

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
21-307**

Medical Review(s)

OTC Medical Officer's Review

NDA 21-307

Drug Name: Butenafine HCl Cream, 1%

Sponsor: Schering-Plough Corporation

Pharmacologic Category: Topical Anti-Fungal

Proposed Indications: Tinea Pedis, Tinea Corporis, Tinea Cruris

Dosage Form/Route of Administration: Topical

Submission Date: 07/18/01

Review Date: 12/08/01

Reviewer Name: Andrea Leonard-Segal, M.D., M.S.

Background:

This submission is an addendum to the January 31, 2001 Safety Update Report for butenafine HCl cream 1%. It provides information from the Toxic Exposure Surveillance System (TESS) compiled by the American Association of Poison Control Center from January 01, 2000 through December 31, 2000.

The sponsor states that they have not received the Japanese Periodic Safety Update Report for the time period July 1, 2000 to December 31, 2000. They state that any new adverse event data for butenafine HCl covered in that report will be submitted to the NDA upon request.

Safety Update Data:

There were 20 unintentional exposures to butenafine HCl, 1% cream. Fifteen involved children \leq 3 years of age and 5 involved adults. There were no deaths or serious adverse events reported. One patient, a child, was treated in a healthcare facility and released.

Routes of unintentional exposure:

- ◊ Ingestion: 17 exposures (13 children, 4 adults)
- ◊ Ocular: 1 exposure (adult)
- ◊ Dermal: 1 (adult)
- ◊ Dermal + ingestion: 1(child)

Three patients reported a total of 4 adverse events, all following product ingestion:

- ◊ Nausea + headache (81-year-old woman)
- ◊ Nausea (51-year-old man)
- ◊ Vomiting (18-month-old child)

Summary:

Data from the TESS reported 20 cases of unintentional exposure to butenafine HCl 1% cream. None were associated with serious adverse events or death. Three of the 20 patients reported minor adverse events.

Conclusion:

The TESS data does not suggest that there is a serious safety concern with butenafine HCl 1% cream.

LS

12/7/01

Andrea Leonard-Segal, M.D., M.S.
Medical Officer
Division of OTC Drug Products

Concurrence:

Labeling Review of NDA

NDA	21-307
Submission Date	28-Sep-2000
Applicant	Schering-Plough Corporation 3 Oak Way P.O. Box 603 Berkeley Heights, NJ 07922-0603
Representative	Mark Gelbert, Ph.D., JD Vice President, Scientific Affairs
Drug	Butenafine HCl Cream, 1%
Pharmacological Category	antifungal
Reviewer	Elizabeth F. Yuan, R.Ph.
Items reviewed	<ol style="list-style-type: none">1. Proposed text of the labeling, submitted for:<ol style="list-style-type: none">a. Athlete's foot cartonb. Jock itch cartonc. Tube labeling2. PDF cartons for:<ol style="list-style-type: none">a. athlete's footb. jock itch

Relevant approvals:

NDA 20-524: Approved on October 18, 1996 for the treatment of interdigital tinea pedis (athlete's foot). Dosing regimen is once daily for 4 weeks.

NDA 20-663: Approved on December 31, 1996 for the treatment of tinea corporis (ringworm) and tinea cruris (jock itch). Dosing regimen is once daily for 2 weeks.

NDA 20-524/S-001: Approved on November 25, 1997 for one week, twice a day treatment of interdigital tinea pedis OR 4 weeks, once a day treatment of interdigital tinea pedis.

Background:

Schering-Plough Corporation submitted NDA 21-307, Tradename® (butenafine) cream, 1% for the switch from prescription status to over-the-counter (OTC) marketing for the treatment of athlete's foot, jock itch, and ringworm on September 28, 2000. Tinea versicolor will remain available in a prescription only status. This drug product was originally marketed by Bertek Pharmaceuticals, Inc. prior to the transfer of ownership to Schering Plough in a letter to the Agency dated August 3, 1999. For the purposes of this review, the tradename of this product will be addressed as "TRADENAME®" until the sponsor submits an appropriate tradename for this drug product. There was no consumer educational brochure submitted by the company. The sponsor later submitted mock up

NDA 21-307

Butenafine cream, 1% Rx-OTC Switch

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labeling for the athlete's foot carton and the jock itch carton. (Attached on the last two pages of this review.)

Butenafine hydrochloride cream, 1% was approved for interdigital tinea pedis on October 18, 1996 to "cover the affected and immediately surrounding skin once daily for four weeks". This drug product was later approved on November 25, 1997 for an additional treatment option of "twice daily for 7 days OR once daily for 4 weeks". The directions used in this review will reflect the 4 week dosing regimen as this gave the best efficacy for this product, which may be more beneficial for the over-the-counter use of this product.

Reviewer recommended additions are identified by highlight. Reviewer recommended deletions are identified by a ~~single strike-out line~~.

**Carton Labeling
For Athlete's Foot**

Principal Display Panel

Cures Most Athlete's Foot Between the Toes, Jock Itch, and Ringworm

TRADENAME®

Butenafine Hydrochloride Cream 1%

Antifungal

DRAFT.

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

OTC Medical Officer's Review

NDA 21-307

Drug Name: Butenafine HCl Cream, 1%

Sponsor: Schering-Plough Corporation

Pharmacologic Category: Topical Anti-Fungal

Proposed Indications: Tinea Pedis, Tinea Corporis, Tinea Cruris

Dosage Form/Route of Administration: Topical

Submission Date: 11/01/01

Review Date: 11/21/01

Reviewer Name: Andrea Leonard-Segal, M.D., M.S.

Background:

In the butenafine HCl 1% cream NDA, submitted on September 28, 2000, the sponsor sought approval for the treatment of athlete's foot, jock itch and ringworm in adults and children 12 years and older. They requested a waiver from the requirements for data to assess the safety and effectiveness of the cream for the treatment of athlete's foot, jock itch, and ringworm in children under the age of 12 years. They stated as their reason that this product does not represent a meaningful therapeutic benefit over current OTC treatments for children between the ages of 2 and 12. The sponsor also stated that butenafine HCl 1% cream is not likely to be used in a substantial number of pediatric patients under the age of 2 because of the low incidence of the above indications in that age group.

Subsequently, the Agency requested that the sponsor provide information on the incidence of tinea corporis in children under the age of 12 years and information to support their contention of the low incidence of tinea pedis, tinea corporis, and tinea cruris in children under the age of 2 years. The sponsor provided an Additional Information Amendment on March 8, 2001 and stated that the incidence of tinea corporis in children under 12 years of age in the United States was predicted to be no more than 1.5%.

The Agency sent the sponsor an Approvable Letter on July 27, 2001, which made the following request:

"Also, you should propose a protocol to satisfy a Post-Marketing Commitment to evaluate the safety and efficacy of tinea corporis in the 12 year old and under pediatric population, especially since the dermatophyte species responsible may vary from the adults."

The sponsor has submitted 3 items in response to this request:

1. A copy of a letter submitted on September 26, 2001 requesting a teleconference with the Agency to discuss the request for the protocol. The letter included a comment that a literature review the sponsor conducted did not reveal information that would suggest that the dermatophyte species differed between children and adults.

2. An identical copy of the draft protocol No. CL2001-10 included in the October 5, 2001 Resubmission for "A Clinical Study to Evaluate the Safety and Efficacy of Butenafine Hydrochloride Cream 1% vs. Vehicle Cream in the Treatment of Tinea Corporis in the Pediatric Population."
3. A copy of one article that the sponsor states appears to support the Agency concern that the dermatophyte species responsible for tinea corporis in children may vary from that in adults.

