeated dose toxicity studies were conducted in rats and dogs given daily topical administrations of butenafine HCl to intact skin for 90 days and in rats given daily subcutaneous injections for 90 days. Based on the results of these studies, the systemic no-adverse effect dose level after topical administration to rats is 15 mg/kg/day and after topical administration to dogs is greater than 100 mg/kg/day. The systemic no- adverse effect dose level after subcutaneous administration to rats is 1 mg/kg/day.

The sponsor states that the human dose of Butenafine HCl Cream 1% is expected to be one gram per day, or 0.2 mg butenafine HCl/kg/day based on an average patient body weight of 50 kg. The no-effect doses calculated from the subchronic rat and dog studies are 75- and 100-fold greater, respectively, than the expected clinical dose.

Long-term repeated dose toxicity studies were conducted in rats given daily subcutaneous injections of butenafine HCl for six months and in dogs given daily topical butenafine HCl to intact skin for 12 months. According to the results of these studies, the systemic no-adverse effect dose level after chronic subcutaneous administration to rats is 0.5 mg/kg/day and after chronic topical administration to the intact skin of dogs is 100 mg/kg/day. The sponsor again states that the human dose of Butenafine HCl Cream 1% is expected to be one gram per day, or 0.2 mg butenafine HCl/kg/day based on an average patient body weight of 50 kg. The no-effect dose calculated from the chronic dog study is 500-fold greater than the expected clinical dose.

Reviewer's Comment: The average adult body weight in the US population is greater than 50 kg. In addition, T.cruris indication will require about 1.5 gm/day, not 1.0 gm. Nonetheless, the numbers indicate that butenafine HCl is likely safe for human use for the intended indication.

Carcinogenicity and Photocarcinogenicity Studies

The duration of treatment for these indications is two weeks. As such, the duration of treatment is not sufficient to require carcinogenicity studies. The data from the chronic toxicity studies give no indication of carcinogenic potential. The proposed labeling indicates that carcinogenicity studies have not been conducted. The data from phototoxicity and photosensitization animal studies indicate there is

no significant potential for photoreactivity, and results from the mutagenicity studies indicate that butenafine HCl is not a mutagen. (As will be noted in Section 8, the sponsor has submitted the results of human photoallergy testing because the current NDA includes tinea corporis).

Special Toxicity Studies

Studies were performed to assess the primary irritation (skin and eye), sensitization, and antigenicity potential of butenafine HCl. Dermal and ocular irritation studies in rabbits indicate that butenafine HCl cream, solution and lotion elicit minimal irritation and are well-tolerated. Studies conducted in guinea pigs indicate that butenafine HCl does not elicit antigenic or contact sensitization responses.

Reproduction and Teratology Studies

The effects of butenafine HCl on reproductive performance and fetal development were assessed after the compound was administered subcutaneously to rats and topically to rabbits. The subcutaneous route was used to provide an effective exaggeration of systemic exposure relative to the low human dose (0.2 mg/kg), since there is relatively low percutaneous absorption of butenafine. The results of these reproductive toxicity tests demonstrate that butenafine HCl has no effect on fertility, reproductive performance or perinatal or postnatal fetal development, even when the subcutaneous route was employed to provide a greatly exaggerated exposure to the compound.

Pharmacokinetics

Pharmacokinetic data in rats and dogs indicate that there is relatively low percutaneous absorption of butenafine.

6 Clinical Background

6.1 Relevant Human Experience Butenafine is an allylamine-class, broad-spectrum antifungal with fungicidal activity against dermatophytes, molds and certain dimorphic fungi. Butenafine's antifungal activity has been substantiated in two Phase III clinical studies where the butenafine cream 1% formulation was found to be superior to vehicle control in the treatment of tinea pedis. The incidence of side effects was low (< 2%) and was limited to minor symptoms such as pruritus and erythema. The sponsor filed a safety update for the tinea pedis NDA (20-524) on 10/8/96. It states that there has been no change in the safety or efficacy profile since that NDA was filed. In addition, post-marketing follow-up in Japan (Kaken) shows that the local adverse event rate in >4000 patients remains in the range of 0.99-2.76%.

6.2 Important Information from Related NDAs Studies supporting NDA 20-524 employed the same formulation of butenafine cream as was used in the current

submission. NDA 20-524 was approved by the Agency on 10/18/96. There were no serious adverse events related to the drug and only two patients withdrew from the studies due to a local AEs, both of whom were in vehicle arms. Overall adverse events, local and systemic, as well as laboratory abnormalities, occurred more frequently in the vehicle arms of the supportive studies.

6.3 Foreign Experience A butenafine cream 1% formulation and a butenafine gel 1% formulation were approved for marketing in Japan in April 1992. The sponsor states that, to the best of their knowledge, neither of these butenafine formulations have been withdrawn from the Japanese market due to safety or effectiveness issues. The package insert for the formulation marketed in Japan (Mentax® Cream/Lotion) was provided.

6.4 Human Pharmacology and Pharmacokinetics 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)

In this open-label plasma level study conducted in the U.S., an exaggerated dose of the cream was used to mimic the use of butenafine cream for indications such as tinea cruris. The objective in this study was to measure levels of butenafine and the major metabolite, M2 (N-4-(2-hydroxy 1,1-dimethylethyl) benzyl-N-methyl -1-naphthalenemethylamine) in the plasma of subjects with normal skin following daily applications of butenafine cream once a day for 14 consecutive days under an exaggerated dosing regimen.

Two groups of subjects received either a 6-gram or a 20-gram topical dose of the new drug formulation for 14 days. These doses represented a 6-fold and 20-fold exaggeration of the clinical dose for tinea pedis, respectively. Blood samples were collected to obtain pharmacokinetic profile on the first and 14 day of treatment. In addition samples were collected at intermediate time points to determine the trough measurements, and at selected time points through day 28 to determine the elimination profile. Plasma was analyzed for butenafine and M2 using a LC/MS/MS method with a level of quantitation of 0.1 ng/mL.

Twenty healthy volunteers in the age range of 20-65 years and within 20% of their ideal body weight participated in this study. A total of twelve subjects were treated for 14 days with a single daily dose of 20 grams of butenafine cream and eight subjects with 6 grams. Drug was applied to the dorsal torso in the 6 gram group and to the trunk, arms and infra mammary and groin/scrotal areas in females and males respectively.

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 against time did not differ significantly from zero for either butenafine or its M2 metabolite.

The results of this study indicate that there is low absorption of butenafine and minimal formation of its M2 metabolite, when administered once-daily for 14 days at doses of 6 grams or 20 grams. These data are consistent with earlier Japanese studies (Study G3) conducted by Kaken, which showed a comparable butenafine plasma level after multiple doses of a 5 gram dose of the new drug formulation. These data are also consistent with the nonclinical pharmacokinetic data which indicate low absorption of butenafine and low plasma levels after topical dosing in rats and dogs.

Review of the CRFs for this study revealed no adverse events other than minor skin irritation. The following items, however, are noted:

Pt [redacted] had WBC in urine with many bacteria and a history of bladder surgery. This result was listed as "not clinically significant".

Pt [redacted] had had a tubal ligation and was therefore not tested for pregnancy.

Pt [redacted] had blood specimens drawn 2.5 hours late.

Pt [redacted] had a baseline blood glucose of 181 with trace gycosuria. This result was listed as "not clinically significant".

Pharmacokinetic Study of Tinea Cruris Trial Patients (PDC 010-005)

All patients at two sites (total 17) donated blood at Day 14 and Day 42 for measurement of butenafine and metabolite levels. After the randomization code was broken, only samples from the butenafine arm were analyzed. The level of detection was 0.1 ng/ml. At Day 14, the mean drug level was 0.91 ng/ml (0-2.52ng/ml) and 0.07 for the metabolite. At Day 42, the drug was detectable in 5 of the 17 patients (0.15-0.28 ng/ml), but none had measurable metabolite. As noted previously, the non-clinical "no-effect" level was 100 ng/ml. See safety review for adverse events.

6.5 Directions for Use

(from the combined indication label submitted 10/25/96)

"Sufficient Mentax™ cream should be applied once daily to cover affected areas and immediately surrounding skin of patients with tinea pedis, tinea corporis, and tinea cruris. Patients with tinea pedis should apply Mentax Cream for four weeks and tinea corporis or tinea cruris for two weeks. If a patient shows no clinical improvement after the treatment period, the diagnosis should be reviewed."

7 Description of Clinical Data Sources

7.1 Tinea Corporis (PDC 010-004)

Ninety-one (91) patients were enrolled in a multicenter, vehicle-controlled, parallel, randomized, double-blind trial of Butenafine HCl Cream 1%. Patients with tinea corporis, diagnosis confirmed by KOH and culture, applied the assigned medications once a day for two weeks. Of the 78 patients who were evaluated for efficacy in the Modified-Intent-To-Treat population, 42 received butenafine and 36 received vehicle. The two groups were demographically and clinically similar.

7.2 Tinea Cruris (PDC 010-005)

Ninety-three (93) patients were enrolled in a multicenter, vehicle-controlled, parallel, randomized, double-blind trial of Butenafine HCl Cream 1%. Patients with tinea cruris, diagnosis confirmed by KOH and culture, applied the assigned medications once a day for two weeks. Of the 76 patients who were evaluated for efficacy in the Modified-Intent-To-Treat population, 37 received butenafine and 39 received vehicle. The two groups were demographically and clinically similar.

7.3 NDA 20-524 Clinical Trials PDC 010-001 and 002 for tinea pedis -see Medical Officer's review dated 2/29/96 (NDA approved 10/18/96)

7.4 Evaluation of Human Photoallergy (PDC 010-008)

Thirty-one subjects (27 females and four males).

7.5 Human Pharmacokinetics

PDC 010-011 20 normal subjects with exaggerated dosing for 14 days
PDC 010-005 26 patients in tinea cruris trial dosed for 14 days

8 Clinical Studies

OVERVIEW CONTROLLED CLINICAL STUDIES

In support of this NDA, 1 multicenter, double-blind, parallel group, vehicle-controlled study was conducted in patients with tinea cruris (Protocol PDC 010-005) and 1 multicenter, double-blind, parallel group, vehicle-controlled study in patients with tinea corporis (Protocol PDC 010-004). The drug product, in both trials, was applied nightly for 2 weeks followed by a 4-week post-treatment period (total length of study was 6 weeks).

Objective/Rationale:
The objective of each study was to evaluate the efficacy and safety of butenafine cream 1% in the treatment of tinea cruris or tinea corporis.

Study Design:
Each study was a multicenter, randomized, double-blind, vehicle-controlled, parallel group study in which patients received treatment for 2 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 (for tinea cruris); age 12 to 65 years (for tinea corporis)
3) If female, must be either post-menopausal or surgically sterilized, or using a medically acceptable form of birth control or abstinent)
4) Symptomatic tinea cruris or tinea corporis with the target site characterized by at least 2 of the 3 major symptoms of tinea cruris/corporis: erythema, scaling, and pruritus. The minimum total score for these 3 major signs and symptoms should be at least 5, based on a scoring scale where 0 = absent, 1 = mild (barely perceptible), 2 = moderate (distinctive presence), and 3 = severe (marked, intense)
5) Positive KOH for fungal elements
6) Positive fungal culture for a fungal pathogen (other than yeast)
7) Signed informed consent

Exclusion Criteria:

1) Pregnancy or lactation
2) Any significant disease of the hepatic, renal, endocrine (e.g., diabetes mellitus or hyperthyroidism), or immune systems

3) Use of any topical drugs (prescription or OTC) on the area of tinea cruris/corporis within 2 weeks prior to starting the study
4) Use of systemic antifungals, corticosteroids, or immunosuppressants within 1 month prior to starting the study
5) Current use of systemic antihistamines or antibiotics
6) Known hypersensitivity to allylamine derivatives or to any ingredients in the formulation
7) Clinically significant abnormal laboratory results at the screening visit
8) Presence of any concomitant skin disease or disease that could interfere with the evaluation
9) Use of any investigational drug in the previous 4 weeks
10) Previous enrollment in this protocol or in any other study involving butenafine HCl
11) Presence of tinea versicolor

Dosage and Duration of Treatment:

The study medication was applied to the affected areas and to the immediately surrounding skin once daily after bathing for 2 weeks. The 2-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 tinea cruris or tinea corporis. A target lesion was selected for clinical assessment and mycologic sampling throughout the study. Baseline laboratory studies were performed and, for women of childbearing potential, a urine pregnancy test was obtained. Patients were allowed to enter the study based on the clinical findings and KOH examination, with results of the fungal culture and laboratory results pending. (Patients who were subsequently found to have a negative baseline fungal culture or clinically significant abnormal laboratory results were considered "delayed exclusions," and were terminated before completing the study [see "Statistical Considerations" section below]). 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 days 7, 14, and 42.

The post-baseline fungal cultures were held for 4 weeks before being declared negative. Repeat laboratory studies were obtained at day 14. Adverse events were recorded at all follow-up visits.

Reviewer's Comment:

It is not clear whether the evaluation of the KOH slide was performed by an investigator other than the one performing the clinical evaluation, which would be preferred.

Endpoints:

The following procedures/examinations were performed at baseline, days 7, 14, and 42, 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:
   - Erythema
   - Scaling
   - Pruritus
   - Maceration
   - Papules
   - Vesiculation

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

0 = absent (none)
1 = mild (barely perceptible)
2 = moderate (distinctive presence)
3 = severe (marked, intense)

The same rating scale was used to evaluate overall tinea cruris/corporis disease severity (excluding the target area)

4) The **Investigator Global Response** was graded using the following 7-point scale:

Cleared	=	100% remission of clinical signs and symptoms compared to baseline
Excellent	=	90% - 99% improvement of clinical signs and symptoms compared to baseline
Good	=	50% - 89% 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 tinea cruris/corporis 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 **day 42** (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 Global Response

3) Overall Cure - Mycological Cure **and** a score of "Cleared" on the Investigator 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 (between the sponsor and Dr. Slifman), the sponsor was informed that the preferred primary efficacy variable in support of an NDA for this drug product for the indication of tinea cruris/corporis would be "Overall Cure" as defined above. A Total Signs and Symptoms score of 0, when used with Mycological Cure, is consistent with 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.

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 and considered a **"delayed exclusion."**

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
3) Patients without clinically significant abnormal baseline laboratory results
4) Patients who had no "noteworthy" protocol violations
5) Patients with at least 1 post-baseline follow-up visit

In the MITT population, to be included in the Day 7 and Day 14 visits, the visit had to be within ±3 days of the intended study day. If the visit was outside the window or the patient was not present for the visit, the most recent assessment prior to the visit was carried forward and used in the analysis (except that Day 1 data were not carried forward to be used for Day

7). However, at Day 42, no visit window restrictions were applied. In the event that only "partial data" were available at Day 42, the missing data were carried forward from Day 14, (e.g., if the Day 42 culture was missing, the Day 14 culture results were carried forward).

The **Per Protocol** study population was defined by the sponsor as being identical to the MITT population with the exception of the day 42 data. The "window" for the day 42 visit was defined as ≥ 23 days from the date of the last study medication use or those who terminated early due to treatment failure or a treatment-related adverse event.

Reviewer's Comment:

1) In the sponsor-defined per protocol analysis, the day 42 visit could have occurred as much as 8 days prior to the scheduled visit (assuming only 11 days of treatment). The "outside" window for the day 42 visit was not stated, but the sponsor clarified that there was no outside limit.

Methods

Baseline Characteristics

Age, sex, race, history of tinea cruris/corporis, presence of concomitant superficial fungal infections, area of the target lesion, and Total Signs and Symptoms at day 1 were examined to rule out any differences in the sample of patients comprising each of the 2 treatment groups. Categorical variables (i.e., gender, race, history of tinea cruris/corporis, and presence of concomitant superficial fungal infections) were analyzed using Fisher's exact test. Age and Total Signs and Symptoms at day 1 were analyzed using a one-way ANOVA, with treatment serving as the only effect of interest. The area of the target lesion was compared between treatment groups using the Wilcoxon rank-sum test.

The analyses of gender, race, and age were carried out using both the Safety population and the MITT population. All other baseline analyses were carried out on the MITT population.

Variables

The efficacy variables (Mycological Cure, Clinical Cure, Overall Cure, Effective Clinical Response and Effective Treatment) were analyzed using the

Cochran-Mantel-Haenszel (CMH)(General Association) test, stratified by investigator.

The Investigator Global Response and the Patient Perception of cure were analyzed using the Cochran-Mantel-Haenszel test on modified ridits, stratified by investigator. The primary conclusions were based on CMH (ANOVA), since this procedure, according to the sponsor, is appropriate when modified ridits serve as the dependent variable.

The Total Signs and Symptoms Scores were summed and analyzed using the Wilcoxon rank-sum test.

All efficacy analyses were carried out for both the MITT population and the Per Protocol population.

8.1.1 STUDY #1

Title: A Double-Blind Evaluation of Butenafine HCl 1% Cream and Vehicle in the Treatment of Tinea Cruris (Protocol PDC 010-005)

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 93 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 93 patients enrolled, 47 were enrolled in the butenafine treatment group and 46 patients in the vehicle group. Of these 93 patients, a total of 17 (10 butenafine/7 vehicle)were excluded either because of lack a of a positive fungal culture at baseline (8 butenafine/6 vehicle), lack of at least 1 post-baseline visit (1 butenafine/1 vehicle), or a significant protocol violation (1 butenafine patient: continued medication for total of 22 days instead of stopping after 14 days). Thus, there were 76 patients (37 butenafine and 39 vehicle) who were considered evaluable (See Table 1).

Table 1: Patients Enrolled and Evaluability (at baseline)

	Butenafine	Vehicle	All patients
# of Patients Enrolled	47	46	93
Not evaluable			
Negative baseline fungal culture	8 (17%)	6 (13%)	14 (15%)
No post-baseline follow-up visit	1	1	2
Significant protocol violation	1	0	1
Total # not evaluable	10 (21%)	7 (15%)	17 (18%)
Total # Evaluable (MITT population)	37 (79%)	39 (85%)	76 (82%)

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

Table 2 : Demographics of Evaluable Patients (MITT population)

	Butenafine	Vehicle
No. of Patients	37	39
Male **Female**	37 (100%) 0 (0%)	38 (97%) 1 (3%)
Age Mean yrs ± SEM **Range (yrs)**	34.49 ± 2.25 18 - 64	37.67 ± 2.34 19 - 70
Caucasian **African-American** **Hispanic** **Asian**	34 (92%) 1 (3%) 1 (3%) 1 (3%)	39 (100%) 0 (0%) 0 (0%) 0 (0%)
Baseline Sign/Symp Score, median	7.0	8.0
Target Lesion Area, mean	49.85	59.79
Dermatophyte, rubrum **other**	36 1	39 0

Reviewer's Comment:

Since tinea cruris occurs much more frequently in males, as expected, there was a preponderance of males versus females in both treatment arms of the study. In addition, the great majority of patients studied were Caucasian. It should also be noted that the youngest patient studied in the butenafine group was only 18 years of age. Note that the baseline Sign Symptom Score and the target lesion size are larger in the vehicle arm.

The percentage of evaluable patients and their enrollment in the active vs. vehicle arms was not significantly different among the 6 study sites.

In addition to the 17 "delayed exclusion" patients who terminated early, a total of 7 patients (5 butenafine/2 vehicle) were not included in the Per Protocol analysis. Five patients (3 butenafine, 2 vehicle) did not attend the day 42 visit. One patient (butenafine) had a missing day 42 culture and for one patient (butenafine), the day 42 visit was less than 23 days after cessation of treatment. There were no patients who were discontinued early from the study due to an adverse event.

Protocol Violations

Fifteen patients had a total of 22 protocol violations; all were allowed to remain in the study. The most common violation was an unnecessary blood draw at the Day 42 follow-up visit (according to the protocol, no laboratory evaluation was required at Day 42 unless a follow-up for previous abnormality.) Significant deviations from protocol included the following notable cases:

Pt [redacted] received an injection of dexamethasone for foot pain unrelated to the study.

Pt [redacted] was not terminated despite a negative baseline mycology. Pt 5111 continued the medication for 22 days. Neither was included in the efficacy analysis.

Pt [redacted] had a baseline HCT of 57 and a platelet count of 40,000. This patient was referred to a hematologist, but allowed to continue in study.

Pt [redacted] was terminated from the butenafine arm due to negative mycology and follow-up labs were erroneously not drawn, excluding this patient from safety analysis.

Pt [redacted] (butenafine) was included in the MITT analysis. The site failed to submit the Day 42 culture. The previous Day 14 culture (negative) was carried forward.

Reviewer's Comment: The last patient listed, [redacted] should be analyzed as a treatment failure. The patient with hematologic abnormalities clearly has a significant disease likely to be associated with compromised defenses against infection. This patient should have been excluded from a study in which treatment for an existing infection is unproven or inactive.

8.1.1.4.2 Efficacy Endpoint Outcomes

Table 3: Efficacy as Calculated by the Sponsor

Patient Outcome Category	Day 14 (End of Rx)		Day 42 (Four Week Follow-up)	
	Butenafine	**Vehicle**	**Butenafine**	**Vehicle**
Mycological Cure	78% (29/38)	11% (4/38)	81% (31/38)	13% (5/39)
Overall Cure Rate	32% (12/37)	8% (3/39)	62% (23/37)	3% (1/39)
Effective Treatment	57% (21/38)	8% (3/39)	73% (28/38)	5% (2/39)

In addition to this physician/laboratory generated outcome, the Patient Perception of outcome is presented below.

Table 4: Patient Perception of Outcome

	Butenafine n=37	Vehicle n=39
Greatly improved	29 (78%)	8 (21%)
Somewhat improved	1	12 (31%)
Same	6 (16%)	8 (21%)
Somewhat worse	1	9 (23%)
Much worse	0	2

Reviewer's Comments:

1) All of the positive culture isolates were T. rubrum, most likely as a result of the low enrollment number. Tinea cruris is, however, also associated with infection by E. floccosum and T. mentagrophytes. Efficacy for non-rubrum infection can only be inferred. The NDA for tinea pedis included a sufficient number of T. mentagrophytes infections, but only 8 cases in which E. floccosum was isolated. This reviewer agrees with the microbiologist consultant that efficacy against this dermatophyte is highly likely and does not have to be excluded in the label.

