

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-484

OTHER REVIEW(S)



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: March 5, 2010

To: Susan Walker, M.D., Director
**Division of Dermatology and Dental
Products (DDDP)**

Renata Albrecht, M.D., Director
**Division of Special Pathogen and
Transplant Products (DSPTP)**

Through: Claudia Karwoski, PharmD, Director
Division of Risk Management (DRISK)

Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer, Acting Team
Leader
Division of Risk Management

From: Latonia M. Ford, RN, BSN, MBA
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Patient
Package Insert)

Drug Name(s): TRADENAME (itraconazole) Tablets

Application
Type/Number: NDA 22-484

Applicant/sponsor: Stiefel Laboratories, Inc.

OSE RCM #: 2009-1146

1 INTRODUCTION

Stiefel Laboratories, Inc. submitted an original 505(b) (1) New Drug Application, NDA 22-484, for TRADENAME (itraconazole) tablets, on March 31, 2009. TRADENAME is indicated for the treatment of onychomycosis of the toenail due to *Trichophyton rubrum* or *T. mentagrophytes* in non-immunocompromised patients. Sporonox (itraconazole), the Reference Listed Drug, was originally approved in September 1992 and is available as a capsule, an oral solution, and an intravenous solution and is indicated for the treatment of Blastomycosis, Histoplasmosis, and Aspergillosis fungal infections in immunocompromised and non-immunocompromised patients.

This review is written in response to a request by the **Division of Dermatology and Dental Products (DDDP)** for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for TRADENAME (itraconazole) tablets.

Please let us know if DDDP would like a meeting to discuss this review or any of our changes prior to sending to the Applicant.

2 MATERIAL REVIEWED

- Draft TRADENAME (itraconazole) tablets Prescribing Information (PI) submitted March 31, 2009, revised by the Review Division throughout the current review cycle, and provided by the Review Division February 22, 2010.
- Draft TRADENAME (itraconazole) tablets Package Insert (PPI) submitted on March 31, 2009 and provided by the Review Division February 22, 2010.

3 RESULTS OF REVIEW

In our review of the PPI, we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the PI
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 RECOMMENDATIONS

Our annotated PPI is appended to this memo. Any additional revisions to the PI should be reflected in the PPI.

In light of the serious risks associated with the use of itraconazole, we recommend that this product have a Medication Guide (MG) as part of a Risk Evaluation and Mitigation Strategy (REMS) rather than a PPI. A PPI does not have distribution requirements. We believe that a MG is necessary because this is a product for which patient labeling could help prevent serious adverse events. This is also a drug product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could effect decision to use or continue to use the product.

We also recommend that a mechanism for requesting a MG only REMS for all oral itraconazole products be investigated in the near future. We understand that the issue of drug interactions and other serious risks may not be a new safety issue for the approved itraconazole product, Sporanox. We also understand that in order to require a MG under the Food and Drug Administration Amendments Act (FDAAA), new safety information is required. If there is currently no new safety information to warrant a MG only REMS under FDAAA, then we recommend that a MG be considered in the future should new safety information become available.

Please let us know if you have any questions.

15 pages of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22484

ORIG-1

STIEFEL
LABORATORIES
INC

HYPHANOX 200MG FILM-
COATED TABLETS

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/s/

LATONIA M FORD
03/05/2010

CLAUDIA B KARWOSKI
03/05/2010

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

******Pre-decisional Agency Information******

Memorandum

Date: February 26, 2010

To: Nichelle Rashid, Regulatory Project Manager
Division of Dermatologic and Dental Products (DDDP)

From: Andrew Haffer, Regulatory Review Officer
Shefali Doshi, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Catherine Gray, Professional Group Leader
Robert Dean, DTC Group Leader
DDMAC

Subject: NDA 22-484

DDMAC labeling comments for TRADENAME (itraconazole) Tablets

In response to DDDP's May 14, 2009 consult request, DDMAC has reviewed the draft labeling (PI and PPI) for TRADENAME (itraconazole) Tablets (NDA 22-484). DDMAC's comments on the PI and PPI are based on the proposed draft marked-up labeling that was accessed in the e-room on February 24, 2010.

DDMAC's comments are provided directly in the document attached (see below).

Thank you for the opportunity to comment on these proposed materials.

If you have any questions regarding the PI, please contact Andrew Haffer at 301.796.2268 or Andrew.Haffer@fda.hhs.gov. If you have any questions regarding the PPI, please contact Shefali Doshi at 301.796.1780 or Shefali.Doshi@fda.hhs.gov.

23 pages of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22484	ORIG-1	STIEFEL LABORATORIES INC	HYPHANOX 200MG FILM-COATED TABLETS

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/s/

ANDREW S HAFFER

02/26/2010

We hid formatting changes so our comments are easier to read.