The protocol and the article are reviewed below.

Protocol CL2001-01: A Clinical Study to Evaluate the Safety and Efficacy of Butenafine Hydrochloride Cream 1% vs. Vehicle Cream in the Treatment of Tinea Corporis in a Pediatric Population.

Objective:

To evaluate the safety and efficacy of butenafine hydrochloride cream 1% vs. vehicle cream in treating tinea corporis with once daily applications for 2 weeks.

Study Design:

This is a double-blind, vehicle-controlled, multi-center randomized, 1:1, parallel-group study to be conducted in approximately 100 randomized subjects to obtain approximately 35 evaluable completed subjects in the active treatment group and 35 evaluable completed subjects in the vehicle group. Participants must be experiencing the clinical signs of tinea corporis infection at the start of the study. A positive dermatophyte culture and KOH mount, and physician examination will be required to confirm the clinical diagnosis.

Inclusion Criteria:

- Males or females, ages 2 through 12 years.
- Erythema and scaling. A total physician-rated lesion score for these 2 major signs must be a minimum of 4 of the following scoring system:
 - 0 = None (absent)
 - 1 = Mild (perceptible, but not pronounced)
 - 2 = Moderate (pronounced)
 - 3 = Severe (marked)
- Positive KOH preparation on Day 1 to be enrolled; however the scraping must grow a positive culture for a dermatophyte for the subjects to be evaluable for and continue in the study.
- Parents/guardians/subjects must be:
 - Willing to refrain from using oral medications and topical medications other than the study drug and non-drug therapy to treat or relieve signs and symptoms of tinea corporis for the length of the study.
 - Willing to refrain from using other topical products other than soap on their skin for the entire length of the study.

- Willing to refrain from topical steroids one week prior to starting study treatment and systemic steroids one month prior to starting study treatment. (Nasal or inhaled steroids is permitted.)
- Capable and willing to comply with the visit schedule, study procedures and dosing regimen.
- Capable of providing informed consent. Subject must give assent, if applicable.

Exclusion Criteria:

- Immunocompromised.
- Analgesic, antihistamine, or anti-inflammatory medication (topical or oral) 24 hours prior to the start of the study that may interfere with ability to experience cutaneous sensations.
- Topical antifungal within 4 weeks or systemic antifungal within 4 weeks (or 8 weeks in the case of terbinafine, fluconazole, or itraconazole).
- Oral or topical antibiotics within 3 days of Day 1.
- Concomitant atopic or contact dermatitis, psoriasis, or other skin disease that could interfere with evaluation of the signs of tinea corporis.
- Fungal infections other than tinea corporis or tinea capitis.
- Received a study drug within the 30 days preceding the study.
- Currently participating in another clinical study.
- Drug or alcohol abuse.
- Cannot comply with study instructions.
- Any condition the Investigator thinks should exclude them.
- Previously enrolled in this protocol.

Study Procedures:

Subjects will be required to make 4 visits to the study site; sites may use a 3-day window to schedule subjects for the Week 2 (Days 14-16) visit and a 5-day window for scheduling subsequent visits (± 2 days from protocol visit). **Table 1** summarizes the study procedures.

**APPEARS THIS WAY
ON ORIGINAL**

Table 1. Study Flow Chart

	Day 1	End of Week 2 Days 14 – 16	End of Week 4 Days 26 – 30	End of Week 8 Days 54 – 60 or Early Termination
Consent Form	X			
Assent Form	X			
Medical History	X			
Physical Examination	X			
KOH Read at Site	X			
KOH Read at Central Laboratory				X
Culture Read at Central Laboratory	X			X
Inclusion /Exclusion Criteria	X			
Clinical Signs Assessment	X	X	X	X
Weigh Medication	X	X		
Dispense medication	X			
Medication Application	X*			
Investigator's Global Assessment		X	X	X
Drug Accountability	X	X		
Collect Medication		X		
Dispense Diary	X**			
Collect and Review Diary		X		
Adverse Experience	X	X	X	X
Serious Adverse Events	Report to Study Management Within 24 Hours			
Concomitant Medication	X	X	X	X

* Study medication should be applied once daily for 14 days.

** Diary should be completed once daily, prior to applying medication.

Each tube of study medication will be weighed prior to dispensing it to the subject (parent/guardian) on Day 1 and after it is returned.

Participants (parent/guardian) will be instructed to avoid application of any topical product (other than that required by the study treatment-dosing regimen) during the study period. Excluded products include creams, lotions, ointments, sprays, etc. All other medications being used at the time of the study initiation except for those specified under the Exclusion Criteria may be continued.

Study Discontinuation:

Subject participation may be terminated during the study for any of the following reasons:

- Delayed Exclusion – Day 1 Culture negative for dermatophyte
- Significant protocol violations
- Adverse event for which the subject of investigator desires discontinuation
- At the discretion of the investigator
- At the request of the subject or parent/guardian.

If a subject discontinues prior to the completion of the study, the subject should be requested to return to the clinic for a final visit. The reason for and date of discontinuation will be obtained.

Data Analysis:

Clinical efficacy of the treatment will be evaluated through observations of the treated lesions with respect to conversion to negative mycology (negative KOH and dermatophyte culture) and regression of sign. The evaluation of safety will be based on the rates of incidence of adverse events.

Efficacy Parameters:

- Conversion to negative mycology will be evaluated at week 8.
- Clinical signs scores – The sum of the erythema, maceration, scaling, papules, and vesiculation scores will be determined at each visit.
- Investigator’s Global Assessment of the tinea corporis will be performed at Weeks 2, 4, and 8. (0 = cleared, 1 = minimal signs, 2 = moderate signs, 3 = severe signs)

Efficacy Criteria

- Effective Treatment (conversion to negative mycology with Investigator’s Global Assessment of 0, or 1)
- Complete Cure (conversion to negative mycology with Investigator’s Global Assessment = 0)

The primary criterion of efficacy will be Effective Treatment at Week 8 or study endpoint. Secondary criteria are the Week 8 rates of Complete Cure and the Investigator’s Global Assessment.

The modified intent-to-treat (MITT) data set will include all subjects randomized to the study with a positive culture at baseline and at least 1 post baseline assessment. Discontinued subjects will be included in the MITT analysis of efficacy on the basis of last observation carried forward. All subjects will be included in the MITT analysis of efficacy, regardless of protocol violations or compliance to treatment. The safety analysis will include all subjects (intent-to-treat data set) who received treatment.

Comments:

The sponsor does not state if the vehicle used as the comparator is identical to the vehicle in butenafine HCl 1% cream.

The sponsor should be sure that the study is adequately powered. It appears that the sponsor expects a high percentage of participants who may not complete the study. It is

unclear whether this will be because of misdiagnosis, noncompliance, or other reasons. The study should be sized to provide meaningful safety data.

The study does not evaluate the pharmacokinetics butenafine HCl 1% cream in 2 – 12 year old children.

It is important to determine how many culture negative participants are initially permitted into the study. The analysis should include the percentage of misdiagnoses and the conditions that were mistaken for tinea corporis.

If the study investigators have difficulty predicting who will be culture positive, it would follow that it may be difficult for the consumer (parents/guardians) to properly diagnose tinea corporis.

The data analysis should consider discontinued participants as treatment failures.

The primary endpoint should be complete cure at Week 8. Effective treatment at Week 8 could be a secondary endpoint.

