CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-307

Administrative Documents

"PARAGRAPH IV CERTIFICATION"

In accordance with 21 CFR § 314.50(i)(1)(i)(A)(4), Schering-Plough HealthCare Products (SPHCP) herewith certifies that it has been granted a patent license from:

Bertek Pharmaceuticals Inc.
373 Vintage Park Drive, Suite D
Foster City, CA 94404

for:

Butenafine HCl cream, 1%
Patent No.US 5021458 (expiry 10/18/2010).

We further certify that Patent No. US 5021458 will not be infringed by the manufacture, use, or sale of Butenafine HCl cream, 1% for which this application is submitted.

Upon receipt of acknowledgement from FDA that the subject application has been filed, SPHCP will comply with the requirements under 21 CFR § 314.52(a)(b)(c), with respect to providing a notice of certification to Bertek Pharmaceuticals, Inc., the owner of the patent and the holder of the approved application for the drug product that is claimed by the patent.

Signed: Mark Gelbert Date: 9/28/00

Mark Gelbert, Ph.D., JD
Vice President Scientific

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PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

View as Word Document

NDA Number:	021307	**Trade Name:**	BUTENAFINE HCL 1% CREAM
Supplement Number:	000	**Generic Name:**	BUTENAFINE HCL 1% CREAM
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	TREATMENT OF ATHLETES FOOT/JOCK ITCH/RINGWORM
Action Date:	9/29/00		

Indication # 1	This new drug application provides for the use without prescription of Lotrimin Ultra butenafine hydrochloride cream, 1%, for the topical treatment of interdigital tinea pedis (athlete's foot between the toes), tinea corporis (ringworm) and tinea cruris (jock itch).
Label Adequacy:	Adequate for SOME pediatric age groups
Formulation Needed:	NO NEW FORMULATION is needed
Comments (if any):	7/26/01: Because of the low prevalence of tinea cruris and tinea pedis in the 12 year old and under pediatric population, these indications would be difficult to study. The Sponsor 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 adults.

Ranges for This Indication

Lower Range	Upper Range	Status	Date
13 years	Adult	Completed	7/26/01

This page was last edited on 7/26/01

/S/ _____ 7/26/01

Signature Date

7/26/01

DEBARMENT STATEMENT

Schering-Plough HealthCare Products 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: Mark Gelbert Date: 9/28/00

Mark Gelbert, Ph.D., JD
Vice President Scientific Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Mark Gelbert, PhD, JD	Vice President, Scientific Affairs
FIRM/ORGANIZATION: Schering-Plough HealthCare Products	
SIGNATURE: Mark Gelbert	DATE: 9/28/00

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

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Team Leader Addendum for NDA 21-307

Submission Date: 9/29/2000
CDER Stamp Date: 10/02/2000
Date Primary Review Completed: 2/21/2001
Date of Team Leader Addendum: 2/23/2001

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.

This addendum is meant to complement the review by the Medical Officer dated 2/21/2001. Specific detail is put forth regarding certain conclusions made and why this Team Leader agrees with the conclusions drawn by the Medical Officer.

Regarding Proposed OTC Dosing Regimen

The Medical Officer recommends a dosing regimen for the indication of tinea pedis interdigitalis, once daily for four weeks. This is different from the dosing regimen proposed by the Applicant of twice daily (morning and night) for one week.

While evidence for efficacy exists for both regimens and both regimens are indicated in the label for the Rx drug product Mentax (butenafine HCl) Cream, 1%, it is clear that the once daily for four week regimen has a significant better "Effective Treatment" rate. The table below is derived from the current labeling for Mentax Cream:

Interdigital Tinea Pedis: 4 Week vs. 1 Week Dosing Regimen								
	4 Week Dosing Regimen				1 Week Dosing Regimen			
	WEEK 4 (End of Treatment)		WEEK 8 (4 Weeks Post-Treatment)		WEEK 1 (End of Treatment)		WEEK 6 (5 Weeks Post-Treatment)	
	Butenafine	Vehicle	Butenafine	Vehicle	Butenafine	Vehicle	Butenafine	Vehicle
Mycological Cure	89% (83/93)	57% (51/90)	90% (66/73)	38% (25/66)	44% (111/253)	28% (75/265)	79% (200/253)	20% (54/265)
Effective Treatment	57% (53/93)	28% (25/90)	74% (54/73)	26% (17/66)	5% (12/253)	3% (7/265)	38% (95/253)	7% (18/265)
Overall Cure	15% (14/93)	8% (7/90)	25% (18/73)	9% (6/66)	0.4% (1/253)	0.4% (1/265)	15% (37/253)	0.7% (2/265)

Patients with interdigital tinea pedis in the absence of moccasin-type tinea pedis and onychomycosis were studied. The term **"Mycological Cure"** is defined as both 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). The 4-week dosing regimen uses the "per protocol" analysis and the 1-week dosing regimen uses "modified-intent-to-treat" analysis.

There may be some reasons for not comparing these two sets of data as has been done in the table above and these have been highlighted on pages 9-10 of the Medical Officer Review of this submission. However, in the background of a scarcity of new comparative studies between the two treatment regimens, statistical evaluation for non-inferiority was performed (See Biostatistics Review).

Looking at the data available, a four-week treatment appears to provide higher cure and treatment rates than the one-week treatment at both the End of Treatment and from 4 to 5 weeks Post-Treatment (See Biostatistics Review for comparisons).

An additional prominent concern is that the one-week regimen does not actually result in any significant overall or clinical cure at 1 week. Rather it is not until 5 weeks Post-Treatment or 6 weeks after initiating treatment that any cure is noticeable.

In an OTC environment, either a treat-until-cured (for a maximum of four weeks) dosing regimen, or a treat for four weeks (see your doctor if not cured) would be most easily understood by the lay public.

There are no significant safety concerns to advocate using a treatment regimen shorter than four weeks. On the contrary, it could be supposed, as described in the Medical Officer Review, that if this drug product were to be used for a shorter time period and a significant number of non-cures resulted, that a safety concern would exist for the 1 week dosing regimen (e.g. secondary infections, etc.). There do not appear to be any drug resistance concerns currently with this product and dermatophytes.

The Applicant appears to have sufficient information from Rx labeling to support OTC use of this product for jock itch and ringworm (tinea cruris and corporis) and with the proposed dosing regimen of twice daily for two weeks as indicated in the Medical Officer Review.

Regarding the Sought Indications

The Applicant seeks the OTC indication of "most athlete's foot." While the Sponsor is correct in asserting that the interdigital variant of tinea pedis is the most common form of tinea pedis (see current edition of Fitzpatrick, et al., *Dermatology in General Medicine*), the statement "most athlete's foot" may not be specific enough. Any OTC labeling for interdigital tinea pedis should be consistent with previous products approved for interdigital tinea pedis (including specific mention of "between the toes" and accompanying graphic).

Regarding the Pediatric Waiver

The Medical Officer Review correctly asserts that the Applicant should provide data to support a waiver of Pediatric studies. No such data was provided in the submission. This data was requested from the Sponsor on February 21, 2001.