SEALD LABELING REVIEW

APPLICATION NUMBER	NDA 22-484
APPLICANT	Stiefel Laboratories, Inc.
DRUG NAME	TRADENAME (itraconazole)
SUBMISSION DATE	March 31, 2009
SEALD REVIEW DATE	January 25, 2010
SEALD REVIEWER(S)	Jeanne M. Delasko, RN, MS

19 pages of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22484

ORIG-1

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COATED TABLETS

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/s/

JEANNE M DELASKO
01/25/2010

LAURIE B BURKE
02/01/2010

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: November 12, 2009

TO: Nichelle Rashid, Regulatory Project Manager
S. Trajkovic, M.D., Medical Officer
Division of Reproductive and Urologic Drugs Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22-484

APPLICANT: Stiefel Laboratories, Inc.

DRUG: Hyphanox™ Film-Coated Tablets, 200 mg (itraconazole)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of onychomycosis of the toenail [REDACTED] (b) (4)
[REDACTED] in non-immunocomprised patients.

CONSULTATION REQUEST DATE: June 17, 2009

DIVISION ACTION GOAL DATE: January 31, 2009

PDUFA DATE: January 31, 2009

I. BACKGROUND:

The conduct of Protocol #BT0300-302-NT entitled " A Phase II Randomized, Evaluator-Blind, Parallel Group Study of the Safety and Efficacy of Itraconazole Tablets, Itraconazole Capsules and Placebo in the Treatment of Onychomycosis of the Toenail" was inspected:

For this study, the primary efficacy endpoint was the complete cure, defined as clinical cure and mycologic cure at Visit 8 (Week 52), the primary evaluation period.

The primary objective of this study was to evaluate the non-inferiority of one itraconazole 200 mg tablet given once daily to two itraconazole 100 mg capsules given once daily and the superiority of itraconazole tablets to placebo.

The clinical sites of Drs. Kempers and Aly were selected for inspection because both were high enrollers. In addition, there was a concern regarding blinding of the study at the site of Dr. Kempers, and the investigational product appeared more efficacious than the comparator product at the site of Dr. Aly.

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ # of Subjects/	Inspection Dates	Final Classification
Site 15 Steven Kempers, M.D. Minnesota Clinical Study Center 7205 University Avenue N.E. 721 Fridley, MN 55432 Phone: (763) 571-4200 Fax: (763) 571-4000	BT0300-302-NT/ 72/	24-31 Aug 2009	VAI
Raza Aly, Ph.D. University of California, San Francisco 1701 Divisadero St., Room 332 San Francisco, CA 94143-0316 Phone: (415)476-3048 Fax: (415) 476-8677	BT0300-302-NT/ 49/	26 Aug-30 Sep,2009	VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field;
EIR has not been received from the field and complete review of EIR is pending.

1. Steven Kempers, M.D.

7205 University Avenue N.E.
Minneapolis, MN 55432-3134

- a. **What was inspected:** At this site, 72 subject records were audited with respect to informed consent and the primary efficacy endpoint. The records for nine subjects were reviewed in depth for adverse event reporting, secondary endpoints, inclusion/exclusion criteria, study related procedures, concomitant medications, randomization protocol deviations, and compliance with study activities.
- b. **General observations/commentary:** A Form FDA 483 was issued at the conclusion of the inspection. Inspection revealed a potential unblinding issue in that drug accountability information was recorded on blinded source documents that had the potential to unblind the study (i.e., whether subjects were taking 100 mg capsules or 200 mg tablets or placebo). There was no indication that any of the investigators at the site were actually unblinded as the result of the inclusion of this information. Blinding does not appear to have been compromised. The unblinding was identified by the unblinded clinical research associate, who then removed all unblinded information from the subjects' files. Site personnel were then re-trained regarding the method(s) by which blinding was to be maintained. Subject 15103 reported blurred vision that was not reported as an adverse event, and three subjects failed to either actually sign the consent form (though the individual pages of the consent form were initialed) or sign it in the correct place.
- c. **Assessment of data integrity:** The deviations noted above would not appear to have a significant impact on data integrity, and the data appear acceptable in support of the respective application.

2. Raza Aly, Ph.D.

University of California, San Francisco
1701 Divisadero St., Room 332
San Francisco, CA 94143-0316

- a. **What was inspected:** At this site, 107 subjects were screened, 49 were enrolled, 41 completed the study, and eight dropped out. All 107 subject records were audited with respect to informed consent. Of the 49 enrolled subjects, the records of 25 subjects were reviewed with respect to inclusion/exclusion criteria, medical histories, baseline status, randomization, primary and secondary efficacy endpoints, concomitant medications, clinical evaluations, safety assessments, adverse events, protocol deviations, subject withdrawals and terminations, and source document information and line listings as compared with corresponding CRFs.
- b. **General observations/commentary:** A Form FDA 483 was issued. Inspection revealed that drug disposition records were extensively revised to accurately reflect the dispensation of capsules or tablets (original records appeared to indicate that both capsules and tablets were administered; the result of a misinformed attempt by the study coordinator to maintain the blind). The investigator, who was not a certified

health professional, routinely reviewed, commented, and signed off on clinical laboratory reports. Subject 38068 was enrolled despite taking Viagra, an excluded medication. All concomitant medications were not reported for Subjects 38087 and 38098. Adverse events were not reported for Subject 38087 (periorbital cellulitis/edema trauma) and Subject 38084 (breast lump, rectal bleeding/hemorrhoids). Medical histories were not accurately reported for Subject 38072 (history of depression), and Subject 38044 (history of neuropsychiatric disease).