Bronson DM, Desai DR, Barsky S, Foley SM: An Epidemic of Infection with Trichophyton Tonsurans Revealed in a 20-Year Survey of Fungal Infections in Chicago. J Am Acad Derm 8:322-330,1983.

This article reports results of a 20-year survey, the objectives of which were:

- To observe the changes in the causative agents of dermatophytosis in Chicago over 20 years from 1961 – 1980.
- To study in detail the infection caused by T. tonsurans.

Materials and Methods:

Specimens from patients suspected of having a superficial mycosis were cultured on Sabouraud's dextrose agar containing chloramphenicol and cycloheximide at the Mycology Laboratory at Cook County Hospital. Plates were incubated at 26 – 30 degrees centigrade and observed for growth for at least 3 weeks. Positive cultures were identified by gross and microscopic morphology. Whenever necessary, confirmatory tests were performed. Dermatophytes isolated between 1961 and 1980 were grouped by species and type of infection. Charts were reviewed to determine the age, race, and sex of affected persons during the last 3 years of the study. In addition, inflammatory response and anatomic location were recorded in cases of tinea capitis and tinea corporis.

Results:

A total of 8,871 specimens of skin, hairs, and nails were submitted between January, 1961 and December, 1980. From them, 1,292 positive cultures of 13 species of dermatophytes were obtained. Tinea capitis accounted for 506 (39%) of the positive cultures, tinea pedis for 293 (23%) and tinea corporis for 272 (21%). Tinea cruris, tinea unguium, and tinea manus accounted for the remaining 221 (17%). The most common

organism cultured was *T. tonsurans*, followed by *T. rubrum*, *T. mentagrophytes*, *M. audouini*, *E. floccosum*, and *M. canis*.

There was a rise in infection with *T. tonsurans* over the 20-year period. From 1961 to 1965 it was responsible for 45% of the cases of tinea capitis; from 1976 to 1980, it accounted for 96%. Similarly, the organism caused 15% of cases of tinea corporis during the first 5 years of the study, whereas during the last 5 years it was responsible for 76% of cases.

Between 1978-1980, 95% of cases of tinea capitis caused by *T. tonsurans* occurred in children under 15 years of age. During this same time period, 62% of cases of tinea corporis caused by *T. tonsurans* occurred in adults. In most cases of tinea corporis caused by *T. tonsurans*, a history of tinea capitis in a family member, schoolmate, or the patient himself/herself was obtained.

Comments:

*The article does not provide the number of total cases of tinea capitis from each organism in adults and in children or the number of total cases of tinea corporis from each organism in adults and in children during the time intervals studied. It is not clear whether the percentage of cases of tinea corporis caused by each organism differs substantially between adults and children. Therefore, the article does not directly address the question of whether *T. corporis* is caused by different organisms in children and adults.*

Conclusion:

The sponsor has proposed a protocol to test efficacy of butenafine HCl 1% cream for tinea corporis in children ages 2 – 12 years. The proposed data analysis could be improved with better handling of noncompleters and a change in primary endpoints. Because of its small size, the study cannot provide meaningful safety data about the use of this drug in children. The study does not gather pharmacokinetic data that may be important, especially in youngsters with widespread skin disease.

*The article by Bronson, et al., does not answer the question as to whether *T. corporis* is caused by different organisms in children and adults.*

Recommendations:

- *The comparator vehicle should be identical to that in butenafine HCl 1% cream.*
- *The primary endpoint should be complete cure at Week 8. Effective treatment at Week 8 could be a secondary endpoint.*
- *The study should be adequately powered.*
- *Discontinued participants should be considered to be treatment failures.*
- *The percentage of misdiagnoses and the percentage of specific conditions that were mistaken for tinea corporis should be analyzed.*
- *The study needs to provide meaningful safety data.*

/S/

12/5/01

Andrea Leonard-Segal, M.D., M.S.
Medical Officer
Division of OTC Drug Products

Concurrence: 12/5/01

MEDICAL OFFICER'S REVIEW OF NDA 21-307 RS
DIVISION OF DERMATOLOGY AND DENTAL DRUG PRODUCTS, HFD-540

NDA	IND	CORRESPONDENCE DATE:	CDER STAMP DATE:
21-307		10/05/01	10/09/01

SERIAL NUMBER: 000-RS REVIEW DATE: 10/19/01
HFD540 #: 018994 REVISION DATE: 11/14/01

SPONSOR: Bertek Pharmaceuticals.

STUDY MANAGEMENT: Schering Plough Healthcare Products.

DRUG: Proposed name: Lotrimin Ultra cream.
 Generic name: Butenafine HCl cream 1%.

PHARMACOLOGICAL CATEGORY: Topical antifungal.

PROPOSED INDICATION: Tinea corporis.

DOSAGE FORM AND
ROUTE OF ADMINISTRATION: Once daily for 2 weeks.

RESUME: Sponsor submitted on September 28, 2000, NDA 21-307 for the indications tinea pedis interdigitalis, tinea corporis and tinea cruris. An approvable letter was issued on 7/27/01 and in it a pediatric study for the indication tinea corporis was requested because there has been substantial use in this age group for this indication. The Sponsor has submitted to this IND a proposed Protocol 2001-10 to study the use of butenafine HCl cream 1% , a topical antifungal, in tinea corporis in patients 2-12 years old. The submitted protocol is for a 2-week, vehicle-controlled, double blind, randomized (1:1), parallel-group, multi-center study in 100 patients with tinea corporis to study safety and efficacy. The principal investigator has not been named. This study represents a Phase 4 commitment agreed to by the Sponsor when granted an approvable. Initially the Sponsor had requested a pediatric waiver on the grounds that this product would not represent a significant therapeutic alternative in children younger than 12 years old, but a review of the materials supplied by the Sponsor with the NDA showed that 20% of all prescriptions written for butenafine cream in the U.S. had been for children under the age of 12, and that for that age, about 15% of the prescriptions had been written for tinea corporis, diaper dermatitis or unspecified tinea/rash. There is a concern that tinea corporis might actually be more common in children than in adults and that the type of pathogen involved might differ from that seen in tinea cruris in adults.

Butenafine cream is currently approved under the name Mentax® cream for tinea pedis interdigitalis, tinea cruris, and tinea corporis.

The proposed study plans to evaluate the effect of two weeks of treatment with butenafine HCl 1% cream in tinea corporis by evaluating the signs and symptoms scores, the Investigator Global Assessment of the disease and mycology results.

REGULATORY BACKGROUND:

- a) Study Phase 4
- b) Regulatory Intent is to comply with pediatric studies requirement
- c) Date/type of previous meetings concerning this submission/protocol
- d) Principal investigators have not been named
- e) The IRB has not been named.
- f) Previous studies with **similar** drugs in humans have been carried out.

CHEMISTRY AND MANUFACTURING CONTROLS: See Chemist's Review

PHARMACOLOGY: See Pharmacology & Toxicology Review.

PLANNED CLINICAL STUDY:

TITLE: A Clinical Study to Evaluate the Safety and Efficacy of Butenafine Hydrochloride Cream 1% vs. Vehicle Cream in the Treatment of Tinea Corporis in a Pediatric Population

PRINCIPAL INVESTIGATORS: Not identified.

INSTITUTIONAL REVIEW BOARD: Not identified.

