CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-484

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	March 19, 2010
From	David Kettl, MD, Clinical Team Leader
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	22-484 Related IND: 69,847 SDN: 1
Applicant	Stiefel Laboratories
Date of Submission	March 31, 2009
PDUFA Goal Date	January 31, 2010, extended to April 30, 2010 by major amendment
Proprietary Name / Established (USAN) names	Tradename Itraconazole
Dosage forms / Strength	200mg tablet
Proposed Indication(s)	Onychomycosis of toenail
Recommended:	*Approval*

1. Introduction

This 505(b)(1) application for a new formulation of itraconazole, 200 mg tablets, is from Stiefel Laboratories, and is submitted for the indication of toenail onychomycosis.

Itraconazole is approved for the treatment of onychomycosis (along with several anti-fungal indications) in the U.S. and has been marketed since the mid-1990s using a once daily (QD) administration for 12 weeks of two 100-mg itraconazole capsules (Sporanox, Janssen Pharmaceutical Products, NDA 20-083). The original approval for Sporanox 100 mg capsules was on September 11, 1992.

Two other approved formulations of Sporanox, Sporanox Oral Solution (NDA 20657, approved 2/21/97) and Sporanox Injectable Solution (NDA 20966, approved 3/30/99) are marketed in the United States, but neither of these formulations is approved for onychomycosis.

Tradename-Itraconazole 200-mg film-coated tablets were developed initially by Janssen Pharmaceutical Products (Johnson & Johnson). Subsequently, Stiefel Laboratories, Inc. (Barrier Therapeutics) assumed ownership of the itraconazole film-coated tablet formulation. Stiefel is currently developing the itraconazole 200-mg film-coated tablet and is the listed sponsor for this application.

Sporanox has had a boxed warning since 2001 for cardiac events, including ventricular dysfunction, negative inotropic events, and congestive heart failure.

The applicant proposes that the advantages of this new 200 mg tablet formulation include a simpler dosing regimen, more tamper resistance, and improved patient compliance, while mirroring the safety and effectiveness of the innovator product, Sporanox 100 mg capsules.

The applicant's development plan was based on pharmacokinetic findings which concluded that the 200 mg tablet was slightly out of bioequivalence boundaries for an ANDA application. One phase 3 trial was conducted to demonstrate efficacy and bridge to safety of the innovator Sporanox formulation.

The applicant provided a Rights of Reference letter from Janssen, who own the Sporanox referenced products. However, most use of Sporanox is in patients who have systemic fungal infections, and current labeling for Sporanox may not reflect the entire adverse event and drug interaction profile that should be considered for prescribers considering treatment of a non-life threatening indication with a high recrudescence rate such as toenail onychomycosis. Discussions with DSPTP are underway to add additional drug interaction information and additional contraindicated drugs to the existing Sporanox boxed warning.

The clinical reviewer, Dr. Trajkovic, initially recommended a Complete Response for this application until further safety and drug interaction information could be provided by the applicant and reviewed by the Agency. The applicant submitted drug interaction information in November, 2009 which included extensive literature on 27 new drug interactions. Due to the nature and size of this submission, and the review time required by the clinical pharmacology and clinical teams, this was characterized as a major amendment and a three month clock extension was made to the existing PDUFA date.

The review of this material is now complete, and updated labeling recommendations appear to be adequate to capture the new drug interaction information. Labeling recommendations have been discussed with the DSPTP clinical and clinical pharmacology review teams so that changes in the Sporanox prescribing information which include this new information can be undertaken once the action for this DDDP product is complete.

The clinical review now recommends an approval action for this application, with which this CDTL review concurs, pending successful conclusion of pending labeling negotiations with the applicant.

There are no outstanding issues from the CMC, Pharmacology/Toxicology and Biostatistics reviews.

2. Background

Tradename-itraconazole 200mg tablet was developed under IND 69,847, initially submitted on January 20, 2005. The initial proposed tradename was Hyphanox, though the DMEPA review

in this cycle rejected that name [redacted] though some letters and reviews referenced here may still refer to that originally proposed name.