2) Examination of the Physician's Global Assessment and Patient Perception by site indicates that one may be problematic. Dr. Lesher's assessment of the per protocol population was that 100% of the 5 butenafine arm patients were clear at the Day 42 visit, but none of the vehicle arm patients. In contrast, the other sites reported 46-71% of their butenafine patients as clear vs. 0-25% of the vehicle arm. This investigator's patients likewise had the most dichotomous perception of efficacy with 80% of the butenafine group reporting the highest efficacy ranking vs. 0% in the vehicle arm. This suggests that either the medication performed better at this one site or that the blind may have been compromised and that physician bias may have unintentionally influenced patient perception.

3) In general, the patients were more enthusiastic in their subjective assessment than their doctor, particularly in the vehicle arm, but overall, there was agreement between the physician's global and the patient perception assessments.

8.1.1.4.3 Safety Outcomes

A total of 45 patients were exposed to butenafine for 2 weeks. Forty-three were exposed to vehicle. Of these patients, 4 could not be evaluated at 2 weeks because they were terminated earlier as treatment failures (1 vehicle) or lost to follow-up (I vehicle, 2 butenafine). No patient withdrew from either arm due to treatment related reasons. No serious adverse events were reported. The most common body system listed was "Body as a Whole" and the most common events were headache (2 butenafine/3 vehicle) and backache (2 butenifane/0 vehicle). One patient is listed as experiencing moderate burning upon butenafine application. This patient completed the study and, in fact, is the same patient ([redacted]) listed under protocol violations for continuing medication for 22 days.

The sponsor states that there were no clinically significant laboratory abnormalities related to medication. Nonetheless, the following cases were noted in the CRF's and line listings:

Butenafine

Pt [redacted] bilirubin increased from 1 to 2.9 over 2 weeks (reference range 0.1-1.2). No follow-up value was recorded.

Pt [redacted] SGOT increased from 17-52 with no follow-up recorded.

Pt [redacted] Baseline SGOT was 236 (ref range 0-50), SGPT_118, but was continued in study because the investigator decided the abnormalities were due to alcohol abuse. There was no change at the Day 14 follow-up.

Vehicle

Pt [redacted] LDH increased from 168-353 (ref range).

Pt [redacted] Baseline hematocrit was 57 with platelet count of 40,000. The patient was referred to a hematologist and allowed to continue in the study.

Reviewer's Comment: The small number of patients in these arms precludes meaningful analysis of these abnormalities, but it is unlikely that they are related to butenafine given the small amounts absorbed (refer to Human PK section of this review and the Pharmacokinetic review).

8.1.2 Study #2

Title: A Multicenter, Double-Blind Study to Evaluate Butenafine HCl Cream 1% and Vehicle in the Treatment of Tinea Corporis (PDC 010-004)

Investigators:

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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 91 patients were enrolled at 5 sites and were randomized to either the butenafine arm or the vehicle arm. 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 91 patients enrolled, 47 were in the butenafine group and 44 in the vehicle group. Two in the vehicle group were excluded due to no post-baseline visit. Of the remaining 89, 11 were excluded from efficacy analysis because of negative baseline culture (5 butenafine/6 vehicle). In the remaining 78 patients who were evaluated for efficacy in the Modified-Intent-To-Treat population, 42 received butenafine and 36 received vehicle. A total of 2 patients in each arm were excluded from the Per Protocol analysis because the Day 42 visit was missing (2

butenafine/1 vehicle) or the Day 42 culture was missing (I vehicle). There were no patients excluded from the study because of clinically significant abnormal Baseline laboratory results. However, one patient with no history of diabetes [redacted]vehicle) had an elevated serum glucose level at Baseline. A diagnosis of diabetes mellitus was confirmed, but the patient was allowed to complete the study. (See Protocol Violations).

Early Terminations

In addition to the patients noted above, a total of 11 eligible patients terminated before the scheduled Day 42 completion visit. Seven patients in the vehicle group withdrew from the study at either Day 7 or Day 14 because of treatment failure . No patients in the butenafine group withdrew because of treatment failure. (However, as noted above, two patients in the butenafine group did not return after the Day 7 visit for undisclosed reasons

Table 6: Patient Evaluability

	Butenafine	Vehicle	All patients
# of Patients Enrolled	47	44	91
Not evaluable			
Negative baseline fungal culture	5 (11%)	6 (14%)	11 (12%)
No post-baseline follow-up visit	0	2	2
Significant protocol violation	0	0	0
Total # not evaluable	5 (11%)	8 (18%)	13 (14%)
Total # Evaluable (MITT population)	42 (89%)	36 (82%)	78 (86%)

Table 7: Patients in MITT Analysis but not in Per Protocol Analysis

Patient Number	Treatment	Investigator	Reason for Exclusion
	Butenafine	Hebert	Withdrew after Day 7 visit
	Butenafine	Hebert	Withdrew after Day 7 visit
	Vehicle	Rodriguez	Day 42 visit <23 days post-TX
	Vehicle	Hebert	No Day 42 culture result

Reviewer's Comment: Patients had negative mycology at their last visit on Day 7, but were not listed as Cleared and thus not analyzed as Cured. However, the application is inconsistent. In the Population Flowchart it states that patient was included only in the MITT analysis; in the Protocol Violations section it describes inclusion of this patient in both the MITT and the PP analyses.

There were no statistically significant differences between the two treatment groups in the distribution of either age, sex, race, tinea corporis history, target lesion area, Total Signs and Symptoms Scores or incidence of concomitant superficial fungal infections at Baseline. The demographic characteristics of each group are shown in Table 8.

Table 8: Patient Demographics MITT Analysis (All Investigators)

	Butenafine HCl Cream 1%	Vehicle
Males	22	17
Females	20	19
Mean age (years)	40.5	40.0
Age range		
Race		
Caucasian	25	21
Hispanic	11	8
Black	5	7
Asian/Other	1	0
Baseline Sign/Symptom Score of Target Lesion	8.40(mean)	8.42(mean)
Target lesion area(mean)	40.04 cm^2	39.39 cm^2
Dermatophyte		
T. rubrum	29	19
T. tonsurans	10	7
M. canis	2	3
T. mentagrophytes	1	3
M. gypseum	0	3
E. floccosum	0	1

Protocol Deviations

There were 16 deviations from the protocol noted. The deviations are listed in Table 9. None of the protocol deviations was deemed by the Sponsor or Investigator to be of sufficient severity to warrant discontinuation of the patient from the study. As noted above, the disposition of patient is not consistently stated in the application.

Table 9: Protocol Deviations (explanations are the sponsor's)

Patient Number	Treatment	Reason
	Vehicle	Patient was enrolled into the study on 9/12/94. Patient has a history of emphysema and was on beclomethasone dipropionate 5 puffs t.i.d. since 9/10/93. Since the patient's concomitant corticosteroid use was not identified until after the patient completed the study, the patient's data was included in the MITT and Per Protocol analyses.
	Vehicle	Patient was enrolled into the study on 9/16/94. Patient was initially scheduled for his Day 42 visit on 10/28/94. Since the patient was out of town, he returned 20 days late (11/17/94) for his Day 42 visit.
	Butenafine HCl Cream 1%	No urine specimen was collected for this patient at the Day 14 visit. A urine specimen could not be obtained from the patient during the visit.
	Vehicle	No urine specimen was collected for this patient at the Day 14 visit. A urine specimen could not be obtained from the patient during the visit.
	Vehicle	No urine specimen was collected for this patient at the Day 1 visit. A urine specimen could not be obtained from the patient during the visit. A urine specimen was collected at the Day 14 visit. Patient was enrolled into the study on 8/17/95. Patient was initially scheduled for his Day 42 visit on 9/22/95. Patient came in on 9/18/95, 4 days early for his Day 42 visit. The patient was leaving town for an indefinite amount of time due to a family emergency.
	Vehicle	Patient was enrolled into the study on 8/4/94. Patient missed his Day 7 (Week 1) visit on 8/11/94 since he was suffering from a cold.
	Vehicle	Patient was enrolled into the study on 3/9/95. Patient's date of birth is 9/15/23. Patient is a healthy working male who was 71 years old (at the time he was enrolled into the study) and met all inclusion/exclusion criteria except the age range of 12-65. The patient is a very active and healthy 71 year old and the site did not realize that the patient exceeded the age limit for this study. Since the patient's age was not discovered until after the patient completed the study, the patient's data was included in the MITT and Per Protocol analyses.
	Vehicle	Blood and urine specimens were collected at the Day 7 visit since the patient was terminated on this date for lack of efficacy.

	Vehicle	Patient was enrolled into the study on 8/17/95. At the Day 14 visit (9/1/95), this patient's L.H. was elevated to 569 IU/L (normal range 100-250 IU/L). The patient's labs were repeated at Day 20 (9/7/95) and the L.H. was 130 IU/L. Since the patient's L.H. at Day 20 and at Baseline (8/17/95) was within the normal range, the patient's elevated L.H. at Day 14 was not considered clinically significant by the investigator. Patient returned 9 days early (9/21/95) for his Day 42 visit. The patient was seen early since he was going on vacation out of town.
	Vehicle	Since the blood specimen collected at Day 1 (10/10/94) for differential analysis was hemolyzed and could not be analyzed by the laboratory, a blood specimen was collected at Day 7 (10/19/94) for analysis.
	Butenafine HCl Cream 1%	Patient was enrolled in the study on 9/19/94. Patient was seen on 10/12/94, 9 days late for her scheduled Day 14 visit (10/3/94) due to an illness. Patient discontinued study medication treatment on 10/3/94 per protocol On 10/3/94, patient started Ceclor® 500 mg b.i.d. p.o. for an upper respiratory infection and discontinued antibiotic therapy on 10/9/94.
	Vehicle	Patient was enrolled into the study on 5/22/95. Site initially sent only one baseline culture tube to the Fungus Testing Lab (FTL). Site was notified that both culture tubes must be sent to FTL. When site received the baseline culture result on 6/8/95 for the first culture tube and no dermatophyte was identified, patient was informed that he did not have to return for a Day 42 visit. Patient had discontinued study medication use on 6/5/95 per protocol. FTL notified site on 6/13/95 that *T. tonsurans* was isolated from the second baseline culture tube. Since a dermatophyte was isolated at baseline and no other medication was used on the corporis lesions other than the study medication and there were no protocol violations, the patient was recontacted by the site to return for a Day 42 visit. This patient's Day 42 mycology cultures which were taken on 7/5/95 were not sent to FTL and were discarded in error by the study coordinator on 7/21/95 since there was no growth. Since the Day 42 mycology cultures were held for only 16 days before being discarded for no growth, the patient's mycology result for Day 14 was carried forward in the MITT analysis. This patient's data was not included in the Per Protocol analysis since the Day 42 mycology cultures were not held for four weeks before being declared negative.

	Butenafine HCl Cream 1%	Patient was enrolled into the study on 6/14/95. This patient's Day 7 mycology cultures taken on 6/22/95 were not sent to FTL and were discarded in error by the study coordinator on 7/21/95 because there was no growth. This patient did not return for any follow-up visits after Day 7 and was terminated from the study for non-compliance. Since the Day 7 mycology cultures were held by the site 4 weeks from the collection date before being declared negative, this patient's data was included in the MITT and Per Protocol analyses.
	Vehicle	Patient was enrolled into the study on 6/27/95. This patient's Day 7 mycology cultures taken on 7/5/95 were not sent to FTL and were discarded in error by the study coordinator on 7/24/95 because there was no growth. This patient returned for his Day 14 and 42 visits and the mycology cultures for these visits were sent to FTL for identification. Since the Day 7 mycology cultures were held by the site for approximately 4 weeks, this patient's data was included in the MITT and Per Protocol analyses.
	Butenafine HCl Cream 1%	The laboratory was not able to obtain any valid results from the blood and urine specimens collected for this patient at Day 14. Blood and urine specimens were collected at Day 42 for analysis
	Butenafine HCl Cream 1%	Patient was enrolled into the study on 7/19/95. This patient's baseline serum glucose level was 327 mg/dl. Patient was referred to an internist for follow-up. Since the patient had completed 5 days of treatment when the site was notified of the elevated glucose level and no diagnosis of diabetes mellitus was confirmed, the patient was allowed to continue in the study. The patient was diagnosed with diabetes mellitus on 8/14/95 and placed on Chlorpropamide 100 mg qd. On 8/14/95 the patient was also diagnosed with a urinary tract infection and placed on Cipro® 500 mg b.i.d. from 8/14/95-8/21/95. Since the patient had completed the treatment phase of the study on 8/1/95, the patient was allowed to complete the study. Blood and urine specimens were collected at Day 42 to follow-up patient's recent diagnosis of diabetes and UTI.

Reviewer's Comment: *Patients had negative mycology at their last visit on Day 7, but were not listed as Cleared and thus not analyzed as Cured. The application is inconsistent regarding case in the Population Flowchart it states that the patient was included only in the MITT analysis; however, in the Protocol Violations section it describes inclusion of this patient in both the MITT and the PP analyses. Case was in the vehicle arm. This case was analyzed as a Cure. Thus, the negative result carried forward had no deleterious impact on the study conclusion.*

8.1.2.4.2 Efficacy Endpoint Outcomes

At the four-week post-treatment follow-up (Day 42), the Overall Cure rate was 67% in the butenafine-treated group compared with 14% in the vehicle-treated group ($p<0.0001$, Table 11).

At the four-week post-treatment follow-up (Day 42), the Mycological Cure rate was 88% in the butenafine-treated group compared with 17% in the vehicle-treated group ($p<0.0001$, Table 11).

Table 10: Efficacy Outcomes (sponsor's analysis)

Patient Outcome Category	Day 14 (End of Rx)		Day 42 (4 Week Follow-up)	
	Butenafine	Vehicle	Butenafine	Vehicle
Mycological Cure	88% (37/42)	28% (10/36)	88% (37/42)	17% (6/36)
Overall Cure	31% (13/42)	3% (1/36)	67% (28/42)	14% (5/36)
Effective Treatment	60% (25/42)	17% (6/36)	81% (34/42)	14% (5/36)

A favorable pattern of improvement in Patient Perception exists in the butenafine group compared to the vehicle group at Day 42, as shown in Table 11.

Table 11: Patient Perception

	Butenafine (n=40)	Vehicle (n=34)
Greatly improved	35 (88%)	7 (21%)
Somewhat improved	4 (10%)	7 (21%)
Same	1	8 (24%)
Somewhat worse	0	8 (24%)
Much Worse	0	4 (12%)

As in trial 005 for tinea cruris, the physicians and the patients showed overall agreement in their subjective scoring with the patients being somewhat more enthusiastic in both arms of the study.

8.1.2.4.3 Safety Outcomes

A total of 91 patients were enrolled in this study, with 47 randomized to butenafine HCl cream 1% and 44 randomized to vehicle. A total of 45 patients were exposed to butenafine HCl cream 1% for the two week treatment period while 40 were exposed to vehicle for at least 12 days. Two of the patients in the vehicle arm terminated before the Day 14 follow-up visit and were not evaluated for safety.

Study medication was dispensed to all patients enrolled into the study, a total of 91 patients (47 butenafine/44 vehicle). The amount of medication used was not

determined for four of these patients (2 butenafine/2 vehicle). Patients (vehicle) did not return for study visits following the Baseline visit and patients (butenafine) did not return for study visits after Day 7. Patient did eventually return study medication to the Investigator; medication was not retrieved from the other three patients.

The sponsor states that there were no adverse events assessed by the investigators as possibly, probably or definitely related to study treatment. Overall, there were very few adverse events identified in this study. A total of 2 patients in the butenafine group and 5 patients in the vehicle group reported adverse events. The body system accounting for 4 of the events in the vehicle arm was Respiratory. One adverse event was reported in this category from the butenafine group and the other was a urinary tract infection.

There were no Serious Adverse Events reported by the sponsor during this study. No patient in either group withdrew from the study because of an adverse event. The sponsor states that there were no laboratory test results judged to be clinically significant and at least possibly related to study medication. However, several patients had additional lab tests to follow-up on out-of-range results from Baseline or end-of-treatment specimens. In addition, examination of CRFs and line listings revealed the following cases in which follow-up is not given:

<u>Butenafine</u>

Pt Creatinine increased from 1.5 to 2.4

Pt SGOT increased from 34 to 69; SGPT from 20-51

<u>Vehicle</u>

Pt LDH increased from 144 to 499 (ref range

Reviewer's Comment: *Since follow-up is not given, it is difficult to evaluate relationship to the study treatment. It is unlikely that these events are related to the treatment, since negligible amounts are absorbed and the overall profile of laboratory abnormalities does not differ in the butenafine and vehicle arms.*

8.1.3 <u>PDC 010-008 - Evaluation of Human Photoallergy</u>

Thirty-one subjects (27 females and four males) completed this blinded photoallergy study. Each subject received duplicate patches of Butenafine HCl Cream 1% and its vehicle (24-hour contact) twice a week for the first three weeks of the study. After each 24-hour period, patches were removed and the sites were evaluated and exposed to two times the subject's MED of UVB radiation from a 1000 Watt Xenon Arc Solar Simulator. The solar simulator source used in this study complies with the FDA Sunscreen Drug Product Over-the-Counter Monograph requirements, which

defines solar light as a continuous emission spectrum from 290 to 400 nanometers with less than 1 percent of its total energy output contributed by nonsolar wavelengths shorter than 290 nanometers. The sites were scored 15 minutes after irradiation. After a two-week rest period (no material applied), each subject received patches of the test materials applied to naive sites. The patches were removed after 24 hours and the sites graded and exposed to UVA/B radiation. Sites were then evaluated at 15 minutes, 24 and 72 hours post irradiation. Unirradiated sites were used to evaluate contact sensitization.

The results indicated no evidence of photo-contact allergy or phototoxicity associated with the application of the test materials in either the induction or challenge phase.

Reviewer's Comment: *While the number of subjects enrolled is consistent with Agency advice, it should be noted that it is insufficient to detect photosensitization potential in the range less than about 5%.*

9 Overview of Efficacy

As shown below and discussed at length in Dr. Thomson's statistical review, the global evaluation of disease compared to baseline correlates well with both the Patient Perception Scale and the Total Signs and Symptoms Scale

Table 12: Validity of Endpoints

	Day=7			Day=14			LOCF			Day=42		
	global	patient	target S&S	global	patient	target S&S	global	patient	target S&S	global	patient	target S&S
global patient	-.73			-.76			-.76			-.90		
target S&S	.86	-.69		.93	-.79		.92	-.81		.94	-.87	
disease S&S	.43	-.35	.41	.60	-.61	.59	.58	-.47	.50	.75	-.60	.68

Dr. Thomson's review confirms the sponsor's analysis that virtually all means favor butenafine over vehicle.

Butenafine cream 1% is clearly efficacious in the treatment of tinea cruris and corporis. However, as discussed at length in the microbiology review, the small study populations did not provide isolates of all of the dermatophytes associated with these infections. For tinea cruris, only T. rubrum was isolated. For tinea corporis, 91% of the isolates treated with butenafine were T. rubrum or tonsurans. There was one isolate of T. mentagrophytes and two isolates of M. canis.

It should be noted that T. mentagrophytes often produces a more inflammatory lesion that the more common isolates; given the small sample represented in this application, efficacy can only be assumed. It should also be noted that the perifollicular form of tinea corporis (Majocchi's granuloma) was not studied. Efficacy for this form of tinea corporis cannot be assumed and is, in fact, unlikely.

Overall, this reviewer agrees with the microbiologist's opinion that efficacy for the less common, but unstudied, dermatophytes can be assumed for typical cases of these two indications, tinea cruris and corporis. Indeed, the overall cure rates for these indications were very similar: 67% and 62%. Data from Japanese trials is difficult to compare because overall cure was not required for efficacy.

10. Overview of Safety

There were no serious adverse events or deaths in these studies, nor were there any significant events likely to be related to the drug other than one case of skin irritation in a patient who used the medication in the crural area for a week longer than indicated. No patient is known to have withdrawn from either study for an adverse event and there were only 4 cases lost to follow-up (1 butenafine, 3 vehicle). The most common complaints during the study were respiratory (5/1), headache (2/3), and backache (2/0). There were no laboratory abnormalities that appear to be related to the drug. The most common were elevated liver function tests, but these appeared as frequently in the vehicle arm, as was true in the tinea pedis studies. It is extremely unlikely that any of these results are due to the drug, since two PK studies confirmed very little systemic absorption.

The sample sizes of the two clinical trials and the normal subject photoallergy study are too small to allow definitive assessment of risk in the larger population. However, the results obtained in the four Japanese trials for these indications are consistent with the excellent safety profile suggested by the studies in this application, as are the results of Japanese post-marketing reports of safety.

The application contains insufficient data to assess drug-demographic effects, but there is no reason to expect differential responses to the drug. There was no data regarding drug-drug interactions nor drug-disease interactions, since concurrent medications or disease in the target areas was an excluding parameter. Likewise, pregnant and lactating women were excluded and no inadvertent exposures were reported.

11 Labeling Review

The sponsor has an Approved label for this drug in the treatment of tinea pedis. The label submitted with this NDA for corporis and cruris is the combined label for all three indications. The comments to follow address items in this combined label which either differ from the Approved label or are specific to the added indications.

11.1 Description: *No change.*

11.2 Clinical Pharmacology: In 17 patients with tinea cruris, Mentax™ Cream, 1%, was applied by the patients to cover the affected and immediately surrounding skin area once daily for 2 weeks. Blood samples were collected 1 to 65 hours after dosing after 2 weeks of treatment and 4 weeks after cessation of treatment. The plasma butenafine HCl concentration ranged from undetectable to 2.52 ng/mL.

Reviewer's Comment: *The sponsor has added the results of the cruris trial PK study to the relevant section of the label.*

Microbiology: Butenafine HCl has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section:

Epidermophyton floccosum

Trichophyton mentagrophytes

Trichophyton rubrum

Trichophyton tonsurans

Microsporum canis

Reviewer's Comment: *The Microbiology section should be amended to state specifically the isolates studied for each indication. Specifically, only T. rubrum was isolated in the cruris trial; in the corporis trial, 91% of the isolates treated with butenafine were T. rubrum or tonsurans. There was one isolate of T. mentagrophytes and two isolates of M. canis.*

Clinical Studies:

Interdigital Tinea Pedis

In the following data presentations, patients with interdigital tinea pedis in the absence of moccasin-type tinea pedis and onychomycosis were studied. The term **"Mycological Cure"** is defined as negative KOH and culture. The term **"Effective**

Treatment" refers to patients who had a "Mycological Cure" **and** an Investigator's Global **of** either "Excellent" (80% to 99% improvement) **or** "Cleared" (100% improvement). The term **"Overall Cure"** refers to patients who had both a "Mycological Cure" **and** an Investigator's Global Assessment of "Cleared"(100% improvement).