DRUG DEVELOPMENT PHASE: 4

NUMBER OF SUBJECTS: 100

AGES OF SUBJECTS: 2-12

INCLUSION CRITERIA:

- Males or females must be between 2 and 12 years of age, inclusively.
- Subjects must have erythema and scaling (clinical signs of tinea corporis). A total physician-rated lesion score for these 2 major signs must be a minimum of 4 (see Section V.B.6.).
- Subjects must have a positive KOH preparation on Day 1 to be enrolled in the study; however, the subjects' scraping must grow a positive culture for a dermatophyte for the subjects to be evaluable for and continue in the study. (Subjects who have a Day 1 culture negative for dermatophytes will be withdrawn from the study as a "delayed exclusion").
- Subjects (or parents/guardians on behalf of the child) must be willing to refrain from using oral medications (prescription or over-the-counter) and topical medications

(prescription or over-the-counter) other than the study treatment and non-drug therapy to treat or relieve the signs and symptom of tinea corporis for the entire length of the study.

- Subjects (or parents/guardians on behalf of the child) must be willing to refrain from using other topical products on their skin for the entire length of the study other than soap used to wash.
- Subjects (or parents/guardians on behalf of the child) must be willing to refrain from using topical steroids one week prior to starting study treatment and systemic steroids one month prior to starting study treatment. (Use of nasal or inhaled steroids is permitted.)
- Subjects (or parents/guardians) must be capable and willing to understand and comply with the visit schedule, study procedures, be able to apply the study treatment and follow the dosing regimen.
- Parents/guardians must be capable of understanding and providing written informed consent. Subjects must give assent, if applicable.

EXCLUSION CRITERIA:

- Subjects who are immunocompromised (e.g., known to be HIV positive, transplant recipients taking immunosuppressant medications, etc.).
- Subjects taking any analgesic, anti-inflammatory medication (topical or oral), 24 hours prior to the start of the study that may interfere with their ability to experience cutaneous sensations.
- Subjects taking any antihistamine drug 24 hours prior to the start of the study that may interfere with their ability to experience cutaneous sensations, unless on a stable dose of antihistamine for at least 6 weeks.
- Subjects who have applied a topical antifungal (prescription or over-the-counter) within 4 weeks or taken a systemic antifungal within 4 weeks (or 8 weeks in the case of terbinafine, fluconazole, or itraconazole) of the start of the study.
- Subjects currently (within three days of Day 1) using either oral antibiotics or topical antibiotics.
- Subjects with any concomitant atopic or contact dermatitis, psoriasis or any other skin disease that could interfere with the evaluation of the subjects' signs of tinea corporis.
- Subjects who have fungal infections other than tinea corporis or tinea capitis.
- Subjects who have received and used a study drug (Investigational New Drug) within the past 30 days immediately preceding this study.
- Subjects who are currently participating in any other type of clinical study.
- Subjects who are active drug and/or alcohol abusers.
- Subjects/guardian/parents who are unable to comply with study instructions.
- Subjects with any condition, which in the Investigator's opinion does not make them an appropriate candidate for the study.
- Subjects who have been previously enrolled in this protocol.

STUDY DESIGN:

This will be a double-blind, vehicle-controlled, multi-center, randomized (1:1), parallel-group study conducted in approximately 100 randomized subjects, to obtain approximately 70 evaluable completed subjects. A positive dermatophyte culture and KOH mount, and physician examination will be required to confirm the clinical diagnosis. Subjects will be followed for 6 weeks after completing the two-week treatment to evaluate effective therapy. Effective therapy consists of either Effective Treatment or Complete Cure, as per the following definitions:

- 1) Mycological Cure will be defined as a negative KOH and negative dermatophyte culture.
- 2) Effective Treatment will be defined as Mycological Cure and an Investigator Global Assessment <2.
- 3) Complete Cure will be defined as a Mycological Cure and complete clearance of signs (an Investigator Global Assessment of 0).

STUDY PLAN:

STUDY FLOW CHART	DAY 1	End of WEEK 2 (Days 14-16)	End of WEEK 4 (Days 26-30)	End of WEEK 8 (Days 54-60) Or Early Termination
Consent & Assent Form	X			
Medical Hx & Physical Exam	X			
KOH read at site	X			
KOH read at central laboratory				X
Culture read at central laboratory	X			X
Inclusion/Exclusion Criteria	X			
Clinical Signs Assessment	X	X	X	X
Medication Weight & Account.	X	X		
Dispense Medication & Diary	X ²			
Medication Application	X ¹			
Investigator's Global Assessment		X	X	X
Collect Medication & Rev. Diary		X		
Adv. Events & Conc. Medication	X	X	X	X
Serious Adverse Events	Report to Study Management Group Within 24 hours			

¹Study medication should be applied once a day for 14 days.

²Diary should be completed once a day, prior to applying medication

OVERVIEW:

Subjects will be required to make 4 visits to the study site. Every effort should be made to schedule the subjects as closely to the protocol required visits as possible. However,

sites may use a three-day window to schedule subjects for the Week 2 (Days 14-16) visit and a five-day window for scheduling subsequent visits (± 2 days from protocol visit).

Reviewer comment: if evaluations are performed outside the three day window, particularly those corresponding to Week-2, adjustments in efficacy analysis might be needed depending on numbers of subjects who might have received treatment for longer than 2 weeks.

VISIT 1—DAY 1—START OF STUDY

1. Subjects will report to the study site with the signs of tinea corporis
Parents/Guardian sign the Informed Consent Form before study participation.
2. The Investigator or designated personnel completes the subject's medical history.
3. Investigator performs a physical examination to evaluate subject's appropriateness for the study.
4. Investigator (physician) examines each subject. The affected tinea corporis areas (lesions) and the location of the sites scraped will be marked in the subject's source documents and on the subject's Case Report Forms. All lesions affected and treated on Day 1 will be evaluated for the entire study.
5. The Investigator or designated study personnel (physician) then evaluates the presence and severity (total score should be at least 4) of the following signs and their severity of the most clinically involved lesion:
 - a) erythema
 - b) scaling
 - c) vesiculation
 - d) maceration
 - e) papules.

The following scoring system will be used to grade the signs:

- 0 = None (absent)
- 1 = Mild (perceptible, but not pronounced)
- 2 = Moderate (pronounced)
- 3 = Severe (marked)

Reviewer comment: these grades should be accompanied by a description that is clinically distinct, to facilitate consistent use by centers and investigators through the study.

6. The Investigator or trained designee will take skin scrapings for KOH preparation and culture only from all affected lesions and surrounding skin (not more than 0.5 inches or 10 millimeters from the lesion) and evaluate the KOH mount for fungal hyphae. It is permissible to repeat the scraping if a negative KOH is obtained. However, only subjects with distinct fungal hyphae will be randomized to study treatment.

Reviewer comment: scrapings should be collected from all areas involved at study entry and pooled. From this pooled sample, a portion taken for direct mount, the remainder used for culture in its entirety.

7. After obtaining the sample, it will be sent to the central laboratory, for culture. Randomize all subjects who meet all inclusion criteria including a positive KOH preparation and assign a subject number in order of presentation and based upon the subject numbers assigned to the site.
8. Weigh each tube of study medication and dispense it according to the randomization code. Two tubes of study treatment will be given for the two-week treatment period.

OTHER VISITS:

These will take place at the end of week-2, week-4 and of week-8.

At each of these visits, there will be evaluation of adverse events, compliance, diary (visit-2 only), signs and symptoms of affected area, global evaluation of treated area

Additional scrapings for mycology will be obtained at week-8 or at study exit.

TREATMENT:

- 30 gm undecorated tube containing butenafine hydrochloride cream, 1%
 - Formula number: P71-021
 - Each gram of active drug contains 10 mg of butenafine HCl in a white cream base of purified water USP, 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, and sodium benzoate NF.
- 30 gm undecorated tube containing vehicle cream
 - Formula number: P71-022
 - Each gram of vehicle cream contains a white cream base of purified water USP, 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, and sodium benzoate NF.

