CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-484

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	April 27th, 2010
From	Susan J. Walker, M.D., F.A.A.D.
Subject	Division Director Summary Review
NDA	22-484
Applicant Name	Stiefel Laboratories
Date of Submission	March 31st, 2009
PDUFA Goal Date	April 30th, 2010
Proprietary Name / Established (USAN) Name	TRADENAME / Itraconazole
Dosage Forms / Strength	Tablet/ 200mg
Proposed Indication(s)	Onychomycosis of toenail
Action	***Approval***

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Snezana Trajkovic, M.D.
CDTL Review	David Kettl, M.D.
Statistical Review	Mat Soukup, Ph.D.
Pharmacology Toxicology Review	Kumar Mainigi, Ph.D.
CMC Review	Christopher Hough, Ph.D.
Microbiology Review	Kerry Snow, Ph.D.
Clinical Pharmacology Review	Seonguen Julia Cho, Ph.D.
DDMAC	Andrew Haffer
DSI	Roy Blay, Ph.D.
OSE/DMEPA	Denise Baugh, PharmD.
SEALD	Jeanne Delasko, RN, MS
OSE/DRISK	Latonia Ford, RN, BSN, MBA

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
CDTL=Cross-Discipline Team Leader
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK=Division of Risk Management
SEALD= Study Endpoints and Labeling Development

Division Director Signatory Review

1. Introduction

This 505(b) (1) application proposes approval of itraconazole formulated in a 200mg tablet for the treatment of onychomycosis. Itraconazole 100 mg capsule was initially developed, and is marketed by Johnson and Johnson, on behalf of Janssen Pharmaceutica. The current applicant has been granted right of reference to NDA 20-083 (Sporanox® oral capsules), NDA 20-657 (Sporanox® oral solution 10mg/ml) and NDA 20-966 (Sporanox® Injection 10mg/ml). The application proposes approval of the product based upon reference to the currently approved product and the outcomes of studies conducted to demonstrate the safety and efficacy of TRADENAME.

2. Background

Itraconazole is a synthetic triazole with broad spectrum antifungal activity. The sponsor proposes treatment of onychomycosis of the toenail with their 200mg product for the same indication and at the same total dosage, route of administration, duration, and frequency as the currently approved Sporanox® 100mg capsule. Additionally, itraconazole is available as a 100mg generic capsule. Itraconazole is not available as an Over the Counter product and is not listed as a Discontinued Drug Product in the Orange Book.

The applicant's development program included an End of Phase 2 meeting December 8th, 2005, and a preNDA meeting on February 4th, 2009. The clinical program consisted of two pharmacokinetic studies, two bioequivalence studies, one bioavailability study, and one safety and efficacy study. Johnson and Johnson Pharmaceutical Research and Development, LLC (J&JPRD) has authorized the Food and Drug Administration to cross-reference to NDA 20-966 Sporanox® (Itraconazole) injection 10mg/mL, 20-803 for Sporanox® (Itraconazole) capsules and NDA 20-657 (Itraconazole Oral Soln 10mg/mL) for clinical, preclinical, and chemistry, manufacturing and control data on behalf of Stiefel Laboratories. J&J has also authorized cross-reference to DMF [redacted] (b) (4), 10725.

3. CMC/Device

The drug substance for this application is itraconazole, manufactured by Janssen Pharmaceutica and complies with the Eur. Pharm. Monograph for itraconazole. The drug product is an oblong biconvex tablet containing 200mg of itraconazole embossed on one side with "Barrier" and on the other with "It 200". The tablet is an immediate release tablet. The chemistry reviewer concludes that the 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. Manufacturing site inspections were acceptable and a final recommendation of Acceptable was received from the Office of Compliance on 11 Dec 2009.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

Cross reference letters were provided authorizing the Agency to cross-reference non-clinical toxicology data to support this application.

No non-clinical studies were conducted with the proposed formulation, however, I concur that adequate information has been obtained via right of reference to approved products. The labeling for this product will reflect conversion to the PLR format.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The applicant conducted 3 bioequivalence/bioavailability studies and 2 pharmacokinetics studies. Studies were conducted in both the fed and fasted states as absorption of itraconazole has been demonstrated to be affected by food.