- c. Assessment of data integrity:** The review division may wish to consider excluding the data from Subject 38068 because of the subject's use of an excluded medication (Viagra); otherwise, the deviations noted immediately above would not appear to have a significant impact on data integrity, and the data appear acceptable in support of the respective application.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical investigator sites were inspected in support of this NDA. Although regulatory violations were noted at both Dr. Aly's and Dr. Kempers's sites, the findings are unlikely to impact data integrity. However, the review division may wish to consider excluding data from Subject 38068 from Dr. Aly's site because of the use of an excluded medication (Viagra). Otherwise, the study appears to have been conducted adequately, and the data generated by the clinical sites of Drs. Kempers and Aly appear acceptable in support of the respective indication.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

Application
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HYPHANOX 200MG FILM-
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/s/

ROY A BLAY
11/13/2009

JEAN M MULINDE
11/16/2009

Signed for Tejashri Purohit-Sheth, M.D.



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: November 5, 2009

To: Susan Walker, MD., Director
Division of Dermatology and Dental Products

Through: Todd Bridges, RPh, Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis
(DMEPA)

From: Denise V. Baugh, PharmD, BCPS, Safety Evaluator
Division of Medication Error Prevention and Analysis
(DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Hyphanox (Itraconazole) Tablets
200 mg

Application Type/Number: NDA# 022484

Applicant: Stiefel Laboratories, Inc.

OSE RCM #: 2009-1146

1 INTRODUCTION

This review is written in response to a request from the Division of Dermatology and Dental Products for assessment of the label and labeling for Hyphanox (Itraconazole) Tablets and their vulnerability to medication errors.

2 METHODS AND MATERIALS

For this product the Applicant submitted the insert labeling on June 26, 2009 and the blister and carton labeling on August 21, 2009 (see Appendices A and B). DMEPA used Failure Mode and Effects Analysis (FMEA)¹ in our evaluation of the label and labeling.

3 RECOMMENDATIONS

Our evaluation noted areas where information on the blister card, carton and insert labeling can be improved to minimize the potential for medication errors. We provide recommendations on the insert labeling in Section 3.1, *Comments to the Division*, for discussion during the review team's label and labeling meetings. Section 3.2, *Comments to the Applicant*, contains our recommendations for the blister card and carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have questions or need clarifications, please contact Janet Anderson, OSE Regulatory Project manager, at 301-796-0675.

3.1 COMMENTS TO THE DIVISION

A. General Comments

1. DMEPA concurs with the ONDQA chemist for this application that the appropriate dosage form designation for this product is "tablet" and not "film-coated tablet". Therefore, we recommend limiting the use of the descriptor, "film-coated" in combination with the dosage form to appropriate areas of the labeling (e.g., Description and How Supplied sections).
2. DMEPA notes the Applicant has presented parts of the boxed warning on the blister card and carton labeling in bold letters. We defer to the Division as to whether these statements are appropriate since they are not a full representation of the boxed warning for this product but may be interpreted as such.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

B. Full Prescribing Information

We note that subsection 16.1 (How Supplied) states ‘Each carton contains the tablets supplied in two unit-dose packs of 2 x 7 tablets (NDC 0145-2500-02)’. To clearly describe the number of tablets in the unit-dose packs, revise to read ‘Each carton contains two blister cards of 14 tablets each (NDC 0145-2500-02)’.

3.2 COMMENTS TO THE APPLICANT

A. GENERAL COMMENTS (BLISTER CARD AND CARTON LABELING)

1. We note the established name is ½ the size of the proprietary name, but it lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
2. The appropriate dosage form designation for this drug product is “tablet”. Revise the dosage form from “film-coated tablet” to “tablet” and ensure that it has prominence commensurate with the active ingredient.
3. Increase the prominence of the statement of product strength by increasing the font size to be commensurate with the proprietary and established names and relocate it after the dosage form which is the customary position for this information.
4. The prominence of the ‘Rx only’ statement on the principal display panel may distract from other important information. We recommend you decrease the prominence of the ‘Rx only’ statement by changing the font color to black.
5. Delete the stand-alone statement of product strength “200 mg” at the top of the principal display panel as it is duplicative and is not associated with the active ingredient or proprietary name.