/S/ 2/23/01

Markham C. Luke, M.D., Ph.D.
Acting Clinical Team Leader, Dermatology

Team Leader's Memorandum to NDA 21-307
OTC Labeling for Rx to OTC Switch

Submission Date: 9/29/2000
CDER Stamp Date: 10/2/2000
Date Primary Review Completed: 2/21/2001
Date TL Review Completed: 2/23/2001
Date of Labeling Memo: 7/26/2001

Drug Product: Lotrimin Ultra (butenafine hydrochloride cream) Cream, 1%
OTC Labeling – Dosage and Administration

In the original clinical review of this Rx to OTC switch for butenafine hydrochloride cream 1% for the indications of interdigital tinea pedis, tinea corporis, and tinea cruris there was discussion regarding how the dosage and administration would be affected by the Rx to OTC switch. It was felt regarding labeling for tinea pedis that in an "OTC environment, either a treat-until-cured (for a maximum of four weeks) dosing regimen, or a treat for four weeks (see your doctor if not cured) would be most easily understood by the lay public."

It was also noted that there were no significant safety concerns to advocate using a treatment regimen for tinea pedis shorter than four weeks.

During labeling discussions this issue was discussed further. It was agreed at a labeling meeting on March 22, after discussion with the Sponsor, that the Rx labeling for dosage and administration could be carried over in spirit to OTC labeling. The Rx labeling states the following:
"In the treatment of interdigital tinea pedis, Mentax [Rx product being switched] should be applied twice daily for 7 days OR once daily for 4 weeks (NOTE: in separate clinical trials, the 7 day dosing regimen was less efficacious than the 4 week regimen, see CLINICAL STUDIES. While the clinical significance of this difference is unknown, these data should be carefully considered before selecting the dosage regimen for patients at risk for the development of bacterial cellulitis of the lower extremity associated with interdigital cracking/fissuring)."

The proposed OTC labeling for "most athlete's foot between the toes" or interdigital tinea pedis allows for use as follows:
"apply to affected skin between and around the toes twice a day for 1 week (morning and night), or once a day for 4 weeks, or as directed by a doctor..."

It was thought that usage in this manner would provide sufficient cure that would not be misleading to the public.

JS 7/26/01

Markham C. Luke, M.D., Ph.D.
Acting Clinical Team Leader, Dermatology

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: June 12, 2001	**DUE DATE:** July 18, 2001	**OPDRA CONSULT #:** 01-0064

TO: Jonathan Wilken, MD
Director, Division of Anesthetics, Critical Care, and Addiction Drug Products
HFD-540

THROUGH: Frank Cross, Project Manager
HFD-540

PRODUCT NAME:	**Manufacturer:** Schering-Plough Corporation
Lotrimin [redacted] (butenafine 1% cream) **NDA #: 21-307**	

SAFETY EVALUATOR: Alina R. Mahmud, RPh.

SUMMARY: In response to a consult from the Division of Dermatologic and Dental Drug Products (HFD-540), OPDRA reviewed Schering-Plough's justification provided for use of the tradename Lotrimin [redacted] for this product.

OPDRA RECOMMENDATION: OPDRA does not recommend the use of the proprietary name "Lotrimin [redacted]

/S/

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
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/S/

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: June 25, 2001

NDA NUMBER: 21-307

NAME OF DRUG: Lotrimin
(butenafine 1% cream)

NDA HOLDER: Schering-Plough Corporation

I. INTRODUCTION

This consult was written in response to a request from the Division of Dermatologic and Dental Drug Products (HFD-540), for assessment of the tradename "Lotrimin regarding potential name confusion with other proprietary/generic drug names.

The sponsor had originally submitted the proprietary names Lotrimin and to OPDRA for consideration. On March 21, 2001, OPDRA responded with a memorandum to the division stating the reasons why the proprietary names Lotrimin or were not appropriate for this NDA. OPDRA stated that the Center for Drug Evaluation and Research is generally opposed to approving the same proprietary name for different active ingredients by the same manufacturer. In addition, OPDRA had safety concerns with the name Lotrimin, which is also the proprietary name for clotrimazole. OPDRA believes that patients may inappropriately use the butenafine product expecting to be treated with Lotrimin and dose with the wrong dose or duration.

On May 22, 2001, Schering-Plough submitted their rationale for the use of the Lotrimin brand name for the butenafine cream. For commercial reasons, the sponsor withdrew the brand name for consideration for this Rx-OTC switch NDA.

II. RESPONSE TO THE SPONSOR'S APPEAL

Sponsor's comment:

1. **There is no demonstrated safety issue (e.g., contact allergic dermatitis) based on a complete review of the butenafine safety database. More adverse events were seen in the vehicle treated subjects than the butenafine treated subjects. No subject withdrew from the butenafine study due to an adverse event associated with butenfine cream 1%. All dermal safety studies located in NDA 20-524 further establish the excellent safety profile, including no evidence of delayed contact sensitization. The spontaneous reports of adverse reactions during the Rx use of topical**

butenafine cream likewise demonstrate this excellent safety profile. The likelihood a consumer would experience a significant or serious allergic reaction to a butenafine 1% cream product is exceptionally minimal. A complete review of this safety data can be found in the Integrated Summary of Safety for NDA 20-524.

OPDRA's response:

We acknowledge that butenafine has demonstrated a safe adverse event profile and that there is no safety issue with the widespread use of the drug. However, unlike the management of an adverse reaction, where the acceptable level of risk is always weighed against its benefits for the indicated use, there is no acceptable level of risk when we manage a medication error. Medication errors are **preventable events** that can be minimized by implementing many different measures such as differentiating product packaging, the use of barcodes in medication administration, computerized prescription order entry, etc. A decision for a proprietary name change is not based solely on the total number of reported cases and serious patient outcome, but also the *potential* to cause an error and *potential* to cause patient harm.

Sponsor's comment:

2. **The proposed labeling incorporates multiple signals to the consumer to minimize or eliminate any potential for confusion.**

OPDRA's response:

We acknowledge your efforts in complying with the "Drug Facts" format for all OTC drug product labels which is supported by the FDA. Therefore, we have no objections to the proposed format.

Sponsor's comment:

3. **There are a number of similar examples in the market place in which the same brand name, with appropriate suffixes, are used for different active ingredients. In these cases, existing brand names currently on the market with OTC Monograph ingredients were used with recently "switched" active ingredients. The following recent similar examples in the market demonstrate FDA's acceptance of the extension of OTC brand names using new switch ingredients:**

   a. **Terbinafine, an antifungal active ingredient for athlete's foot that was approved as an OTC product in March 1999 under the prescription brand name Lamisil, was also launched under the Desenex brand name in May 2000. The Desenex brand name has traditionally been an currently is marketed with undecolenic acid, miconazole nitrate and clotrimazole active ingredients.**
   b. **Tioconazole, an antifungal ingredient introduced as Vagistat-1 in February 1997 for OTC treatment of vaginal yeast infections, was also launched in June 1999 under the Monistat brand name, which continues to be used for marketing similar products containing the active ingredient miconazole nitrate.**
   c. **Famotidine, an H2 receptor antagonist, was launched under the Pepcid brand name in 1995. Later in 1997, this ingredient was also marketed under the Mylanta brand name, traditionally and currently used to market aluminum and magnesium hydroxide, and calcium carbonate antacids. In this case, a systemic ingredient with a completely different mode of action was marketed under the same brand name (Mylanta) that is also marketed with a completely different pharmacologic class of compounds (antacids).**

As we understand, these changes were made with the notification to the FDA in respective NDA Annual Reports and apparently without FDA action. Although each situation presents unique facts, the above examples present identical issues to those of our own butenafine product. These examples indicate that issues of potential consumer confusion between products of similar brand names can be effectively dealt with, and that there is an acceptable level of safety if confusion results even in situations where systemic actives are involved. In order to assure a "level playing field," FDA should permit the use of the proposed Lotrimin name for the approved butenafine product.