Bioavailability

Studies comparing bioequivalence/bioavailability of TRADENAME 200mg formulation with the two 100-mg Sporanox® capsules were open label, randomized, cross-over, single-dose studies in healthy male and female subjects. Study BT0300-BEL-005 included a high-fat, high calorie breakfast, study BT300-BEL-002 included a “standard breakfast” and studyBT300-BEL-006 was administered without food (fasting). Outcomes are summarized by the biopharm reviewer and replicated below.

Study BT0300-BEL-005 (High-fat, high-calorie breakfast)

Parameter		Itraconazole Capsule 2 x 100 mg - Reference - Mean ± STD	Itraconazole 200-mg film-coated tablet 1 x 200 mg - Test - Mean ± STD	Geometric Mean Ratio, % Test/Reference Ratio (90% CI)
Itraconazole				
T_{max}	(h)	4.0 (2.0-8.0)[a]	5.0 (2.5-8.0)[a]	0.50 (0.00-0.75)[b]
C_{max}	(ng/mL)	227±106	185±112	80.4 (70.1-92.4)
AUC_t[c]	(µg·h/mL)	3.22±1.83	2.28±152	69.6 (60.4 -80.2)
AUC_∞	(µg·h/mL)	3.38±1.96	2.41±1.62	70.4 (61.4-80.6)
$t_{1/2term}$	(h)	24.9±6.2	23.9±7.6	
Hydroxy-itraconazole				
T_{max}	(h)	5.0 (2.5-12.0)[a]	5.0 (3.5-8.0)[a]	0.01 (-0.01-0.50)[b]
C_{max}	(ng/mL)	354±130	288±108	82.3 (73.5-92.0)
AUC_t[c]	(µg·h/mL)	7.02±4.08	4.85±2.96	69.8 (60.3-80.8)
AUC_∞	(µg·h/mL)	7.25±4.16	5.04±2.99	70.1 (60.9-80.8)
$t_{1/2term}$	(h)	9.8 ±2.9	8.7±2.7	

Study BT0300-BEL-002 (Standard breakfast)

Parameter		Itraconazole Capsule 2 x 100 mg - Reference - Mean ± STD	Itraconazole 200-mg film-coated tablet 1 x 200 mg - Test - Mean ± STD	Geometric Mean Ratio, % Test/Reference Ratio (90% CI)
Itraconazole				
T_{max}	(h)	5.0 (2.0-8.0)[a]	3.5 (2.0-8.0)[a]	-0.50 (-0.99--0.25)[b]
C_{max}	(ng/mL)	306±146	294±114	101.0 (91.3-111.7)
AUC_t	(µg·h/mL)	3.60±1.69	3.98±1.74	114.8 (103.9-126.9)
AUC_∞	(µg·h/mL)	3.87±1.85	4.28±1.96	114.7 (103.7-126.8)
$t_{1/2term}$	(h)	26.0±8.8	28.4±9.5	
Hydroxy-itraconazole				
T_{max}	(h)	5.0 (2.0-8.0)[a]	4.0 (2.0-12.0)[a]	-0.25 (-0.50-0.025)[b]
C_{max}	(ng/mL)	460±166	470±115	105.9 (98.2-114.2)
AUC_t	(µg·h/mL)	7.79±3.70	8.64±3.80	114.9 (103.3-127.8)
AUC_∞	(µg·h/mL)	8.01±3.75	8.85±3.87	113.9 (102.6-126.5)
$t_{1/2term}$	(h)	9.0±2.3	9.3±2.4	

Study BT0300-BEL-006 (fasting condition)

Parameter		Itraconazole 200-mg film-coated tablet 1 x 200 mg - Fasted - Mean ± STD	Itraconazole 100-mg Capsule 2 x 100 mg - Fasted - Mean ± STD	Geometric Mean Ratio, % Tablet/Capsule Ratio (90% CI)
Itraconazole				
T_{max}	(h)	3.0 (1.02-4.0)[a]	3.0 (2.0-5.0)[a]	-0.50 (-1.00--0.00)[b]
C_{max}	(ng/mL)	162±107	135±68.2	105.3 (84.2-131.7)
AUC_t[c]	(µg·h/mL)	2.12±1.38	1.73±0.95	114.0 (93.0-139.7)
AUC_∞	(µg·h/mL)	2.27±1.44	1.87±0.99	114.7 (94.6-139.1)
$t_{1/2term}$	(h)	25.9±5.68	24.4±6.98	
Hydroxy-itraconazole				
T_{max}	(h)	3.25 (2.50-5.0)[a]	3.5 (2.5-6.0)[a]	-0.50 (-0.99-0.00)[b]
C_{max}	(ng/mL)	264±109	232±70	106.7 (89.8-126.7)
AUC_t[c]	(µg·h/mL)	4.42±2.79	3.57±1.95	116.3 (94.3-143.4)
AUC_∞	(µg·h/mL)	4.58±2.80	3.73±2.00	116.3 (95.1-142.2)
$t_{1/2term}$	(h)	12.3±3.67	10.1±2.02	