B. BLISTER CARD

Increase the prominence of the statement beginning with “Each tablet contains . . .” to help minimize the potential for misinterpreting the strength of each tablet.

C. CARTON LABELING

Currently, you use the term (b) (4) to describe the blister card. Use of this terminology may be (b) (4) (b) (4), with the blister card. Revise (b) (4) to read ‘blister card’ throughout the labeling.

2 pages of Draft Carton and Container Labels have been Withheld in Full immediately following this page as B4 (CCI/TS)

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NDA-22484	ORIG-1	STIEFEL LABORATORIES INC	HYPHANOX 200MG FILM- COATED TABLETS

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/s/

DENISE V BAUGH
11/05/2009

TODD D BRIDGES
11/05/2009

DENISE P TOYER
11/05/2009

CAROL A HOLQUIST
11/06/2009

NDA/BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information		
NDA # 22-484 BLA# NA	NDA Supplement #:S- NA BLA STN # NA	Efficacy Supplement Type SE- NA
Proprietary Name: Hyphanox Established/Proper Name: itraconazole Dosage Form: Tablets Strengths: 200 mg		
Applicant: Steifel Laboratories, Inc. Agent for Applicant (if applicable): NA		
Date of Application: March 31, 2009 Date of Receipt: March 31, 2009 Date clock started after UN:		
PDUFA Goal Date: January 31, 2010	Action Goal Date (if different):	
Filing Date: May 30, 2009 Date of Filing Meeting: May 18, 2009		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed Indication(s): oral treatment of onychomycosis of the toenail (b) (4)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
Refer to Appendix A for further information.		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	<input type="checkbox"/> Tropical disease Priority review voucher submitted
Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR	

601.42)	
Collaborative Review Division (if OTC product):	
List referenced IND Number(s): 69,847	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ora/compliance_ref/aiplist.html If yes, explain: If yes, has OC/DMPQ been notified of the submission? Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status Comments:	<input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
Exclusivity	

<p>Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</i></p> <p>If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES # years requested: 3 <input type="checkbox"/> NO
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<input checked="" type="checkbox"/> Not applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
<ol style="list-style-type: none"> 1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)). 3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? 	<input checked="" type="checkbox"/> Not applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>	
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<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</p>		<input type="checkbox"/> YES <input type="checkbox"/> NO	
<p>If yes, please list below:</p>			
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>			
Format and Content			
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p>Comments:</p>		<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)	
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>		<p>NA</p>	
<p>If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p>Comments:</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	
<p>If electronic submission, does it follow the eCTD guidance? (http://www.fda.gov/cder/guidance/7087rev.pdf)</p> <p>If not, explain (e.g., waiver granted):</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO	

<p>Form 356h: Is a signed form 356h included?</p> <p><i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Index: Does the submission contain an accurate comprehensive index?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Controlled substance/Product with abuse potential:</p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BLAs/BLA efficacy supplements only:</p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Patent Information (NDAs/NDA efficacy supplements only)	
<p>Patent information submitted on form FDA 3542a?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Debarment Certification	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, both the applicant and the U.S. Agent must</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>sign the certification.</p> <p><i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p> <p>Comments:</p>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Financial Disclosure	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Pediatrics	
PREA	
<p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	
<p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> • <i>If no, request in 74-day letter.</i> • If yes, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) 	<p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Comments:	

BPCA (NDAs/NDA efficacy supplements only):	
Is this submission a complete response to a pediatric Written Request? <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Comments:	
Prescription Labeling	
Check all types of labeling submitted. Comments:	<input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format? <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
Package insert (PI) submitted in PLR format? If no , was a waiver or deferral requested before the application was received or in the submission? If before , what is the status of the request? <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
REMS consulted to OSE/DRISK?	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	

OTC Labeling	
<p>Check all types of labeling submitted.</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Meeting Minutes/SPA Agreements	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES Date(s): December 8, 2005 <input type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES Date(s): February 4, 2009 <input type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES Date(s): April 21, 2006; July 14, 2006 September 13, 2006 <input type="checkbox"/> NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 18, 2009

NDA/BLA #: 22-484

PROPRIETARY/ESTABLISHED NAMES: Hyphanox (itraconazole)

APPLICANT: Steifel Laboratories, Inc.

BACKGROUND: NDA 22-484, Hyphanox™ (itraconazole) Film-Coated Tablets, 200 mg, submitted March 31, 2009 is indicated for the treatment of onychomycosis of the toenail (b) (4) in non-immunocomprised patients. This application was submitted as a 505(b)(1).