OPDRA's response:

We recognize that brand name line extensions were allowed by the Agency in the past. However, new policies and procedures involving proprietary name reviews have been implemented since approval of the cited examples. The Agency routinely discourages the use of the same proprietary name for different active ingredients by the same manufacturer.

Mylanta AR Acid Reducer containing famotidine was taken off the market in 2000 and has been replaced with the Pepcid brand name. Famotidine is now available as an over-the-counter active ingredient under the proprietary name Pepcid AC and Pepcid Complete. Famotidine is no longer marketed under the brand name Mylanta.

We acknowledge that certain labeling changes can be made in an annual report, however, the Agency reserves the right to address or re-address issues that have safety implications including proprietary names used by distributors, etc.

Sponsor's comment:

4. **It is well established under trademark law and FDA precedent that the use of the brand name Lotrimin( ) is appropriate. FDA may not prohibit the use of an extended brand name unless it is inherently misleading and no other measure (such as clarification in the labeling) will eliminate consumer confusion. The extreme remedy of forbidding the use of a trademark is appropriate only where gross confusion among consumers would be experienced if the use of the mark were permitted. As discussed above, no demonstrated safety issue exists with the use of the proposed brand name, and the proposed labeling further aids the consumer in choosing the appropriate product.**

OPDRA's response:

Although such measures as label clarification is being implemented to eliminate consumer confusion, the use of two proprietary names for the same active ingredient by the same manufacturer is inherently misleading. Per 201.10 (c)(5), "The labeling of a drug may be misleading by reason (among other reasons) of: Designation of a drug or ingredient by a proprietary name that, because of similarity in spelling or pronunciation, may be confused with the proprietary name or the established name of a different drug or ingredient". Please note that the Regulations do not state that the drug must be "inherently" misleading. Furthermore, the Food, Drug, and Cosmetic Act, section 502 [352](a), states that "A drug or device shall be deemed to be misbranded: if its labeling is false or misleading in any particular." Based on the aforementioned regulations and current policies and procedures, the Center for Drug Evaluation and Research discourages the use of the two proprietary names for the same active ingredient by the same manufacturer as it finds this practice to be misleading to the consumer.

III. RECOMMENDATIONS

OPDRA does not recommend the use of the proprietary name "Lotrimin[redacted]

If you have any questions concerning this review please contact Sammie Beam at 301-827-3231.

S 7/17/01

Alina R. Mahmud, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

S 7/18/01

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: July 18, 2001	**DUE DATE:** July 27, 2001	**OPDRA CONSULT #:** 01-0163

TO: Jonathan Wilken, MD
Director, Division of Dermatologic and Dental Drug Products
HFD-540

THROUGH: Frank Cross, Project Manager
HFD-540

PRODUCT NAME:	**Manufacturer:** Schering-Plough Corporation
Lotrimin [redacted] (butenafine hydrochloride cream) 1% **NDA #: 21-307**	

SAFETY EVALUATOR: Alina R. Mahmud, RPh.

SUMMARY: In response to a consult from the Division of Dermatologic and Dental Drug Products (HFD-540), OPDRA reviewed the labeling and packaging of "Lotrimin [redacted] for possible interventions that may help minimize medication errors. In addition, OPDRA refers the Division to consult 01-0064, which addresses the use of the existing proprietary name "Lotrimin" with the current NDA (21-307).

OPDRA RECOMMENDATION: OPDRA does not recommend the use of the proprietary name "Lotrimin [redacted]. In addition, OPDRA has made recommendations for labeling revisions to minimize potential errors with the use of this product (see section III).

/S/

Carol Holquist, R.Ph. for
Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
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/S/

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: **July 24, 2001**

NDA NUMBER: **21-307**

NAME OF DRUG: **Lotrimin**
(butenafine hydrochloride cream) 1%

NDA HOLDER: **Schering-Plough Corporation**

I. INTRODUCTION

This consult was written in response to a request from the Division of Dermatologic and Dental Drug Products (HFD-540), for assessment of the packaging and labeling of Lotrimin regarding preventable medication errors.

The sponsor had originally submitted the proprietary names Lotrimin and to OPDRA for consideration. On March 21, 2001, OPDRA responded with a memorandum to the Division stating the reasons why the proprietary names Lotrimin or were not appropriate for this NDA. OPDRA stated that the Center for Drug Evaluation and Research is generally opposed to approving the same proprietary name for different active ingredients by the same manufacturer. In addition, OPDRA had safety concerns with the name Lotrimin, which is also the proprietary name for clotrimazole. OPDRA believes that patients may inappropriately use the butenafine product expecting to be treated with Lotrimin and therefore administer an incorrect dose.

On May 22, 2001, Schering-Plough submitted their rationale for the use of the Lotrimin brand name for the butenafine cream. For commercial reasons, the sponsor withdrew the brand name for consideration for this Rx-OTC switch NDA.

In response to the sponsor's May 22, 2001 memorandum, OPDRA conducted a secondary review (consult 01-0064). Once again, OPDRA objected to the use of the same proprietary name for different active ingredients by the same manufacturer.

II. SAFETY EVALUATOR RISK ASSESSMENT

OPDRA searched the FDA Adverse Event Reporting System *(AERS)* database for all post-marketing safety reports of medication errors reported for terms "OTC" and "name confusion%", using the Meddra Preferred Term, DRUG MALADMINISTRATION. In addition, the Drug Quality Reporting System (DQRS) database was searched for similar reports with "OTC" and "name confusion". This search strategy retrieved seventeen ***potential*** medication error reports, all of which were related to confusion with use of the same proprietary name for two different active ingredients.