A preIND meeting was held on October 25, 2005, and reviewed advice for conduct of pharmacokinetic protocols. An End of Phase 2 meeting was held on December 8, 2005. The meeting discussion centered on [redacted]

A Special Protocol Assessment was submitted on March 7, 2006, but the indication, dose and dosing regimen were changed from what was proposed at the prior meetings. The sponsor proposed to evaluate safety and efficacy of itraconazole tablets, itraconazole capsules and placebo in the treatment of onychomycosis of toenail. Specifically, the study was designed to evaluate the non-inferiority of one itraconazole 200mg tablet given once daily to two itraconazole 100mg capsule given once daily and superiority of itraconazole tablet to placebo.

A second Special Protocol Assessment was submitted on May 31, 2006, which reflected the Agency recommendations from the initial SPA review.

A guidance teleconference was conducted on July 25, 2006, and identified agreement on the primary endpoint…:

> *"The Agency is in agreement with your proposed primary endpoint, which should be the difference in percentage of patients achieving both clinical cure (an IGA of 0 with no evidence of onychomycosis in target nail - normal nail unit without subungual hyperkeratosis or onycholysis) and mycologic cure (negative KOH and negative culture for dermatophytes of the target toenail)."*

…but did not specify with the choice and definition of secondary endpoints for clinical success, [redacted], and multiplicity adjustments.

The applicant was also informed that:

> *"If Hyphanox is more bioavailable than Sporanox, additional safety information to support systemic safety will be needed."*

A preNDA meeting was scheduled for February 4, 2009. After receiving the Agency's draft responses, the sponsor cancelled the meeting.

A single Phase 3 trials was conducted, Study 302, with the efficacy objective of demonstrating Tradename-Itraconazole Tablets would be non-inferior to Itraconazole Capsules (Sporanox) and superior to Placebo Tablets for the treatment of toenail onychomycosis.

The primary efficacy parameter was the Complete Cure rate defined as both Clinical Cure and Mycological Cure at Visit 8 (Week 52). In Study 302, Tradename-Itraconazole Tablets were found to be superior to Placebo Tablets ($p < 0.05$) and non-inferior to Itraconazole Capsules (NI margin $< -10\%$). This study was conducted in accordance with Agency recommendations of the SPA reviews.

While the efficacy objectives were met in this trial, and the safety profile seen in the phase 3 trial was similar to that predicted given the Sporanox experience, the clinical team concluded that the safety information contained in the Sporanox labeling, from which this applicant has liberally borrowed, was not sufficient for the patient population who will use this product for onychomycosis. More complete labeling descriptions of the pharmacokinetic profile of this product and the potential for additional drug interactions have been added to the proposed draft labeling to augment the currently known safety information. Labeling negotiations with the applicant are ongoing as of the date of this CDTL review.

3. CMC/Device

CMC data was reviewed by the Drug Product and Drug Substance Reviewer, Christopher Hough, Ph.D.

Review of the CMC information submitted to the NDA was sufficient to conclude that this NDA has provided sufficient information to assure identity, strength, and quality of the drug product.

The Sponsor 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.

Issues involving container/carton labels have been resolved. In addition, a recommendation from the Office of Compliance on manufacturing site acceptability has been received and is acceptable.

Early concerns regarding the drug product manufacturing process, microbiological testing, and assay validation were successfully resolved during the review cycle. A degradant (b) (4) (b) (4) that minimally exceeded the qualification threshold recommended by ICH guidelines was qualified by the Pharmacology/Toxicology reviewer.

The proposed post-marketing stability testing commitment is adequate.

No outstanding CMC issues remain that would impact on an approval action for this application.

4. Nonclinical Pharmacology/Toxicology

The original IND (69, 847, submitted 01-20-2005) for the proposed formulation was submitted by Barrier Therapeutics, Inc. Since August 2008, Stiefel Laboratories, Inc. is the legal owner of Barrier Therapeutics, Inc. Right of Reference letters for NDA 20-083 (Sporanox capsules) and NDA 20-657 (Sporanox oral solution) were included in the NDA submissions which authorized the Agency to reference the nonclinical toxicology data contained in NDA 20-083 and NDA 20-657 to support this NDA submission. There was no limitation on the data referenced in those reference authorization letters.