While Hyphanox™ (itraconazole) Film-Coated Tablets, 200 mg is a new formulation, itraconazole is already an approved drug in the US and marketed as Sporanox®.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Nichelle Rashid	Y
	CPMS/TL:	Barbara Gould/Margo Owens	N/Y
Cross-Discipline Team Leader (CDTL)	David Kettl		
Clinical	Reviewer:	Snezana Trajkovic	Y
	TL:	David Kettl	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
Labeling Review (for OTC products)	Reviewer:		
	TL:		
OSE	Reviewer:		
	TL:		
Clinical Microbiology (for antimicrobial	Reviewer:	Kerry Snow	N

<i>products)</i>			
	TL:	Frederick Marsik	N

Clinical Pharmacology	Reviewer:	Julia Cho	Y
	TL:	Dennis Bashaw	Y
Biostatistics	Reviewer:	Matthew Soukup	Y
	TL:	Mohamed Alesh	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Daivender Kumar Mainigi	Y
	TL:	Barbara Hill	N
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Christpher Hough	Y
	TL:	Shulin Ding	Y
Facility (<i>for BLAs/BLA supplements</i>)	Reviewer:		
	TL:		
Microbiology, sterility (<i>for NDAs/NDA efficacy supplements</i>)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Roy Blay	N
	TL:		
Other reviewers			

OTHER ATTENDEES: Susan Walker, Division Director, DDDP
Elaine Smoot, Regulatory Health Project Manager, DDDP
Paul Loebach, Regulatory Health Project Manager, DDMAC
Janet Anderson, Regulatory Health Project Manager, OSE

505(b)(2) filing issues? If yes, list issues:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Per reviewers, are all parts in English or English translation? If no, explain:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>Electronic Submission comments</p> <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
BIOSTATISTICS	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments: Unblinding issues; Pdf files requested	<input checked="" type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments: Blister-packet child resistant issues	<input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Establishment(s) ready for inspection? <ul style="list-style-type: none"> Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Sterile product? <p>If yes, was Microbiology Team consulted for</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES

validation of sterilization? (NDAs/NDA supplements only)	<input type="checkbox"/> NO
FACILITY (BLAs only)	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Susan Walker

GRMP Timeline Milestones:

ACTIVITY/MILESTONE	GRMP DATE
Team Meeting	June 16, 2009
Team Meeting	July 21, 2009
Mid-Cycle Meeting	August 27, 2009
Labeling	November 17, 2009
Labeling	December 1, 2009
Discipline Complete Reviews (TL Signed off)	December 1, 2009
CDTL Completed Review	January 7, 2010
Labeling Discussion with Sponsor	January 7, 2010
DD Briefing/Wrap-Up Meeting held by	January 7, 2010
Action Package and Letter to DD	January 7, 2010
Complete DD Review/Sign Off	January 31, 2010
PDUFA Date	January 31, 2010

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <input checked="" type="checkbox"/> Standard Review

	<input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

NICHELLE E RASHID
08/07/2009

MARGO L OWENS
08/07/2009

DSI CONSULT: Request for Clinical Inspections

Date: June 17, 2009

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief (Acting), GCP2
Roy Blay, Director Regulatory
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Snezana Trajkovic/Medical Officer/DDDP

From: Nichelle Rashid, Regulatory Project Manager, HFD-540

Subject: **Request for Clinical Site Inspections**
Hyphanox (itraconazole) Film Coated Tablets, 200 mg

I. General Information

Application#: NDA-22-484

Applicant/ Applicant contact information (to include phone/email): Stiefel Laboratories, Inc.
20 T.W. Alexander Drive
P.O. Box 14910
Research Triangle Park, NC 27709
(919) 990-6207
Devon.Allen@stiefel.com

Drug Proprietary Name: Hyphanox™ Film-Coated Tablets, 200 mg

NME or Original BLA (Yes/No): No

Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): Yes (16 years of age or older)

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Treatment of onychomycosis of the toenail (b) (4)
in non-immunocomprised patients.

PDUFA: January 31, 2010

Action Goal Date: January 31, 2010

Inspection Summary Goal Date: November 15, 2009

II. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site 15 Kempers, Steven MD Minnesota Clinical Study Center 7205 University Avenue N.E. Fridley, MN 55432 Phone: 763-571-4200 Fax: 763-571-4000	BT0300-302-NT	72	treatment of onychomycosis of the toenail
Site 38 Aly, Raza PhD University of California, San Francisco 533 Parnassus Ave, Rm U350 San Francisco, CA 94143-0517 Phone: 415-476-3048 Fax: 415-476-8677	BT0300-302-NT	49	treatment of onychomycosis of the toenail

III. Site Selection/Rationale

The reasons for inspection of these sites are:

1. Site 15 was selected because of reported unblinding issues.
2. Site 38 was selected because of high rate of response in Itraconazole tablet and capsule groups and the high number of subjects enrolled.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects (Site 38)
- High treatment responders (specify): High rate of response in Itraconazole tablet and capsule groups
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): Reported unblinding issues (Site 15)

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

IV. Tables of Specific Data to be Verified (if applicable)

NA

Should you require any additional information, please contact Nichelle Rashid at 301-796-3904 *or* Snezana Trajkovic at 301-796-4782.