The following reports were retrieved from the AERS and DQRS database:

AERS/DQRS Accession Number	**Date Received**	**Narrative**
3680163-6	03/14/01	**UNISOM** name confusion. Two different drug products sold under the same name by the same manufacturer.
3698813-7	03/19/01	Two generics marketed under the same brand name. No incident, but confusion and potential incident. Bayer markets two Nasal **NEO-SYNEPHRINE** brand products: One is "Neo-Synephrine 12 Hour Nasal Spray." The other is "Neo-Synephrine Regular Nasal Spray". The former contains oxymetazoline 0.05%! The later contains phenylephrine 0.5%. Two generics marked under the same brand name. Also Neo-Synephrine is so closely aligned with phenylephrine, no one would imagine that if they buy, prescribe, dispense, or administer Neo-Synephrine, if might be oxymetazoline.
U-15907	10/17/92	This complaint is mainly with the FDA for allowing a drug company to change product formulations in a way that will be apt to deceive customers, and is confusing at best. For years there was an **ANUSOL** ointment and there was and Anusol HC Cream, with 1% Hydrocortisone. Now there is not Anusol HC Cream with the old formula. There is still a plain Anusol, but the product labeled "Anusol-HC 1" has no Anusol in it.
M-122403	07/17/96	See attached letter regarding confusion between **BETADINE** Ointments containing either PVP Iodine or else Polymixin B and Bacitracin. Reporter is concerned about frequent confusion between two products with virtually the same name but different ingredients. The name "Betadine" has always referred to a line of products whose chief ingredient is PVP Iodine. A relatively new product has been introduced which contains Polymixin B and Bacitracin, and is referred to as clear Betadine.
U-42116	10/10/96	Manufacturer has two products with the same name but different ingredients. **BOROFAX** Topical Ointment contains 5% Boric Acid and Borofax Skin Protectant contains 5% Zinc Oxide. This similarity in names can cause the wrong product to be selected without realizing that the desired actions are different.

M-123890	02/23/97	OTC 8 hour product has 8 mg of **CHLORPHENIRAMINE**. OTC 4 hour product has 4 mg Chlorpheniramine and 60 mg of Pseudoephedrine. This is misleading labeling. This could present a problem with patient who have BP problems and they by the product that contains Pseudoephedrine.
M-121851	05/01/96	Reporter is writing to express concern about the labeling for **CHLORTRIMETON** brand of Pseudoephedrine sold by Schering-Plough. The name "Chlortrimeton" has, for many years, been closely associated with Chlorpheniramine. The association has been so close that the terms are now used interchangeably. When people wish to recommend Chlorpheniramine, they occasionally say "Chlortrimeton". When patients with hypertension, coronary or peripheral vascular disease want OTC medicine to treat upper respiratory infections, reporter often suggests Chlorpheniramine. For some of these patients, Pseudoephedrine could do harm. Reporter's concern is that someone with sever hypertension could grab a box of "Chlortrimeton" thinking hat it was Chlorpheniramine, take Pseudoephedrine instead, and have an adverse event as a result.
M-123860	02/20/97	Product name is misleading: **DIABETIC TUSSIN EX** = Guiafenesin, Diabetic Tussin DM = Guiafenesin plus Dextrometorphan, Diabetic Tussin Allergy Relief = Chlorpheniramine Maleate. One would be lead to believe the product contains Guiafenesin.
U-50421	08/21/97	Ads state "**EXCEDRIN** Aspirin-Free" but there are Excedrin products with Aspirin. May confuse consumers.
M-123868	02/21/97	Who approves drug names at FDA? It is done without any regard for patient safety. **MYLANTA AR** is the next accident waiting to happen. Allowing manufacturers to use a brand name for an entirely different product just by adding a suffix is stupid and dangerous.
U-40262	04/26/95	The reporter is concerned about the product's name change. Some confusion has occurred between **MYLANTA** and Mylanta Gas.
D-121460	03/20/96	**NEO-SYNEPHRINE** Nasal Spray and Drops as well as the injectable form is the brand name for Phenylephrine HCl. Apparently in the fall of 1994, a 12 hour spray was developed with the use of Oxymetazoline 0.05%. The name Neo-Synephrine was used for this new application. Oxymetazoline is on the package label in very small type. People who are allergic or who may have had a bad reaction to Oxymetazoline but not to Phenylephrine might purchase the new 12-hour spray inadvertently and not realize that it is a totally different product. Another potential problem would be if the user was used to the more frequent Neo-Synephrine products and starts to use Oxymetazoline more often than recommended.
D-121920	05/09/96	Report received on USP Veterinary Practicioner's Reporting form. Owner was sent to purchase **NEO-SYNEPHRINE** 0.125% (phenylephrine) Nasal Spray. Owner purchased Neo-Synephrine but it contained oxymetazoline. Poorly named product. Name implies Phenylephrine.
U-50268	06/25/97	The name of this new product, **TAVIST** Sinus (shipping will begin in August), implies that it will contain the same ingredient as other Tavist products. This will cause problems with consumers, especially those with little knowledge of medical products, when they unknowingly consume a product they believe to be Tavist (clemastine fumarate) and is, in fact, Pseudoephedrine and acetaminophen.
U-41995	07/08/96	**TYLENOL** PM might be misunderstood to be just another form of regular Tylenol rather than Tylenol that has an antihistamine, diphenhydramine, in it. The PM label might give patients and/or consumers the idea that the product is just plain Tylenol that works better in the evening comparison to regular Tylenol.
D-124378	05/14/97	Reporter relayed his concerns for the name of these two products (**UNIFED** and Uni fed). These are 2 different products with different ingredients, but have the same name. Unifed is a liquid containing pseudoephedrine Hcl and Uni Fed is a syrup (and tablet) that contains Triprolidine 2.5 mg and pseudoephedrine 60 mg. This could cause confusion.

U-19669	06/23/94	**Unisom** contains 25 mg of doxylamine succinate. Unisom Plus pain relief contains two other ingredients but no doxylamine succinate. The reporter stated that because of confusing names of these products and many others, every day thousands of patients are taking the wrong medications.

In regards to the use of the proprietary name "Lotrimin", OPDRA refers you to consult 01-0064. In addition, the aforementioned reports reinforce our concerns that the use of the same proprietary name (with or without a modifier) creates confusion among consumers where the safe and effective use of the intended medication may be jeopardized.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In the review of the labeling, OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified one area of possible improvement, in the interest of minimizing potential user error.

- The net weight statement has a greater prominence than the established name and strength. The established name is not as legible as the rest of words on the label. Therefore, we recommend increasing the prominence of the established name and strength and decreasing the prominence of the net quantity statement.

III. RECOMMENDATIONS

A. OPDRA does not recommend the use of the proprietary name "Lotrimin" (see OPDRA consult 01-0064).

B. OPDRA has recommended a labeling intervention that might minimize user error.

If you have any questions concerning this review please contact Sammie Beam at 301-827-3231.

/S/

Alina R. Mahmud, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur: /S/

Carol Holquist, R.Ph. for
Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

Butenafine HCl Cream 1%
NDA #21- 307

September 26, 2001
Request for Teleconference

SPONSOR PARTICIPANTS

Mark Gelbert, Ph.D., JD.
VP Scientific Affairs

Robert Nowak, Ph.D.
Director Clinical Research

Mary Williams
Associate Director Regulatory Affairs

KEY QUESTIONS

Background:
In the original application (9/28/00) SPHCP requested a waiver from the requirements for data to assess the safety and effectiveness of butenafine HCl cream, 1% for the treatment of athlete's foot, jock itch, and ringworm in children under the age of 12 years. As allowed under 21 CFR § 314.55(c)(3)(i), the justification for this partial waiver of the requirements was based on the knowledge that butenafine HCl cream, 1% does not represent a meaningful therapeutic benefit over existing treatments (e.g., OTC Monograph Topical Antifungal products) for children 2 years up to 12 years of age. In addition, butenafine HCl cream, 1% is not likely to be used in a substantial number of pediatric patients under the age of two because of the low incidence of the above indications in that age group.