Adequate medication will be packaged so that each subject may be given a maximum of two cartons each containing two (2) undecorated tubes of cream.

Reviewer comment: earlier it was said each subject would receive two tubes. Here it is said up to four tubes. Sponsor should clarify this discrepancy.

The tubes and cartons will bear a label and the tear-off part will be attached to the subjects' case report forms when the product is dispensed. The carton's tear-off part will contain the blinded treatment code and randomization (computer generated). The carton will also have an additional 1-part warning label. Inside the carton will be an Instruction Sheet for the subjects in both treatment groups describing study procedures and warnings. Study treatment will not be shipped until Schering-Plough HealthCare Products has received the following documentation:

1. Completed and signed Form FDA 1572

2. A signed final Protocol
3. Investigators' Curriculum Vita
4. Financial Disclosure Statements for all Investigators
5. An IRB approval of the protocol
6. A sample of the IRB approved consent form

SUBJECT INSTRUCTION PROCEDURES AND WARNINGS:

- At the first visit, you will be given a carton containing two tubes of study medication for your child.
- Wash the affected areas with mild soap and water and dry thoroughly.
- Apply the study medication to all affected areas and the immediately surrounding skin of each affected area once daily for fourteen (14) days even if your child's skin may appear to have healed. Record the date and time of application each day on the diary.
- Do not allow your child to use or take any other medication (over-the-counter or prescription) without first notifying the study center. Please notify the study center immediately since using another medication can affect your child's participation in the study.
- Remember to bring tubes of your child's study medication, the carton, and the diary to your child's next visit to the study site.

MYCOLOGY

1. Specimen Collection Procedure From Tinea Corporis (for KOH preps and Fungal Cultures)

- Thoroughly clean the areas on the treated (or on Day 1 areas to be treated) with an alcohol swab.

Reviewer comment: cleansing skin with alcohol swab could decrease culture yields. It would be more appropriate to cleanse with saline solution.

- Using a sterile scalpel blade, scrape the dry, scaly epithelium from the peripheral edge of all the treated (or on Day 1 areas to be treated) areas.
- Obtain as generous sample as possible to improve ability to visualize the fungal pathogen in the microscopic preparation (KOH) and to send sufficient specimen for isolation of a dermatophyte on fungal culture at the reference laboratory.

2. Fungal Culture

- Place a generous portion of the subject specimen into a ' — ' specimen transport kit and seal edges with tape to prevent leakage of scale. The more specimen the higher the yield.

Reviewer comment: skin scrapings should be obtained from all affected areas at each visit and pooled. If the sites affected at study entry appear cured, skin scrapings should be obtained from the sites that were affected at study entry. A portion of the sample

should be used for direct examination and the entire remaining sample should be cultured.

- Identify the subject initials and randomization number, Investigator's name, date of sample and visit number.
- Return _____ to its zip lock bag and seal.
- Store at room temperature and send to reference laboratory so that the sample arrives within 72 hours. The _____ will provide pre-printed, postage paid airbills. Specimens may be batched daily and shipped to:

- Upon receipt by the reference laboratory, subject specimens will be inoculated on fungal culture media for isolation of pathogens.
- Positive culture of dermatophyte isolate will be identified to their genus and species and reported within 28 days. Negative cultures will be reported as "No dermatophyte isolated" at Day 28.

STUDY DISCONTINUATION

Subject participation may be terminated during the study for any of the following reasons:

- Delayed Exclusion Day 1 Culture Negative for dermatophyte.
- Significant protocol violations.

Reviewer comment: sponsor needs to define what will constitute a significant protocol violation before conducting the study, and indicate whether participants meeting such description will be analyzed any differently.

- Adverse event for which the subject desires to discontinue treatment or if the Investigator determines that participation by the subject should be discontinued.
- At the discretion of the Investigator-If subject's health or well being may be threatened by continuation in this study.
- At the request of the subject or parent/guardian.

If a subject discontinues prior to the completion of the study the subject should be requested to return to the clinic for a final visit. The reason for and date of discontinuation will be obtained. This information will be documented in the source documents and on the Case Report Form.

EVALUATION CRITERIA

The clinical efficacy of the treatment will be evaluated through observations of the treated lesions with respect to conversion to negative mycology (negative KOH and dermatophyte culture) and regression of sign.

1. Efficacy Parameters

- a) Conversion to negative mycology: the conversion of the treated lesions from positive mycology (both positive microscopy and positive culture) at the start of the study to negative mycology (both negative microscopy and negative culture). This parameter will be evaluated at Weeks 8.
- b) Clinical signs scores: The signs of the most clinically involved treated lesion will be graded, erythema, maceration, scaling, papules, and vesiculation. The sum of scores will be determined for each subject at each visit.

Reviewer comment: signs should be graded for all areas affected at the time of study entry.

Investigator's Global Assessment: The Investigator will provide a global evaluation of all the subjects' tinea corporis condition at Weeks 2, 4, and 8, using this scoring system:

- 0 = Cleared, no signs present.
- 1 = Minimal signs present.
- 2 = Moderate signs present.
- 3 = Severe signs present.

Reviewer comment: this scoring system needs to be accompanied of clinically distinct descriptions, to facilitate consistent and reproducible use through the study.

2. Efficacy Criteria

The effectiveness of the tinea Corporis therapy will be evaluated using the following criteria:

- a) Effective Treatment. Conversion to negative mycology, with no residual signs or minimal signs (Investigator's Global Assessment=0,1)
- b) Complete cure. Conversion to negative mycology, with no residual signs (Investigator's Global Assessment=0)

The primary criterion of efficacy will be Effective Treatment at Week-8 or study endpoint. Secondary criteria are the Week-8 rates of complete cure and the Investigator's Global Assessment at Week-8. All other efficacy parameters are to be statistically analyzed as supportive criteria.

Reviewer comment: if evaluation is planned for week 8, which is 6 weeks after completion of treatment, the presence of signs or symptoms at that point would not be representative of cure, since the skin has had sufficient time to normalize if a cure had been obtained. Therefore, only complete cure would be representative of success.

The modified intent-to-treat (MITT) data set will include all subjects randomized to the study with confirmed diagnosis (positive dermatophyte culture at baseline and at least 1 post baseline assessment).

Reviewer comment: MITT should be defined as including all subjects who were randomized and given treatment, whether or not a subsequent evaluation was available.

Discontinued subjects will be included in the MITT analysis of efficacy on the basis of last observation carried forward. All subjects will be included in the MITT analysis of efficacy, regardless of protocol violations or compliance to treatment. A missing or non-evaluable status with respect to effective treatment or cure will be imputed by carrying forward the status at the last evaluable assessment.

3. Safety Parameters and Analysis

The evaluation of safety will be based on the rates of incidence of adverse events, summarized as overall frequency counts, and by body system, by maximum severity, by relationship to study medication, and by preferred term. The safety analysis will include all subjects (ITT data set) who received treatment.

DATA ANALYSIS AND JUSTIFICATION OF SAMPLE SIZE: See Biostatistics Review

CONCLUSIONS:

Before conducting the study, Sponsor needs to supply clinically distinct descriptions for the scales that will be used.

Once such scales are defined, if they are relevant, the study may produce useful information in evaluating safety and efficacy of butenafine HCl cream 1% in children 2-12 years old with tinea corporis.