Data from the two controlled studies in which Mentax™ Cream, 1%, was used once daily for 4 weeks have been combined in the table below. Patients were treated for 4 weeks and evaluated 4 weeks post-treatment. In the "per protocol" analysis shown in the table below, statistical significance (Mentax™ vs. vehicle) was achieved for all patient outcome categories at 4 weeks post-treatment.

Patient Outcome Category	WEEK 4 (End of Treatment)		WEEK 8 (4 Weeks Post-Treatment)	
	Butenafine	Vehicle	Butenafine	Vehicle
Mycological Cure	89% (83/93)	57% (51/90)	90% (66/73)	38% (25/66)
Effective Treatment	57% (53/93)	28% (25/90)	74% (54/73)	26% (17/66)
Overall Cure	15% (14/93)	8% (7/90)	25% (18/73)	9% (6/66)

Tinea Corporis and Tinea Cruris

In the following data presentations, patients with tinea corporis or tinea cruris were studied. The term **"Mycological Cure"** is defined as negative KOH and culture. The term **"Effective Treatment"** refers to patients who had a "Mycological Cure" **and** an Investigator's Global of either "Excellent" (90% to 99% improvement) **or** "Cleared" (100% improvement). The term **"Overall Cure"** refers to patients who had both a "Mycological Cure" **and** an Investigator's Global Assessment of "Cleared"(100% improvement).

Separate studies compared Mentax™ Cream to vehicle applied once daily for 2 weeks in the treatment of tinea corporis and tinea cruris. Patients were treated for 2 weeks and evaluated 4 weeks post-treatment. In the "modified intent-to-treat" analysis shown in the table below, statistical significance (Mentax™ vs. vehicle) was achieved for all patient outcome categories at Week 2 (end of treatment) and 4 weeks post-treatment.

Tinea Corporis

Patient Outcome Category	WEEK 2 (End of Treatment)		WEEK 6 (4 Weeks Post-Treatment)	
	Butenafine	Vehicle	Butenafine	Vehicle
Mycological Cure	88% (37/42)	28% (10/36)	88% (37/42)	17% (6/36)
Effective Treatment	60% (25/42)	17% (6/36)	81% (34/42)	14% (5/36)
Overall Cure	31% (13/42)	3% (1/36)	67% (28/42)	14% (5/36)

Tinea Cruris

Patient Outcome Category	WEEK 2 (End of Treatment)		WEEK 6 (4 Weeks Post-Treatment)	
	Butenafine	Vehicle	Butenafine	Vehicle
Mycological Cure	78% (29/37)	11% (4/38)	81% (30/37)	13% (5/39)
Effective Treatment	57% (21/37)	8% (3/39)	73% (27/37)	5% (2/39)
Overall cure	32% (12/37)	8% (3/39)	62% (23/37)	3% (1/39)

Reviewer's Comment: *In the ' section under tinea pedis, the sponsor has changed the Approved wording to state that instead of This statement is also made in the section that follows for corporis and cruris. Either statement is technically correct.*

It should be noted that the pedis trial results are for the Per Protocol Population, while the corporis/cruris trials list the MITT results.

11.3 Indications and Usage:

INDICATIONS AND USAGE

Reviewer's Comment: *The term ' is misleading. Dermatophytoses, by definition, are confined to the superficial layer of the skin. Since there are very serious dermal mycotic infections that would not be amenable*

to topical treatment, this wording should be changed to "superficial skin infections".

This section should state that the perifollicular form of tinea corporis has not been studied.

11.4 Contraindications: *No change.*

11.5 Warnings: *No change.*

11.6 Precautions:

Information for Patients

The patient should be instructed to:

1. Use Mentax™ Cream, 1%, as directed by the physician. The hands should be washed after applying the medication to the affected area(s). Avoid contact with the eyes, nose, mouth, and other mucous membranes. Mentax™ Cream, 1%, is for external use only.
2. Dry the affected area(s) thoroughly before application, if he/she wishes to apply Mentax™ Cream, 1%, after bathing.
3. Use the medication for the full treatment time recommended by the physician, even though symptoms may have improved. Notify the physician if there is no improvement after 4 weeks, sooner, if the condition worsens (see below).
4. Inform the physician if the area of application shows signs of increased irritation, redness, itching, burning, blistering, swelling, or oozing.
5. Avoid the use of occlusive dressings unless otherwise directed by the physician.
6. Do not use this medication for any disorder other than that for which it was prescribed.

Reviewer's Comment: *The label continues to state that patients should notify their physician if not improved after 4 weeks, although the treatment period for corporis and cruris is 2 weeks.*

Pediatric Use:

Pediatric Use

Safety and efficacy in pediatric patients below the age of 12 years have not been studied. Use of Mentax™ Cream, 1%, in pediatric patients 12 to 16 years of age is supported by evidence from adequate and well-controlled studies of Mentax™ Cream, 1%, in adults.

Reviewer's Comment: *The tinea corporis trial included 4 patients age 13-16. The label states that this is "evidence from adequate and well-controlled studies". In fact, the sample is very small, one of the 4 was a failure, there were only 2 patients in this age group in the vehicle arm, and tinea corporis in pediatric patients is often associated with M. canis, which was poorly represented in the study (2 isolates). For these reasons, this section should be changed to simply state the facts as noted.*

Adverse Reactions:

ADVERSE REACTIONS

In controlled clinical trials, 3 (approximately 1%) of 230 patients treated with Mentax™ Cream, 1%, reported adverse events related to the skin. These included burning/stinging and worsening of the condition. No patient treated with Mentax™ Cream, 1%, discontinued treatment due to an adverse event. In the vehicle-treated patients, one of 205 patients discontinued because of severe burning/stinging and itching at the site of application.

In uncontrolled clinical trials, the most frequently reported adverse events in patients treated with Mentax™ Cream, 1%, were: contact dermatitis, erythema, irritation, and itching, each occurring in less than 2% of patients.

Reviewer's Comment: *No changes were made other than the additional local AE noted by the sponsor; the total numbers exposed are accurate.*

See next page for Conclusion and Recommendation

12 Conclusions

Butenafine HCl Cream, 1% is safe and effective for the topical treatment of tinea pedis, tinea corporis, and tinea cruris.

13 Recommendation

Approval with changes in label noted above.

Kathryn O'Connell MD

Kathryn A. O'Connell, M.D., Ph.D.
Medical Officer, Dermatology

MD 12/3/96.

cc: HFD-540
HFD-540/CSO/Cross
HFD-540/Micro/
HFD-540/Chem/
HFD-540/Pharm/
HFD-540/Stats/Thomson
HFD-540/MO/OConnell
HFD-540/DivDir/Wilkin

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 020663

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

OCT 31 1996

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA: 20-663 **SUBMISSION DATE:** 12/22/95
PRODUCT: Butenafine HCl Cream 1% (Mentax™)
SPONSOR: Penederm Incorporated
320 Lakeside Drive, Suite A
Foster City, CA 94404
TYPE OF SUBMISSION: Original NDA **REVIEWER:** Sue-Chih Lee, Ph.D.

I. BACKGROUND:

Butenafine HCl, a benzylamine derivative, is closely related to allylamine antifungal agents in that it inhibits the squalene epoxidase. Previously, the sponsor has submitted a NDA (#20-524) for the same product for the treatment of interdigital tinea pedis. In this NDA, the product is proposed for the treatment of tinea corporis and tinea cruris. Provided in this submission are plasma concentrations of butenafine and its metabolite in 24 tinea cruris patients participating in a pivotal clinical trial. Also included are reports of a PK study (Protocol PDC-010-011) which was previously submitted in NDA 20-524. The sponsor refers to NDA 20-524 for information on other in vivo and in vitro percutaneous absorption studies.

II. FORMULATION AND DOSAGE REGIMEN:

The formulation intended for marketing (PD-010-C-003) is given below. The cream is to be applied oyer the affected and immediately surrounding skin once daily after bathing for two weeks. The sponsor indicates that the expected daily dose is approximately 2 g.

Ingredient	%w/w
Butenafine HCl	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	

III. STUDIES INCLUDED IN AND REVIEWED UNDER NDA 20-524:

1) 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, Penederm Study 9425201D):

Plasma concentrations of butenafine and the major metabolite (M2) were determined following once daily application to normal volunteers for 14 days under exaggerated dosing regimens. This study used the formulation intended for marketing.

At a daily dose of 6 g, the mean (±SD) steady state Cmax values for butenafine and the metabolite M2 were 1.43±0.78 and 0.17±0.34 ng/ml, respectively. At a daily dose of 20 g, the mean steady state Cmax values for butenafine and the metabolite M2 were 5.03±2.04 ng/ml and 0.20±0.11 ng/ml, respectively. The mean total daily urinary excretion (including butenafine and the metabolites) was very small and the highest value was 0.01% of the applied dose.

2) Single and Multiple Application Study of KP-363, a New Antifungal Agent, in Healthy Adults 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 12 hours after application), the mean Cmax was 4.1±1.7 ng/ml for Day 1 and 4.8±2.3 ng/ml for Day 7.

3) In Vitro Percutaneous Absorption of Butenafine Cream Formulations

This study was conducted to verify that the two formulations, PD-010-C-001 and PD-010-C-003, evaluated in clinical trials and some preclinical studies, deliver comparable amounts of butenafine percutaneously. The results for the two formulations were found not to be significantly different.

IV. NEW PK INFORMATION:

Study Title: A Multicenter, Double-Blind Study To Evaluate Butenafine HCl 1% Cream and Vehicle in the Treatment of Tinea Cruris (PDC 010-005)

A summary of the study results are given below. The detailed information is attached in Appendix I.

Ninety-three patients were enrolled in the pivotal clinical tinea cruris study of butenafine HCl cream 1%. The cream was applied by the patient once daily for 2 weeks. The plasma concentrations of butenafine and M2 metabolite during and after treatment were determined in 24 male patients. Blood samples were obtained at pre-dose, and on Days 14 and 42.

The mean plasma concentration on Day 14 was 0.91±0.15 ng/mL for butenafine and 0.07±0.02 ng/mL for M2. On Day 42, five patients (out of 17) had measurable plasma butenafine concentrations ranging from 0.15-0.28 ng/mL and no patients had detectable M2 (LOQ of 0.1 ng/mL).

V. COMMENTS:

A. General Comment:

The existing PK study (Penederm Study 9425201D) conducted in healthy volunteers used exaggerated doses (6 and 20 g/day) and all adverse events considered possibly related to the drug were mild and were dermatological in nature.

B. Labeling Comments:

1. The labeling as we proposed for NDA 20-524 is unclear regarding the sampling time in tinea pedis patients (Paragraph 2, Line 3). Please revise as follows:

   ... a single blood sample was collected between 10 and 20 hours following dosing at 1, 2 and 4 weeks after treatment. The plasma butenafine HCl concentration ranged from undetectable to 0.3 ng/mL.

2. The PK information in tinea cruris patients should be added to the labeling.

   In 24 patients with tinea cruris, Mentax™ Cream 1% was applied by the patients to cover the affected and immediately surrounding skin area once daily for 2 weeks. The resultant mean average daily dose was 1.3±0.2 g. A single blood sample was collected between 0.5 and 65 hours after last dose and the plasma butenafine HCl concentration ranged from undetectable to 2.52 ng/mL (mean±SD: 0.91±0.15 ng/mL).

VI. RECOMMENDATION:

From the biopharmaceutics standpoint, the application is acceptable. Please convey all Labeling Comments to the sponsor.

10/29/96

Sue-Chih Lee, Ph.D.
Division of Pharmaceutical Evaluation III

RD Initialed by Dennis Bashaw, Pharm.D. 10/30/96
FT Initialed by Dennis Bashaw, Pharm.D. 10/31/96

CC:
NDA 20-524
HFD-540 (2 copies)
✓HFD-880 (Division File)
HFD-880 (TL - Bashaw)
✓HFD-880 (Reviewer - Lee)
HFD-340 (Viswanathan)
✓Drug File (Clarence Bott, HFD-870, Pkln 13B31)

APPENDIX 1

Penederm Clinical Study PDC 010-005:

A MULTICENTER, DOUBLE-BLIND STUDY TO EVALUATE BUTENAFINE HCL 1% CREAM AND VEHICLE IN THE TREATMENT OF TINEA CRURIS

INVESTIGATOR AND LOCATION:

OBJECTIVES:
The objective of this Phase III study was to determine the efficacy of the cream when compared to the vehicle in tinea cruris patients. 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 two specific sites.

FORMULATION: PD-010-C-003 (To-be-marketed formulation)

STUDY DESIGN:
The clinical trial included six centers totaling 93 patients. Butenafine HCl cream 1% was applied by the patient once daily for 2 weeks. Out of the 76 evaluable patients, 37 patients (age: 18-64 yrs.) received the drug. Plasma samples were obtained from all patients participating at Sites

Sample Collection - Blood samples were obtained before the initiation of treatment (baseline) and on Day 14 (end of treatment) and Day 42 (4 weeks post-treatment) visits.

ASSAY:
Plasma samples from 12 butenafine-treated patients were analyzed for the presence of butenafine and M2 metabolite using a LC/MS/MS method with a quantitation limit of 0.1 ng/mL.

RESULTS:
Only plasma samples from patients receiving the drug were analyzed which resulted in plasma concentration data from 24 patients. The individual data are given in Tables 1 and 2.

The average daily dose for each individual patient ranged from 0.34 to 4.13 g (mean$\pm$SD: 1.3$\pm$0.2 g). No patients had measurable plasma concentrations of butenafine or M2 before treatment. On Day 14, the mean plasma concentration was 0.91$\pm$0.15 ng/mL for butenafine (range: ng/mL) and ng/mL for M2 with less then half of the patients having measurable levels of the latter. Of the 17 patients who had plasma samples analyzed at

the Day 42 time point, five patients had measurable plasma butenafine concentrations ranging from ng/mL and no patients had detectable M2.

Comments (not to be sent to the sponsor):

1. The highest average daily dose was 4.1 g (Patient in the PK study subset of patients. The highest plasma butenafine concentration observed on Day 14 (2.52 ng/mL) came from a patient with an average daily dose of 2.3 g.

2. The sampling time for each individual patient on Day 14 varied from 0.45 to 65.15 hours after last dose with 8 patients having sampling time greater than 24 hours. This variation as well as the variation in the dose (both the average daily dose and the actual last dose) could affect the observed plasma concentrations. A linear regression analysis indicated a statistically significant effect of the average daily dose but not of the sampling time. (Note: This does not prove that the sampling time is not a factor in the observed plasma concentrations.)

   The sponsor did not provide a demographic table specifically for the patients participating in the PK arm of the study. Weight, age and the diseased skin condition could also affect the observed plasma drug concentration.

3. The study protocol did not exclude female patients but only one female patient was enrolled in this clinical trial due to the nature of the disease being almost exclusively a male dermatophytosis in the United States.

TABLE 8

PDC 010-005

Plasma Levels of KP-363 (Butenafine) and M2 (ng/ml)

Patient No.	Average Daily Dose (g)	Baseline		Day 14		Day 42	
		KP-363	M2	KP-363	M2	KP-363	M2
	1.07						
	2.9						
	1.94						
	0.95						
	0.37						
	3.05						
	0.79						
	0.75						
	2.29						
	4.13						
	1.38						
	0.74						
	0.84						
	0.66						
	0.34						
	1.02						
	0.51						
	1.73						
	0.92						
	1.95						
	1.25						
	0.5						
	1.47						
	0.47						
Mean	1.3	0.0	0.0	0.91	0.07	0.07	0.0
SEM	0.20	0.0	0.0	0.151	0.021	0.03	0.0

N.D. = No data for that patient at that time point

A value of "0" was assigned if level was below limit of quantitation (0.1 ng/ml)

2A

TABLE ~~9.A~~

PDC 010-005 - CLINICAL SITE #51

PLASMA LEVELS (ng/ml) OF BUTENAFINE (KP-363) AND M-2

Patient No.	BASELINE VISIT				DAY 14 VISIT					DAY 42 VISIT (Four Weeks Post-Treatment)			
	Date	Time	KP-363	M-2	Date	Time	HSLD	KP-363	M-2	Date	Time	KP-363	M-2
					9/1/94		42.0	1.13	0.12	10/4/94		0.00	0.0
	8/25/94		0.0	0.0	9/8/94		3.1	0.84	0.0	10/7/94		0.27	0.0
	12/9/94		0.0	0.0	12/23/94		2.25	2.32	0.22				
					4/25/95		1.45	1.66	0.32	5/23/95		0.24	0.0
	5/3/95		0.0	0.0	5/17/95		1.15	0.31	0.0	6/14/95		0:00	0.0
	5/24/95		0.0	0.0	6/14/95		11.10	2.48	0.29	7/19/95		0.00	0.0
	6/2/95		0.0	0.0									
	7/5/95		0.0	0.0	7/21/95		12.05	0.37	0.0	8/16/95		0.0	0.0
	7/5/95		0.0	0.0									
	7/24/95		0.0	0.0	8/7/95		2.0	1.20	0.0				
	7/27/95		0.0	0.0	8/10/95		11.00	2.52	0.18	9/7/95		0.22	0.0
	7/28/95		0.0	0.0	8/14/95		4.00	1.93	0.23				

KEY

HSLD = Hours Since Last Dose

☐ Data unavailable

A value of "0" was assigned if level was below limit of quantitation (0.1 ng/ml).

2B

TABLE ~~9.B~~

PDC 010-005 - CLINICAL SITE #53

PLASMA LEVELS (ng/ml) OF BUTENAFINE (KP-363) AND M2

Patient No.	BASELINE VISIT				DAY 14 VISIT					DAY 42 VISIT (Four Weeks Post-Treatment)			
	Date	Time	KP-363	M-2	Date	Time	HSLD	KP-363	M-2	Date	Time	KP-363	M-2
	9/1/94		0.0	0.0	9/15/94		34.30	0.81	0.11	10/11/94		0.0	0.0
	9/1/94		0.0	0.0	9/16/94		48.15	0.0	0.0	10/14/94		0.0	0.0
	9/15/94		0.0	0.0	9/28/94		6.15	0.59	0.0				
	9/27/94		0.0	0.0	10/11/94		12.75	0.29	0.0	11/8/94		0.0	0.0
	10/6/94		0.0	0.0	10/20/94		3.15	0.34	0.0	11/17/94		0.0	0.0
	10/7/94		0.0	0.0	10/20/94		5.30	0.76	0.10				
	10/7/94		0.0	0.0	10/20/94		4.40	0.44	0.0	11/16/94		0.0	0.0
	10/13/94		0.0	0.0	10/28/94		53.30	0.20	0.0				
	10/27/94		0.0	0.0	11/10/94		29.45	0.56	0.0	11/29/94		0.0	0.0
	11/1/94		0.0	0.0	11/17/94		65.15	0.72	0.0	12/14/94		0.15	0.0
	11/3/94		0.0	0.0	11/17/94		30.45	0.96	0.0	12/14/94		0.0	0.0
	11/9/94		0.0	0.0	11/22/94		5.0	0.52	0.0	12/19/94		0.0	0.0
	6/16/95		0.0	0.0	6/29/95		0.45	0.68	0.0	7/26/95		0.28	0.0
	6/28/95		0.0	0.0	7/12/95		28.30	0.25	0.0				

KEY

HSLD = Hours Since Last Dose

☐ Data unavailable

A value of "0" was assigned if level was below limit of quantitation (0.1 ng/ml).

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 020663

PHARMACOLOGY REVIEW

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

NDA 20-663 (Original submission 01-05-1996)

DRUG: Butenafine Hydrochloride, Cream 1%

SPONSOR: Penderm Incorporated
Lakeside Drive, Suite A
Foster City, CA 94404
Barry Calvarese: 415-358-0100

Number of Volumes: Two (2)
Date CDER Received: 01-11-1996
Date Assigned: 01-18-1996
Date Review Started: 09-10-1996
Date Review Completed: 09-13-1996

Dosage and Route of Administration: Cream, topical
Category: Antifungal
Indication: For the treatment of Tinea Corporis and Tinea Cruris

Comments: Butenafine Hydrochloride, Cream 1% was approved for the treatment of *Tinea pedis* under NDA 20-524 on April 3, 1996. In the current NDA, the sponsor has proposed to use the same formulation for the treatment of *Tinea Corporis* and *Tinea Cruris*, and has cross-referred all the non-clinical studies to NDA 20-524. Since the dosing regimen and duration of treatment for the additional indications are identical to the treatment of *Tinea pedis*, no new animal studies are required to further support the safety of Butenfine hydrochloride. Similarly, the non-clinical portion of the label should remain identical to that approved for NDA 20-524.

Regulatory Conclusion: I have no objection to the approval of this new drug application.

Kumar D. Mainigi, Ph.D., M.P.H., DABT
Toxicologist

CC: Original NDA 20-663
HFD-82
HFD-540
MO / O'Connell
Pharm / Mainigi
Chem / Pappas
Micro-HFD-520 / Dionne
CSO / Cross
Pharm / Jacobs

Concurrence:
A. Jacobs, TL, HFD-540 9/13/96
J.Wilkin, Dir, HFD-540 9/17/96

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 020663

STATISTICAL REVIEW

DEC 9 1996

Statistical Review and Evaluation

NDA/ Drug Class:	20-663 / 6S
Name of Drug:	Butenafine Hydrochloride Cream, 1%.
Applicant:	Penederm, Inc. 320 Lakeside Drive, Suite A Foster City, CA 94404
Type of Report:	Clinical/Statistical
Indication:	Tinea Corporis and Tinea Cruris
Documents Reviewed:	Volumes 1.1, 1.19 through 1.28 (Statistical Data) and diskettes containing SAS data sets from the sponsor
Medical Officer:	Dr. K. O'Connell (HFD-540)

Introduction

According to the sponsor "Butenafine HCl Cream 1% was originally developed in Japan by and subsequently licensed by the Sponsor . . . The product tested outside the United States is very closely related to the proposed new drug formulation. It differs only by the presence of an additional preservative, 0.5% benzyl alcohol, in the new drug formulation."

"The clinical efficacy and safety of Butenafine HCl Cream 1% was evaluated in six Japanese, one European, and nine U.S. studies. Two of the Japanese and five of the U.S. clinical studies were dermal safety studies conducted in normal volunteers. One European and four Japanese efficacy studies were conducted in patients with dermatomycosis. Of these patients, 443 were diagnosed with tinea pedis, with the remaining patients distributed among tinea corporis, tinea cruris, tinea versicolor, and cutaneous candidiasis infections."