Subsequently, the Agency requested that SPHCP provide: (1) information on the incidence of tinea corporis in children under the age of 12 years, and (2) information to support the low incidence of fungal infections (tinea pedis, tinea corporis, and tinea cruris) in children under the age of 2 years. SPHCP conducted an extensive literature search and provided this information in an Additional Information Amendment (3/8/01). Based on this information, the incidence of tinea corporis in children under 12 years of age in the US was predicted to be no more than 1.5%.

In the July 27, 2001 Approvable Letter for Butenafine HCl Cream 1%, NDA #21-307, the Agency 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."

Butenafine HCl Cream 1%
NDA #21- 307

September 26, 2001
Request for Teleconference

The above referenced literature search on the incidence of fungal tinea infections in children did not reveal any information which indicated that the dermatophyte species responsible for tinea corporis in children may vary from that in adults. SPHCP is now conducting a more extensive literature search on this issue and will provide any information found on this matter to the Agency as soon as it is available.

Questions:

1) Does the Agency agree with SPHCP's original assessment that Butenafine HCl Cream 1% (1) does not represent a meaningful therapeutic benefit over existing treatments for children 2 to 12 years of age, and (2) is not likely to be used in a substantial number of pediatric patients under the age of two because of the low incidence of the above indications in that age group?

2) What information does the Agency have that demonstrates that the dermatophyte species responsible for tinea corporis in children may vary from that in adults?

LABELING REVIEW OF AN NDA
RESUBMISSION

NDA: 21-307	**NDA Resubmission:**	October 5, 2001
	Label Review:	October 24, 2001
Applicant:	Schering-Plough Corporation 3 Oak Way P.O. Box 603 Berkeley Heights, NJ 07922-0603	
Applicant's Representative:	Mark Gelbert, Ph.D., JD Vice President, Scientific Affairs	
Drug:	Butenafine hydrochloride cream, 1%	
Pharmacologic Category:	Antifungal	
Reviewer:	Nahid Mokhtari, Ph.D.	
Items Reviewed:	Copies of the final printed labeling for 12, 15, 24 and 30 gram package sizes	

Background

On October 5, 2001, the sponsor submitted 20 copies of the final printed labeling as amendment to NDA 21-307 in response to the agency approvable letter of July 27, 2001 (FPL). The sponsor indicated that the FPL was identical in content to the labeling in the agency's approvable letter.

Reviewer's Comments

The FPL was compared to the labeling in the approvable letter of July 27, 2001. The FPL is identical in content to the labeling enclosed in the approvable letter (Attachment A) and is acceptable.

/S/

Nahid Mokhtari, Ph.D.
DOTCDP (HFD-560)

LABELING REVIEW OF AN NDA
ADDENDUM

NDA: 21-307	**NDA Submission:**	September 28, 2000
	Label Review:	May 25, 2001
	Addendum:	July 26, 2001
Applicant:	Schering-Plough Corporation 3 Oak Way P.O. Box 603 Berkeley Heights, NJ 07922-0603	
Applicant's Representative:	Mark Gelbert, Ph.D., JD Vice President, Scientific Affairs	
Drug:	Butenafine hydrochloride cream, 1%	
Pharmacologic Category:	Antifungal	
Reviewer:	John D. Lipnicki	
Items Reviewed:	Carton and tube labeling for the 12, 15, 24, and 30 gram package sizes	

Background

On June 8, 2001, the sponsor submitted draft revised labeling for NDA 21-307 in response to agency comments facsimilied on March 2, 2001 and a meeting with the agency on March 22, 2001. The agency provided comments on the June 8, 2001 revised labeling at a teleconference with the sponsor on July 19, 2001 (with written comments facsimilied to the sponsor on July 23, 2001).

In their subsequent response letter on July 23, 2001, the sponsor agreed with all changes recommended in the agency's facsimile of July 23, 2001 and included draft carton labeling for the 12 gram athlete's foot product with the agency's recommendations. The sponsor noted that identical carton and tube labeling would be submitted for the 12, 15, 24, and 30 gram package sizes if the labeling submitted on July 23, 2001 was found acceptable by the agency.

On July 24, 2001, the sponsor was notified of the acceptability of the draft labeling submitted on July 23, 2001. This addendum concerns those changes made by the sponsor (per their letter of July 23, 2001) to the 12, 15, 24, and 30 gram package sizes as received by the agency on July 25, 2001.

Reviewer Comments

Athlete's Foot and Jock Itch Products – Front Panel Carton Labeling:

1. The "Flag the Label" banner has been expanded from "—" to "NEW! DIFFERENT INGREDIENT".

2. The tradename is "LOTRIMIN® ultra™" (noted as acceptable in the agency's July 23, 2001 comments).

3. The prominence of the statement of identity has been enhanced in relation to the size of the most prominent printed matter on the front panel (approximately 0.4 times the size of the Lotrimin tradename).

Athlete's Foot and Jock Itch Products – Back Panel Carton Labeling:

The sponsor has indicated that the website referenced in the carton labeling (www.lotrimin.com) will direct consumers to both Lotrimin AF® and Lotrimin® ultra™ products.

Athlete's Foot Product – Back Panel Carton Labeling and Tube Labeling:

Under the Drug Facts heading "Directions", the phrases "to affected skin between and around the toes" and "or as directed by a doctor" have been added to the "**for athlete's foot between the toes**" bullet to read: "apply to affected skin between and around the toes twice a day for 1 week (morning and night), or once a day for 4 weeks, or as directed by a doctor." However, the phrase "or once a day for 4 weeks," in the latter bullet is repeated (i.e., "...or once a day for 4 weeks, or once a day for 4 weeks,...") on the 15, 24, and 30 gram athlete's foot product carton labeling.

Jock Itch Product – Front Panel Carton Labeling:

1. The "Flag the Label" banner has been expanded from "—" to "NEW! DIFFERENT INGREDIENT".

2. The tradename is "LOTRIMIN® ultra™".

3. The prominence of the statement of identity has been enhanced in relation to the size of the most prominent printed matter on the front panel.

Conclusion

Labeling content for the 12, 15, 24, and 30 gram package sizes is acceptable except for the repetition of the phrase "or once a day for 4 weeks," under the "Directions" heading in the "for athlete's foot" bullet on the 15, 24, and 30 gram athlete's foot product carton labels. This review considered labeling content only and does not address appropriate font, type size, or barline/hairline thickness as specified in 21 CFR 201.66. In their July 25, 2001 submission, the sponsor has stated that the labeling meets all of the content and format requirements of 21 CFR 201.66. The sponsor also states that the labeling for their 12, 15, 24, and 30 gram package sizes is identical to that included with their July 23, 2001 response to the agency's July 23, 2001 recommendations (except for package size).

Recommendations

We recommend approval of the submitted labeling for the 12, 15, 24, and 30 gram package sizes with the deletion of the repeat of the phrase "or once a day for 4 weeks," on the 15, 24, and 30 gram athlete's foot product carton labels (as noted on the attached labeling). The sponsor should be reminded to comply with applicable content and format requirements of 21 CFR 201.66.