Concurrence: (as needed)

- _____ Medical Team Leader
- _____ Medical Reviewer
- _____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

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this page is the manifestation of the electronic signature.**

/s/

David Kettl
7/2/2009 09:28:48 AM

DSI CONSULT: Request for Clinical Inspections

Date: June 17, 2009

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief (Acting), GCP2
Roy Blay, Director Regulatory
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Snezana Trajkovic/Medical Officer/DDDP

From: Nichelle Rashid, Regulatory Project Manager, HFD-540

Subject: **Request for Clinical Site Inspections**
Hyphanox (itraconazole) Film Coated Tablets, 200 mg

I. General Information

Application#: NDA-22-484

Applicant/ Applicant contact information (to include phone/email): Stiefel Laboratories, Inc.
20 T.W. Alexander Drive
P.O. Box 14910
Research Triangle Park, NC 27709
(919) 990-6207
Devon.Allen@stiefel.com

Drug Proprietary Name: Hyphanox™ Film-Coated Tablets, 200 mg

NME or Original BLA (Yes/No): No

Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): Yes (16 years of age or older)

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Treatment of onychomycosis of the toenail (b) (4)
in non-immunocomprised patients.

PDUFA: January 31, 2010

Action Goal Date: January 31, 2010

Inspection Summary Goal Date: November 15, 2009

II. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site 15 Kempers, Steven MD Minnesota Clinical Study Center 7205 University Avenue N.E. Fridley, MN 55432 Phone: 763-571-4200 Fax: 763-571-4000	BT0300-302-NT	72	treatment of onychomycosis of the toenail
Site 40 Matheson, Robert T. MD Oregon Medical Research Center 9495 SW Locust Street, Suite G Portland, OR 97223 Phone : 503-245-1525 Fax : 503-245-0315	BT0300-302-NT	79	treatment of onychomycosis of the toenail
Site 38 Aly, Raza PhD University of California, San Francisco 533 Parnassus Ave, Rm U350 San Francisco, CA 94143-0517 Phone: 415-476-3048 Fax: 415-476-8677	BT0300-302-NT	49	treatment of onychomycosis of the toenail
Site 64 Pollak, Richard DPM, MS Endeavor Clinical Trials James G. Trevino and San Antonio Podiatry Associates, PC 8042 Wurzbach Road Suite 450 San Antonio, TX 78229 Phone: 210-949-0807 Fax: 210-692-7646	BT0300-302-NT	30	treatment of onychomycosis of the toenail

III. Site Selection/Rationale

The reasons for inspection of these sites are:

1. Sites 15 and 64 were selected because of reported unblinding issues.
2. Sites 40 and 38 were selected because of high rate of response in Itraconazole tablet and capsule groups and the high number of subjects enrolled.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects (Sites 40 & 38)
- High treatment responders (specify): High rate of response in Itraconazole tablet and capsule groups
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): Reported unblinding issues (Sites 15 & 64)

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

IV. Tables of Specific Data to be Verified (if applicable)

NA

Should you require any additional information, please contact Nichelle Rashid at 301-796-3904 *or* Snezana Trajkovic at 301-796-4782.

Concurrence: (as needed)

- _____ Medical Team Leader
- _____ Medical Reviewer
- _____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

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/s/

David Kettl
6/22/2009 01:04:29 PM

NDA/BLA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

Application Information		
NDA # 22-484 BLA# NA	NDA Supplement #:S- NA BLA STN # NA	Efficacy Supplement Type SE- NA
Proprietary Name: Hyphanox Established/Proper Name: itraconazole Dosage Form: Tablets Strengths: 200 mg		
Applicant: Steifel Laboratories, Inc. Agent for Applicant (if applicable): NA		
Date of Application: March 31, 2009 Date of Receipt: March 31, 2009 Date clock started after UN:		
PDUFA Goal Date: January 31, 2010	Action Goal Date (if different):	
Filing Date: May 30, 2009 Date of Filing Meeting: May 18, 2009		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 5		
Proposed Indication(s): oral treatment of onychomycosis of the toenail (b) (4)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Refer to Appendix A for further information.	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical disease Priority review voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/> Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR	

601.42)	
Collaborative Review Division (if OTC product):	
List referenced IND Number(s): 69,847	
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> http://www.fda.gov/ora/compliance_ref/aiplist.html If yes, explain: If yes, has OC/DMPQ been notified of the submission? Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status Comments:	<input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
Exclusivity	