Earlier the sponsor provided the results of two vehicle controlled studies comparing Butenafine Hydrochloride Cream with vehicle in the treatment of tinea pedis. Apparently those studies were very similar to those reviewed here. Defining "effective treatment" as in the Methods section below, at the end of treatment (week 4) 57% (out of 93) patients scored with "effective treatment" in the Butenafine 1% treatment group versus 27% (out of 92) in the vehicle group. At the end of week, after a four-week follow-up period without treatment, 69% in the Butenafine 1% treatment group and 24% in the vehicle group had "effective treatment." Apparently patient symptoms continued to improve up to four weeks after treatment was discontinued.

Methods

The sponsor conducted two pivotal studies in the U.S. to provide evidence of the effectiveness and safety of Butenafine HCl Cream 1% in the treatment of tinea corporis and tinea cruris. The review of these studies is the objective of this report.

The designs used in the studies are summarized in the following table:

Table 1. Phase III Clinical Studies
Tinea Corporis/Tinea Cruris

Protocol no	design	objective	duration of study	No. enrolled*
PDC 010-004	multicenter, double blind, randomized, parallel-group	safety/efficacy vs vehicle once daily for treatment of tinea corporis	2-week treatment with a 4 week untreated follow-up	B 1% 47 V 44
PDC 010-005		safety/efficacy vs vehicle once daily for treatment of tinea cruris	2-week treatment with a 4 week untreated follow-up	B 1% 47 V 46

*B=Butenafine HCl Cream 1%, V=vehicle.

For the studies, protocols were virtually identical. Patient visits were recorded at baseline, the end of the first week (approximately day 7), the end of the treatment (roughly day 14), plus at the end of the sixth week (nominally day 42). A number of endpoints were available:

For both studies, at baseline, and at days 7, 14 (end of treatment), and at day 42, there was a KOH examination for hyphae and a fungal culture. In addition, the following **signs and symptoms** were evaluated at both the target lesion site and as well as an overall assessment of the disease (excluding the target area):

Erythema	Maceration
Scaling	Papules
Pruritus	Vesiculation

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

0 = absent (none)
1 = mild (barely perceptible)
2 = moderate (distinctive presence)
3 = severe (marked, intense)

In addition to the individual signs and symptoms scores, for both the target lesion and the overall disease, **total signs and symptoms scores** were computed by summing the respective target lesion scores. However, for a number of subjects the sole site of

infection was the target lesion. Thus their disease signs and symptoms, excluding baseline, were not defined. Hence the target lesion total signs and symptoms score is considered to be of more relevance than the disease sign and symptoms score.

At days 7, 14 (end of treatment) and 42 (end of study) the **Investigator Global Response** of the tinea corporis/cruris condition was evaluated using the following 7-point scale:

Cleared	100% remission of clinical signs and symptoms compared to baseline.
Excellent	90-99% remission of clinical signs and symptoms compared to baseline.
Good	50-89% remission of clinical signs and symptoms compared to baseline.
Fair	25-49% remission of clinical signs and symptoms compared to baseline.
Poor	<25% remission 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.

The primary efficacy variables were defined by the sponsor as below:

Mycological Cure: Negative KOH and negative Culture

Effective Treatment: Mycological cure and a score of "excellent" or "cleared" on the investigator global response above.

Overall Cure: Mycological cure and a score of "cleared" on the investigator global response.

The **Patient Perception of Treatment Response** was the answer to the question "How does your tinea cruris/corporis condition appear to you now versus when you began the study," graded using the following 5 point scale:

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

In the sponsor's report the primary efficacy endpoints above were to be evaluated at day 42 (four weeks post-treatment). The secondary efficacy tables were defined by the sponsor as the patient perception of treatment response as well as the total signs and symptoms scores, apparently also evaluated at day 42.

The Medical Officer proposed using the overall cure, the investigator global response, the patient perception of response, and the total signs and symptoms scores as primary endpoints, with particular emphasis upon the overall cure. The Medical Officer was also interested in the association of the global response with the total signs and symptoms scores as evidence of the validity of each.

The tables in this report are based on a modified intent-to-treat (MITT) population, using the proposed Division IV definition. Thus these tables are based on every subject who was dispensed a study treatment who additionally had a baseline positive dermatophyte mycology (i.e. both KOH and culture). These tables differ from the tables based on the sponsor's MITT definition for two reasons:

i)The sponsor's definition of MITT deleted cases who had no post-baseline visits, plus, in the PDC 010-005 study, one extreme protocol violator. Thus the sponsor's definition of MITT differed considerably from that used by Division IV.

ii)The sponsor reported all tables at the 14th day of treatment using a last observation carried forward technology, where any case missing the value of some variable at 14th day of treatment has that value imputed from the corresponding day 7 measurement.

Recall that only the signs and symptoms scores were available at baseline. Hence most in this report tables begin with the first measurement at day 7, followed by day 14, and finally at the end of treatment, at nominal day 42. In addition an LOCF (last observation carried forward) entry was tabulated for the end of treatment. That is, for each case, if the day 14 is unavailable for some reason, the day 7 is carried forward. If the day 7 value is unavailable the baseline (day one) value is carried forward. Presumably, at least within treatment, such LOCF assessments are conservative. To this reviewer the LOCF assessments, plus the day 42 entries, seem to be reasonable endpoints for each variable. The LOCF endpoints correspond to the last known day under treatment, while the nominal 42 day measurements are roughly 4 weeks post-treatment.

Results:

I. Tinea Corporis - Study PDC 010-004:

1. Patient Demographics:

The objective of this study was to evaluate the safety, efficacy and duration of therapeutic effect of Butenafine Hydrochloride 1% Cream versus vehicle gel applied once daily in the treatment of tinea corporis (a.k.a. ringworm).

The following table summarizes the demographics of the subjects.

Table 2. Patient Demographics

		Butenafine HCL 1% Cream	Vehicle
Mean (Std. Dev.)			
Age		40.5 (15.0)	40.4 (15.8)
Area of target lesion		4.5 (8.9)	5.6 (11.9)
Sex	M	20	19
	F	22	19
Race	White	25	22
	Hispanic	11	8
	Black	5	8
	Asiatic	1	0
Total patient no		42	38

As indicated by an ANOVA (not displayed) with investigator, treatment group, and interactions as factors, there were no statistically significant differences in age or baseline area of the target lesion across treatment groups or interaction contrasts. So it seems reasonable to ignore the apparent active treatment group advantage in size of lesions. There were significant differences across investigators. Further loglinear models with gender, treatment group, and investigator showed no statistically significant interactions. In particular, there is no evidence to reject the hypothesis that gender is homogeneous over treatment. Similarly, when race was dichotomized into "white" and "non-white", again there is no evidence to reject the hypothesis that race was homogeneous over treatment. Note that a very detailed flow chart of patient disposition appears as Figure A. in their report.

2. Efficacy Assessments

The following tables display the overall cure as well as the sponsor defined effective treatment, the global response, the total signs and symptoms scores, and the patient assessment of treatment response. The Cochrane-Mantel-Haenszel (CMH) p-value is the a p-value of a test of treatment mean differences over investigators using integer (trend) scores.

Statistical Note:
This reviewer has a mild preference for such scores over alternative scores, such as ranks or ridits as used by the sponsor. However, the statistical tests should not be too sensitive to the choice of such scores.

From the following table 3, note that both overall cure and effective treatment are statistically significant by week 14 for overall cure, and week 7 for effective treatment ($p \leq .001$).

Table 3. Overall Cure and Effective Treatment

Nominal Day	7		14		locf		42	
	Active	Vehicle	Active	Vehicle	Active	Vehicle	Active	Vehicle
Overall Cure:								
Cure	1	.	13	1	13	1	28	5
	2%		33%	3%	31%	3%	70%	18%
Fail	41	35	26	33	29	35	12	23
	98%	100%	67%	97%	69%	97%	30%	82%
CMH p-value	.338		.001		.001		.001	
Sponsor Defined Effective Treatment:								
Cure	14	.	23	6	25	6	32	5
	33%		59%	18%	60%	17%	80%	18%
Fail	28	35	16	28	17	30	8	23
	67%	100%	41%	82%	40%	83%	20%	82%
CMH p-value	.001		.001		.001		.001	

So, again, by the end of treatment (day 14) the butenafine group is statistically significantly better than the vehicle group with respect to both "overall cure" and "effective treatment." For the variable "effective treatment," by the end of the first week of treatment the butenafine group is statistically significantly better than the vehicle group. These discrepancies seem to generally increase over time, even up to six weeks after the conclusion of treatment.

Note that the investigator's global assessment of the disease response was a component of each of the scores above. These assessments are tabulated below:

Table 4. Investigator Global Response (of target lesion)

Investigator Global Response	7		14		locf		42	
	Active	Vehicle	Active	Vehicle	Active	Vehicle	Active	Vehicle
Cleared	1 2%	.	13 33%	1 3%	13 31%	1 3%	30 75%	6 21%
Excellent	16 38%	2 6%	12 31%	8 24%	14 33%	8 22%	4 10%	1 4%
Good	12 29%	7 20%	9 23%	5 15%	9 21%	5 14%	1 3%	3 11%
Fair	8 19%	4 11%	2 5%	6 18%	3 7%	6 17%	1 3%	3 11%
Poor	3 7%	11 31%	1 3%	7 21%	1 2%	7 19%	3 8%	4 14%
Unchanged	2 5%	7 20%	2 5%	4 12%	2 5%	4 11%	1 3%	6 21%
Worse	.	4 11%	.	3 9%	.	5 14%	.	5 18%
CMH p-value	.001		.001		.001		.001	

Again, even by the seventh day of treatment the butenafine group is statistically significantly better than the vehicle group with respect to the global evaluation of the response to the disease. As before, the discrepancy increases over time, even up to six weeks after the conclusion of treatment.

The total sum of the signs and symptoms scores was compared using an ANOVA with factors for treatment, investigator, and interaction. An ANCOVA with the area of the target lesion was also performed, but results differ little from those summarized here. Note that the Medical Officer expressed some interest in the individual scores. These are displayed in table 18 and 19 of the appendix.

From table 5 below, one can see that both sums show statistically significant differences between treatment groups, with the difference in sum of the target lesion signs and symptoms between Butenafine and vehicle particularly increasing over the course of experiment. The second variable is the sum of signs and symptoms excepting the target lesion. Since a substantial number of patients had no involvement except at the target lesion this variable was ignored by the sponsor. This reviewer agrees with this point and suggests that this variable is of less importance. Still, for completeness, it is included.

Table 5. Sums of Signs and Symptoms Scores (of target lesion and excepting target lesion)

Nominal Day		Baseline		7		14		locf		42	
		Active	Vehicle	Active	Vehicle	Active	Vehicle	Active	Vehicle	Active	Vehicle
Sum of Target Lesion Signs & Symptoms	n	42	38	42	35	39	34	42	38	40	28
	Mean	8.4	8.3	3.1	6.0	1.5	4.8	1.6	5.1	0.8	4.7
	Std Dev	1.8	1.7	2.1	2.5	1.9	3.4	2.0	3.4	1.6	3.4
	P-value*	0.7777		0.0011		0.0022		0.0004		0.0001	
Sum of Other Disease Signs & Symptoms	n	34	32	34	29	32	28	34	32	32	26
	Mean	4.4	3.5	1.4	3.1	0.5	2.4	0.5	2.3	0.6	2.4
	Std Dev	4.0	4.1	1.5	3.3	0.9	3.1	0.9	3.1	1.8	3.3
	P-value*	0.8367		0.033		0.0187		0.0197		0.0403	

* From p-value of F-test for treatment in an ANOVA with factors for investigator, treatment, and interaction.

Finally the patient was requested to evaluate their own improvement in their tinea corporis. This was the response to the question "How does your tinea corporis condition appear to you now versus when you began the study?"

Table 6. Patient Perception of Improvement in Tinea Corporis

Patient Perception of Response	7		14		locf		42	
	Active	Vehicle	Active	Vehicle	Active	Vehicle	Active	Vehicle
Greatly improved	27 (64%)	6 (17%)	33 (85%)	10 (29%)	34 (81%)	10 (28%)	35 (88%)	8 (29%)
Somewhat improved	12 (29%)	16 (46%)	4 (10%)	16 (47%)	6 (14%)	17 (47%)	4 (10%)	5 (18%)
No change	3 (7%)	6 (17%)	2 (5%)	4 (12%)	2 (5%)	4 (11%)	1 (3%)	7 (25%)
Somewhat worse	.	6 (17%)	.	3 (9%)	.	3 (8%)	.	6 (21%)
Much worse	.	1 (3%)	.	1 (3%)	.	2 (6%)	.	2 (7%)
CMH P-value	0.001		0.001		0.001		0.001	

Again by the seventh day of treatment the butenafine group is statistically significantly better than the vehicle group with respect to both overall cure and "effective treatment". The discrepancy increases over time, even up to six weeks after the conclusion of treatment.

3. Validity of Scales::

The Medical Officer expressed interest in assessing the validity of some of the scales used in the analysis. Validity refers to the notion that a measurement actually measures the criterion that it proposes to measure. Operationally this usually justified by the concepts of either criterion or construct validity of an instrument, computed by assessing the association, usually correlation, of the instrument to some specified criterion variable, or among some set of objects associated with the criterion to be measured, respectively. For either definition the correlations lead to several sets of recommendations for specifying "validity" . One simple rule of thumb seems to be there is evidence for strong association if the absolute value of the correlation is greater than .5 (or .4) among the objects and instruments. A more strict notion of validity involves the notion that instruments should be proportional to the same "true" quantity, incorporating the concept of reliability. At least roughly, this is also sometimes addressed with simple correlations. Alternatively one must pose and estimate measurement error models. Note that if one assumes a simple model where each response is a sum of some scale times the "true" score plus error, then the maximum observed correlation between responses is a lower bound to validity. Again, using the correlations as a simple descriptive, one (of many differing) rules of thumb for such a measure of validity is that an instrument is valid, perhaps weakly valid, if the correlation of the instrument with the target criterion or among the other objects is ,7 or more. The validity is strong if this correlation is .8 or more, and superb if the correlation is .9 or more.

The following are the pooled within investigator correlations of the investigator's global assessment of the disease condition compared to baseline (labeled global), the patient's perception of improvement (labeled patient), and the two sums of signs and symptoms scores (labeled target or disease). The pooled within investigator correlation should adjust for differences in mean due to different investigators. However, treatment differences in mean treatment within investigators is forced to essentially zero. This probably will attenuate correlation, though hopefully only slightly. So, to some extent, this correlation will be an underestimate of validity. The Medical Officer expressed the opinion that once measure of validity would be the association of the global score with the target signs and symptoms total score. This would be naturally defined as "criterion-referenced validity" as noted above. Alternatively we could consider the correlation of the global score with the other three indicators of treatment success. . Note that correlations are provided for the different points in time.

Table 7. Validity of Endpoints

	Day=7			Day=14			LOCF			Day=42		
	global	patient	target S&S	global	patient	target S&S	global	patient	target S&S	global	patient	target S&S
global												
patient	-.73			-.76			-.76			-.90		
target S&S	.86	-.69		.93	-.79		.92	-.81		.94	-.87	
disease S&S	.43	-.35	.41	.60	-.61	.59	.58	-.47	.50	.75	-.60	.68

In general, all endpoints are associated. Note that the numeric order of responses to the patient's perception of response is inversely related to the order of the other questions. That is, for the other questions small values suggest less impact of the disease, while for the patient perception of response large values are associated with less disease impact.

Correlations between endpoints generally become larger as time increases. This seems to be largely due to a reduction in variance due to the large proportion of patients showing general alleviation of symptoms. This reduces variance, and increases correlation. But, without using measurement theory models, it does appear that the global score has generally high criterion related validity for estimating that feature described by the target sum of signs and symptoms (i.e. correlations are .86, .93, .92, and .94). The patient score has somewhat less, but still somewhat respectable, validity for the same feature. Although the disease sum of signs and symptoms appears to be associated with the other variables it does seem to be measuring something slightly different.

The final conclusion to the question posed by the Medical Officer is that the investigator global evaluation of disease compared to baseline does appear to be a valid measurement.

4. Subset Analysis

The following table summarizes the analysis for each response variable, at each end point. When the test statistic is statistically significant, in favor of the Butenafine HCl Cream at the 0.10 level (This was chosen instead of the more usual 0.05 level, to "correct" for the reduced sample size and limited discrimination due to the binary response coding. However, the choice of level is largely a matter of taste), a '+' is coded; when not statistically significant in favor of the test drug a '-' is coded. When the test statistic is undefined, as happens with some configurations of the data, an 'N' is coded. The first four variables indicate the statistical significance of the associated CMH tests, the last two, the associated ANOVA tests. A more detailed breakdown of effective treatment and overall cure appears in the appendix, in tables 22 and 23. More detailed tables for the other variables were not included, primarily due to limitations of space.

Table 8. Summary of Subset Analysis

	Overall Cure Day				Effective Treatment Day				Investigator Global Day				Patient Perception Day			
	7	14	LOCF	42	7	14	LOCF	42	7	14	LOCF	42	7	14	LOCF	42
Age 13-24	N	-	-	-	-	-	-	-	+	+	+	-	-	+	+	N
25-45	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
46+	N	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+
Sex Female	N	-	-	+	+	-	-	+	+	+	+	+	+	+	+	+
Male	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Race Caucasian	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Other	N	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+

	Target Lesion Signs and Symptoms Day					Disease Signs and Symptoms Day				
	Baseline	7	14	LOCF	42	Baseline	7	14	LOCF	42
Age 13-24	-	+	+	+	+	-	+	+	+	N
25-45	-	+	+	+	+	+	-	-	-	-
46+	-	+	+	+	+	-	+	+	-	+
Sex Female	-	-	+	+	+	-	-	-	-	-
Male	-	+	+	+	+	-	+	+	-	+
Race Caucasian	-	+	+	+	+	-	+	+	+	-
Other	-	+	+	+	+	-	-	-	-	+

- denotes not statistically significant, i.e. p>.10
+ denotes statistically significant, i.e. p≤.10
N denotes statistic not defined, or too few degrees of freedom

Except at baseline virtually all means favor Butenafine over vehicle. Generally, the results within each subgroup are statistically consistent with the overall results presented in tables 3-6 above.

II. Tinea Cruris - Study PDC 010-005:

1. Patient Demographics:

The following table summarizes the demographics of the subjects.

Table 9. Demographics

		Butenafine HCL 1% Cream	Vehicle
Mean (Std. Dev.)			
Age		34.5 (13.3)	37.2 (14.6)
Area of target lesion		5.4 (4.5)	5.9 (5.9)
Sex	M	39	39
	F	0	1
Race	White	36	40
	Hispanic	1	0
	Black	1	0
	Asiatic	1	0
Total patient no.		39	40

Note that virtually all patients are Caucasian and male. As indicated by an ANOVA with investigator, treatment group, and interactions as factors (not displayed), there were no statistically significant differences in age or baseline area of target lesion across treatment groups or interaction terms. There were significant differences across investigators. There were insufficient females and insufficient numbers of non-Caucasian patients to make any subgroup comparisons for these groups.

The following tables display the overall cure as well as the sponsor defined effective treatment, the global response, the total signs and symptoms scores, and the patient assessment of treatment response. The CMH p-value is the a p-value of a test of treatment mean differences over investigators using integer (trend) scores.

Table 10. Overall Cure and Effective Treatment

Nominal Day	7		14		locf		42	
	Active	Vehicle	Active	Vehicle	Active	Vehicle	Active	Vehicle
Overall Cure:								
Cure	4	1	12	3	12	3	23	1
	11%	3%	33%	9%	32%	8%	72%	4%
Fail	32	38	24	31	26	37	9	27
	89%	97%	67%	91%	68%	93%	28%	96%
CMH p-value	.079		.004		.004		.001	

Table 10.(cont.) Overall Cure and Effective Treatment

Sponsor Defined Effective Treatment								
Cure	10	2	21	3	21	3	27	2
	28%	5%	58%	9%	57%	8%	84%	7%
Fail	26	37	15	32	16	36	5	26
	72%	95%	42%	91%	43%	92%	16%	93%
CMH p-value	.006		.001		.001		.001	

Note that even by the end of treatment (day 14) the butenafine group is statistically significantly better than the vehicle group with respect to both overall cure and "effective treatment". Strictly speaking the 0.079 p-value for overall cure at day 7 is not below the often chosen .05 level. But it is close to statistical significance. As in the previous study, this statistical significance increases over time, even up to six weeks after the conclusion of treatment.

Recall that the investigator's assessment of the tinea cruris response was a component of each of the scores above. These assessments are tabulated below:

Table 11. Investigator Global Response

Investigator Global Response	7		14		locf		42	
	Active	Vehicle	Active	Vehicle	Active	Vehicle	Active	Vehicle
Cleared	5	1	15	3	14	3	23	3
	14%	3%	42%	9%	38%	8%	72%	11%
Excellent	7	1	9	3	9	3	5	4
	19%	3%	25%	9%	24%	8%	16%	14%
Good	12	14	4	8	6	9	.	4
	33%	36%	11%	23%	16%	23%		14%
Fair	9	11	3	9	3	10	3	1
	25%	28%	8%	26%	8%	26%	9%	4%
Poor	2	4	3	3	3	3	.	6
	6%	10%	8%	9%	8%	8%		21%
Unchanged	.	5	1	5	1	5	.	5
		13%	3%	14%	3%	13%		18%
Worse	1	3	1	4	1	6	1	5
	3%	8%	3%	11%	3%	15%	3%	18%
CMH p-value	.001		.001		.001		.001	

Again, even by the seventh day of treatment the butenafine group is statistically significantly better than the vehicle group with respect to the global evaluation of the response to treatment. As before, the discrepancy increases over time, even up to six weeks after the conclusion of treatment.

The total sum of the signs and symptoms scores was compared using an ANOVA with factors for treatment, investigator, and interaction. An ANCOVA with the area of the target lesion was also performed, but results differ little from those summarized here. Note again that the Medical Officer expressed some interest in the individual scores. These are displayed in table 20 and 21 of the appendix.