/S/

John D. Lipnicki
Team Leader, Team 2
DOTCDP (HFD-560)

cc:
HFD-560/Ganley
HFD-560/Katz
HFD-560/Lipnicki
HFD-560/Segal
HFD-560/Keravich
HFD-540/Cross

7-26-01

n:/team2/nda/butenafine/addendum.doc

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

Meeting Date: November 22, 1999 Time: 1030 Location: S300
Meeting ID # 5127

Rx to OTC Switch Meeting for NDA's 20-524 and 20-663, Mentax® (butenafine hydrochloride cream) Cream, 1%

Sponsor: Bertek Pharmaceuticals, Inc.

Meeting Chair: Jonathan K. Wilkin, M.D.

Meeting Recorder (Project Manager): Frank Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
Wilson DeCamp, Ph.D., Chemistry Team Leader, DNDCIII, HFD-540
Kumar Mainigi, Ph.D., Pharmacologist/Toxicologist, DDDDP, HFD-540
Dennis Bashaw, Pharm. D., Biopharmaceutics Team Leader, DPEIII, HFD-880
Martin Okun, M.D., Ph.D., Clinical Team Leader, DDDDP, HFD-540
R. Srinivasan, Ph.D., Biostatistics Team Leader, DOBIV, HFD-725
Steve Thomson , Biostatistician, DOBIV, HFD-725
Charles Ganley, M.D., Division Director, DOTCDP, HFD-560
Linda Katz, M.D., M.P.H., Deputy Division Director, DOTCDP, HFD-560
John Lipnicki, Team Leader, DOTCDP, HFD-560
Andrea Segal, M.D., Medical Officer, DOTCDP, HFD-560
Donald Dobbs, Labeling Reviewer, DOTCDP, HFD-560
Gail Gantt, DOTCDP, HFD-560
Babette Merritt, Regulatory Health Project Manager, DOTCDP, HFD-560
Frank Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Sponsor Attendees, titles and offices:

Bertek Pharmaceuticals:

Bhaskar Chaudhuri, Ph.D., Vice President and General Manager
Mary Treuhaft, Ph.D., Vice President, Regulatory and Clinical Affairs

Schering-Plough HealthCare Products:

John Clayton, Ph.D., Senior Vice President and Regulatory Affairs
Mark Gelbert, Ph.D., J.D., Vice President, Scientific Affairs
Mary Williams, Associate Director, Regulatory Affairs
Doreen Frank, Associate Director, Regulatory Affairs
Clover Bergman, Vice President Footcare Marketing

Discussion:

With reference to the briefing package of November 5, 1999, submitted to NDA 20-524 and 20-663, the Agency offered the following advice/recommendations:

Chemistry, Manufacturing and Controls:

The meeting package did not include any CMC questions. All CMC information pertinent to NDA 20-524 and NDA 20-663 since their approval has been kept current via the NDA supplement route.

2. CMC changes after NDA submission may affect the review of this proposed NDA.

2. Regarding the container/closure system, three sizes (2 g, 15 g and 30 g) were approved for NDA 20-524 and NDA 20-663. Will the same container/closure system be used? If a size outside the present range is used, appropriate stability data should be submitted to support that size.

3. A statement should be given that the same CMCs will be used as performed for NDA 20-524 and NDA 20-663. This statement should also assure that the identity, strength, quality and purity of the drug product will be maintained for OTC use.

4. An Environment Assessment should be submitted since the drug products may affect a greater population for OTC use than the Rx.

5. It is important that the drug product labeling for NDA 20-524 and NDA 20-663 be exhausted before OTC marketing. In the interim, if the Rx labeling is not used up before OTC launch, the OTC labeling should be different from that used for Rx use.

Pharmacology/Toxicology:

No comments.

Biopharmaceutics:

No comments.

Clinical (Division of Dermatologic and Dental Drug Products):

1) Question 1 of November 5, 1999, Meeting Briefing Package: "Does the Agency agree with *b.i.d.* applications for one week as the dosing regimen for the OTC treatment of tinea pedis with butenafine HCl cream?"

Agency:

Under NDA 20-524/SE2-001, butenafine HCl cream, 1% was approved for *b. i. d.* applications for one week in treatment of *interdigital* tinea pedis. Efficacy and safety of butenafine HCl cream, 1% has not been demonstrated in treatment [redacted] To address this question, the Sponsor is strongly encouraged to perform clinical efficacy studies in patients with [redacted] Product labeling would be reflective of the specific indications studied in the clinical trials.

Issues of potential concern regarding the bi.d. applications for one week as the O.T.C. dosing regimen, as opposed to the q.d. regimen for four weeks, include:

a. 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 OTC 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 a one week or four week dosing regimen.

Sponsor:

In response to the Agency's above recommendation, the suggestion was made that the clinical trial results for the different dosing regimens are not directly comparable because of differences in the definitions of the primary efficacy variable and baseline characteristics.

Agency:

The Agency expressed willingness to review Sponsor's supplementary analyses that attempted to adjust for these differences, but that any conclusions based on these supplementary analyses would be a review issue.

b. According to the draft educational brochure, patients who use butenafine for one week but do not see any improvement within 4 weeks would be encouraged to "see a doctor". This creates the possibility that many patients may be encouraged to seek attention of a learned intermediary for a condition that might otherwise have been treated more effectively with a q.d. regimen for four weeks, without needing the attention of a learned intermediary.

2) Question 2 of November 5, 1999, Meeting Briefing Package: "Does the Agency agree with the use of the "apply to the affected area" in the directions for use in the labeling of butenafine HCl cream?"

Agency:

Interdigital-type tinea pedis was the indication studied in clinical trials conducted under NDA 20-524 and NDA 20-524/SE2-001. In those studies, patients were instructed to rub the study medication into all interdigital spaces and immediately surrounding skin of the affected foot or feet. The OTC directions should specify the treatment site (e.g., between the toes) approved under the NDA. A diagram can be used to direct proper consumer use for the interdigital-type tinea pedis indication.

3) Question 3 of November 5, 1999, Meeting Briefing Package: "Does the Agency agree that the current safety database supports the switch of butenafine to OTC status?"

Agency:

Adequacy of the current safety database to support switch of butenafine to OTC status is a review issue and cannot be addressed at this time. In addition to the sources listed by the sponsor, the World Health Organization database and regional poison control databases should be queried for adverse event reports.

4. Additional Comments:

The drug product is indicated for use in children 12 years of age and older. Tinea corporis and pedis occurs in children younger than 12 years of age. The sponsor has not addressed pediatric plans for this age group.

Clinical (Division of Over the Counter Drug Products):

1. After 1 week of treatment, the treatment effective rate is 38% for interdigital T. pedis. If the product is approved for the OTC market, the 4 week treatment regimen, with its higher efficacy rate, may make more sense. The word "cures" is misleading when fewer than 50% of subjects with a particular indication actually "cure". This may require an advisory committee to discuss the directions for use (duration of therapy) in an OTC setting. The indications' language in labeling may include "most".

2. Since Mentax® has not been studied in [redacted] this needs to be done before a general [redacted] indication could be approved.