Table 8: Summary of the Equivalence Statistics of the Bioequivalence Studies (BT300-BEL-002, BT0300BEL005, and BT0300BEL006) Conducted in Various Food Conditions

Parameter	Itraconazole 200-mg film-coated tablet versus Itraconazole 100-mg capsules Point Estimate [90% Confidence Interval], %[a]		
	Standard breakfast n = 52	High-fat, high-calorie breakfast n = 56	Fasting conditions n = 18
Itraconazole			
T_{max}	-0.50 [-0.99--0.25]	0.50 [0.00-0.75]	-0.50 [-1.00-0.00]
C_{max}	101.0 [91.3-111.7]	80.4 [70.1-92.4]	105.3 [84.2-131.7]
AUC_t	114.8 [103.9-126.9]	69.6 [60.4-80.2]	114.0 [93.0-139.7]
AUC_∞	114.7[103.7-126.8]	70.4 [61.4-80.6]	114.7 [94.6-139.1]
Hydroxy-itraconazole			
T_{max}	-0.25 [-0.50-0.025]	0.01 [-0.01-0.50]	-0.50 [-0.99-0.00]
C_{max}	105.9 [98.2-114.2]	82.3 [73.5-92.0]	106.7 [89.8-126.7]
AUC_t	114.9 [103.3-127.8]	69.8 [60.3-80.8]	116.3 [94.3-143.4]
AUC_∞	113.9 [102.6-126.5]	70.1 [60.9-80.8]	116.3 [95.1-142.2]

As noted by the primary clinical and biopharm reviewers, the effects of food on the comparative bioavailability of itraconazole in TRADENAME vs. itraconazole in Sporanox® are not unidirectional and depend upon the composition of the meal. These studies demonstrate that exposure of itraconazole from TRADENAME under the high-fat/high calorie meal was 30% lower than exposure from Sporanox®. However, there is high inter-subject variability in the exposure and it is anticipated that the mean plasma concentration of TRADENAME will fluctuate around the mean plasma concentrations expected from Sporanox®, depending upon the composition of the daily meal. Under the standard meal, the Cmax for TRADENAME was equivalent to that of Sporanox®, while the exposure was approx 15% higher than Sporanox®. Observations from this study also demonstrate that the coefficient of variation of AUC is large for both products and I concur with the biopharm and clinical reviewers that the 15% difference is unlikely to have impacts upon efficacy or safety.

Pharmacokinetics: Single and multiple dose profiles

Two studies were conducted to characterize itraconazole and its active metabolite, hydroxy-itraconazole, after administration of TRADENAME.

Reference	Design	Treatments	No. of Subjects	Age, yrs mean (range)	Weight, kg mean (range)
BT300-BEL-004	Open	Two itraconazole 200-mg film-coated tablets dosed after a high-fat, high-calorie breakfast.	16F	35.8 (19-58)	63.6 (46-81)
BT0300-108-USA	Open	One itraconazole 200-mg film-coated tablet after a standard breakfast, QD for 14 days	8M/8F	36.3 (23-53)	69.6 (49.9-93.4)

Study BT0300-108-USA demonstrated the pharmacokinetics of itraconazole and its major metabolite at steady state after administration of TRADENAME once daily for two weeks, with a 10 day followup period. Product was administered with the sponsor's standard breakfast of approximately 500 calories (20% from protein, 50% from carbohydrate, and 30% from fat). As with other studies, inter-subject variability was relatively high. However, the mean plasma profile data demonstrates that a steady state level of itraconazole was reached by day 10.

Study BT300-BEL-004 assessed the pharmacokinetics of itraconazole in healthy women after single administration of 400mg of itraconazole in the new 200mg tablet formulation. Cmax and AUC of itraconazole were 307ng/ml and 5.53 ug.h/mL respectively. Single administration was well tolerated.