Table 12. Sums of Signs and Symptoms Scores

Nominal Day		Baseline		7		14		locf		42	
		Active	Vehicle	Active	Vehicle	Active	Vehicle	Active	Vehicle	Active	Vehicle
Mean of Target Lesion Signs & Symptoms	n	39	40	36	39	36	35	38	40	32	28
	Mean	7.9	8.1	3.4	5.2	2.3	5.0	2.5	5.4	1.1	5.3
	Std Dev	1.8	1.8	2.6	2.9	3.0	3.1	3.1	3.3	2.7	3.6
	P-value*	0.8706		0.0901		0.0344		0.0323		0.0039	
Mean of Other Disease Signs & Symptoms	n	39	40	36	39	36	35	38	40	32	28
	Mean	6.4	6.5	2.7	4.8	1.8	4.3	2.0	4.5	0.9	4.3
	Std Dev	3.0	3.0	2.6	3.4	2.5	3.6	2.7	3.6	2.3	3.9
	P-value*	0.3494		0.048		0.0656		0.0602		0.0123	

* From p-value of F-test for treatment in an ANOVA with factors for investigator, treatment, and interaction.

Finally the patient was requested to evaluate their own improvement in their tinea cruris, as in table 13 below:

Table 13. Patient Perception of Improvement in Tinea Corporis

Patient Perception of Response	7		14		locf		42	
	Active	Vehicle	Active	Vehicle	Active	Vehicle	Active	Vehicle
Greatly improved	15 41%	7 18%	25 69%	9 26%	25 68%	9 23%	27 84%	8 29%
Somewhat improved	18 49%	18 46%	5 14%	16 46%	6 16%	17 44%	1 3%	8 29%
No change	4 11%	10 26%	6 17%	6 17%	6 16%	6 15%	3 9%	6 21%
Somewhat worse	.	3 8%	.	4 11%	.	6 15%	1 3%	5 18%
Much worse	.	1 3%	.	.	.	1 3%	.	1 4%
P-value	0.004		0.001		0.001		0.001	

Again by the seventh day of treatment the butenafine group is statistically significantly better than the vehicle group with respect to the patient's perception of their disease condition compared to baseline. The discrepancy increases over time, even up to six weeks after the conclusion of treatment.

3. Validity of Scales:

As note before, the Medical Officer expressed interest in assessing the validity of some of the scales used in the analysis. The following are the pooled within investigator correlations of the investigator's global assessment compared to baseline (labeled global), the patient's perception of improvement (labeled patient), and the two sums of signs and symptoms scores (labeled target or disease). Again, these may be biased to underestimate validity.

Table 14. Validity of Endpoints

	Day=7			Day=14			LOCF			Day=42		
	global	patient	target S&S	global	patient	target S&S	global	patient	target S&S	global	patient	target S&S
global												
patient	-.72			-.78			-.77			-.88		
target S&S	.86	-.69		.91	-.78		.91	-.77		.96	-.89	
disease S&S	.79	-.61	.92	.86	-.71	.86	.86	-.72	.86	.75	-.84	.92

In general, all endpoints are associated. Observe that the correlations between endpoints generally become larger as time increases. As before, the global response seems to be reasonably valid for what is estimated by the target signs and symptoms score, and vice versa. Similarly, the disease signs and symptoms score and the patient evaluation of response seemed to be strongly associated, with both somewhat less strongly associated with the global evaluation and the target lesion sum score.

The final conclusion to the question posed by the Medical Officer is that the investigator global evaluation of condition relative to baseline does appear to be a valid measurement. In this study, the patient response seems to be roughly equally valid for the disease signs and symptoms.

4. Subset Analysis

The following table summarizes the analysis for each response variable, at each end point. When the test statistic is statistically significant, in favor of the Butenafine HCl Cream at the .10 level a '+' is coded; when not statistically significant in favor of the test drug a '-' is coded. When the test statistic is undefined an 'N' is coded. The first four variables indicate the coded ('+' or '-') significance levels of CMH tests. The two signs and symptoms scores indicate coded p-values of ANOVA tests. Note that only one female was included in the trial, and all patients except three were Caucasian, and these three all received the active treatment. Hence subgroup analysis for race and gender was not performed. As before, a more detailed breakdown of effective treatment and overall cure appears in the appendix, in table 24 and 25.

Table 15. Summary of Subset Analysis

	Overall Cure Day				Effective Treatment Day				Investigator Global Day				Patient Perception Day			
	7	14	LOCF	42	7	14	LOCF	42	7	14	LOCF	42	7	14	LOCF	42
Age 13-24	N	N	N	+	N	-	-	+	-	-	-	+	-	-	-	+
25-45	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
46+	-	-	-	+	+	+	+	+	+	-	-	+	+	+	+	+

	Target Lesion Signs and Symptoms Day					Disease Signs and Symptoms Day				
	Baseline	7	14	LOCF	42	Baseline	7	14	LOCF	42
Age 13-24	N	N	N	N	N	N	N	N	N	N
25-45	-	+	+	+	+	-	+	+	+	+
46+	-	-	+	+	+	-	+	-	+	+

- denotes not statistically significant, i.e. p>.10
+ denotes statistically significant, i.e. p≤.10
N denotes statistic not defined or too few degrees of freedom

Except at baseline, virtually all means favor Butenafine over vehicle. As before, the results within each subgroup are statistically consistent with the overall results presented in tables 10-13 above.

Safety Data

A. Adverse Events

Tables 16 and 17 below summarize the adverse events identified by the sponsor in the two trials. Note that it evident that none of these counts would show statistically significant differences across treatments.

Table 16. Adverse Events
Study PDC 010-004

Body System	Adverse Event Description	# individuals Treatment Active	Vehicle	# events Treatment Active	Vehicle
Body	Common Cold	.	1	.	1
	Cut on arm with electrical wire	.	1	.	1
Man.	Hyperglycemia; glucosuria consistent w/diabetes mellitus	1	.	1	.
Respiratory	Bronchitis	.	1	.	1
	Cough	.	2	.	2
	Throat pain	.	1	.	1
	Uri	1	.	1	.
Skin	New ringworm lesion lower rt back	.	1	.	1
Uro-genital	Urinary tract infection	1	.	1	.
Overall		3	7	3	7

Overall, there appears to be little difference in adverse events due to treatment.

Note that for any adverse event with no outcomes, by the "rule of three", a 95% confidence interval for the true proportion associated with this adverse event ranges from 0% - 3x(1/40)=7.5% (Assuming 40 subjects in a group). So we can predict that most adverse events will have a true proportion in this range.

Table 17. Adverse Events
Study PDC 010-005

Body	Basal cell carcinoma	.	1	.	1
	Head cold	1	.	1	.
	Headache	2	2	2	3
	Lower left back pain	1	.	1	.
	Muscle pull - mid back	1	.	1	.
	Pain foot	.	1	.	1
	Possible bacterial infection in crural area due to scratching	1	1	1	1
CV	Migraine headache	.	1	.	1
Digestive	Aphthous ulcer	1	.	1	.
Respiratory	Sinusitis	.	1	.	1
	Sore throat	1	.	1	.
Skin	Burning upon medication application	1	.	1	.
Sensory	Dry eyes	1	.	1	.
	Puffy rt. eyelid	.	1	.	1
	Overall	10	8	10	9

Again, there is no statistically significant differences between treatment groups with respect to these adverse events. No p-values are given but the results are clear.

Conclusions (Which may be conveyed to the Sponsor):

1. Two randomized, multicenter, double-blind studies were provided to support the claim of efficacy of Butenafine Hydrochloride (HCl) Cream 1% versus its vehicle in the treatment of tinea corporis and tinea cruris. Both studies had (nominally) two weeks of treatment, once daily, followed by four weeks of an untreated follow-up period.

2. This review used the proposed Division IV definition of a modified intent-to-treat (MITT) population, based on every subject who was dispensed a study treatment who additionally had a baseline positive dermatophyte mycology (i.e. both KOH and culture). Thus the tables in this report differ from the tables based on the sponsor's MITT definition for two reasons:

i)The sponsor's definition of MITT deleted all subjects that had no post-baseline visits, plus, in the PDC 010-005 study, one extreme protocol violator. Thus the sponsor's definition of MITT differed considerably from that used by Division IV.

ii)The sponsor reported all tables at the 14th day of treatment using a last observation carried forward (LOCF) technology, where any case missing the value of some variable at 14th day of treatment has that value imputed from the corresponding day 7 measurement.

3. Complete cure was defined as a physician's global response of cleared plus a mycological cure. From tables 3-6, and tables 10-14, in both studies, for each of the response variables: complete cure, a 7 point scale assessing physician's global assessment of disease compared to baseline, the sum of the target lesions signs and symptoms scores (defined on page 2 of this report), and the patient's assessment of treatment response were all highly statistically significant, both at the LOCF end of treatment and at the end of the four week follow-up period, nominally day 42 (all $p \leq 0.001$, except for the target lesion sum of signs and symptoms in the PDC 010-005 study, where $p \leq 0.0323$ at the LOCF endpoint and $p \leq 0.0039$ at the end of day 42). Even by day 7, most of these endpoints showed statistically significant differences between Butenafine HCl Cream 1% and vehicle. The magnitude of these differences increased over the course of the experiment.

4. There was question about the validity of the measures used, particularly the relevance of the physician's global assessment of disease with the target lesion signs and symptoms. However correlations of these measures were quite high in both studies (.86 and above in both studies, with most correlations above .9), which suggest these measures are coherent.

5. Note that overall, combining studies the number of adverse events was numerically higher for the vehicle group than for the treatment group. One subject did experience burning when the medication was applied. However, it is clear that there were no statistically significant differences in rates of adverse events favoring the vehicle over Butenafine HCl Cream 1%.

6. Thus, it is this reviewer's opinion that the sponsor has demonstrated that Butenafine HCl Cream 1% is statistically significantly more effective than its vehicle for the treatment of tinea corporis and tinea cruris. While safety is harder to establish with such a small trials (i.e. by the so-called "rule of three", for any particular adverse event that did not occur, a 95% confidence interval the proportion of times that particular adverse event would occur is roughly 0-7.5%), there appears to be no particular pattern associated with treatment.

Steven F Thomson 12/9/96

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Dec 9, '96

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HFD-540/Division File
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This review has 20 pages, with 14 pages of tables in an appendix.
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Table 18. Target Lesion Signs and Symptoms Subscales Study PDC 010-004

The following tables present detailed displays of subcomponents of the two signs and symptoms scores, and the overall cure and sponsor defined effective treatment, broken down by demographic subgroup.

Nominal Day	Baseline		7		14		locf		42	
	Active	Veh.	Active	Veh.	Active	Veh.	Active	Veh.	Active	Veh.
Target Lesion Erythema										
Absent (none)	.	1	4	1	18	3	18	4	30	6
		3%	10%	3%	46%	9%	43%	11%	75%	21%
Mild (barely perceptible)	2	.	28	8	18	18	20	18	9	11
	5%		67%	23%	46%	53%	48%	47%	23%	39%
Moderate (distinctive)	23	23	8	19	2	6	3	8	1	7
	55%	61%	19%	54%	5%	18%	7%	21%	3%	25%
Severe (marked, intense)	17*	14	2	7	1	7	1	8	.	4
	40%	37%	5%	20%	3%	21%	2%	21%		14%
CMH p-value	.863		.001		.001		.001		.001	
Target Lesion Maceration										
Absent (none)	38	34	42	33	39	31	42	35	40	26
	90%	89%		94%		91%		92%		93%
Mild (barely perceptible)	3	3	.	2	.	3	.	3	.	2
	7%	8%		6%		9%		8%		7%
Moderate (distinctive)	1	1	.	.	.	.	.	.	.	.
	2%	3%								
CMH p-value	.691		.131		.077		.099		.134	
Target Lesion Papules										
Absent (none)	17	12	30	16	33	19	35	21	35	17
	40%	32%	71%	46%	85%	56%	83%	55%	88%	61%
Mild (barely perceptible)	15	15	10	14	4	10	5	12	5	7
	36%	39%	24%	40%	10%	29%	12%	32%	13%	25%
Moderate (distinctive)	5	9	1	4	1	3	1	3	.	4
	12%	24%	2%	11%	3%	9%	2%	8%		14%
Severe (marked, intense)	5	2	1	1	1	2	1	2	.	.
	12%	5%	2%	3%	3%	6%	2%	5%		
CMH p-value	.581		.026		.025		.013		.006	

Table 18. (cont.) Target Lesion Signs and Symptoms Subscales
Study PDC 010-004

Target Lesion Pruritus										
Absent (none)	.	.	24	7	32	14	34	14	36	9
			57%	20%	82%	41%	81%	37%	90%	32%
Mild (barely perceptible)	6	4	13	7	7	9	8	9	2	8
	14%	11%	31%	20%	18%	26%	19%	24%	5%	29%
Moderate (distinctive)	11	17	5	13	.	4	.	6	2	7
	26%	45%	12%	37%		12%		16%	5%	25%
Severe (marked, intense)	25	17	.	8	.	7	.	9	.	4
	60%	45%		23%		21%		24%		14%
CMH p-value	.457		.001		.001		.001		.001	
Target Lesion Scaling										
Absent (none)	.	.	10	3	25	8	25	8	35	7
			24%	9%	64%	24%	60%	21%	88%	25%
Mild (barely perceptible)	2	2	25	12	12	14	14	14	1	7
	5%	5%	60%	34%	31%	41%	33%	37%	3%	25%
Moderate (distinctive)	27	26	6	18	2	7	3	9	4	9
	64%	68%	14%	51%	5%	21%	7%	24%	10%	32%
Severe (marked, intense)	13	10	1	2	.	5	.	7	.	5
	31%	26%	2%	6%		15%		18%		18%
CMH p-value	.562		.001		.001		.001		.001	
Target Lesion Vesiculation										
Absent (none)	35	30	40	30	37	29	40	32	39	25
	83%	79%	95%	86%	95%	85%	95%	84%	98%	89%
Mild (barely perceptible)	4	6	2	5	2	5	2	6	1	3
	10%	16%	5%	14%	5%	15%	5%	16%	3%	11%
Moderate (distinctive)	2	2	.	.	.	.	.	.	.	.
	5%	5%								
Severe (marked, intense)	1	.	.	.	.	.	.	.	.	.
	2%									
CMH p-value	.732		.189		.210		.110		.280	

Table 19. Overall Disease Signs and Symptoms Subscales
Study PDC 010-004

Nominal Day	Baseline		7		14		locf		42	
	Active	Veh.	Active	Veh.	Active	Veh.	Active	Veh.	Active	Veh.
Disease Severity- Erythema										
Absent (none)	14 41%	18 56%	16 47%	15 52%	24 75%	16 57%	25 74%	19 59%	29 91%	16 62%
Mild (barely perceptible)	1 3%	1 3%	18 53%	2 7%	7 22%	6 21%	8 24%	6 19%	1 3%	5 19%
Moderate (distinctive)	11 32%	9 28%	.	11 38%	1 3%	3 11%	1 3%	4 13%	2 6%	3 12%
Severe (marked, intense)	8 24%	4 13%	.	1 3%	.	3 11%	.	3 9%	.	2 8%
CMH p-value	.221		.026		.020		.026		.010	
Disease Severity-Maceration										
Absent (none)	33 97%	29 91%	34	28 97%	32	27 96%	34	31 97%	32	25 96%
Mild (barely perceptible)	.	2 6%	.	1 3%	.	1 4%	.	1 3%	.	1 4%
Moderate (distinctive)	1 3%	1 3%	.	.	.	.	.	.	.	.
CMH p-value	.344		.296		.273		.317		.190	
Disease Severity-Papules										
Absent (none)	25 74%	24 75%	29 85%	22 76%	30 94%	23 82%	32 94%	27 84%	30 94%	22 85%
Mild (barely perceptible)	8 24%	4 13%	5 15%	6 21%	2 6%	4 14%	2 6%	4 13%	2 6%	2 8%
Moderate (distinctive)	.	4 13%	.	1 3%	.	1 4%	.	1 3%	.	2 8%
Severe (marked, intense)	1 3%	.	.	.	.	.	.	.	.	.
CMH p-value	.468		.127		.113		.131		.162	

Table 19. (cont.) Overall Disease Signs and Symptoms Subscales Study PDC 010-004

Disease Severity-Pruritus

Absent (none)	14	17	26	17	31	20	33	23	29	16
	41%	53%	76%	59%	97%	71%	97%	72%	91%	62%
Mild (barely perceptible)	2	1	7	3	1	3	1	3	.	6
	6%	3%	21%	10%	3%	11%	3%	9%		23%
Moderate (distinctive)	5	7	1	6	.	3	.	3	2	2
	15%	22%	3%	21%		11%		9%	6%	8%
Severe (marked, intense)	13	7	.	3	.	2	.	3	1	2
	38%	22%		10%		7%		9%	3%	8%
CMH p-value	.318		.010		.004		.004		.035	

Disease Severity-Scaling

Absent (none)	14	17	19	14	28	15	29	18	29	16
	41%	53%	56%	48%	88%	54%	85%	56%	91%	62%
Mild (barely perceptible)	4	3	14	4	4	6	5	6	1	3
	12%	9%	41%	14%	13%	21%	15%	19%	3%	12%
Moderate (distinctive)	12	9	1	9	.	3	.	4	2	2
	35%	28%	3%	31%		11%		13%	6%	8%
Severe (marked, intense)	4	3	.	2	.	4	.	4	.	5
	12%	9%		7%		14%		13%		19%
CMH p-value	.458		.013		.001		.001		.004	

Disease Severity-Vesiculation

Absent (none)	34	32	34	28	32	28	34	32	32	25
				97%						96%
Mild (barely perceptible)	.	.	.	1	.	.	.	.	.	1
				3%						4%
CMH p-value	NA		.157		NA		NA		.439	

Table 20. Target Lesion Signs and Symptoms Subscales Study PDC 010-005

Target Lesion Erythema										
Absent (none)	.	.	8	1	19	7	18	7	25	6
			22%	3%	53%	20%	47%	18%	78%	21%
Mild (barely perceptible)	.	1	15	21	11	8	13	9	3	6
		3%	42%	54%	31%	23%	34%	23%	9%	21%
Moderate (distinctive)	26	24	11	11	3	12	3	15	3	10
	67%	60%	31%	28%	8%	34%	8%	38%	9%	36%
Severe (marked, intense)	13	15	2	6	3	8	4	9	1	6
	33%	38%	6%	15%	8%	23%	11%	23%	3%	21%
CMH p-value	.674		.041		.001		.001		.001	
Target Lesion Maceration										
Absent (none)	24	31	33	36	31	30	33	33	30	22
	62%	78%	92%	92%	86%	86%	87%	83%	94%	79%
Mild (barely perceptible)	8	5	2	3	3	4	3	5	1	6
	21%	13%	6%	8%	8%	11%	8%	13%	3%	21%
Moderate (distinctive)	6	4	1	.	2	1	2	2	1	.
	15%	10%	3%		6%	3%	5%	5%	3%	
Severe (marked, intense)	1	.	.	.	.	.	.	.	.	.
	3%									
CMH p-value	.154		.753		.982		.561		.260	
Target Lesion Papules										
Absent (none)	22	18	31	20	30	16	32	17	30	14
	56%	45%	86%	51%	83%	46%	84%	43%	94%	50%
Mild (barely perceptible)	10	8	4	8	5	8	5	10	2	7
	26%	20%	11%	21%	14%	23%	13%	25%	6%	25%
Moderate (distinctive)	7	11	1	9	1	9	1	11	.	6
	18%	28%	3%	23%	3%	26%	3%	28%		21%
Severe (marked, intense)	.	3	.	2	.	2	.	2	.	1
		8%		5%		6%		5%		4%
CMH p-value	.082		.001		.001		.001		.001	

Table 20. (cont.) Target Lesion Signs and Symptoms Subscales Study PDC 010-005

Target Lesion Pruritus										
Absent (none)	1	.	15	9	21	11	22	12	28	8
	3%		42%	23%	58%	31%	58%	30%	88%	29%
Mild (barely perceptible)	3	1	14	12	9	13	8	14	.	6
	8%	3%	39%	31%	25%	37%	21%	35%		21%
Moderate (distinctive)	18	25	3	12	2	9	4	10	2	8
	46%	63%	8%	31%	6%	26%	11%	25%	6%	29%
Severe (marked, intense)	17	14	4	6	4	2	4	4	2	6
	44%	35%	11%	15%	11%	6%	11%	10%	6%	21%
CMH p-value	.891		.015		.060		.034		.001	
Target Lesion Scaling										
Absent (none)	.	.	10	4	22	7	21	7	27	7
			28%	10%	61%	20%	55%	18%	84%	25%
Mild (barely perceptible)	9	8	18	20	10	14	12	16	2	7
	23%	20%	50%	51%	28%	40%	32%	40%	6%	25%
Moderate (distinctive)	21	21	7	12	3	13	4	14	2	12
	54%	53%	19%	31%	8%	37%	11%	35%	6%	43%
Severe (marked, ntense)	9	11	1	3	1	1	1	3	1	2
	23%	28%	3%	8%	3%	3%	3%	8%	3%	7%
CMH p-value	.683		.025		.001		.001		.001	
Target Lesion Vesiculation										
Absent (none)	36	40	35	39	36	33	38	38	32	28
	92%		97%		94%		95%			
Mild (barely perceptible)	3	.	1	.	.	2	.	2	.	.
	8%	.	3%	.		6%		5%		
CMH p-value	.067		.292		.168		.167		NA	

Table 21. Overall Disease Signs and Symptoms Subscales
Study PDC 010-005

Disease Severity-Erythema

Absent (none)	5	4	12	6	21	11	21	11	27	9
	13%	10%	33%	15%	58%	31%	55%	28%	84%	32%
Mild (barely perceptible)	1	5	15	17	11	8	12	9	2	7
	3%	13%	42%	44%	31%	23%	32%	23%	6%	25%
Moderate (distinctive)	24	22	7	9	1	8	1	12	2	8
	62%	55%	19%	23%	3%	23%	3%	30%	6%	29%
Severe (marked, intense)	9	9	2	7	3	8	4	8	1	4
	23%	23%	6%	18%	8%	23%	11%	20%	3%	14%
CMH p-value	.769		.041		.004		.003		.001	

Disease Severity-Maceration

Absent (none)	27	34	34	36	31	30	33	34	30	22
	69%	85%	94%	92%	86%	86%	87%	85%	94%	79%
Mild (barely perceptible)	10	5	2	3	5	5	5	6	2	5
	26%	13%	6%	8%	14%	14%	13%	15%	6%	18%
Moderate (distinctive)	2	1	.	.	.	.	.	.	.	1
	5%	3%								4%
CMH p-value	.115		.631		.815		.675		.074	

