

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-484

CHEMISTRY REVIEW(S)

NDA 22-484

**Hyphanox
Itraconazole Tablets
200 mg**

Stiefel Laboratories, Inc.

Christopher Hough

Review Chemist

**Office of New Drug Quality Assessment
Division of Office of New Drug Quality Assessment
Pre-Marketing Division II, Branch III**

CMC REVIEW OF NDA 22-484

**For the Division of Gastroenterology Products
(HFD-540)**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 22-484
2. REVIEW #: 1
3. REVIEW DATE: 15-Oct-2009
4. REVIEWER: Christopher Hough, Ph.D.
5. PREVIOUS DOCUMENTS: None
6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	31-Mar-2009
Correspondence (C)	
Amendment, Clinical	11-Jun-2009
Amendment, Proprietary name review request	26-Jun-2009
Amendment, Safety update	24-Jul-2009
Amendment, Labeling/Container-Carton Draft	31-Aug-2009
Response to Information Request	01-Sep-2009

7. NAME & ADDRESS OF APPLICANT:

Name: Stiefel Laboratories, Inc.
Address: 20 T.W. Alexander Drive, PO Box 14910,
Research Triangle Park, NC 27709
Representative: Salisa Hauptmann, Global Vice President,
Regulatory Affairs
Telephone: (919) 990-6133

8. DRUG PRODUCT NAME/CODE/TYPE:

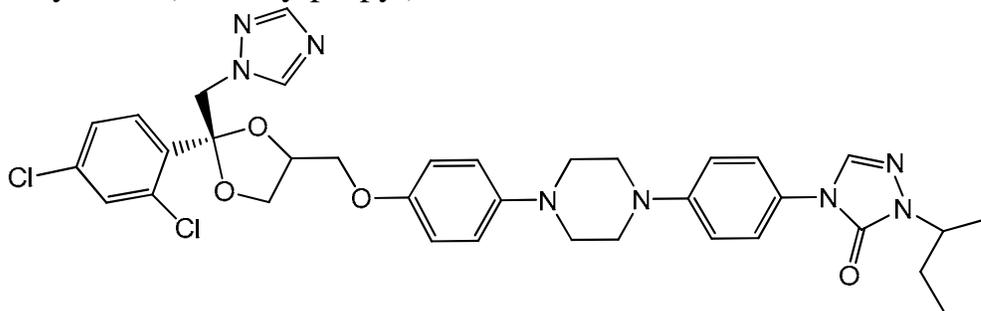
- a) Proprietary Name: (Pending)
- b) Non-Proprietary Name: itraconazole
- c) Code Name/# (ONDQA only): R021511
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 5
 - Submission Priority: Standard

CMC Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
10. PHARMACOL. CATEGORY: Antifungal
11. DOSAGE FORM: tablet
12. STRENGTH/POTENCY: 200 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx OTC
15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)
 SPOTS product – Form Completed
 Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(±)-cis-4-[4-[4-[4[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolane-4-yl]methoxy]methoxy]phenyl-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one



$C_{35}H_{38}Cl_2N_8O_4$
MW 705.64

CMC Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
10725	II	Johnson&Johnson	Drug Substance	1	Adequate	14-Oct-2009	
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	14-Oct-2009	
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	14-Oct-2009	
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate	n/a	
(b) (4)	III	(b) (4)	(b) (4)	4	Adequate	n/a	
(b) (4)	IV	(b) (4)	(b) (4)	4	Adequate	n/a	
(b) (4)	IV	(b) (4)	(b) (4)	4	Adequate	n/a	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	IND (b) (4)	Itraconazole coated tablet, Stiefel
NDA	NDA 20-083 NDA 20-657	Sporanox Oral Capsules Sproanox Oral Solution

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	pending	10-Nov-2009	
Pharm/Tox	N/A		
Biopharm	N/A		
LNC			
Methods Validation	N/A		
DMETS	Proprietary name not acceptable. "Film-coated" not acceptable. Some formatting changes needed.	22-Sept-2009	Baugh, Denise V
EA	Categorical exclusion (see review) granted	15-Oct-2009	Hough, Christopher
Microbiology	Adequate	01-May-2009	Snow, Kerry

Executive Summary Section

The CMC Review for NDA 22-484

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient information to assure identity, strength, and quality of the drug product.

However, all issues involving container/carton labels have not been resolved. In addition, a recommendation from the Office of Compliance on manufacturing site acceptability has not been made as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until the site acceptability and label issues have been resolved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable :

The proposed post-marketing stability testing commitment is adequate.

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

The drug substance of this application is itraconazole, manufactured by Janssen Pharmaceutica NV. Reference is made to the DMF#10725 for the drug substance and to the (b) (4) materials used in the synthesis of itraconazole. The drug substance complies with the Eur. Pharm. monograph for itraconazole and is tested by the Sponsor before releasing the drug substance for the manufacture of drug product. The testing involves largely compendial methods. The compendial method for assay by titration is replaced by an in-house HPLC method. Stress testing of the drug substance indicates that this substance is stable to heat, light, acid, or alkali, but is sensitive to oxidation. The drug substance is neither water soluble nor hygroscopic. Stability testing demonstrates that the itraconazole is stable when stored at 15-25° C/30-65% relative humidity in the manufacturer's container/closure.

(2) Drug Product

The drug product is an oblong biconvex tablet, containing 200 mg of itraconazole, embossed on one side with the word "BARRIER" and with "It 200" on the other. (b) (4)



Executive Summary Section

(b) (4)
The finished product is packaged in (b) (4) blister package that is placed in a thin cardboard card containing 14 dosage units, and those are packaged into two card cartons. The tablet is an immediate release tablet. (b) (4)

(b) (4) Excipients, the drug substance and processes are optimized and controlled to insure consistency and uniformity of composition and performance of the drug product. Specifications and validated analytical methods of the drug product control the key attributes of the drug product to assure product identity, strength, purity, and quality. Stability studies have demonstrated the stability of the finished product in the proposed blister pack for up to 48 months. This is the recommended expiration dating period until further data are obtained.

B. Description of How the Drug Product is intended to be used

The drug product is intended as a treatment for Onychomycosis of the toenail (b) (4) in non-immunocompromised patients. The dosage form is a tablet for oral administration. The strength is that which is recommended for a single day for this indication (200 mg).

C. Basis for Approvability or Not-Approval Recommendation

The Sponsor has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability information for the drug product to assure strength, purity, and quality of the drug product during the expiration dating period. However, all issues involving labels and final recommendation from the Office of Compliance concerning establishment acceptability have not been resolved as of the date of this review. Therefore, this NDA will not be recommended for approval until these issues are resolved.

Executive Summary Section

III. Administrative**A. Reviewer's Signature:**

(See appended electronic signature page)

Christopher Hough, Ph.D., CMC reviewer, ONDQA

B. Endorsement Block:

(See appended electronic signature page)

Moo-Jhong Rhee, Ph.D., Branch Chief, Branch #II, ONDQA

C. CC Block: entered electronically in DARRTS

**56 page(s) 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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTOPHER J HOUGH
11/17/2009

MOO JHONG RHEE
11/17/2009
Chief, Branch III