SUMMARY STATEMENTS REGARDING THE ADEQUACY OF THE PROTOCOL:

- 1) The risks of the proposed study are acceptable in view of its objectives.
- 2) Adequate precautions are being taken.
- 3) The study objectives are clear and are based on a sound rationale.
- 4) The study protocol is adequate to provide data that will achieve the study objectives.
- 5) The informed consent form has not been reviewed.

RECOMMENDED COMMENTS TO BE CONVEYED TO SPONSOR:

1.-Treatment. Sponsor should clarify whether each subject will receive two tubes (page 009) or 4 (page 013).

2.-Scales for efficacy evaluation:

2.a.The scale grades should be accompanied by a description that is clinically distinct, to facilitate consistent use by centers and investigators through the study.

2.b. If evaluations are performed outside the three day window, particularly those corresponding to Week-2, adjustments in efficacy analysis might be needed depending on numbers of subjects who might have received treatment for longer than 2 weeks.

3. Efficacy evaluation.

3.a. If evaluation for efficacy is planned for week 8, which is 6 weeks after completion of treatment, the presence of signs or symptoms at that point would not be representative of cure, since the skin has had sufficient time to normalize if a cure had been obtained. Therefore, only complete cure would be representative of success.

3.b. MITT should be defined as including all subjects who were randomized and given treatment, whether or not a subsequent evaluation was available.

3.c. Sponsor needs to define what will constitute a significant protocol violation before conducting the study, and indicate whether participants meeting such description will be analyzed any differently.

4.-Mycology sampling:

4.a. Scrapings should be collected, after washing with sterile saline rather than with alcohol, from all areas involved at study entry, and should be pooled. From this pooled sample, a portion taken for direct mount, the remainder used for culture in its entirety.

4.b. In addition to obtaining mycology samples at study entry and at study end, it would seem appropriate to study scrapings obtained on the other intermediary two visits.

Investigator and I.R.B need to be identified and a form 1572 and copy of the Curriculum Vitae supplied for each investigator.

151

12/4/01

Joseph M. Porres M.D., Ph.D.
Medical Officer/Dermatology

cc: Orig IND []
NDA 21-307 RS
HFD-540 file
HFD-540/DIVDIR/Wilkin
HFD-540/Acting Clinical TL/Luke
HFD-540/Biophram/Badshaw
HFD-540/PHARM/Jacobs
HFD-540/CHEM/DeCamp
HFD-540/STATS/Al-Osh
HFD-540/CSO/Cross
HFD-550/Microbiology/Altaie
HFD- 560/Ganley
Entered to DFS on: 11/15/01

IND [] MOR

ADDENDUM TO MEDICAL OFFICER'S REVIEW OF NDA 21-307

Submission Date: 9/29/2000

CDER Stamp Date: 10/02/2000

Date Primary Review Completed: 2/21/2001

Date of Medical Reviewer Addendum: 12/05/2001

Applicant: Schering-Plough HealthCare Products

Drug Product: Butenafine HCl Cream, 1% Rx to OTC Switch

OTC Indications Sought:

- 1) cures most athlete's foot, jock itch, and ringworm
- 2) relieves itching, burning, cracking, and scaling which accompany these conditions.

Financial Disclosure

The Sponsor has provided the required certification (FDA Form 3454) regarding financial interests and arrangements of clinical investigators. The Sponsor has certified that the value of compensation to the investigator was not influenced by the outcome of the study. Further, no investigator had a proprietary interest in the product or a significant equity interest in the Sponsor and no investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

JS *12/5/01*

Joseph M. Porres M.D., Ph.D.
Medical Officer, Dermatology

CC: NDA 21-307
HFD-540
HFD-540/CSO/Cross
HFD-520/Micro/Altaie
HFD-540/Chem/DeCamp
HFD-540/Pharm/Mainigi
HFD-540/Stats/AlOsh
HFD-540/Derm/MO/Porres
HFD-540/Derm/TL/Luke
HFD-540/Derm/DivDir/Wilkin

Entered to DFS on: 12/05/01

Reviewer Recommendation:

As this product has significant use in the pediatric population, including up to age 12 years old, and Sponsor has not submitted sufficient information to make a decision regarding their waiver request, it is appropriate to defer pediatric studies in this age group for this product/indication. For the pediatric population age 12-18, such information is not needed due to sufficient similarity to the adult population.

/S/

7/25/01

Joseph M. Porres M.D., Ph.D.
Medical Officer, Dermatology

CC: NDA 21-307
HFD-540
HFD-540/Derm/DivDir/Wilkin
HFD-540/Derm/Act.TL/Luke
HFD-540/Derm/MO/Porres
HFD-540/CSO/Cross
HFD-520/Micro/Altaie
HFD-540/Chem/DeCamp
HFD-540/Pharm/Mainigi
HFD-540/Stats/Al-Osh

Entered to DFS on: 7/25/01

MEDICAL OFFICER'S REVIEW OF NDA 21-307

1 Title and General Information

- 1.1 Title/Heading - Medical Officer's Review.
 - 1.1.1 NDA # 21-307.
 - 1.1.2 Submission date: 9/29/00
 - 1.1.3 CDER date: 10/02/00
 - 1.1.4 Review date: 1/02/01
 - 1.1.5 Review completed: 2/21/01
- 1.2 Drug name:
 - 1.2.1 Generic name: Butenafine hydrochloride.
 - 1.2.2 Proposed trade name: Not given.
 - 1.2.3 Chemical name (structure optional) N-4-*tert*-butylbenzyl-N-methyl-1-naphthalenemethylamine hydrochloride.
 - 1.2.4 Formulation:

<u>Ingredient:</u>	<u>Theoretical %w/w</u>
Butenafine HCl	1.0
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	

1.2.5 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.

Using a wild-type strain and several tolclate-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

An Rx to OTC Switch Meeting took place on November 22, 1999 pre-NDA. At that meeting the sponsor asked whether the Agency would agree with the b.i.d. application for one week as the dosing regimen for the O.T.C. treatment of tinea pedis with butenafine HCL cream. The Agency's response pointed to the lack of studies demonstrating efficacy for the _____ which would affect labeling of the product. The Agency also pointed out that issues of potential concern regarding the b.i.d applications for one week as the O.T.C. dosing regimen, as opposed to the q.d. regimen for four weeks, included:

"In the pivotal clinical trials in NDA 20-524/S-001, a minority of patients (38%) treated for one week with b.i.d. applications experienced effective treatment at 5 weeks post-treatment. In comparison, the majority of patients (74%) treated for four weeks with q.d. applications experienced effective treatment at 4 weeks post-treatment. Concerns about the comparative efficacy of the one week and four week treatments resulted in inclusion of the following statement in the package label, included especially for the benefit of learned intermediaries: "While the clinical significance of this difference is unknown, these data should be carefully considered, especially in selecting the dosage regimen for patients at risk for the development of bacterial cellulitis of the lower extremity associated with interdigital cracking/fissuring." In the O.T.C. setting, with no learned intermediary, it is unclear if and how patients would be able to factor in their risk for developing bacterial cellulitis into their choice of one week or four week dosing regimen."

The Agency expressed willingness to review Sponsor's supplementary analysis that attempted to adjust for differences in the definitions of the primary efficacy variable and baseline characteristics but made it clear that any conclusions based on these supplementary analyses would be a review issue.

Sponsor is requesting a waiver from the requirements for data to assess the safety and effectiveness of butenafine HC cream, 1% for the treatment of athlete's foot, jock itch, and ringworm in children under the age of 12, based on the knowledge that it does not represent a meaningful therapeutic benefit over existing treatments for this age group and it is not likely to be used in a substantial number of pediatric patients under 2 years old because of the low incidence of these indications in that age group.