Disease Severity-Papules

Absent (none)	26	23	32	23	31	21	33	23	30	17
	67%	58%	89%	59%	86%	60%	87%	58%	94%	61%
Mild (barely perceptible)	8	6	2	5	4	4	4	5	2	5
	21%	15%	6%	13%	11%	11%	11%	13%	6%	18%
Moderate (distinctive)	5	8	2	7	1	8	1	10	.	6
	13%	20%	6%	18%	3%	23%	3%	25%		21%
Severe (marked, intense)	.	3	.	4	.	2	.	2	.	.
		8%		10%		6%		5%		
CMH p-value	.133		.004		.003		.001		.001	

Table 21. (cont.) Overall Disease Signs and Symptoms Subscales Study PDC 010-005

Disease Severity-Pruritus

Absent (none)	5	4	18	12	24	16	24	17	28	12
	13%	10%	50%	31%	67%	46%	63%	43%	88%	43%
Mild (barely perceptible)	2	5	13	11	8	9	8	11	1	6
	5%	13%	36%	28%	22%	26%	21%	28%	3%	21%
Moderate (distinctive)	19	19	2	12	2	7	4	8	2	5
	49%	48%	6%	31%	6%	20%	11%	20%	6%	18%
Severe (marked, intense)	13	12	3	4	2	3	2	4	1	5
	33%	30%	8%	10%	6%	9%	5%	10%	3%	18%
CMH p-value	.679		.027		.052		.058		.001	

Disease Severity-Scaling

Absent (none)	5	4	15	7	24	12	24	12	28	12
	13%	10%	42%	18%	67%	34%	63%	30%	88%	43%
Mild (barely perceptible)	12	9	15	17	9	12	10	14	2	4
	31%	23%	42%	44%	25%	34%	26%	35%	6%	14%
Moderate (distinctive)	16	22	5	12	3	8	4	10	1	10
	41%	55%	14%	31%	8%	23%	11%	25%	3%	36%
Severe (marked, intense)	6	5	1	3	.	3	.	4	1	2
	15%	13%	3%	8%		9%		10%	3%	7%
CMH p-value	.739		.014		.002		.001		.001	

Disease Severity-Vesiculation

Absent (none)	37	40	35	39	36	34	38	39	32	28
	95%		97%			97%		98%		
Mild (barely perceptible)	2	.	1	.	.	1	.	1	.	.
	5%		3%			3%		3%		
CMH p-value	.146		.292		.346		.343		NA	

Table 22. Subgroups for Overall Cure
Study PDC 010-004

Overall Complete Cure

Nominal Day	7		14		locf		42	
	Active	Vehicle	Active	Vehicle	Active	Vehicle	Active	Vehicle
Age = 13-24								
Cure	.	.	2	.	2	.	6	1
			29%		29%		86%	50%
Fail	7	4	5	3	5	4	1	1
			71%		71%		14%	50%
CMH p-value	NA		.285		.244		1.000	
Age = 25-45								
Cure	1	.	6	.	6	.	9	1
	7%		50%		43%		75%	8%
Fail	13	15	6	14	8	16	3	11
	*93%		50%		57%		25%	92%
CMH p-value	.617		.033		.015		.072	
Age = 46+								
Cure	.	.	5	1	5	1	13	3
			25%	6%	24%	6%	62%	21%
Fail	21	16	15	16	16	17	8	11
			75%	94%	76%	94%	38%	79%
CMH p-value	NA		.099		.108		.002	

Complete Cure

Nominal Day	7		14		locf		42	
	Active	Vehicle	Active	Vehicle	Active	Vehicle	Active	Vehicle
Sex of Patient = Female								
Cure	.	.	4	1	4	1	14	3
			24%	6%	20%	5%	78%	23%
Fail	20	19	13	17	16	18	4	10
			76%	94%	80%	95%	22%	77%
CMH p-value	NA		.428		.404		.007	
Sex of Patient = Male								
Cure	1	.	9	.	9	.	14	2
	5%		41%		41%		64%	13%
Fail	21	16	13	16	13	19	8	13
	95%		59%		59%		36%	87%
CMH p-value	.439		.007		.004		.002	

Table 22.(cont.) Subgroups for Overall Cure
Study PDC 010-004

Complete Cure

Nominal Day	7 Active	7 Vehicle	14 Active	14 Vehicle	locf Active	locf Vehicle	42 Active	42 Vehicle
Race = Caucasian								
Cure	1	.	8	.	8	.	16	2
	4%		35%		32%		67%	13%
Fail	24	20	15	20	17	22	8	14
	96%		65%		68%		33%	88%
CMH p-value	.317		.003		.003		.001	
Race = Other								
Cure	.	.	5	1	5	1	12	3
	*		31%	7%	29%	6%	75%	25%
Fail	17	15	11	13	12	15	4	9
			69%	93%	71%	94%	25%	75%
CMH p-value	NA		.168		.116		.020	

Table 23. Subgroups for Effective Treatment
Study PDC 010-004

Effective Treatment

Nominal Day	7 Active	7 Vehicle	14 Active	14 Vehicle	locf Active	locf Vehicle	42 Active	42 Vehicle
Age = 13-24								
Cure	3 43%	.	3 43%	1 33%	3 43%	1 25%	7	1 50%
Fail	4 57%	4	4 57%	2 67%	4 57%	3 75%	.	1 50%
CMH p-value	.163		.695		.533		.317	
Age = 25-45								
Cure	6 43%	.	11 92%	2 14%	13 93%	2 13%	10 83%	1 8%
Fail	8 57%	15	1 8%	12 86%	1 7%	14 88%	2 17%	11 92%
CMH p-value	.030		.002		.001		.030	
Age = 46+								
Cure	5 24%	.	9 45%	3 18%	9 43%	3 17%	15 71%	3 21%
Fail	16 76%	16	11 55%	14 82%	12 57%	15 83%	6 29%	11 79%
CMH p-value	.034		.058		.068		.001	

Effective Treatment

Nominal Day	7 Active	7 Vehicle	14 Active	14 Vehicle	locf Active	locf Vehicle	42 Active	42 Vehicle
Sex of Patient = Female								
Cure	6 30%	.	9 53%	4 22%	11 55%	4 21%	17 94%	3 23%
Fail	14 70%	19	8 47%	14 78%	9 45%	15 79%	1 6%	10 77%
CMH p-value	.032		.168		.102		.001	
Sex of Patient = Male								
Cure	8 36%	.	14 64%	2 13%	14 64%	2 11%	15 68%	2 13%
Fail	14 64%	16	8 36%	14 88%	8 36%	17 89%	7 32%	13 87%
CMH p-value	.013		.004		.001		.001	

Table 23. (cont.) Subgroups for Effective Treatment
Study PDC 010-004

Effective Treatment

Nominal Day	7		14		locf		42	
	Active	Vehicle	Active	Vehicle	Active	Vehicle	Active	Vehicle
Race = Caucasian								
Cure	8	.	13	3	14	3	17	2
	32%		57%	15%	56%	14%	71%	13%
Fail	17	20	10	17	11	19	7	14
	68%		43%	85%	44%	86%	29%	88%
CMH p-value	.012		.004		.003		.001	
Race = Other								
Cure	6	.	10	3	11	3	15	3
	35%		63%	21%	65%	20%	94%	25%
Fail	11	15	6	11	6	13	1	9
	65%		38%	79%	35%	80%	6%	75%
CMH p-value	.014		.041		.011		.001	

Table 24. Subgroups for Overall Cure
Study PDC 010-005

Complete Cure

Nominal Day	7		14		locf		42	
	Active	Vehicle	Active	Vehicle	Active	Vehicle	Active	Vehicle
Age = 13-24								
Cure	-	-	1 (17%)	-	1 (17%)	-	4 (80%)	-
Fail	6	3	5 (83%)	3	5 (83%)	4	1 (20%)	3
CMH p-value	NA		NA		NA		.066	
Age = 25-45								
Cure	3 (14%)	1 (5%)	8 (38%)	1 (7%)	8 (36%)	1 (5%)	13 (68%)	1 (9%)
Fail	18 (86%)	19 (95%)	13 (62%)	14 (93%)	14 (64%)	19 (95%)	6 (32%)	10 (91%)
CMH p-value	.337		.052		.022		.006	
Age = 46+								
Cure	1 (11%)	-	3 (33%)	2 (13%)	3 (30%)	2 (13%)	6 (75%)	-
Fail	8 (89%)	16	6 (67%)	14 (88%)	7 (70%)	14 (88%)	2 (25%)	14
CMH p-value	.114		.269		.340		.001	

All but one patient was male.

For race, all were white except three, all three in the active treatment group.

Hence these subgroups are virtually identical to the pooled group and subgroup analyses are ignored.

Table 25. Subgroups for Effective Treatment
Study PDC 010-005

Effective Treatment

Nominal Day	7		14		locf		42	
	Active	Vehicle	Active	Vehicle	Active	Vehicle	Active	Vehicle
Age = 13-24								
Cure	.	.	3 50%	.	3 50%	.	5	.
Fail	6	3 50%	3	3 50%	3	4	.	3
CMH p-value	NA		.237		.176		.014	
Age = 25-45								
Cure	7 33%	1 5%	13 62%	1 6%	13 59%	1 5%	16 84%	1 9%
Fail	14 67%	19 95%	8 38%	15 94%	9 41%	19 95%	3 16%	10 91%
CMH p-value	.032		.001		.001		.001	
Age = 46+								
Cure	3 33%	1 6%	5 56%	2 13%	5 50%	2 13%	6 75%	1 7%
Fail	6 67%	15 94%	4 44%	14 88%	5 50%	14 88%	2 25%	13 93%
CMH p-value	.100		.033		.057		.003	

All but one patient was male.

For race, all were white except three, all three in the active treatment group.

Hence these subgroups are virtually identical to the pooled group and subgroup analyses are ignored.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 020663

CHEMISTRY REVIEW

NOV 15

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-663 **CHEM.REVIEW #:** 1 **REVIEW DATE:** 11/05/96

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	12/22/95	1/11/96	1/18/96
AMENDMENT/BC	3/1/96	3/4/96	3/7/96
NC	3/1/96	3/4/96	3/7/96

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

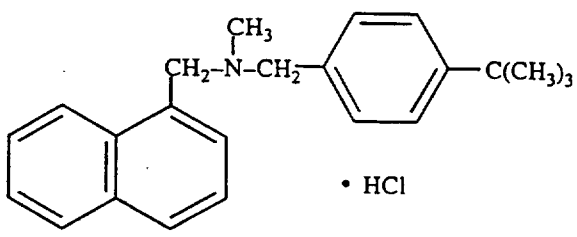
Chem.Type/Ther.Class: 6 S

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:

Butenafine HCl is designated chemically as N-4-tert-butylbenzyl-N-methyl-1-napthalenemethylamine hydrochloride. The structural formula is:



Mol.Wt. 353.93

SUPPORTING DOCUMENTS:
N/A

RELATED DOCUMENTS (if applicable): IND
NDA 20-524; Mentax (butenafine HCl) Cream, 1%.

CONSULTS:

EA review and FONSI will be performed by Nancy Sager (HFD-357).
See Trade Name Consult dated 3/12/96

REMARKS/COMMENTS:

In accordance with 21 CFR 314.50, the applicant filed a New Drug Application on 12/22/96 for Butenafine Hydrochloride Cream 1% to treat tinea corporis and tinea curis. This NDA is also the subject of a marketed product, Mentax (butenafine HCl) Cream, 1% (NDA 20-524), approved on 10/18/96 for the treatment of interdigital tinea pedis. Since the subject NDA was originally submitted before NDA 20-524 was approved, it was classified as a 1-S product. However the approval of NDA 20-524 resulted in the reclassification of NDA 20-663 ~~as a line extension~~ (Type 6 S) to the presently approved product in accordance with 21 CFR 314.54.

The subject NDA only contains Clinical and Statistical Data in support of the application. Since no changes have been made in the manufacturing of the currently approved product, no Chemistry, Manufacturing and Controls information was submitted. However, the applicant has cross-referenced NDA 20-524 for information relating to the CMCs used in that NDA. **Note: The CMCs were approved for NDA 20-524 (see Chemist Review #5 dated 10/18/96).**

Environmental Assessment:

A type 6 NDA for Mentax cream requires an Environmental Assessment in accordance with regulation 21 CFR Part 25.22 (a)(14). In this regard, the applicant provided EA information as per this regulation. This information was sent on 1/29/96 to Nancy Sager (HFD-357) for review.

Note: The review chemist would ordinarily review the EA and draft of FONSI because this NDA is a type 6 drug. However, Nancy Sager has agreed to review the EA since she has

initiated the original review, while it was classified as 1 S product. To date, this EA and FONSI is pending.

Establishment Evaluation Review:

EERs (ID #9510) were requested on 2/8/96 for the following facilities: (1) Penederm Inc., 320 Lakeside Dr., Inspection # 23246) (Raw Material, Finished Product and Stability Testing); (2) (Inspection ID #23244) (Bulk); (3) (Inspection ID #23250) (Raw Material Testing); (4) (Inspection ID #23245) (Manufacturing, packaging and testing of finished product); (5) (Inspection ID #23247) (Micro Testing); (6) (Inspection ID #23249) (Micro Testing); (7) (Inspection ID #23248) (Micro Testing).

These facilities were found acceptable for GMPs

CONCLUSIONS & RECOMMENDATIONS:

The NDA is approved for manufacturing and controls under section 505 of the Act.

EERs: All manufacturing facilities are currently in acceptable GMP compliance (see memo dated 4/30/96 from HFD-324).

Environmental Assessment: Acceptable pending EA review and FONSI from Nancy Sager (HFD-357). EA information sent HFD-357 on 1/29/96.

Labeling: Technical portion of labeling was reviewed for NDA 20-524. The labeling is the same for the subject NDA. Tradename approved on 3/1/96 by the L&NC.

Ernest G. Pappas 11/6/96

Ernest G. Pappas
Review Chemist

cc: Orig. NDA 20-663
HFD-540/Division File
HFD-540/Pappas
HFD-540/OConnell
HFD-540/Mainigi
HFD-160/Conney
HFD-540/Cross
HFD-540/DeCamp HMR 11/13/96

GW 11/15/96

MAR 11 1996 (383)

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: 3/11/96

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark: Mentax NDA # 20-663
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 lengthily): Treatment of Interdigital Tinea Corporis and Tinea Cruris

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

Log out 3/12/96
[illegible]
[illegible]

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

RWBering 4/1/96, Chair

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 020663

CHEMISTRY REVIEW

JAN 24 1996

1.1

REVIEW FOR HFD-540
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #1 OF NDA 20-663

23 January 1996

A. 1. NDA 20-663
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 intended for use in the treatment of tinea corporis and tinea cruris.

B. 1. DATE OF INITIAL SUBMISSION: 22 December 1995

2. DATE OF AMENDMENT: (none)

3. RELATED DOCUMENTS:

Table 1. Documents referenced in this NDA.

Document	Subject/ Document Holder
IND	IND for Butenafine HCl Cream 1%/ Penederm
DMF	
DMF	
DMF	
DMF	

4. ASSIGNED FOR REVIEW: 22 January 1996

C. REMARKS: The application is from the same applicant, for the same formulation, using the same

manufacturing facilities as NDA 20-524 which was recommended for approval on 7 September 1995. The major difference between the two applications is the indications for product use. The review that follows is also the same as the review for NDA 20-524.

D. CONCLUSIONS: The submission is recommended for approval on the basis of microbial integrity and preservative effectiveness.

23 January 1996

Paul Stinavage, Ph.D.

cc: Original NDA 20-663
HFD-805/Stinavage/Consult File
HFD-540/Div File/E. Pappas

PMC 1/24/96

Drafted by: P. Stinavage, 23 January 1996
R/D initialed by P. Cooney, 23 January 1996

Consultative Review for HFD-540
Division of Topical Drug Products
Division of Anti-Infective Drug Products (HFD-520)
Microbiological Clinical Review

Requestor: Frank Cross, CSO, HFD-540

Date of Request: Feb 1, 1996

Reason for Request: Microbiological Review of antifungal activity

NDA #: 20-663 **MICRO REVIEW #:** 1 **REVIEW DATE:** 11-Apr-96

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL NDA	22-DEC-95	05-JAN-96	02-FEB-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

Proprietary:	None
Nonproprietary/USAN:	Butenafine Hydrochloride Cream
Code Names/#'s:	KP-363
Chemical Type/	Allylamine (a benzylamine derivative)
Therapeutic Class:	Antifungal-Dermatophyte

ANDA Suitability Petition/DESI/Patent Status:
Not Applicable

PHARMACOLOGICAL CATEGORY/INDICATION:
Anti-fungal: Interdigital Tinea pedis, Tinea Corporis, Tinea Cruris

DOSAGE FORM:	Cream
STRENGTHS:	1%
ROUTE OF ADMINISTRATION:	Topical
DISPENSED:	_X_ Rx ___ OTC

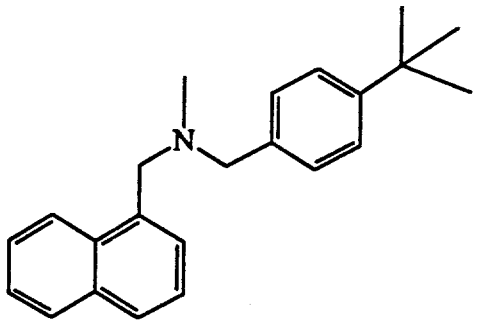
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL. WT:

Chemical Name: N-4-tert-Butylbenzyl-N-methyl-1-naphthalene methylamine Hydrochloride

Structural Formula:

F.W. $C_{23}H_{27}N \cdot HCl$

M.W.353.93



SUPPORTING DOCUMENTS:
DMF
DMF
DMF
DMF

DMF
IND

RELATED DOCUMENTS (if applicable): Consultative microbiological clinical review for NDA 20-524 which reviews Tinea pedis for the identical product.

CONSULTS: HFD-540 placed the consultative microbiological reviews for this application in two separate Divisions.

REMARKS/COMMENTS: This microbiological review is concerned with the clinical aspects and not the manufacturing controls. The Pre-clinical microbiology for this NDA is identical to that of NDA 20-524 and therefore the reader is referred to the review of NDA 20-524 for a detailed discussion of the pre-clinical studies which is attached as an appendix to this review.

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 9-10 of this review (pending medical input) and pages 62-64 of the review for NDA 20-524, which is included as an appendix to this review.

NDA 20- 524 (Butenafine HCL Cream 1% for the treatment of tinea pedis) has been reviewed by Mr. Peter Dionne. Since the pre-clinical information for NDA 20- 524 is identical to that for NDA 20- 663 (Butenafine HCL Cream 1% for the treatment of tinea corporis and tinea

cruris), Mr. Dionne's review is attached to this review as an appendix which should be consulted for that information. Therefore the preclinical efficacy *in vitro and invivo* are not included in the text of the review for NDA 20-663 and the reader is referred to the attached appendix for that information. The table of contents for Mr. Dionne's consultative review for NDA 20- 524 is included on page 6 of this review. It also be should be kept in mind that the three indications from the two reviews, tinea pedis from Mr. Dionne's review and, tinea corporis and tinea cruris from this review are to be included in one package insert.

TABLE OF CONTENTS
(Review of NDA 20-663)

TABLE OF CONTENTS
(Review 20-524)

INTRODUCTION:

This NDA is for a product, Butenafine HCL 1% Cream, developed to treat dermatomycosis including tinea pedis, tinea cruris and tinea corporis. Most drugs currently used against dermatophytes belong to one of five chemical groups: 1. The imidazoles (clotrimazole, miconazole, ketoconazole, and econazole),2. The thiocarbamates (tolnaftate and tolciclate), 3. polyenes (nystatin and amphotericin B), 4. Griseofulvin, and 5. the allylamines (naftifine, terbinafine, and butenafine). The drug product includes an active ingredient, Butenafine which has not been previously approved by the FDA for medicinal usage. Butenafine HCL is a benzylamine derivative with a chemical structure and mode of action that is similar to the allylamine class of antifungal agents and has therefore been included in that class. In common with the azole class of antifungal drugs, it acts at an early stage in ergosterol biosynthesis by inhibiting squalene epoxidase. Ergosterol is an essential component of fungal cell membranes. Depending on the conditions, concentration of drug and fungal species tested, Butenafine can be either bacteriocidal or bacteriostatic. The drug substance is manufactured by Most of the pre-clinical studies included in and referred to in these NDAs and discussed in Mr. Dionne's review are from unpublished final reports from

CLINICAL EFFICACY (TINEA CORPORIS)

CLINICAL MICROBIOLOGY

One pivotal multicenter clinical study was conducted in the United States, protocol PDC 010-004. The clinical studies were conducted at five different sites under five investigators. Butenafine HCl Cream 1% was

evaluated in a double-blind, randomized, parallel, vehicle controlled study in 91 patients. Patient entry required a clinical diagnosis of tinea corporis confirmed microscopically by viewing KOH mounts and further coroborated by culture isolation on two separate media and identification of genera and species to give a positive fungal identification, other than yeast. The isolation media used were Mycobiotic agar and Sabouraud's dextrose agar without cycloheximide. All culture tubes were sent to a central laboratory for identification. **The mycological methods used for isolation and identification of cultures appeared to be satisfactory by present standards.** Patients received either drug or placebo once daily for two weeks and were evaluated for cure at the end of treatment and four weeks after the end of treatment. There were three primary efficacy endpoints, 1. Mycological Cure, negative microscopy (KOH mounts) and culture, 2. Effective Treatment (Mycological Cure and Investigator Global Response assessment of "Cleared" or "Excellent") and 3. Overall Cure (Mycological Cure and Investigator Global Response assessment of "Cleared"). Assessments including Mycological were conducted at baseline, day 7, 14 and 42. There were 42 evaluable patients who received treatment and 36 who received placebo.