3. The Division of Dermatologic and Dental Drug Products will investigate whether subjects develop an increase in skin irritation early in treatment. If not, the proposed label needs to be changed.

4. Depending on the treatment duration, a labeling comprehension study may need to be done to insure that subjects understand the likely clinical outcome of treatment and where to apply if [redacted] is not an approved indication.

Sponsor:

The Sponsor expressed its reluctance to include language in the proposed label for this drug that patients be specifically directed to apply this drug between and around the toes.

Agency:

The Agency indicated that the decision as to the specific language to be incorporated into the label is a review issue.

Sponsor:

The Sponsor inquired about the willingness of the Agency to review a clinical study protocol that has a 1 week dosing regimen and incorporates a contingency for a longer treatment regimen for the subset of those patients who are not cleared at the end of the 1 week treatment period.

Agency:

The Agency said it would be willing to consider the feasibility of such a protocol. The treatment groups would need to be adequately defined. Issues related to multiple hypotheses being tested and a possible need for nesting of those multiple hypotheses would also have to be addressed in the Sponsor's proposed protocol.

Biostatistics:

No comments.

Project Management:

1. The Food and Drug Administration Modernization Act [FDAMA] of 1997, Section 111, Pediatric Studies of Drugs, effective April 1, 1999, requires the following:

   Per 21CFR 314.50(d)(7), NDA applications are required to contain "A section describing the investigation of the drug for use in pediatric populations, including an integrated summary of the information (the clinical pharmacology studies, controlled clinical studies, or uncontrolled clinical studies, or other data or information) that is relevant to the safety and effectiveness and benefits and risks of the drug in pediatric populations for the claimed indications, a reference to the full descriptions of such studies provided under paragraphs (d)(3) and (d)(5) of this section, and information required to be submitted under Section 314.55."

   In addition, per 21CFR 314.55(a), each NDA "application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration shall contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective...." Under 21CFR 314.55(d) "this section does not apply to any drug for an indication or indications for which orphan designation has been granted under part 316, subpart C, of this chapter."

   A waiver can be requested in accordance with 21CFR 314.55(c).

2. For applications submitted after February 2, 1999, per 21CFR 54.3 and 21CFR 54.4, an NDA applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests.

3. If the Sponsor has an Information for Patients leaflet/labeling, please submit it with the proposed NDA.

Signature, minutes preparer: /S/
Concurrence Chair (or designated signatory): /S/
Attachment/Handouts:
Briefing Package, dated November 5, 1999

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: October 19, 2000 Number of Pages (including cover sheet) - 3

TO: Mary Williams, Associate Director, Regulatory Affairs
COMPANY: Schering-Plough HealthCare Products
FAX #: 908-679-1741

MESSAGE: Minutes from our October 13, 2000, teleconference are attached to this facsimile transmission.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

Teleconference Date: October 13, 2000 Time: 1230 Location: N225

User Fee Discussion for NDA 21-307, Mentax (butenafine hydrochloride cream) Cream, 1%

Applicant: Schering-Plough HealthCare Products

Meeting Chair: Frank Cross, Jr., M.A., CDR, Project Manager, DDDDP, HFD-540

Meeting Recorder (Project Manager): Frank Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Beverly Friedman, Consumer Safety Officer, User Fee Staff, Office of the Center Director
Frank Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Sponsor Attendees, titles and offices:

Schering-Plough HealthCare Products

Mary Williams, Associate Director, Regulatory Affairs

Background:

To date, the Agency has received one half of the full User Fee for this Application. Schering believed they could submit one Type 6 NDA for an RX to OTC switch and one supplement fee.

Discussion:

This application is requesting a switch of RX to OTC use for three separate indications. The three indications were approved with 4 clinical studies in 2 separate NDAs. Schering raised the following questions:

Applicant:

1. Since the clinical data have already been reviewed, why would three separate supplements be required for approval?

Agency:

These three indications are all antifungal uses of the product, but are not the same syndrome. The three indications require consideration of separate issues. So, three supplements are required.

Applicant:

2. The data that are required for review are safety versus efficacy data. Why would a fee be assessed?

Agency:

Although the data to be reviewed are only safety data, they are still considered clinical data for user fee purposes. The analysis for the indications changing population still require clinical review, hence the User Fee assessment.

3. After some additional discussion, the Agency offered the following:

   Since the Applicant seeks approval of this NDA 21-307, Mentax (butenafine hydrochloride cream) Cream, 1%, for three indications, Tinea pedis, Tinea corporis and Tine cruris, the Agency informed the Applicant that additional User Fee monies need to be submitted. The Applicant has two options:

   a. The Applicant may choose to consider this submission as an original NDA and submit the remaining fee ($142,870). or

   b. Since the submission requests approval of three indications, the Applicant may choose to consider this submission as three Efficacy Supplements and submit two additional supplement User Fees. This would be an additional $285,740.

4. The Applicant was also informed of the following:

   a. Since the submission was received in FY 2000 and the Applicant has shown a good faith effort to pay what they believed to be the appropriate application fee, no change of the receipt date of the submission is required and the assessed fees will be based on the FY 2000 schedule of fees.

   b. Additional User Fee monies should reference the previously issued User Fee ID number for this submission.

   c. Provided that the additional User Fee Monies are received promptly, the PDUFA Due Date will be unaffected.

   d. A revised Form FDA 356h should be submitted by the Applicant

Applicant:

The Applicant agreed with the Agency and will promptly submit the requested items.

The teleconference ended amicably.

Signature, minutes preparer: /S/

Concurrence Chair (or designated signatory): /S/

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: March 19, 2001 Number of Pages (including cover sheet) - 3

TO: Mary Williams, Associate Director, Regulatory Affairs
COMPANY: Schering-Plough HealthCare Products
FAX #: 908-679-1741

MESSAGE: Minutes of our February 27, 2001, teleconference concerning NDA 21-307, TRADENAME (butenafine hydrochloride) Cream, 1%, are attached to this facsimile transmission.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

Teleconference Date: February 27, 2001 Time: 1100 · Location: N225

Sponsor: Schering-Plough HealthCare Products

Meeting Chair: Jonathan K. Wilkin, M.D.

Meeting Recorder (Project Manager): Frank Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
Ernie Pappas, Chemist, DNDCIII, HFD-540
Kumar Mainigi, Ph.D., Pharmacologist/Toxicologist, DDDDP, HFD-540
Abi Adebowale, Ph.D., Biopharmaceutist, DPEIII, HFD-880
Markham Luke, M.D., Ph.D., Acting Dermatology Team Leader, DDDDP, HFD-540
Joe Porres, M.D., Ph.D., Medical Officer, DDDDP, HFD-540
Valeria Freidlin, Biostatistician, DOBIV, HFD-725
Charles Ganley, M.D., Division Director, DOTCDP, HFD-560
Linda Katz, M.D., M.P.H., Deputy Division Director, DOTCDP, HFD-560
John Lipnicki, Team Leader, DOTCDP, HFD-560
Andrea Segal, M.D., Medical Officer, DOTCDP, HFD-560
Elizabeth Yuan, R.Ph., LTJG, Labeling Reviewer, DOTCDP, HFD-560
Daniel Keravich, Regulatory Health Project Manager, DOTCDP, HFD-560
Marilyn Pitts, R.Ph., Labeling Reviewer, OPDRA, HFD-430
Frank Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Applicant Attendees, titles and offices:

Mary Williams, Associate Director, Regulatory Affairs, Schering-Plough HealthCare Products

The following discussion took place:

Agency:

1. The Agency has some safety concerns about the proposed Tradenames (submission dated February 21, 2001) for this product.