During the NDA review the division pursued additional discussions with the sponsor regarding drug-drug interactions. Expanded information regarding drug-drug interactions will be included in the TRADENAME approved labeling. Currently approved itraconazole products are anticipated to have similar labeling updates.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

I concur with the conclusions of the clinical microbiology reviewer that 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

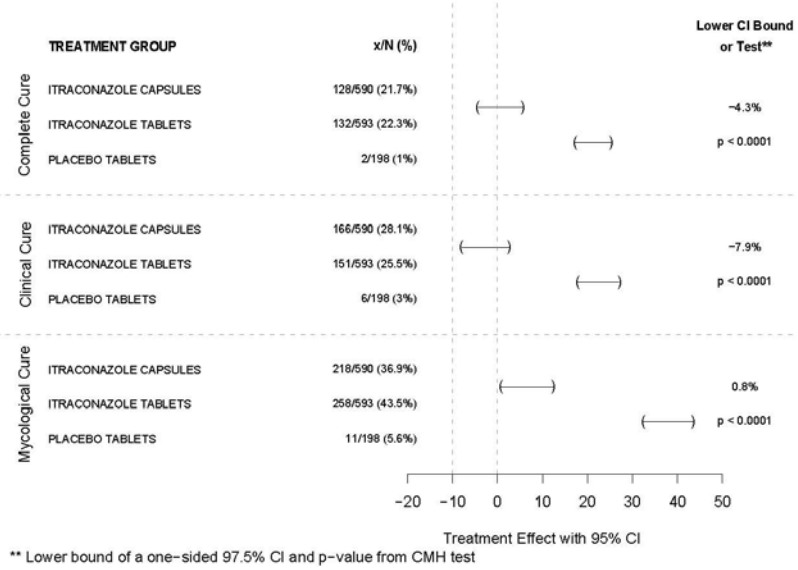
KOH and fungal culture at the End of Study Visit) were comparable between the two active arms, in subjects infected by either species of the *Trichophyton* genus, but insufficient data was available to evaluate comparative efficacy in cases of infection by *E. floccosum*. No notable decreased susceptibility of dermatophytes to itraconazole was observed during the study.

There are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

The applicant conducted one Phase 3 efficacy study, randomizing across 62 sites in 7 countries. 517 subjects treatment with TRADENAME completed the study. The study population included male and female subjects from 16 years to 75 years with a clinical diagnosis of distal and/or lateral subungual onychomycosis of the great toenail. The target nail involvement was greater than 25% but less than 75% of the nail unit, an unaffected length of 2mm, and a positive KOH and culture. The study was a parallel group, evaluator blinded trial designed to evaluate the safety and efficacy of daily administration of TRADENAME tablet compared to 2 itraconazole 100mg capsules and 1 placebo tablet. Subjects were randomized 3:3:1 to administer 1 itraconazole 200mg tablet, 2 itraconazole 100mg capsules or 1 placebo tablet after a standard breakfast consisting of approximately 500 calories and including 20% protein, 50% carbohydrates and 30% fat. The objective of the trial was to demonstrate that TRADENAME 200mg tablets taken daily for 12 weeks are non-inferior to two 100mg itraconazole capsules and superior to placebo tablets for the treatment of onychomycosis. The study consisted of 8 visits, which comprised the 12 week dosing evaluation period as well as a 40 week follow-up period. The primary efficacy parameter was Complete Cure, defined as clinical cure and mycologic cure at visit 8, which was at week 52. The comparisons of itraconazole tablets to itraconazole capsules and placebo each met the pre-specified efficacy objectives and demonstrated that TRADENAME is effective for the treatment of onychomycosis.

These outcomes are summarized by the biostatistics reviewer and replicated below:



8. Safety

Across all 6 studies, 1516 subjects were enrolled and evaluated for safety. Of these subjects, 744 were exposed to the TRADENAME (itraconazole 200mg tablet), 711 subjects were exposed to Sporanox® itraconazole 2- 100mg capsules, and 191 subjects were exposed to placebo.

In the Phase 3 study BT0300- 302-INT at week 0, subjects were randomized (3:3:1) to study drug were instructed to self-administer 1 Tradename-itraconazole 200mg tablet, 2 itraconazole 100mg capsules, or 1 placebo tablet QD for 12 weeks. Dosing began the day after the week 0 visit and ended on the day prior to the week 12 visit. The mean (STD) number of doses administered within the TRADENAME-itraconazole 200mg tablet, itraconazole 2- 100mg capsule, and placebo tablet dosing groups, respectively, was 79.5 (14.82), 76.7 (17.23), and 77.6 (16.30). In general, the largest proportion of subjects in each dosing group ingested between 68 and 100 doses of the assigned study drug. Approximately 95% or more of the subjects in each dosing group remained on the study drug for more than 6 weeks; more than 90% of the subjects remained on the study drug for more than 10 weeks.