The non-clinical safety profile of the proposed tablet formulation is essentially based on studies conducted to support the safety of Sporanox 100 mg capsules (NDA 20-083 approved in 1992) for blastomycosis and histoplasmosis in AIDS patients, and Sporanox Solution for oropharyngeal candidiasis (NDA 20-657 approved in 1997), which are referenced by the current applicant under the right of reference.

.

Both drugs were reviewed and approved by the Division of Antiviral Drug Products.
Most of these studies were conducted prior to the issuance of ICH guidelines in early 1990s.

A degradant (b) (4)) that minimally exceeded the qualification threshold recommended by ICH guidelines was qualified by the Pharmacology/Toxicology reviewer. The organic impurity caused no toxicity, genotoxicity, or cellular cytotoxicity, and this issue does not affect approvability.

Labeling recommendations for the nonclinical sections are taken directly from the Sporanox labeling. Proposed labeling for this section is adequate and is supported by the reviews of the innovator product. The nonclinical reviewer concluded that there were no outstanding issues from the non-clinical perspective.

5. Clinical Pharmacology/Biopharmaceutics

Itraconazole belongs to the first generation of systemic triazoles. As a class, triazoles act predominantly by inhibiting cytochrome P450 (CYP)-dependent conversion of lanosterol to ergosterol, the main sterol in the cell membrane of most fungi, resulting in inhibition of cell growth and replication.

Five of the six clinical studies conducted to support this application were related to clinical pharmacology, among which were 3 bioequivalence/bioavailability studies and 2 pharmacokinetic studies. To evaluate if a 200-mg film-coated tablet is bioequivalent to two

100-mg Sporanox capsules, comparative PK studies were conducted using the to-be-marketed tablet product and commercially available Sporanox capsules.

Previous studies conducted to support the approval of Sporanox have shown that the absorption of itraconazole is affected by food and the label of Sporanox indicates that the drug is to be taken with food. Therefore comparative BE studies in this submission were conducted under both fasting and fed conditions.

The BE studies reviewed by the primary Biopharmaceutics reviewer, Dr. Seongeun Cho, PhD, demonstrated significant variability from food effects despite claims by the applicant that their "melt extrusion" technology would limit such variability.

The results from all three BE studies collectively show that itraconazole 200-mg film-coated tablets and two 100-mg Sporanox capsules are not bioequivalent in any conditions, exceeding 80-125 % boundary for 90 % confidence interval. In addition, the effects of food on the PK of Hyphanox, compared to Sporanox, are not uniform and depend on the composition of the meal. The total exposure of itraconazole was about 15% higher with the 200-mg film-coated tablet than with the 100-mg capsules, when dosing occurred in the fasted state as well as after a standard breakfast, while tablets had 30% lower bioavailability compared to capsules, when dosing occurred after a high-fat, high-calorie breakfast.

The Biopharmaceutics review also notes that there was high inter-subject variability in the exposure in all studies with coefficient of variations (CV) for AUC in the range of 43-66 %.

Also noted by Dr. Cho is that in a real world environment, it is unlikely that patients will have a same fat content breakfast everyday for 12 weeks, affecting the plasma concentrations of itraconazole toward a consistent direction following administration of Hyphanox relative to Sporanox. Rather, it is anticipated that the mean plasma concentrations of Hyphanox will fluctuate around the mean plasma concentrations expected from Sporanox, depending on the composition of a daily meal.

Dr. Cho concludes:

> "*Therefore it is this reviewer's opinion that the differences in the exposure between Hyphanox and Sporanox under studied meal conditions are clinically insignificant and will not have impacts on efficacy or safety.*"

The pivotal Phase 3 safety and efficacy trial was conducted following a standard breakfast. No PK parameters were examined, however, during the phase 3 trial and thus no determination of exposure-safety and/or efficacy correlation can be made.

No independent Qt/Qtc evaluations were performed for this formulation of itraconazole. The applicant intends to rely on the existing labeling for Sporanox for issues related to Qt prolongation.

The issue of drug interactions, and the adequacy of labeling to address these concerns, is discussed in section 8, Safety.

6. Clinical Microbiology

Kerry Snow, PhD, the clinical microbiology reviewer, concluded that from a clinical microbiology perspective, the application is approvable.