<p>Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</i></p> <p>If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES # years requested: 3 <input type="checkbox"/> NO
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<input checked="" type="checkbox"/> Not applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
<ol style="list-style-type: none"> 1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? 2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)). 3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? 	<input checked="" type="checkbox"/> Not applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>	
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<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm</p>		<input type="checkbox"/> YES <input type="checkbox"/> NO																
<p>If yes, please list below:</p> <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>			Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration												
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																		
<p>Format and Content</p>																		
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p>Comments:</p>		<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)																
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>		<p>NA</p>																
<p>If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p>Comments:</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO																
<p>If electronic submission, does it follow the eCTD guidance? (http://www.fda.gov/cder/guidance/7087rev.pdf)</p> <p>If not, explain (e.g., waiver granted):</p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO																

<p>Form 356h: Is a signed form 356h included?</p> <p><i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Index: Does the submission contain an accurate comprehensive index?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input type="checkbox"/> legible <input type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p>If no, explain:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Controlled substance/Product with abuse potential:</p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>BLAs/BLA efficacy supplements only:</p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p>If yes, BLA #</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Patent Information (NDAs/NDA efficacy supplements only)	
<p>Patent information submitted on form FDA 3542a?</p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Debarment Certification	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, both the applicant and the U.S. Agent must</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>sign the certification.</p> <p><i>Note: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p> <p>Comments:</p>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Financial Disclosure	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Pediatrics	
PREA	
<p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	
<p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p>If no, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> • <i>If no, request in 74-day letter.</i> • If yes, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) 	<p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
Comments:	

BPCA (NDAs/NDA efficacy supplements only):	
Is this submission a complete response to a pediatric Written Request? <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
Comments:	
Prescription Labeling	
Check all types of labeling submitted. Comments:	<input type="checkbox"/> Not applicable <input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input type="checkbox"/> MedGuide <input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format? <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
Package insert (PI) submitted in PLR format? If no , was a waiver or deferral requested before the application was received or in the submission? If before , what is the status of the request? <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (<i>send WORD version if available</i>)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
REMS consulted to OSE/DRISK?	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Comments:	

OTC Labeling	
<p>Check all types of labeling submitted.</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p>Comments:</p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
Meeting Minutes/SPA Agreements	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES Date(s): December 8, 2005 <input type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES Date(s): February 4, 2009 <input type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p>Comments:</p>	<input checked="" type="checkbox"/> YES Date(s): April 21, 2006; July 14, 2006 September 13, 2006 <input type="checkbox"/> NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 18, 2009

NDA/BLA #: 22-484

PROPRIETARY/ESTABLISHED NAMES: Hyphanox (itraconazole)

APPLICANT: Steifel Laboratories, Inc.

BACKGROUND: NDA 22-484, Hyphanox™ (itraconazole) Film-Coated Tablets, 200 mg, submitted March 31, 2009 is indicated for the treatment of onychomycosis of the toenail (b) (4) in non-immunocomprised patients. This application was submitted as a 505(b)(1).

While Hyphanox™ (itraconazole) Film-Coated Tablets, 200 mg is a new formulation, itraconazole is already an approved drug in the US and marketed as Sporanox®.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Nichelle Rashid	Y
	CPMS/TL:	Barbara Gould/Margo Owens	N/Y
Cross-Discipline Team Leader (CDTL)	David Kettl		
Clinical	Reviewer:	Snezana Trajkovic	Y
	TL:	David Kettl	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
Labeling Review (for OTC products)	Reviewer:		
	TL:		
OSE	Reviewer:		
	TL:		
Clinical Microbiology (for antimicrobial	Reviewer:	Kerry Snow	N

<i>products)</i>			
	TL:	Frederick Marsik	N

Clinical Pharmacology	Reviewer:	Julia Cho	Y
	TL:	Dennis Bashaw	Y
Biostatistics	Reviewer:	Matthew Soukup	Y
	TL:	Mohamed Alesh	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Daivender Kumar Mainigi	Y
	TL:	Barbara Hill	N
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Christpher Hough	Y
	TL:	Shulin Ding	Y
Facility (<i>for BLAs/BLA supplements</i>)	Reviewer:		
	TL:		
Microbiology, sterility (<i>for NDAs/NDA efficacy supplements</i>)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Roy Blay	N
	TL:		
Other reviewers			

OTHER ATTENDEES: Susan Walker, Division Director, DDDP
Elaine Smoot, Regulatory Health Project Manager, DDDP
Paul Loebach, Regulatory Health Project Manager, DDMAC
Janet Anderson, Regulatory Health Project Manager, OSE

505(b)(2) filing issues? If yes, list issues:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Per reviewers, are all parts in English or English translation? If no, explain:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p>Electronic Submission comments</p> <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input type="checkbox"/> NO
BIOSTATISTICS	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments: Unblinding issues; Pdf files requested	<input checked="" type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments:	<input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC)	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
Comments: Blister-packet child resistant issues	<input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Establishment(s) ready for inspection? <ul style="list-style-type: none"> Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Sterile product? <p>If yes, was Microbiology Team consulted for</p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES

validation of sterilization? (NDAs/NDA supplements only)	<input type="checkbox"/> NO
FACILITY (BLAs only)	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
Comments:	