All species of dermatophytes belonging to the genera *Trichophyton, Microsporium, or Epidermophyton* are capable of causing tinea corporis. The most common species are *T. Rubrum, M. Canis, and T. Mentagrophytes.* Only patients that had the organism present at baseline and had a 4-week follow-up visit are listed. In order to be cured mycologically, both a negative KOH mount and culture had to be present at the 4-week follow-up time point. Shown below in table 1 are results by organism for butenafine and vehicle, the sponsor's table 17a from NDA #20-663, from the sponsor's submission of additional information, Volume 2 of 3 and table 2, the sponsor's table of results, Tinea Corporis, from the same volume. As seen in Table 1, significantly more butenafine-treated patients than vehicle-treated patients remained negative by culture and microscopy, 88% versus 17% 4-weeks post therapy, $p<0.0001$. As

TABLE 1

Penederm Incorporated
Protocol PDC 010-004 (Tinea Corporis)
Butenafine HCl 1%

Table 17a
Mycological Cure Rates at Day 42 by Baseline Dermatophyte
(Modified Intent-to-Treat Population)

Dermatophyte	BUTENAFINE	VEHICLE	Odds Ratio	Fisher's Exact p-value
T. RUBRUM	25/29 (86%)	3/19 (16%)	33.33	<0.0001
T. TONSURANS	9/10 (90%)	2/ 7 (29%)	22.50	0.0345
T. MENTAGROPHYTES	1/ 1 (100%)	0/ 3 (0%)	non-est	0.2500
M. CANIS	2/ 2 (100%)	0/ 3 (0%)	non-est	0.1000
M. GYPSEUM	0/ 0 (%)	1/ 3 (33%)	non-est	------
E. FLOCCOSUM	0/ 0 (%)	0/ 1 (0%)	non-est	------
TOTAL	37/42 (88%)	6/36 (17%)	37.00	<0.0001

95% C.I. Around Difference in Total Cure Rates (52.7% , 89.3%)

Cochran-Mantel-Haenszel (General Association)	<0.0001
Cochran-Mantel-Haenszel (ANOVA)	<0.0001
Cochran-Mantel-Haenszel (Correlation)	<0.0001
Breslow-Day	0.6757

Mycological Cure = KOH and culture negative

Source Data: Appendix A.8 & B.2
j:\penederm\010-004\saspgms\tables\mc_42mD.sas 13DEC95:17:18 FINAL

TABLE 2 PAGE 8B

ABSTRACT

Ninety-one (91) patients were enrolled in a multi-center, vehicle-controlled, parallel, randomized, double-blind trial of butenafine HCl cream 1%. Patients with tinea corporis, diagnosis confirmed by KOH and culture, applied the assigned medications once a day for two weeks. Of the 78 patients who were evaluated for efficacy in the Modified-Intent-To-Treat population, 42 received butenafine and 36 received vehicle. The two groups were demographically and clinically similar. Three primary efficacy endpoints, Mycological Cure (negative KOH and culture), Effective Treatment (Mycological Cure and Investigator Global Response assessment of "Cleared" or "Excellent") and Overall Cure (Mycological Cure and Investigator Global Response assessment of "Cleared") were determined. Significantly more butenafine-treated patients than vehicle-treated patients showed conversion to negative culture and microscopy four weeks (Day 42) after the end of therapy (88% versus 17% respectively, $p<0.0001$). Effective Treatment cure rate four weeks after the end of therapy (Day 42) was also significantly greater in the butenafine group (81%) than in the vehicle group (14%) ($p<0.0001$). Overall Cure rate four weeks after the end of therapy (Day 42) was also significantly greater in the butenafine group (67%) than in the vehicle group (14%) ($p<0.0001$). There were no adverse events reported as possibly, probably, or definitely related to treatment during this pivotal clinical trial.

The results are shown in the following table.

Tinea Corporis

Patient Outcome Category	Day 14 (End of Rx)		Day 42 (Four Week Follow-up)	
	Butenafine	Vehicle	Butenafine	Vehicle
Mycological Cure	88% (37/42)	28% (10/36)	88% (37/42)	17% (6/36)
Overall Cure	31% (13/42)	3% (1/36)	67% (28/42)	14% (5/36)
Effective Treatment	60% (25/42)	17% (6/36)	81% (34/42)	14% (5/36)

shown, *T. Rubrum,* 25/29 cured and *T. Tonsurans,* 9/10 cured were the most common infecting organisms encountered in these studies. Smaller numbers of *T. Mentagrophytes,* 1/1 cured and *M.canis,* 2/2 cured were seen. *M. Gypsum and E. Floccosum* were not isolated from the treated patients. As seen in table 2, the numbers of mycological cures decreased in the vehicle control group from 10/36 to 6/36 between day 14 and 42 while the numbers of mycological cures in the butenafine treated patients remained constant at 37/42.

CLINICAL EFFICACY (TINEA CRURIS)

CLINICAL MICROBIOLOGY

One pivotal multicenter clinical study was conducted in the United States, protocol PDC 010-005. The clinical studies were conducted at six different sites under six investigators. Butenafine HCl Cream 1% was evaluated in a double-blind, randomized, parallel, vehicle controlled study in 93 patients. Patient entry required a clinical diagnosis of tinea cruris confirmed microscopically by viewing KOH mounts and further coroborated by culture isolation on two separate media and identification of genera and species to give a positive fungal identification, other than yeast. The isolation media used were Mycobiotic agar and Sabouraud's dextrose agar without cycloheximide. All culture tubes were sent to a central laboratory for identification. The mycological methods used for isolation and identification of cultures appeared to be satisfactory by present standards. Patients received either drug or placebo once daily for two weeks and were evaluated for cure at the end of treatment and four weeks after the end of treatment. There were three primary efficacy endpoints, 1. Mycological Cure, negative microscopy (KOH mounts) and culture, 2. Effective Treatment (Mycological Cure and/ Investigator Global Response assessment of "Cleared" or "Excellent") and 3. Overall Cure (Mycological Cure and Investigator Global Response assessment of "Cleared"). Assessments

TABLE 3

ABSTRACT

Ninety-three (93) patients were enrolled in a multi-center, vehicle-controlled, parallel, randomized, double-blind trial of butenafine HCl cream 1%. Patients with tinea cruris, diagnosis confirmed by KOH and culture, applied the assigned medications once a day for two weeks. Of the 76 patients who were evaluated for efficacy in the Modified-Intent-To-Treat population, 37 received butenafine and 39 received vehicle. The two groups were demographically and clinically similar. Three primary efficacy endpoints, Mycological Cure (negative KOH and culture), Effective Treatment (Mycological Cure and Investigator Global Response assessment of "Cleared" or "Excellent") and Overall Cure (Mycological Cure and Investigator Global Response assessment of "Cleared") were assessed. Significantly more butenafine-treated patients than vehicle-treated patients showed conversion to negative culture and microscopy four weeks (Day 42) after the end of therapy (81% versus 13% respectively, $p<0.0001$). Effective Treatment cure rate four weeks after the end of therapy (Day 42) was also significantly greater in the butenafine group (73%) than in the vehicle group (5%, $p<0.0001$). Overall Cure rate four weeks after the end of therapy (Day 42) was also significantly greater in the butenafine group (62%) than in the vehicle group (3%, $p<0.0001$). Adverse events possibly, probably, or definitely related to treatment were reported in one (1) patient treated with butenafine during this pivotal clinical trial.

Tinea Cruris

Patient Outcome Category	Day 14 (End of Rx)		Day 42 (Four Week Follow-up)	
	Butenafine	Vehicle	Butenafine	Vehicle
Mycological Cure	78% (29/38)	11% (4/38)	81% (31/38)	13% (5/39)
Overall Cure Rate	32% (12/37)	8% (3/39)	62% (23/37)	3% (1/39)
Effective Treatment	57% (21/38)	8% (3/39)	73% (28/38)	5% (2/39)

including Mycological were conducted at baseline, day 7, 14 and 42. There were 37 evaluable patients who received treatment and 39 who received placebo.
Tinea cruris is a dermatophytosis and in the United States the infection is mainly caused by *Trichophton rubrum,* followed by *T. Mentagrophytes and Epidermophyton flocossum.* Only patients that had the organism present at baseline and had a 4-week follow-up visit were listed. In order to be cured mycologically, both a negative KOH mount and culture had to be present at the 4-week follow-up time point. In this study the only organism that was isolated was *T. rubrum. As* seen in table1, the sponsor's table, "**Tinea Cruris,**" from NDA #20-663, additional information Volume 2 Of 3, p.6-2677, significantly more butenafine -treated patients than vehicle-treated patients remained mycologically cured at the four-week follow-up time period, 81% versus 13%, $p<0.0001$. Changes in mycological cure rates from day 14 to day 42 were of little significance.

Concerning the package insert for:

1). **Tinea pedis,** It should be adjusted as indicated by Mr. P. Dionne in his review for NDA 20-524 (included as an appendix to this review).

2). **Tinea corporis,** Concerning the organisms and mycological cures seen in the clinical studies involved in NDA 20-663 for tinea corporis, significant numbers of *T. Rubrum and T. Tonsurans* were encountered clinically and mycologically cured. Although there was only one clinical case of infection and mycological cure involving *T. Mentagrophytes,* it is similar to the other Trichophyton species and can be included in the indications from the mycological point of view. *In vitro* data is limited for *E. Floccosum and M. Gyppseum* and no mycological infections and therefore no cures were observed. Adequate *in vitro* susceptibility testing was conducted for *M. Canis* but clinical mycological infection and cure was only demonstrated in two patients.

3). **Tinea cruris,** The only organism isolated clinically from infections and cured mycologically was *T. Rubrum.* Because of the basic similarities, other species of trichopyhton can be assumed to be sensitive to butenafine.

In vitro susceptibiity testing is not conducted for topical anti-fungal products. There are no established methods and quantitative correlations have not been established between *in vitro* testing and clinical results. Since the pre-clinical studies were identical for NDA 20-524 and 20-663, changes in the package insert as recommended my Mr. Peter Dionne in his review for NDA 20-524 can be considered as common to NDA 20-663. (See relevevant sections of Mr. Dionne's review, attached as an appendix to this review, p. 62).

The sponsor's proposed labeling includes all organisms with all three indications whether they have been proven directly in clinical studies or not. We have pointed out that infections and subsequent mycological cures have not been shown for all combinations of organisms and the three infections (indications) in these clinical studies. The specific organisms including indications and usage for Butenafine HCL cream would depend on a medical evaluation of the similarities and/or differences in the three listed infections and potential Butenafine effectiveness at the site of infection against the listed organisms and whether direct and/or indirect clinical evidence is sufficient.

Joel Unowsky

Joel Unowsky. Ph.D.
Microbiologist, HFD-520

cc: Orig. NDA 20,663
HFD-520/Division File
HFD-540/Division File
HFD-520/Micro/J.Unowsky
HFD-540/MO/N.Slifman
HFD-520/Pharm/K.Manigi
HFD-540/Chem/E.Papas

Concurrence Only:
HFD-520/DepDIR/L. Gavrilovich 5/8/96
HFD-520/SMicro/ATSheldon
RD#1 & Final init. 5/3/96 ATS

HFD-540/CSO/F.Cross 5/13/96

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 020663

EA/FONSI

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 27, 1996

FROM: Nancy Sager, Team Leader, Environmental Assessment Team

SUBJECT: Review of EA and FONSI for NDA 20-663

TO: Frank Cross, HFD-540

I am returning the EA for NDA 20-663 (butenafine hydrochloride cream). The EA has not been reviewed. As previously discussed the applicant should update their confidential and non-confidential EA for this NDA in accordance with the EA for NDA 20-524 which has been finalized. Please ask the applicant to include the signed compliance statements in the non-confidential EA for NDA 20-663 and also to identify any sections of the EA that contain information that differs from NDA 20-524 (e.g., indications, format item 4.b.).

Please consult the revised EA to me as soon as possible after receipt.

c.c.
EA file 20-663

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

NDA 20-663

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 20-663

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), tinea corporis (ringworm), and tinea cruris (jock itch). 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.

11/14/96
DATE

PREPARED BY
Nancy B. Sager
Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

11/14/96
DATE

CONCURRED
Charles P. Hoiberg
Division Director
Office of New Drug Chemistry-Division 1
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

NDA #20-663: BUTENAFINE HCl CREAM 1%
ENVIRONMENTAL ASSESSMENT
ABBREVIATED FORMAT 25.31a(b)(3)
TABLE OF CONTENTS

NDA #20-663: BUTENAFINE HCl CREAM 1%
ENVIRONMENTAL ASSESSMENT
ABBREVIATED FORMAT 25.31a(b)(3)
TABLE OF CONTENTS (CONTINUED)

NDA #20-663: BUTENAFINE HCl CREAM 1%
ENVIRONMENTAL ASSESSMENT
ABBREVIATED FORMAT 25.31a(b)(3)

1. DATE

October 18, 1996

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 HCl, and the finished product manufacturing, testing, packaging, and use of the topical product designated as Butenafine HCl Cream 1%.

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), tinea corporis (ringworm), and tinea cruris (jock itch). 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:

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 discussed in Section 4.E. The Confidential Environmental Assessment (Attachments 1 and 2) provides information on the license and permit numbers, the issuing authorities and their identification numbers, and the expiration dates.

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 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.

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 the Confidential Environmental Assessment (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 the Confidential Environmental Assessment (Attachment 1).

Water for cleaning and cooling used in the manufacturing of the drug product is discharged into the sewage treatment system. The permits for this purpose are identified in the Confidential Environmental Assessment (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 the Confidential Environmental Assessment (Attachment 2) for a list of environmental permits.

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, 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.

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. 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.

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:

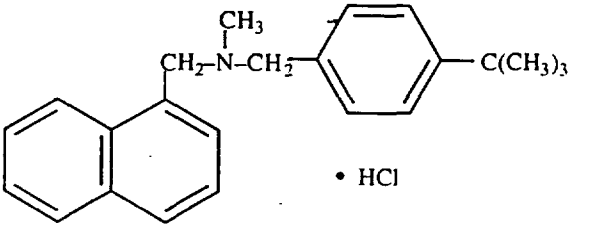
Penederm Incorporated
320 Lakeside Drive
Suite A
Foster City, CA 94404

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 in Japan. 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 HCl is provided in Attachment 1.

A. 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:	$C_{23}H_{27}N \bullet HCl$
Molecular Weight:	353.93
Description:	White crystals or crystalline powder, odorless or with a faint characteristic odor
Melting Point:	210° to 217°C

B. OTHER INGREDIENTS IN THE FORMULATION

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.

- 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 located in 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 provided in the Confidential Environmental Assessment (Attachment 4). 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).

B. PATIENT DISPOSAL

The maximum amount of drug that could enter the wastewater system is provided in the Confidential Environmental Assessment (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 certificate of compliance for the drug substance manufacturer, and compliance statements from the drug product manufacturer and Penederm Incorporated. These compliance statements are included in the Confidential Environmental Assessment.

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 the Confidential Environmental Assessment (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

* 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.

12. LIST OF PREPARERS

This document was prepared by:

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Formulations and Product Development

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Executive Director
Pharmaceutical Sciences

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Toxicologist
Pharmacology and Toxicology

Barry Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

13. CERTIFICATION

The undersigned official certifies that the information presented is true, accurate, and complete to the best of his knowledge.

Terry Gutshall
Vice President, Operations

10/18/96
Date

14. REFERENCES

Berg D., Plempel M. Inhibitors of fungal sterol synthesis: squalene epoxidation and ^{14}C demethylation. J Enzyme Inhibition 3:1-11 (1989).

Hiratani E. *et al.* Studies on antifungal mechanism of action of butenafine HCl. Kaken Study E-11.

Iwatani W., Arika T., Yamaguchi H. Mechanisms of antifungal action of butenafine HCl 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. J.R. Prous Science Publishers, SA 451-459 (1987).

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
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
415-358-0100
FAX 415-358-0101

ATTACHMENT 1

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

MATERIAL	%	TLV (Units)	HAZARD
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 1 (CONTINUED)

PRODUCT NAME: Butenafine Hydrochloride (KP-363)

IV. FIRE AND EXPLOSION HAZARD DATA

FLASH POINT: N/A

FLAMMABLE LIMITS IN AIR, % by volume: N/A

EXTINGUISHING MEDIA: Apply alcohol-type or all-purpose-type foams by manufacturer's recommended techniques for large fires. Use CO_2 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.

Last Revised: 3/27/96

ATTACHMENT 1 (CONTINUED)

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.

Last Revised: 3/27/96

ATTACHMENT 1 (CONTINUED)

PROTECTIVE GLOVES: PVC-coated

EYE PROTECTION: Safety glasses

OTHER PROTECTIVE EQUIPMENT:
Eye bath and safety shower

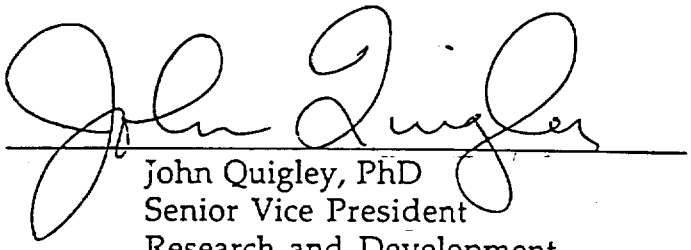
NOTE ---
The opinions expressed herein are those of qualified experts within Penederm Incorporated We believe that the information contained herein is current as of the date of this Material Safety Data Sheet. Since the use of this information and of these opinions and the conditions of the use of the 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.

FDA ADDENDUM

In a separate communication to CDER, the applicant stated that the signed compliance statements could be included in the non-confidential EA.

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
Senior Vice President
Research and Development

10/18/96
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

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 020663

ADMINISTRATIVE DOCUMENTS

JAN 31 1996

NDA 20-663

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

Dear Mr. Calvarese:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Butenafine HCl Cream, 1%

Date of Application: December 22, 1995

Date of Receipt: January 5, 1996

Our Reference Number: NDA 20-663

Unless we find the application not acceptable for filing, the filing date will be March 5, 1996.

Please begin any communications concerning this application by citing the NDA number listed above. Should you have any questions concerning the NDA, please contact:

Frank Cross
Project Manager
(301) 827-2020

Sincerely yours,

Maria Cook 1/29/96

Maria Rossana R. Cook, M.B.A.
Supervisor, Project Management Staff
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation & Research

cc: Orig. NDA 20-663
HFD-82
HFD-540
HFD-540/CSO/Cross
SMO/Katz
MO/Slifman
PH/Mainigi
CH/Pappas
ACKNOWLEDGMENT LETTER

RECORD OF A FORWARD PLANNING MEETING

DATE: February 5, 1996

PARTICIPANTS FROM FDA:

Jonathan Wilkin, Division Director
Linda Katz, Deputy Director
Nancy Slifman, Medical Officer
Ernest Pappas, Chemist
Wilson DeCamp, Supervisory Chemist
Kumar Mainigi, Pharmacologist
Abby Jacobs, Supervisory Pharmacologist
Sue Lee, Biopharmaceutist
Dennis Bashaw, Supervisory Biopharmaceutist
Joel Unowsky, Microbiologist
R. Srinivasan, Biostatistician
Frank Cross, Project Manager
Rosemary Cook, Supervisory Project Manager

SUBJECT: **butenafine HCl cream, 1%**
NDA 20-663

OBJECTIVE: To determine the fileability of NDA 20-663

The meeting was convened to determine the adequacy of NDA 20-663 for filing. All sections of the New Drug Application (NDA) were evaluated in terms of the general content and format requirements.

From a preliminary evaluation of the general content and format, as well as the chemistry, manufacturing, and controls, microbiology, nonclinical pharmacology and toxicology, human pharmacokinetics and bioavailability, clinical data, and statistical sections of the application, it was recommended that NDA 20-663 be filed.

It was concluded that the application was generally complete and was therefore acceptable for filing. However, the need for the following submissions was cited:

1. The CRF's for all patients that terminated have been submitted in the appendix of each clinical report.

2. The weight of the tubes and amount used are in the line listings.

3. The range, mean and standard deviation for each of the two studies, with reference to the second point,

4. The results should be submitted by investigator, if not already submitted.

5. Phototoxicology and allergy testing should be conducted (the timing of this communication is still under discussion at this time).

6. Current patent information.

7. Current marketing history.

The meeting ended amicably.

Frank Cross, Jr., MA, LCDR
Project Manager

cc:
Orig NDA 20-663
HFD-540
HFD-540/DIR/Wilkin
HFD-540/DEP DIR/Katz
HFD-540/SChem/DeCamp
HFD-540/SPharm/Jacobs
HFD-880/SBiopharm/Bashaw
HFD-725/SBiostat/Harkins
HFD-520/SMicro/Sheldon
HFD-540/SPM/Cook
HFD-540/PM/Cross
HFD-540/MO/Slifman
HFD-540/Chem/Pappas
HFD-540/Pharm/Mainigi
HFD-880/Biopharm/Lee
HFD-725/SBiostat/Srinivasan
HFD-520/Micro/Unowsky
HFD-160/Micro/Stinavage
HFD-160/SMicro/Cooney

FORWARD PLANNING MEETING MINUTES

TIMELINE FOR NDA 20-663
BUTENAFINE HCL CREAM, 1%

DAY	DATE	EVENT/ACTION
0	1/5/96	NDA is received. User Fee - SBA
31	2/5/96	Forward Planning Meeting • Fileability decision • Draft review completion dates are requested from each team member Project Manager will bring the following: • 21-day checklist • 21-day Agenda • Most recent Pre-Rounds Report • Gantt Chart • Meeting Minutes
60	3/5/96	Filing Date Chemistry consults for: • Inspections • Methods validation • Tradename • Environmental Assessment
120	5/4/96	Team Meeting as necessary to discuss outstanding issues & assess progress of reviews
180	7/3/96	Regulatory Due Date

Final Review Stage:
Dates for the following activities will be calculated from the timeframes provided by reviewers at the 21-day meeting.

- All reviews finalized
- Labeling Meeting
- Outstanding issues (allow 6 weeks duration)
- Circulation of NDA Action package with letter (allow 2.5 weeks duration)
- NDA package to be provided to Division Director (allow 3 weeks duration)

275	10/6/96	90 Days left until User Fee Due Date
365	1/5/97	User Fee Due Date

FORWARD PLANNING AGENDA

NDA 20-663 BUTENAFINE HCL CREAM, 1%
February 5, 1996

Sponsor:	Penederm
Pharmacologic Class:	Antifungal
Type:	1S
Indication:	Tinea corporis and cruris
Ingredients:	butenafine HCl cream, 1%
Filing Date:	March 5, 1996
Regulatory Due Date:	July 3, 1996
Use Fee Due Date:	January 5, 1997

Expected date of draft review

Project Management	F. Cross	
Chemistry	E. Pappas	
Site of manufacture:		
Name of company:		
Inspections Required?		
Dates submitted:		
Particip. in GMP inspec.:		
Microbiology (CMC)	P. Stinavage	
Microbiology	J. Unowsky	
Pharmacology	K. Mainigi	
Biopharmaceutics	S. Lee	
Biostatistics	S. Thomson	
Clinical	N. Slifman	
Fileability	J. Wilkin	YES NO
	Review Team	

YES **NO**

1.This application is judged sufficiently complete to permit a substantive review, and is hereby filed.
2. Do I have all checklists?