The majority of isolates, identified as fungal pathogens in subjects diagnosed with onychomycosis of the large toenail, were identified as *Trichophtyon rubrum* (1005 of 1057 isolates recovered at the Baseline Visit, ITT data set). Forty-four isolates of *T. mentagrophytes* were recovered, and 8 isolates of *Epidermophyton floccosum* were recovered. Microbiological success rates (negative KOH and fungal culture at the End of Study Visit) were comparable between the two active arms, in subjects infected by either species of the *Trichophyton* genus, but insufficient data was available to evaluate comparative efficacy in cases of infection by *E. floccosum*.

No notable decreased susceptibility of dermatophytes to itraconazole was observed during the study.

The applicant assembled a reference list of studies from the literature, describing the *in vitro* activity of itraconazole against fungal pathogens commonly associated with onychomycosis. No new data have been submitted in this application, regarding the *in vitro* antifungal activity of itraconazole.

Labeling recommendations were made in the clinical microbiology review, but these were not disclosed to the applicant pending decisions regarding safety requirements for labeling. These included:

(b) (4)

(b) (4)

7. Clinical/Statistical- Efficacy

One well-controlled Phase 3 trial was conducted to establish the noninferiority of 12 week treatment of onychomycosis of toenail with once daily itraconazole 200mg tablet to once daily treatment of two itraconazole 100mg capsules (Sporanox) and to demonstrate superiority to placebo.

Despite the major changes in the direction of the development program subsequent to the December 8, 2005 End of Phase 2 meeting, which included changes in the dosing regimen and intended indication, the phase 3 trial was conducted in general agreement with the Agency advice and guidance presented during the SPA reviews and subsequent guidance meeting. The applicant agreed that any endpoints for (b) (4) would be exploratory only and have no bearing on future labeling.

In this study, 1381 subjects were randomized to study drug; 593 subjects in the Tradename-itraconazole 200-mg tablet group, 590 subjects in the itraconazole 100-mg capsule group, and 198 subjects in the placebo tablet group. Of these subjects, 1226 (88.8%) were enrolled at 47 sites in the US, 77 (5.6%) were enrolled at 4 sites in Latin America, 53 (3.8%) were enrolled at 6 sites in Canada, and 26 (1.9%) were enrolled at 1 site in South Africa.

1169 (84.6%) of subjects completed the study, of which 517 (87.2%) in Tradename-itraconazole 200mg group, 469 (84.1%) in itraconazole 100mg capsule group and 156 (78.8%) in placebo tablet group. The population of subjects enrolled in this study was consistent, in terms of age and gender, with the population affected by onychomycosis. In terms of race and ethnicity, there was no significant difference in numbers between treatment subgroups.

(b) (4) only one subject in itraconazole tablet group, no subjects in itraconazole capsule group and one subject in placebo group were included in the trial from age 16-18 years of age. No conclusions regarding safety or efficacy can be made in this group, and any recommended action will be for the adult population 18 years of age and older.

Almost all subjects (96%) had an IGA of moderate to severe, and 99% had > 25% to <75% nail involvement. 84.6% of subjects completed the trial.

The primary efficacy endpoint was Complete Cure rate at Visit 8 (week 52) the primary evaluation visit. In this study, Complete Cure was defined as both a Clinical Cure and a Mycological Cure. A Clinical Cure was considered an IGA score of 0 for the target toenail, and that a Mycological Cure must have included both a negative KOH examination and a negative culture for dermatophytes of the target toenail.

Based upon the definitions of the primary endpoint and analysis populations, both efficacy objectives met the pre-specified statistical criteria (Table 11). The treatment effects (Tradename-itraconazole Tablets - comparator) for each population were:

Non-Inferiority: 0.6% (ITT) and 0.9% (PP)
Superiority: 21.3% (ITT) and 23.8% (PP)

These statistical aspects of efficacy were in accordance with Agency recommendations made following review of the Special Protocol Assessments.