Reviewer comment:

*The sponsor provides a rationale for requesting a waiver from the requirement to supply data to assess the safety and effectiveness, in children below the age of 12 years old, of butenafine HCL cream 1% for the treatment of athlete's foot and for jock itch, which are not very common in children 12 or younger, and for the treatment of ringworm which is encountered more often in that age group. To be consistent with other topical antifungals approved for OTC use, the waiver should be granted, if the sponsor can supply data showing there is a very low potential exposure to the product below the age of 12 years old, both because the product is actually not being prescribed below that age and because of the frequency with which ringworm (tinea corporis) is expected in children below the age of 12. The rationale that it does not represent a meaningful benefit over existing treatments for this age group is interesting. The proposed label indicates for children 12 or younger: **ask a doctor**, which is consistent with the labeling for other OTC antifungals.*

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. A summary of previous studies is provided in the NDA submission.

6.1 Relevant human experience:

Butenafine 1% cream has been sold in South Korea, Indonesia, Canada, the U.S.A., and Japan,, which is the largest market. It is estimated butenafine 1% cream sales, up to June 2000, have totaled _____ The estimated total number of patients treated , up to June 2000, is over _____ which was estimated on the basis of one patient using _____ of product.

6.2 Important information from related INDs and NDAs -see below under Clinical.

6.3 Foreign experience. Butenafine 1% is approved in the following countries:

Table 1. Approval of butenafine topical products

Country	Approval date	Marketing date	Trade name	Indication	Dosage & type	Rx/OTC
Japan	1/21/92	4/92	Mentax/ Volley	Pedis, cruris, corporis, versicolor	Cream & lotion	RX
South Korea	1/17/94 cream 7/6/96 lotion	3/95	Mentax	Pedis, cruris, corporis, versicolor	Cream & lotion	Rx
USA	10/18/96	1/97	Mentax	Pedis	Cream	Rx
USA	12/31/96	12/97	Mentax	Cruris, corporis	Cream	Rx
Canada	4/15/97	9/97	Dr. Scholl's	Pedis	Cream	OTC
Indonesia	7/2/97	8/97	Dermax	Pedis, manus, cruris, corporis, versicolor	Cream	Rx

According to the submission, butenafine cream has not been withdrawn from any market.

6.4 Human Pharmacology, Pharmacokinetics, Pharmacodynamics: No new data is being presented. Previous studies include:

Evaluation of Human Photoallergy (PDC 010-008) see Medical Officer's review dated 2/29/96 (NDA 20-524, approved 10/18/96).

Plasma levels in normal volunteers (PDC 010-011) see Medical Officer's review dated 2/29/96 (NDA 20-524, approved 10/18/96).

Plasma levels in tinea cruris patients (PDC 010-005) e Medical Officer's review dated 2/29/96 (NDA 20-524, approved 10/18/96).

The results of these studies indicate that there is low absorption of butenafine and minimal formation of its M2 metabolite. 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.

7 Description of Clinical Data Sources: No new studies are being presented. Previous studies include:

Tinea Corporis (PDC 010-004) r tinea corporis -see Medical Officer's review dated 11/18/96 (NDA 20-663, approved 12/31/96).

Tinea Cruris (PDC 010-005) r tinea cruris -see Medical Officer's review dated 11/18/96 (NDA 20-663, approved 12/31/96).

Tinea pedis interdigitalis (PDC 010-001 and 002) e Medical Officer's review dated 2/29/96 (NDA 20-524, approved 10/18/96).

7.2 Post-Marketing Experience. See below, under Safety

7.3 Literature. See below, under Safety.

8 Clinical Studies: no new clinical studies are provided. A summary of previous studies is provided.

9 Overview of Efficacy - Comparative results between studies data obtained from original review of NDA 20-524 and from original review of NDA ~~20-263~~ (see Table 2, below).
20-663

Data from the controlled studies in which Mentax® Cream, 1%, was used for tinea pedis interdigitalis, once daily for 4 weeks (with evaluation at 8 weeks), twice daily for one week (with evaluation at 6 weeks), twice daily for two weeks for tinea cruris and twice daily for two weeks for tinea corporis, have been combined in the table below.

APPEARS THIS WAY
ON ORIGINAL

Table 1. Comparative efficacy of two regimens in the treatment of tinea pedis interdigitalis

INDICATION	Tinea pedis						Tinea corporis	Tinea Cruris
	NDA 20-524			Sup 001			NDA 20-663	
Protocol	PDC 010-001	PDC 010-002	Combined	PDC 010-014	PDC 010-015	Combined	PDC 010-004	PDC 010-005
Dose	q.d	q.d	q.d	b.i.d	b.i.d	b.i.d	q.d	q.d
Weeks Rx	4	4	4	1	1	1	2	2
Evaluation at weeks	8	8	8	6	6	6	6	6
# Total / Evaluable Subjects	150/105	119/80	269/185	451/247	393/271	844/518	91/78	93/76
% Overall cure / placebo	21/8 <0.035	23/5 <0.001	25/9	9/1	20/1	15/0.7	67/14	62/5
% Effective treatment / placebo	68/21 <0.001	70/23 <0.001	74/26	35/4	40/9	38/7	81/14	73/5
% Mycological cure / placebo	83/38 <0.001	88/33 <0.001	90/38	82/42	72/22	79/20	88/14	81/13

Reviewer comment:

Effective treatment was found to be safe and statistically better for butenafine cream 1% than for placebo for both tinea interdigitalis regimens. However, the rate of effective treatment following 5 weeks of observation after the one week twice daily regimen (38%) was of low clinical significance and much lower than for the four weeks once daily (74%). The effective treatment rates when examined at the completion of the one week of treatment were even lower (5%) than for the four week treatment (57%). Therefore, for OTC use, the more effective treatment of once daily for four weeks should be selected

10 Overview of Safety (including data quality): A summary of previous studies (NDA 20-524 [PDC 010-001, PDC 010-002] and Sup 001 [PDC 010-014, PDC 010-015] for tinea pedis, NDA 20-663 for tinea cruris [PDC 010-005] and for tinea corporis [PDC 010-004] is provided. Sponsor claims an overall 2 % level of mild irritation without serious adverse events and no treatment-related hematological and biochemical effects.

In addition to these 6 studies, there have been 5 uncontrolled studies and 7 dermal safety studies, including 1339 subjects, with an average rate of adverse events below 15%. Those related to the skin were below 2%, most of them being very mild and not requiring discontinuation of treatment: erythema, irritation, itching.

Sponsor submitted on 1/31/01 a 4 month safety update, which includes safety data from IND (—) for the indication of tinea versicolor [PDC 010-033], in which one patient experienced a possibly related taste disturbance, and from ongoing studies

with no adverse events reported so far.

The NDA submission includes a report of data from the FDA's AERS system, dated as run on 3/10/2000 and it includes two reports:

49 y.o. female	Reported by health professional 4/06/98	Nail discoloration
69 y.o. female	Reported direct 2/15/00	Dermatitis

The NDA also includes several periodic safety reports from Japan: B-1, B-2, B-3, B-4, B-5, covering 1-97 through 12/99. They record events reported directly to sponsor in Japan or elsewhere as well as those reported in the medical literature. There is one event labeled as severe, with local irritation that resolved, and the others are reported as mild, mostly local irritation, generally resolved; some were incompletely reported, only a few were probably related. Isolated cases have been reported with altered laboratory test results, with unproven relation and outcome. ✓

There is a WHO Adverse Reaction Monitoring Programme report, dated 28 June, 2000 which covers 1992-2000 and includes one adverse event, from Japan, without details.