MEMORANDUM OF TELEPHONE CONFERENCE

NDA: 20-663 DATE: 3/11/96

FROM: Frank Cross, Jr., MA, LCDR, Project Manager, HFD-540, (301) 827-2020

TO: Barry Calvarese, Penederm Incorporated, Foster City, CA (415) 378-6479

SUBJECT: butenafine HCl cream, 1%

SPONSOR: Penederm Incorporated

Barry Calvarese was informed that NDA 20-663 was fileable, but that the following information should be submitted:

1. The CRF's for all patients that terminated have been submitted in the appendix of each clinical report.

2. The weight of the tubes and amount used are in the line listings.

3. The range, mean and standard deviation for each of the two studies, with reference to the second point.

4. The results should be submitted by investigator, if applicablen.

Regarding point 3, Mr. Calvarese said these parameters will be calculated and submitted sometime in the next few days. Regarding points 1, 2, and 4, Mr. Calvarese said that these items are already in the original NDA submission. Mr. Calvarese said that he would submit all information requested as an official submission to the NDA. Mr. Calvarese also asked if we want a tabulation of those patients with a negative baseline culture that had experienced no problems. I informed him that we would get back to him on that point.

The telecon ended amicably.

Frank Cross, Jr., MA, LCDR
Project Manager

cc: Orig NDA 20-663
HFD-540
HFD-540/DIR/Wilkin
HFD-540/DEP DIR/Katz
HFD-540/SChem/DeCamp
HFD-540/SPharm/Jacobs
HFD-880/SBiopharm/Bashaw
HFD-725/SBiostat/Harkins
HFD-520/SMicro/Sheldon
HFD-540/SPM/Cook
HFD-540/PM/Cross
TELEPHONE MEMO
HFD-540/MO/Slifman
HFD-540/Chem/Pappas
HFD-540/Pharm/Mainigi
HFD-880/Biopharm/Lee
HFD-725/SBiostat/Srinivasan
HFD-520/Micro/Unowsky
HFD-160/Micro/Stinavage
HFD-160/SMicro/Cooney

RECORD OF TELECON WITH PENEDERM

DATE: June 20, 1996

PARTICIPANTS FROM THE FDA:

J. Wilkin, M.D., Division Director
N. Slifman, M.D., Medical Officer
F. Cross, Project Manager

PARTICIPANTS FROM THE APPLICANT

B. Calvarese, M.S., Executive Director
E. Buehler, Ph.D., Hilltop Research, Inc.

SUBJECT: IND butenafine HCl Cream and gel, 1%, for tinea pedis, cruris, and corporis; NDA 20-663, butenafine HCl Cream, 1% for tinea cruris/corporis.

OBJECTIVE: Telecon to Discuss Additional Photoallergy and Phototoxicity Issues

The **agency** advised the sponsor as follows:

1) 2mg/cm^2 of butenafine cream may be on the sparse side. We would recommend at least 5mg/cm^2 up to 10mg/cm^2

2) We would recommend testing the UVB MED after the same application time that will be used for the challenge patch (probably 24 or 48 hours).

3) We appreciate Penederm's concerns regarding the potential for burning of the control site during the induction phase. If it turns out that the MED in the presence of butenafine cream is significantly higher than the patient's "inherent" MED, then we would agree that an MED should not be used that might result in burning of the patient.

4) During the challenge phase, the photoexposed sites are compared to the non-photoexposed sites. Using the butenafine MED may not represent a problem for a one-time exposure, unless the butenafine MED greatly exceeds the "inherent" MED. Alternatively, it may be possible to expose the vehicle site to 0.75 of the "inherent" MED and the butenafine site to 0.75 of the butenafine MED, with the caveat that the "blind" should be maintained.

Finally, if neither of these seems workable, then, for ethical reasons, we will have to be satisfied with using 0.75 of the "inherent" MED at the butenafine site, knowing that lack of erythema at the time of challenge may represent a sunprotective effect rather than lack of photoallergy.

The **sponsor** outlined its proposal as follows:

- At baseline, 2-3 mg/cm^2 will be applied to a Webril patch for 24 hours. The MED will be determined with a MED at the naive and patch site. No vehicle or saline control is needed. The sponsor felt that a larger amount of drug would result in "caking" on the patch.

- During the induction phase, the MED used will be based on the subject's "inherent" MED.

- During the challenge phase, the vehicle will be exposed to 0.75 of the "inherent" MED, whereas, the butenafine site will be exposed to 0.75 of the MED previously determined in the presence of butenafine. The operator does not need to be blinded but the scorer **does** need to be blinded.

- The rechallenge phase will be data driven. However, it is recommended that subjects with a 1+ or greater reaction be rechallenged. Plus/minus reactions will be rechallenged at the discretion of the investigator.

The **agency** agreed to the sponsor's proposal, provided that the sponsor resubmit its revised protocol for agency review.

The **sponsor** will redesign its proposal and resubmit it to the agency for review.

The telecon ended amicably.

Frank H. Cross, Jr., MA, LCDR
Project Manager, HFD-540

cc:
Orig. IND
Orig. IND
Orig. NDA 20-524
Orig. NDA 20-663
HFD-540
HFD-540/DIV DIR/Wilkin
HFD-540/DEP DIR/Katz
HFD-540/MO/Slifman/6.26.96
HFD-713/BIOSTAT SUPV/Srinivasan
HFD-825/BIOPHARM SUPV/Bashaw
HFD-825/BIOPHARM/Lee
HFD-520/SPHARM/Jacobs
HFD-540/PHARM/Mainigi
HFD-540/SCHEM/DeCamp
HFD-540/CHEM/Pappas
HFD-540/SPM/Cook
HFD-540/PM/Cross/rev1-6.21.96/rev2-6.25.96/rev3-6.27.96

MEMORANDUM OF TELECON

DUPLICATE

PENEDERM INCORPORATED
LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
415-358-0100
FAX 415-358-0101

PENEDERM

NEW CORRESPONDENCE

November 15, 1996

CENTER FOR DRUG
REC'D
NOV 16 1996
MEGA DOC RM

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 20-663, Mentax™, Butenafine HCl 1% Cream
Electronic copies of Clinical Study Reports PDC010-004/PDC010-005 and draft package insert labeling

Dear Dr. Wilkin:

An updated electronic copy (WordPerfect 6.1 for Windows) of the above referenced documents has been sent directly to Mr. Frank Cross. Mr. Cross requested this updated version because the original version, submitted as WordPefect 5.1, could not be read in its entirety by the medical reviewer's computer. Please call if you have any questions about this submission.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION
[ ] LETTER [ ] N.A.I. [ ] MEMO
CSO INITIALS DATE

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
15-358-0100
FAX 415-358-0101

DUPLICATE

PENEDERM

March 1, 1996

X R -
NDA ORIG AMENDMENT

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

EDERM INCORPORATED
AKESIDE DRIVE. SUITE A
ER CITY. CA 94404
358-0100
415-358-0101

PENEDERM

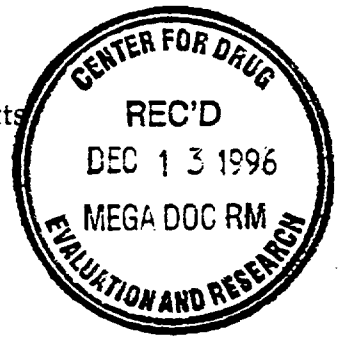
ORIGINAL

ORIG AMENDMENT

SJ

Safety Update Contents

December 12, 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 #20-663, Mentax™ (Butenafine HCl) Cream 1%
Safety Update

Dear Mr. Cross:

As requested, the most recent safety update for Mentax (Butenafine HCl) Cream 1% is enclosed.

This update is nearly identical to the one submitted to NDA #20-524 (Mentax Cream 1% for the treatment of interdigital tinea pedis) on October 8, 1996. The only new safety information provided is from Clinical Study PDC 010-022, Evaluation of Human Photoallergy of Butenafine HCl Cream 1% and Vehicle. The final report for Clinical Study PDC 010-022 was submitted to NDA #20-663 on October 24, 1996.

Please call me at 415-638-3008 if you have any questions or require additional information for this application.

Sincerely,

John Quigley, PhD
Senior Vice President
Research and Development

desk copy: Lt. Cmdr. Frank Cross

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
-358-0100
FAX 415-358-0101

PENEDERM

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,

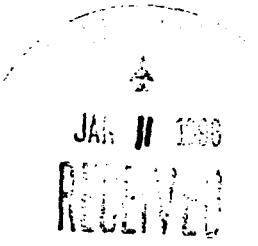
Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
415-358-0100
\X 415-358-0101

PENEDERM

December 22, 1995

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
5600 Fishers Lane, HFD-540
Division Document Room
Rockville, MD 20857



Subject: New Drug Application #20-663
Butenafine HCl Cream 1%
For the Treatment of Tinea Corporis and Tinea Cruris

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 a New Drug Application (NDA) for Butenafine HCl Cream 1% to treat tinea corporis and tinea cruris.

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.

Study reports for this application are listed by section in the Application Summary and are cross-referenced to NDA #20-524, an NDA filed for the identical formulation for the treatment of interdigital tinea pedis. The agreement to cross-reference to NDA #20-524 was communicated by Ms. Kennerly Chapman of your division, and confirmed in writing in a November 13, 1995 letter from Penederm. The tabular listing clearly identifies all reports submitted in NDA #20-524 by name, type, and location by volume and page number.

The complete NDA #20-663 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 1.3	1.1 and 1.2 to 1.3
Nonclinical Pharmacology and Toxicology	1.4	1.1 and 1.4
Human Pharmacokinetics	1.5 to 1.7	1.1 and 1.5 to 1.7
Microbiology	Not Applicable	1.1
Clinical Data	1.8 to 1.18	1.1 and 1.8 to 1.18
Statistical Data	1.19 to 1.28	1.1 and 1.19 to 1.28
Sample and Labeling	1.29	Not Applicable
Total Number of Volumes	29	34

In addition, four desk copies of Section I., Application Summary, Volume 1.1, are included at the request of the Agency.

Penederm Incorporated and will be prepared for a pre-approval inspection by December 22, 1995.

- 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.

- The pharmacology/toxicology studies for NDA #20-663 are designed to define the product safety profile and to allow comparisons to other compounds studied according to similar protocols.

- The studies complied 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 available safety data for the drug product from domestic and foreign sources.

- The cut-off date for clinical data inclusion and preparation of the integrated summary of safety in this new drug application is December 22, 1995.

- Reference is made to the pre-IND meeting that occurred on , and the pre-NDA meeting held IND , Serial Number #020).

- All nonclinical toxicology studies performed by (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 disks, each containing the following:

- 1 disk with SAS data sets for the tinea corporis U.S. pivotal study in SAS transport format. Each file includes a README file of instructions

- 1 disk with SAS data sets for the tinea cruris U.S. pivotal study in SAS transport format. Each file includes a README file of instructions

- A data management user's guide is provided for each SAS data set disk. The data management user's guide provides all information necessary to use the SAS data sets provided.

Also included are disk copies (in DOS WordPerfect 5.1 format) of the Application Summary text and the technical overview text for Nonclinical Pharmacology and Toxicology, Human Pharmacokinetics, Clinical Section, and Statistical Section. The archival copy contains all sections and the review copies contain only the Application Summary and the applicable technical section.

- In addition, disk copies of the Integrated Clinical/Statistical Reports for Clinical Studies PDC 010-004 and PDC 010-005 are provided in DOS WordPerfect 5.1 format for the archival copy and the Clinical review copy.

Note: The conversion of documents from Microsoft Word 6.0 for the Macintosh to DOS WordPerfect 5.1 may result in distortion of some graphic elements. However, all text should be readable and identical to the hard copies provided.

The electronic copies of the application summary, technical sections, and clinical/statistical reports immediately follow this letter. The SAS data set disks are located in Volume 1.28.

All pivotal trial statistical calculations were performed on PC compatible computers containing Intel Pentium chips (free of the floating point error present in earlier versions of the Pentium 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: OMB No. 0910-0001.
Expiration Date: April 30, 1994.
See OMB Statement on Page 3.

FOR FDA USE ONLY

DATE RECEIVED	DATE FILED
5Jan96	
DIVISION ASSIGNED	**NDA/ANDA NO. ASS.**
540	20-663

NOTE: No application may be filed unless a completed application form has been received *(21 CFR Part 314)*.

NAME OF APPLICANT	DATE OF SUBMISSION
Penederm Incorporated	December 22, 1995
ADDRESS *(Number, Street, City, State and Zip Code)*	**TELEPHONE NO.** *(Include Area Code)*
320 Lakeside Drive, Suite A Foster City, CA 94404	415-358-0100
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued) 20-663

DRUG PRODUCT

ESTABLISHED NAME *(e.g., USP/USAN)*	PROPRIETARY NAME *(If any)*
Butenafine Hydrochloride Cream 1%	—

CODE NAME *(If any)*	CHEMICAL NAME
KP-363	N-4-tert-Butylbenzyl-N-methyl-1-naphthalenemethylamine Hydrochloride

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
Cream	Topical	1%

PROPOSED INDICATIONS FOR USE

Indicated for topical application in the treatment of tinea corporis and tinea cruris.

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 *(21CFR 314.420)* REFERRED TO IN THIS APPLICATION:

IND Penederm's IND for Butenafine HCL Cream 1%
DMF
DMF
DMF
DMF

CENTER FOR DRUG ... RECD

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)*

☐ PRESUBMISSION ☐ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☒ ORIGINAL APPLICATION ☐ 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 *(Rx)* ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT *(OTC)*

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 020663

CORRESPONDENCE

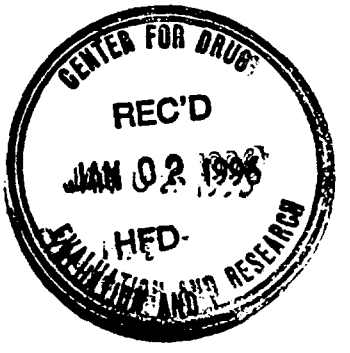
PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
-358-0100
AX 415-358-0101

PENEDERM

2/1/96
hand.

FEB 6 1996

December 27, 1995



Mr. 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
Building 2, Room N229
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA #20-663, Butenafine HCl Cream 1%
For the Treatment of Tinea Corporis and Tinea Cruris

Dear Mr. Cross:

Enclosed with this letter please find a desk copy of the Application Summary for NDA #20-663, Butenafine HCl Cream 1%.

Please call me if you have any questions regarding this NDA. We look forward to working with you and your colleagues to resolve any issues related to approval of this NDA application.

Your time and efforts are greatly appreciated.

Sincerely,

Barry Calvarese

Barry Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

EDERM INCORPORATED
LA[illegible]SIDE DRIVE, SUITE A
I [illegible]TY, CA 94404
3[illegible].00
415-358-0101

PENEDERM

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 #20-663, Butenafine HCl Cream 1%
for the treatment of Tinea Corporis and Tinea Cruris

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

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
415-358-0100
FAX 415-358-0101

ORIGINAL

NEW CORRESP
NC

FEB 5 2/1/96

PENEDERM

January 19, 1996

Mr. 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
Building 2, Room N229
9201 Corporate Blvd.
Rockville, MD 20850

Re: NDA #20-663, Butenafine HCl Cream 1%
For the Treatment of Tinea Corporis and Tinea Cruris

Dear Frank:

It was a pleasure speaking with you yesterday, January 18th. At your request I have enclosed 10 desk copies of the Application Summary (Volume 1.1) and one desk copy of the Human Pharmacokinetics technical section (Volumes 1.5 through 1.7) of NDA #20-663, Butenafine HCl Cream 1%. In addition, two disks are provided, each containing an electronic copy of Protocol PDC 010-004 and Protocol PDC 010-005 in WordPerfect 5.1 format.

Please call me at 415-378-6479 if you have any questions regarding this NDA.

Sincerely,

Barry Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

DUPLICATE

PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
FOSTER CITY, CA 94404
415-358-0100
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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 20-663 Butenafine HCl Cream 1%
For the Treatment of Tinea Corporis and Tinea Cruris
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

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PENEDERM INCORPORATED
320 LAKESIDE DRIVE, SUITE A
'STER CITY, CA 94404
)-358-0100
.X 415-358-0101

PENEDERM

March 27, 1996

NEW CORRESPONDENCE

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

20-663 Shaddox

Re: NDA ~~#20-524~~, Butenafine HCl Cream 1%
for the treatment of ~~Interdigital Tinea Pedis~~ Tinea Cruris & Tinea Corporis Shaddox } Error h.s.

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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Table A
Amount (g) of Drug Used

Investigator	BUTENAFINE N *	Mean	SD	Range	Pts with Unknown Amount	VEHICLE N *	Mean	SD	Range	Pts with Unknown Amount
Greer (#41)	13	15.17	12.6		0	12	17.60	15.0		1
Rodriguez (#42)	11	25.17	15.6		0	10	22.30	14.7		0
Swinehart (#43)	4	14.77	9.7		0	4	12.10	10.4		0
Weiss (#44)	9	16.54	16.3		2	10	9.07	12.4		0
Hebert (#45)	8	16.75	12.3		0	6	15.33	11.4		1
TOTAL	45	18.14	14.0		2	42	15.84	13.8		2

* N, Mean, Standard Deviation based on number of patients with known amount used.

Table A
Amount (g) of Drug Used

	BUTENAFINE					VEHICLE				
Investigator	N *	Mean	SD	Range	Pts with Unknown Amount	N *	Mean	SD	Range	Pts with Unknown Amount
Stewart (#51)	12	22.64	17.2		0	11	27.05	13.3		0
Goldman (#52)	1	12.70			0	2	12.70	11.5		0
Jones (#53)	16	14.27	6.7		0	13	14.26	8.6		1
Weintraub (#54)	2	20.60	13.4		0	1	12.20			0
Lesher (#55)	6	19.92	15.4		0	7	36.71	18.4		1
Kaminester (#56)	10	26.63	15.2		0	10	26.24	12.8		0
TOTAL	47	19.99	13.6		0	44	23.63	14.6		2

* N, Mean, Standard Deviation based on number of patients with known amount used.

:DERM INCORPORATED
.AKESIDE DRIVE, SUITE A
'ER CITY, CA 94404
58-0100
415-358-0101

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REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

March 28, 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 #20-663, Butenafine HCl Cream 1%
for the treatment of Tinea Corporis and Tinea Cruris

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

CITY, CA 94404
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-358-0101

PENEDERM

Confidential Environmental

Non-Confidential Environmental

ober 23, 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

CENTER FOR DRUG
REC'D
OCT 2 4 1996
HFD
EVALUATION AND RESEARCH

Re: NDA #20-663, Butenafine HCl Cream 1%
Confidential and Non-Confidential Environmental Assessments

Dear Dr. Wilkin:

At the request of the Agency, Penederm Incorporated is submitting an updated Environmental Assessment for NDA #20-663. Two versions of the ronmental Assessment are provided; one is confidential; and one is ..-confidential.

This information is submitted in triplicate. We consider all the information contained in this application proprietary. Please be advised that the confidentiality of the enclosed information is provided for under 18 USC, Section 1905 and/or 21 USC, Section 331j.

Please contact us if you have any questions or require additional information for this application.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

ORIGINAL

NEDERM INCORPORATED
0 LAKESIDE DRIVE, SUITE A
'STER CITY, CA 94404
158-0100
415-358-0101

PENEDERM

October 24, 1996

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NDA ORIG AMENDMENT

CENTER FOR DRUG
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OCT 25 1996
HFD
EVALUATION AND RESEARCH

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 #20-663, Butenafine HCl Cream 1%

PDC 010-022 Final Report:
Evaluation of Human Photoallergy of
Butenafine HCl Cream 1% and Vehicle

Dear Dr. Wilkin:

At the request of the Agency, Penederm Incorporated is submitting the final report for PDC 010-022, Evaluation of Human Photoallergy of Butenafine HCl Cream 1% and Vehicle.

This information is submitted in triplicate. We consider all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of the enclosed information is provided for under 18 USC, Section 1905 and/or 21 USC, Section 331j.

Please contact us if you have any questions or require additional information for this application.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.L. ☐ MEMO

CSO INITIALS DATE

ORIGINAL

DERM INCORPORATED
AKESIDE DRIVE, SUITE A
ER CITY, CA 94404
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415-358-0101

PENEDERM

October 25, 1996

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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 #20-663, Butenafine HCl Cream 1%

Mentax™ (butenafine HCl cream) Cream, 1%
Revised Package Insert

Dear Dr. Wilkin:

At the request of the Agency, Penederm Incorporated is submitting the revised package insert for NDA #20-663. A disk with the electronic version in WordPerfect 5.1 DOS format is included in the desk copy.

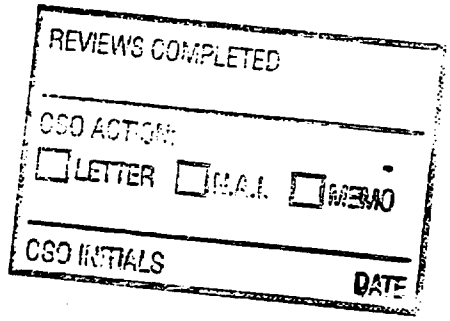
This information is submitted in triplicate. We consider all the information contained in this application proprietary and confidential. Please be advised that the confidentiality of the enclosed information is provided for under 18 USC, Section 1905 and/or 21 USC, Section 331j.

Please contact us if you have any questions or require additional information for this application.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

Desk Copy: Lt. Cmdr. Frank Cross



DUPLICATE

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PENEDERM

NEW CORRESPONDENCE

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
NOV 0 6 1996
HFD

November 5, 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 #20-663, Butenafine HCl Cream 1%
Non-confidential Environmental Assessment

Dear Dr. Wilkin:

At the request of the Agency, Penederm Incorporated is submitting the Environmental Assessment non-confidential compliance statements for the above referenced NDA. Additionally, there are no significant changes from the Environmental Assessment submitted to NDA 20-524 other than the listing of the additional indications of tinea corporis and tinea cruris.

Please contact us if you have any questions or require additional information for this application.

Sincerely,

Barry M. Calvarese, MS
Executive Director
Clinical/Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION
☐ LETTER ☐ N.A.I ☐ MEMO
CSO INITIALS DATE

PENEDERM INCORPORATED
` LAKESIDE DRIVE, SUITE A
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PENEDERM

December 31, 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 20-663, Mentax™ (butenafine Hcl cream) Cream, 1%

Dear Dr. Wilkin:

We have received and reviewed a copy of the proposed labeling for the package insert for Mentax Cream, 1%. Penederm accepts the labeling as worded. Thank you for you efforts.

Sincerely,

John W. Quigley, Ph.D.
Senior Vice President
Research & Development