The primary efficacy results are summarized in the following table:

Complete Cure Results

	Itraconazole Tablet 200mg	Itraconazole Capsule 100mg	Placebo Tablet
ITT Population			
Sample Size	593	590	198
Success (%)	132 (22.3%)	128 (21.7%)	2 (1.0%)
Statistical Comparison	-	(-4.3%, 5.5%)[†]	p< 0.0001[*]
PP Population			
Sample Size	502	488	155
Success (%)	126 (25.1%)	118 (24.2%)	2 (1.3%)
Statistical Comparison	-	(-4.7%, 6.5%)[†]	p<0.0001[*]

As noted in the primary Clinical and Biostatistical reviews, the primary endpoint is essentially a composite endpoint, consisting of two components: Clinical Cure and Mycological Cure. For Clinical Cure, the Sporanox 100 mg capsule formulation had a slightly improved response rate than the Tradename-itraconazole 200 mg tablet formulation. For Mycological Cure, Tradename-itraconazole 200mg tablet was superior to both placebo tablets and itraconazole 100mg capsule. Overall response rates for the proposed Tradename-itraconazole 200 mg tablet were higher for Mycological Cure rates than Clinical Cure rates.

In the study report, the sponsor stated that the blind may have been broken in several sites.

In the 74 day letter the Division requested the sponsor provide additional information on the nature of the unblinding. The sponsor responded, stating that study coordinators who dispensed study product, received returned study product, and were responsible for product accountability inadvertently recorded the number of units dispensed which would have the potential to break the blind as the Tradename tablets are 200 mg and the capsules 100 mg (i.e. twice as many capsules were dispensed as tablets). The sponsor claims that the investigators at the seven sites where this occurred did not notice this information to actually break the blind with the exception of one investigator (Dr. Matheson) who enrolled a single subject.

To insure that potential unblinding issues did not affect efficacy determinations, the Agency Biostatistics reviewer, Dr. Soukup, performed sensitivity analyses which discard the data from the seven sites where the blind was potentially broken. Despite the removal of 301 subjects from the total number of enrolled subjects in these analyses, efficacy was again demonstrated for the non-inferiority objective comparing Tradename-itraconazole 200mg tablets to itraconazole 100mg capsules for both the ITT and PP population as well demonstrated for the superiority objective for comparing the itraconazole 200mg tablets to placebo tablets

Success rates were not affected greatly by gender, baseline IGA score, or nail involvement percentage. There was a slight difference in age subgroups that favored younger subjects. The persistence of efficacy and tolerance effects was not evaluated during the conduct of the Phase 3 trial. Recurrence or recrudescence was not evaluated.

Overall, both the Clinical and Biostatistical reviewers were in agreement that the efficacy endpoints were successfully demonstrated in the Phase 3 clinical trial, and this CDTL review also concurs with this assessment.

8. Safety

Phase 3 Trial:

The safety of 200mg Tradename-itraconazole tablet for treatment of onychomycosis of toenail was evaluated in one pivotal clinical trial enrolling 1,354 subjects (BT0300-302-INT), two Phase 1, bioequivalency trials (BT0300-BEL-002 and BT0300-BEL-005) enrolling 112 subjects, one Phase 1 bioavailability trial (BT0300-BEL-006) enrolling 18 subjects and two Phase 1 PK trials enrolling 32 subjects. Four of the 5 Phase 1 studies were open-label, single-center studies intended to evaluate the Tradename-itraconazole 200mg tablet in healthy, adult volunteers.

Safety data from these 6 trials conducted under the Tradename-itraconazole 200mg tablet clinical development program included 744 subjects exposed to the Tradename-itraconazole 200 mg tablet. 711 subjects received treatment with the Sporanox-itraconazole 100 mg capsule in four of the studies, and 191 subjects received placebo, all in the phase 3 trial.

Tradename-itraconazole 200mg tablet product was evaluated specifically for adverse events that are considered common for the drug class: hepatotoxicity, cardiotoxicity and ototoxicity.

No deaths were reported during clinical development of Tradename-itraconazole 200mg tablet.

There were no serious AEs reported in any of the Phase 1 studies.

During the Phase 3 trial, 25 subjects reported 29 serious adverse events, 13 (2.2%) in Tradename-itraconazole 200mg tablet group, 13 (2.2%) in itraconazole 100mg capsule group, and 3 (1.5%) in the placebo group.

During the 12 week dosing period of Phase 3 trial, 6 subjects (two in each dosing group) reported serious adverse events. The remaining 23 serious adverse events occurred during the follow-up period.