The evaluation of safety was conducted on all subjects who were randomized to study drug, had documented use of at least 1 dose of the assigned drug, and presented for at least 1 post-baseline assessment. This included 1,354 subjects, 582 of whom were randomized to the TRADENAME itraconazole 200mg tablet group, 581 of whom were randomized to the itraconazole 100mg capsule group, and 191 of whom were randomized to the placebo tablet group. The safety analysis is based on an evaluation of the extent of exposure to study drug, adverse events, and other safety related parameters including 12-lead ECG findings, auditory outcomes, clinical laboratory analyses (chemistry, hematology, and urinalysis), and the outcomes of urine pregnancy tests.

There were no fatalities in the phase 3 study. 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 the TRADENAME itraconazole 200mg tablet group, 13 (2.2%) in itraconazole 2-100mg capsule group, and 3 (1.5%) in the placebo group. During the dosing period of Phase 3 trial, 6 subjects (two in each dosing group) reported serious adverse events.

There were reports of serious adverse events of cardiovascular disease and cerebrovascular disease in both TRADENAME 200mg tablet and the itraconazole 2- 100mg capsule groups. These were reviewed by the primary reviewer who concludes that the adverse events were not unusual in number or unexpected, and that the incidence of adverse events related to both itraconazole formulations tested was comparable to the incidence of adverse events for currently marketed Sporanox®. A consultation was obtained with the Cardio-Renal division who also noted that "clinically significant QT prolongation is not expected in this trial since patients with concomitant medications that cause QT prolongation were excluded. Similarly, since patient with history or risk factors for CHF and patients taking calcium channel blockers were excluded, AE's similar to those reported post-marketing and in the literature with Sporanox® are unexpected". DCRP also recommends that similar contra-indications and warnings for CHF and concomitant medications that cause QT prolongation be included in the TRADENAME label, and that this list should be updated.

I concur with these recommendations.

9. Advisory Committee Meeting

No advisory committee was convened for this application because this is not a new molecular entity and no novel issues requiring advisory committee discussion were raised by this application.

10. Pediatrics

The application was discussed with the Pediatric Review Committee (PeRC) who concurred with the recommendation for a waiver for pediatric patients less than 18 years of age.

11. Other Relevant Regulatory Issues

There are no unresolved regulatory issues.

12. Labeling

OSE/Division of Medication Error Prevention and Analysis (DMEPA) has determined that the proposed propriety name HYPHANOX is unacceptable because it is (b) (4)

The applicant relied upon reference to the currently approved product for portions of labeling. During the review, drug-drug interactions were identified that are not included in the current Sporanox® labeling. Some of these interactions may lead to significant adverse events and may provide a basis for contraindicating concomitant use of the drug product with administration of itraconazole. TRADENAME labeling reflects these interactions and similar revisions to the labeling of currently approved itraconazole products are appropriate.

I have reviewed the primary clinical review, the cross discipline team leader review and the DRISK review in regards to risk management. The approved labeling will include a boxed warning and also a Patient Package Insert, and will be consistent with the labeling currently approved for Sporanox®. Patients will receive the Patient Package Insert as an attachment inside the blister pack. While it may appear reasonable to mandate a medication guide for this product, it is also reasonable to maintain a consistent risk management approach for oral itraconazole products. TRADENAME will be used at the same dosage and for the same indication as the currently approved products, and there is reasonable concern that disparity in product risk management approaches could infer differences in the safety profile. I concur with the conclusions of the review team that this product has a safety profile similar to the currently approved Sporanox® product. A medication guide for both products should be considered in the future if new safety information becomes available for itraconazole.

The carton and container labeling has been discussed with the applicant and agreement has been reached.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action – The application will be approved.

- Risk Benefit Assessment – The sponsor has provided information to support the safety and efficacy of TRADENAME when used as labeled. This product has a safety profile consistent with currently approved itraconazole products intended for use for the same indication, at the same dosage and duration. The risks and benefits of this product are clearly delineated in labeling.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  The risk management approach for this product will be consistent with currently approved itraconazole products.

- Recommendation for other Postmarketing Requirements and Commitments
  There are no postmarketing requirements or commitments for this application.

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/

SUSAN J WALKER
04/28/2010