A Toxic Exposure Surveillance Data report, dated March 23, 2000, covers 1998-1999, and it includes 16 unintentional, residential, acute, mostly children, human exposures by ingestion, with vomiting and which were treated by irrigation/wash or simply observed

Treatment during pregnancy and during lactation has been reported in some of the above quoted studies without adverse events in those cases that could be followed up.

A Postmarketing Safety draft report, PID # D010048, by OPDRA, on butenafine 1% cream, includes a review of the AERS database up to January 31, 2000. It found three US adverse event cases associated with the use of topical butenafine. Two of these were already included in the AERS report provided by the sponsor. The reactions were largely described as local, which included dermatitis (NOS), hypersensitivity reaction, nail discoloration, and skin ulcer (NOS). One report described both a rash and an allergic reaction. All cases involved females. There were no serious outcomes of death, hospitalization, or life threatening events. The outcome for two cases was drug discontinuation, and the third was treatment with a prescription drug product. One case reported a positive dechallenge and a second case reported a negative dechallenge. The three AERS cases were not believed indicative of a serious safety concern, since local reactions are labeled events. Additionally, the report included A MEDLINE search of the English-language literature published from 1966 to 2001 and it did not produce any case reports of butenafine associated adverse drug events. ✓

10.1 Significant/Potentially Significant Events

10.1.1 Deaths: No deaths have been reported

10.1.2 Other Significant/Potentially Significant Events: None have been reported

10.1.3 Overdosage exposure: No overdosage events have been reported

10.2 Other Safety Findings

10.2.1 Laboratory Findings, Vital Signs, and EKGs: No significant changes reported

10.2.2 Special Studies have included human repeat insult test (PDC 010-006), human photosensitization (PDC 010-010), human phototoxicity (PDC 010-007) (performed with UVA although the absorption spectrum of butenafine is mostly UVC/UVB), human photoallergy test (PDC 010-008), showed little or no reactivity

10.2.3 Drug-Demographic Interactions: None reported

10.2.4 Drug-Disease Interactions: None reported

10.2.5 Drug-Drug Interactions: None reported

10.2.6 Withdrawal Phenomena/Abuse Potential: None reported

10.2.7 Human Reproduction Data: None reported

10.2.8 Conclusion on safety: From the available data, it can be concluded there is no significant adverse report profile.

11 Labeling Review: See label review

Sponsor is seeking a change in the label for tinea pedis

From:

DRAFT

To: Directions:

DRAFT

In support of this change, the sponsor has submitted a supplementary statistical analysis comparing the two dosing regimens: one week twice daily versus four week once daily. Sponsor claims that this study shows that it is not possible to demonstrate superiority of one regimen over the other, based on the available clinical trials.

Reviewer comment:

Comparison of the results from the one-week and 4 week study cannot be made for the following reasons:

- *Patients were not randomized at the same time into one or another study*

- *Both studies were conducted at different times and they included different parts of the country*
- *Protocols differed, one accepting patients with onychomycosis and the other did not*
- *Mycology methods might have been different for both studies*
- *Concomitant therapy, washout periods, personal hygiene and skin preparation prior to application of treatment, and other study variables might have been quite different for both studies*
- *Exclusion criteria were not identical and the delayed exclusion rate varied widely from one study to another*
- *The number of subjects was quite different from one study to another*
- *The investigator response of "excellent" in the four week study was defined as 80-99% improvement while on the one week study it was defined as 90-99% improved and it would be impossible to decide how many "excellent" from one study would correspond to "excellent" as defined in the second study, and the sponsor recognizes (page 3,125) that **an unbiased comparison of effective treatment rates across studies is not possible***

Sponsor goes on to make a comparison of the rates of mycology cure and of mycology cure plus clinical cure through Week 2.

Reviewer comment:

It would not be adequate to compare data at week 2, assuming that such data would remain the same if the study stopped there as compared to the known outcome of subjects who were treated for the remainder of the protocol time and then observed post-treatment as per protocol. It cannot be determined whether subjects who showed improvement at 2 weeks would or would not have retained their improvement unless their treatment was continued. In fact, the only way to actually compare data of the two treatment regimens would be to conduct a randomized study comparing one treatment versus the other. Therefore, the sponsor's hypothesis would remain just a hypothesis unless backed by data. Drug approval cannot be assigned on hypothesis but requires data to back it up.

Sponsor has submitted on January 25, 2001 a proposed carton and tube label, which will be reviewed separately. What follows is a series of clinical comments on such label:

DRAFT

Reviewer comment:

Sponsor gives directions for use over the age of 16 and below the age of 12 but fails to give instructions in the age bracket 12 to 16. The Mentax ® Cream 1% label included the following: "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."

The label for Mentax ® Cream 1% included the following recommendations:

- *" Dry the affected area(s) thoroughly before application, if you wish to apply Mentax ® Cream 1% after bathing."*
- *"Avoid the use of occlusive dressing unless otherwise instructed by the physician." The first 4 words of this recommendation should remain in the label of the OTC product*
- *"Do not use this medication for any disorder other than that for which it was prescribed." The new label could change the word prescribed into "indicated"*

*In the absence of studies supporting a **clinically** significant rate of effective treatment for the twice daily treatment for one week, the labeling for butenafine HCL 1% OTC cream should direct the patient to use the treatment once a day for 4 weeks. Although butenafine cream 1% was found safe and statistically more effective than placebo in the one week twice daily study, the rate of effective treatment in this study was only 30%, well below the clinically desirable minimum of at least 50%, and about half the rate of the effective treatment obtained with the four week once daily regimen. In an OTC environment, where a patient would not seek the assistance of a learned intermediary, it would be inappropriate to approve a regimen with such low rate of effective treatment when there is data showing the other regimen to be far more effective and without added adverse events. A higher rate of effective treatment would bring about a decrease in secondary infections which may result from a lack of improvement in tinea pedis interdigitalis. In an OTC situation, a patient who feels better after one or two weeks of treatment, and does not know whether there is a mycological, would most likely continue treatment because some signs and symptoms would still persist.*

12 Conclusions:

The sponsor has demonstrated safety and effectiveness for the claimed indications for butenafine 1% cream under the conditions of use prescribed but is proposing a change in the label from that previously approved. Comments are made on why such changes are not appropriate as per the data which has been made available to the Agency until now.

13 Recommendations

13.1 This reviewer recommends approval for Rx-to-OTC for the treatment of adults for the indication of tinea pedis interdigitalis, once daily for four weeks, and for the indication of tinea corporis and cruris, twice daily for two weeks.

13.2 This reviewer also recommends the granting of a waiver from pediatric

studies, if and when the Sponsor can supply data showing the potential exposure to children is such that it can backup the request for a waiver from pediatric studies.

13.3 Labeling. See separate review of label.

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2/21/01

Joseph M. Porres M.D., Ph.D.
Medical Officer, Dermatology

CC: NDA 21-307
HFD-540
HFD-540/CSO/Cross
HFD-520/Micro/Altaie
HFD-540/Chem/DeCamp
HFD-540/Pharm/Mainigi
HFD-540/Stats/Al-Osh
HFD-540/Derm/MO/Porres
HFD-540/Derm/TL/Okun
HFD-540/Derm/Act.TL/Luke
HFD-540/Derm/DivDir/Wilkin

Entered to DFS on: 2/21/01