One case of cholelithiasis (Subject #24090 in Tradename-itraconazole 200mg group) was considered related to the study drug by the sponsor. The other serious adverse event in the Tradename-itraconazole 200mg group was a new diagnosis of prostate cancer, which did not result in study discontinuation and was not suspected to be related to the treatment.

Of the remaining 23 serious adverse events which occurred during the post-dosing follow-up period, three subjects treated with Tradename-itraconazole 200mg were related to cardiovascular events (angina, carotid artery aneurysm, and myocardial infarction-[MI]) which was of particular interest due to the existing boxed warning in the Sporanox 100 mg capsule prescribing information. By comparison, the Sporanox-itraconazole 100 mg group had four events in three subjects (MI, congestive heart failure, MI, and cerebrovascular accident). Of note is that most of these events occurred well after the dosing period in a range of subjects whose average age was 47 years (range 17-75 years).

The nature and number of cardiovascular adverse events were similar to adverse events reported for Sporanox. The proposed updated draft labeling for Tradename-itraconazole, which restates the Boxed Warning contained in the Sporanox label, as well as additional language in the Warnings and Precautions sections, should adequately address these adverse events upon eventual approval.

Three serious adverse events reported in the itraconazole 100-mg capsule group (myocardial infarction, cerebrovascular accident, and glioblastoma multiforme) did lead to study drug discontinuation. All other subjects completed the trial.

The analyses of overall adverse event profiles for the treatment phase of the Phase 3 trial for the two active doses of itraconazole were quite similar. 829 subjects (61%) reported 1 or more adverse events. Of those, 341 (41%) were in Tradename-itraconazole 200mg tablet group, 373 (44%) in itraconazole 100mg capsule group, and 115 (13%) in placebo group.

Review of adverse event occurring in frequency of ≥1% during the dosing period revealed that most frequent adverse events were upper respiratory tract infections, elevation of hepatic enzymes and abdominal pain.

The hepatic enzyme adverse events were not unexpected given the Sporanox experience; however, this was the leading cause of discontinuation from the trial for adverse events. 7 (1.2%) subjects in Tradename-itraconazole 200mg tablet group and 7 (1.2%) subjects in itraconazole 100mg capsule group discontinued due to abnormal liver function tests. One from each group had AST/ALT elevation >10x the ULN. No subjects in placebo group had abnormal hepatic enzymes.

Clinically significant changes from baseline to week 52 were observed in 4% of subjects in Tradename-itraconazole 200mg tablet group, 4% of subjects in itraconazole 100mg capsule group and, 4% in placebo group. This adverse event is described in the Sporanox label, and will be included in the Tradename-itraconazole 200mg label should the product be eventually approved.

This CDTL review concurs with the primary clinical reviewer, Dr. Trajkovic, who concluded,

"The analysis of safety results revealed that reported adverse events in itraconazole tablet group were similar to adverse events reported for itraconazole capsule group and consistent with expected adverse events for the drug class to which both of drug formulations belong to. No additional unexpected adverse events have been reported."

Drug-Drug Interactions:

Triazoles have significant potential for drug-drug interactions through interference with the hepatic CYP3A4 metabolic pathway and potential for hepatic toxicity, including liver failure and death.

No additional drug dependent effects on the disease course of onychomycosis were evaluated during the development of the Tradename-itraconazole 200mg tablet, and the applicant originally proposed to include only those currently contained in the Sporanox prescribing information.

The Sporanox label was last updated in March, 2009. At that time, the DSPTP decided against including the complete list of contraindicated products in the Boxed Warning that could potentiate cardiovascular adverse events despite including them in other sections of the label.

DDDP sent an information request to the applicant on November 5, 2009 regarding any additional information on drug-drug interactions that would inform these labeling considerations. The applicant replied on November 23, 2009 with an extensive literature review bibliography searching back to 1992.

The list of products with unvetted literature reports included 27 drugs not currently listed in the Sporanox label. Literature citations referenced common drugs, including over-the-counter products such as cimetidine and loperamide. These references had not been fully reviewed by the applicant due to time constraints, and specific conclusions about the purported drug-drug interactions were not verified by them.