2. The Agency is most comfortable with either:

   a. A 4-week dosing regimen for athletes' foot between the toes

   OR

   b. Both a 4-week dosing and a 1-week dosing for athletes' foot between the toes along with a patient package insert that could explain the two dosing regimens and expectations.

3. With regard to the proposed packaging size for this product, the Agency recommended that the Applicant ascertain if the proposed tube sizes for this product are of sufficient size for a 4-week dosing regimen.

Applicant:

The Applicant thanked the Agency for its comments and will request a follow-up teleconference in the near future.

The teleconference ended amicably.

Signature, minutes preparer: /S/

Concurrence Chair (or designated signatory): /S/

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: April 16, 2001 Number of Pages (including cover sheet) - 4

TO: Mary Williams, Associate Director, Regulatory Affairs
COMPANY: Schering-Plough HealthCare Products
FAX #: 908-679-1741

MESSAGE: Minutes of our March 22, 2001, meeting concerning NDA 21-307, TRADENAME (butenafine hydrochloride) Cream, 1%, are attached to this facsimile transmission.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

Meeting Date: March 22, 2001 Time: 1000 Location: S300

NDA 21-307, butenafine hydrochloride cream, 1%

Applicant: Schering-Plough HealthCare Products

Meeting Chair: Jonathan K. Wilkin, M.D.

Meeting Recorder (Project Manager): Frank Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
Abby Jacobs, Ph.D., Pharmacology/Toxicology Team Leader, DDDDP, HFD-540
Kumar Mainigi, Ph.D., Pharmacologist/Toxicologist, DDDDP, HFD-540
Abi Adebowale, Ph.D., Biopharmaceutist, DPEIII, HFD-880
Markham Luke, M.D., Ph.D., Acting Dermatology Team Leader, DDDDP, HFD-540
Joe Porres, M.D., Ph.D., Medical Officer, DDDDP, HFD-540
Mohamed Alosh, Ph.D., Biostatistics Team Leader, DOBIV, HFD-725
Atiar Rahman, Ph.D., Biostatistician, DOBIV, HFD-725
Charles Ganley, M.D., Division Director, DOTCDP, HFD-560
John Lipnicki, Team Leader, DOTCDP, HFD-560
Andrea Leonard-Segal, M.D., Medical Officer, DOTCDP, HFD-560
Elizabeth Yuan, R.Ph., LTJG, Labeling Reviewer, DOTCDP, HFD-560
Daniel Keravich, R.Ph., M.S., M.B.A., Regulatory Health Project Manager, DOTCDP, HFD-560
Frank Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Applicant Attendees, titles and offices:

John Clayton, Ph.D. Senior Vice President, Scientific & Regulatory Affairs
Mark Gelbert, Ph.D., J.D., Vice President, Scientific and Regulatory Affairs
Robert Nowak, Ph.D., Director, Clinical Research

Christine Krause, Manager, Clinical Research
Mary Williams, Associate Director, Regulatory Affairs

With regard to the March 14, 2001, Briefing Package, the following discussion took place:

Applicant:

The Applicant presented information that they believe shows there is no difference between a one week b.i.d., dosage regimen versus a four week q.d., dosage regimen in terms of efficacy for the treatment of interdigital tinea pedis with the butenafine cream.

Agency:

The Agency requested:

1. A tabular representation of those patients studied in the four week/q.d., dosage regimen which had patients having onychomycosis listed as having an adverse event. Ideally, if post-hoc analysis is done to exclude onychomycosis patients, such patients should also be excluded.

2. Table 2S (Attachment 2, page 2 of 14 of the March 14, 2001, Meeting Briefing Package) should be revised and submitted to the Agency for its review.

3. While the NDA (Rx to OTC switch) has not been approved, the Agency suggested that the Applicant could label the drug for a both a 1 and 4 week dosage regimen, provided that the Applicant conduct a post-marketing study which directly compares the 1 week/b.i.d. and 4 week/q.d., dosing regimens in terms of safety and efficacy.

Applicant:

1. The Applicant will submit the requested items.

2. The Applicant was amenable to labeling the drug with both dosing regimens provided that no inferences are made about the comparative efficacy of the dosing regimens.

3. The Applicant also was amenable to conducting the requested post-marketing study.

Agency:

After some additional discussion, the Agency said that it will meet internally to further discuss the Applicant's proposed dosage regimen, and will get back to the Applicant.

The meeting ended amicably.

/S/

Signature, minutes preparer: _____

Concurrence Chair (or designated signatory): /S/

Teleconference Date: March 13, 2001 Time: 1315 Location: N225

NDA 21-307, butenafine hydrochloride cream, 1%

Applicant: Schering-Plough HealthCare Products

Meeting Chair: Jonathan K. Wilkin, M.D.

Meeting Recorder (Project Manager): Victoria Lutwak

FDA Attendees, titles and offices:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
Victoria Lutwak, Regulatory Management Officer, DDDDP, HFD-540

Applicant Attendees, titles and offices:

John Clayton, Ph.D. Senior Vice President, Scientific & Regulatory Affairs
Mark Gelbert, Ph.D., J.D., Vice President, Scientific and Regulatory Affairs
Robert Nowak, Ph.D., Director, Clinical Research
Christine Krause, Manager, Clinical Research
Mary Williams, Associate Director, Regulatory Affairs

Purpose:

Clarification of issues regarding the Agency's proposed treatment regimen conveyed during the February 27, 2001, teleconference so as to prepare for the upcoming March 22, 2001, meeting.

Agency:

To assist the Applicant with their preparations for the aforementioned March 22, 2001, meeting, the following issues were conveyed to the Applicant. Per the review team:

1. With regard to the Tradename proposals of February 21, 2001, we have concerns about the different active ingredients and how this will impact on safety.

2. The tube size/package should contain sufficient product for four weeks of dosing.

3. Although the safety profile is the same for both the one and four week dosing regimens for interdigital tinea pedis, the efficacy is better with an endpoint of cure for the 4-week dosing regimen..

Applicant:

1. The March 22, 2001, meeting briefing package will be submitted later this week.

2. The aforementioned briefing package will present the data in a new way.

3. The present problems with the study outcomes presented in the NDA are an anomaly of the original trial design. When the two studies are normalized, i.e., the symptom scores using negative mycology with total signs and symptoms of less than 2, then there is no difference between the one and four-week trials. This post hoc analysis makes for a fair comparison.

Agency:

The Agency said that is willing to review with the Applicant various pathways for re-analysis of the data as well as subsets of those data and definitions of success.

The teleconference ended amicably.

Signature, minutes preparer: /S/

Concurrence Chair: /S/ 4/14/01