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Susan Walker

GRMP Timeline Milestones:

ACTIVITY/MILESTONE	GRMP DATE
Team Meeting	June 16, 2009
Team Meeting	July 21, 2009
Mid-Cycle Meeting	August 31, 2009
Labeling (TBD)	Mid November
Labeling (TBD)	Early December
Discipline Complete Reviews (TL Signed off)	December 1, 2009
CDTL Completed Review	January 7, 2010
Labeling Discussion with Sponsor	January 7, 2010
DD Briefing/Wrap-Up Meeting held by	January 7, 2010
Action Package and Letter to DD	January 7, 2010
Complete DD Review/Sign Off	January 31, 2010
PDUFA Date	January 31, 2010

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <input checked="" type="checkbox"/> Standard Review

	<input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
<input type="checkbox"/>	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
<input type="checkbox"/>	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	If BLA or priority review NDA, send 60-day letter.
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

Nichelle Rashid
6/19/2009 09:11:15 AM
CSO

Margo Owens
6/19/2009 11:13:57 AM
CSO

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Dermatology and Dental Products

Application Number: NDA 22-484

Name of Drug: Hyphanox™ (itraconazole) Film-Coated Tablets, 200 mg

Applicant: Stiefel Laboratories, Inc.

Material Reviewed:

Submission Date(s): March 31, 2009

Receipt Date(s): March 31, 2009

PDUFA Due Date: January 31, 2010

Submission Date of Structure Product Labeling (SPL): March 31, 2009

Type of Labeling Reviewed: PLR Labeling

Background and Summary

NDA 22-484, Hyphanox™ (itraconazole) Film-Coated Tablets, 200 mg, submitted March 31, 2009 is indicated for the treatment of onychomycosis of the toenail [REDACTED] (b) (4) in non-immunocomprised patients. This application was submitted as a 505(b)(1).

While Hyphanox™ (itraconazole) Film-Coated Tablets, 200 mg is a new formulation, itraconazole is already an approved drug in the US and marketed as Sporanox®.

Review

This review provides a list of formatting revisions for proposed labeling that should be conveyed to the applicant in the 74-day letter. These comments are based on 21 CFR 201.1 and FDA recommendations to provide labeling quality and consistency across review divisions. When a reference is not cited, consider the comment as a recommendation only.

The following issues/deficiencies have been identified in your proposed labeling.

Highlights Section:

1. According to 21 CFR 201.57(d)(8), the Highlights must be limited in length to one-half page.
2. According to 21 CFR 210.57(a)(4), the boxed warning is not to exceed a length of 20 lines.
3. Do not use the “TM” symbols after the drug names.
4. Do not include the pregnancy category C, see comment #34 to Preamble.
5. For pregnancy category C drugs, list pregnancy under Use in Specific Populations in the Highlights section followed by the following statement: “Based on animal data, may cause fetal harm,” or “No human or animal data. Use only if clearly needed. If a pregnancy registry exists, state “Pregnancy registry available.” Conclude the entire statement with a cross-reference to Pregnancy subsection (8.1).
6. The revision date should be the month/year that the application is approved.

Contents (Table of Contents) Section:

7. The same title for the boxed warning that appears in the HL and FPI must also appear at the beginning of the Table of Contents in upper-case letters and bold type.
8. Avoid using acronyms, CHF and HMG, in subsection headings. These acronyms should be spelled out.

Full Prescribing Information (FPI) Section:

9. The cross-references should be the section heading followed the numerical identifier. The cross-reference should be in brackets. The use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print.
10. Use “TM” symbol only once in the content of labeling.
11. Other than the required bolding in 21 CFR 201.57(d)(1), (d)(5) and (d)(10), use bold print sparingly. Use another method for emphasis such as italics and underline.
12. Do not include NDC Numbers in the DOSAGE FORMS AND STRENGTHS section.
13. Do not include “How Supplied” information (i.e. packaging) in the DOSAGE FORMS AND STRENGTHS section.
14. Include following statement (or appropriate modification) preceding presentation of adverse reactions from clinical trials in the ADVERSE REACTIONS section:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rate observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

15. Reference the Patient Packaging Insert (PPI) in the Patient Counseling Information section.

Recommendations

The labeling deficiencies/issues identified above should be addressed by the applicant. A revised label should be submitted by August 31, 2009. The updated version of labeling will be used for further labeling discussions.

Nichelle Rashid
Regulatory Project Manager

Supervisory Comment/Concurrence:

Margo Owens
Project Manager Team Leader

Drafted: NER/051109; 051509
Revised/Initialed: MO/051309
Finalized: NER/051509
Filename: Labeling Review (initial PLR).doc

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