Upon Agency review of this IR response, and consultations from SEALD, DMEPA, DRISK, and DDMAC regarding the proposed labeling for Tradename-Itraconazole, the DDDP review team concluded that the Sporanox prescribing information was neither complete nor up-to-date, and that both labels would need to include additional drug-drug interaction information to inform prescribers regarding the likelihood of possible adverse events. The applicant's initial approach of using the labeling from Sporanox, essentially verbatim, would have to be amended to incorporate this new information.

Given the time required for the applicant to examine the literature and determine its significance, and them allow time for the Agency to review the conclusions and determine the impact on product labeling, a major amendment clock extension of three months was applied in January, 2010 for this application.

Subsequent to the review of that information, additional safety information, including additional studies involving drug-drug interactions and metabolism studies were recommended by the DDDP Biopharmaceutics review team, and have been discussed and shared with the DSPTP teams. These recommendations have been added to the proposed draft labeling. Final labeling negotiations are still in process with the applicant.

9. Advisory Committee Meeting

No Advisory Committee meetings were held for this application.

10. Pediatrics

(b) (4)

DDDP recommended a full waiver below age 18 be granted.

The Pediatric Review Committee considered this application on 10/28/2009. The PeRC recommendation concurred with the Division recommendations to restrict this product to adult use in patients 18 years of age and older. A waiver for patients under 18 years of age was granted.

11. Other Relevant Regulatory Issues

The most complex regulatory issue for this application concerned the applicant's proposed labeling, which copied extensive sections of the currently approved Sporanox prescribing information.

DDDP is not aware of any precedent products that have used existing labeling from another approved product this extensively. The applicant did provide an unrestricted right of reference letter to the Sporanox capsule product.

The Food, Drug, and Cosmetic Act defines a 505(b)(2) application as:

> An application that contains ***full reports*** of investigations of safety and effectiveness, where at least some of the information ***relied upon*** for approval comes from studies ***not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use.***
>
> *21 USC 355(b)(2)*

Since the right of reference letter was provided, this reviewer concurs with the assignment of a 505(b)(1) application. The Office of Regulatory Policy concluded that reliance on the innovator product's label fell within the right of reference. They also commented that the innovator company, having provided the applicant with the data and authorization to develop and market the tablet product, would be unlikely to object the applicant's use of the labeling language, trademarks or patents, however extensively borrowed.

Two study sites were inspected for DSI inspection, one (site 15) for the possibility of unblinding, and the other (site 38) due to the number of enrolled subjects and number of treatment responders.

Both site reports noted that the deviations did not appear to have a significant impact on data integrity, and the data appear acceptable in support of the respective application.
There were no financial disclosures that impacted on data assessment or integrity.

12. Labeling

Review of the proposed label supplied by applicant was based on evaluation of clinical studies for the NDA, as well as DMEPA, SEALD, DRISK, and DDMAC consultative reviews. A Patient Package Insert (PPI) has been included and reviewed by the Division and appropriate OSE consults.

These recommendations have been added to the proposed draft labeling. Final labeling negotiations are still in process with the applicant.

Following discussions with DSPTP, it is anticipated that a labeling supplement request letter will be issued to the sponsor of Sporanox to include the appropriate additions gleaned from this application to the Sporanox prescribing information.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The clinical team leader concurs with the primary clinical reviewer that this application should be approved for the treatment of toenail onychomycosis pending completion of labeling negotiations with the applicant.

- Risk Benefit Assessment

The efficacy for the indication of onychomycosis in patients 18 years of age and older has been adequately demonstrated. The safety findings in the single trial approximate those of the previous experience with the previously approved Sporanox formulation of itraconazole. The benefits of this product outweigh the risks when used as the prescribing information recommends and CDTL concurrence is given for the approval recommendation.

There are no outstanding issues from the CMC, nonclinical, or biostatistics review teams.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

It was determined, after discussion with DSPTP, that a REMS would not be required for this product purely on the basis of the presence of a boxed warning. Labeling is adequate to communicate risks for this product.

- Recommendation for other Postmarketing Requirements and Commitments

No recommendations for post-marketing requirements or commitments are suggested for this application.

- Recommended Comments to Applicant

None.

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/

DAVID L KETTL
03/29/2010