CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number 020694

Trade Name SPORANOX 100mg Capsules

Generic Name Itraconazole Capsules

Sponsor Janssen Research Foundation

DEC - 6 1996

NDA 20-694

Janssen Research Foundation
Attention: Cynthia Chianese
Manager, Regulatory Affairs
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

Dear Ms. Chianese:

Please refer to your December 13, 1995, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SPORANOX® (itraconazole capsules) Capsules, 100 mg.

We acknowledge receipt of your amendments and correspondence dated February 29, March 28, and 29, April 5 (2), 15, and 19, May 20, August 26, and 27, September 10 (2), 20, and 23, October 22, 28, 29 (2), and 31, November 1, 4, 13, 18, 19, 21, and 25, and December 3, 1996.

This new drug application provides for the treatment of onychomycosis of the fingernail without concomitant onychomycosis of the toenail with a pulse dosing regimen.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed revised draft labeling submitted November 25, 1996. Accordingly, the application is approved effective the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed revised draft labeling submitted on November 25, 1996. The enclosed revised draft labeling was stated to be acceptable in your letter dated December 3, 1996. Marketing the product with FPL that is not identical to this enclosed revised draft labeling may render the product misbranded and an unapproved new drug.

Please submit sixteen copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy weight paper or similar material. For administrative purposes this submission should be designated "FINAL PRINTED LABELING for approved NDA 20-694." Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your agreed upon Phase 4 commitment specified in your submission dated December 3, 1996. This commitment is listed below:

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. Should an IND not be required to meet your Phase 4 commitment, please submit protocol, data, and final reports to this NDA as correspondences. For administrative purposes, all submissions, including labeling supplements, relating to Phase 4 commitments must be clearly designated "Phase 4 Commitments."

We also request that you submit the following within 6 months of this Approval Letter:

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Dermatologic and Dental Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Frank H. Cross, Jr., M.A., LCDR
Project Manager
(301) 827-2023

Sincerely yours,

12/6/96

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and
Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

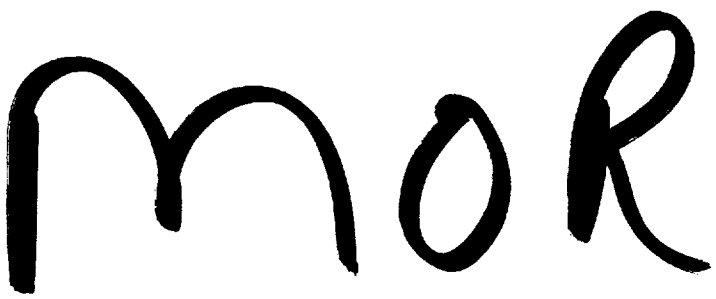
Enclosure

cc:
Original NDA 20-694
HFD-540/Division File
HFD-105/Weintraub (with draft labeling)
HFD-2/Lumpkin (with draft labeling)
HFD-735 (with draft labeling)
HFD-92 (with draft labeling)
HFD-222
District Office
HF-2/Medwatch (with draft labeling)
HFD-40/ (with draft labeling)
HFD-613 (with draft labeling)
HFD-540/MO/Labib
HFD-540/MO/Ko 12-4-96
HFD-540/CHEM/Higgins 12/4/96
HFD-520/MICRO/King 12/4/96
HFD-540/PHARM/Mainigi 12/4/96
HFD-160/MICRO/Stinavage
HFD-725/ BIOSTAT/Thomson 12/4/96
HFD-880/BIOPHARM/Wang 12/4/96
HFD-530/PROJ MGR/Kinsey
HFD-540/PROJ MGR/Cross

Concurrence:

HFD-540/CHEM TM LDR/DeCamp 12/4/96 HFD-160/MICRO TM LDR/Cooney 12/4/96 per FAX
HFD-540/PHARM TM LDR/Jacobs 12/4/96 HFD-880/BIOPHARM TM LDR/Bashaw 12/4/96
HFD-725/BIOSTAT TM LDR/Srinivasan 12/4/96 HFD-540/PM SUPV/Kozma-Fornaro/12.3.96
HFD-520/MICRO TM LDR/Sheldon 12/4/96
drafted: fhc/November 22, 1996/n20694a.ap
r/d Initials:
Final:

APPROVAL
PHASE 4 COMMITMENT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PATENT AND EXCLUSIVITY INFORMATION

Active Ingredient:	Itraconazole
Strength:	100 mg
Trade Name:	SPORANOX®
Dosage Form:	Capsule
Sponsor's Name:	Janssen Research Foundation 1125 Trenton-Harbourton Road P.O. Box 200 Titusville, NJ 08560-0200
NDA Number:	20-694
Approval Date:	pending
Applicable Patent Number:	4,267,179 Expiration date: June 23, 2000

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PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA # 20-694 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-540 Trade (generic) name/dosage form: Sporanox (itraconazole capsules), 100mg Action: (AP) AE NA

Applicant Janssen Therapeutic Class 6S

Indication(s) previously approved Histoplasmosis, Blastomycosis, Onychomycosis (toenail), Dermatophyte skin infections

Pediatric labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application Onychomycosis of the fingernail without concomitant onychomycosis of the toenail

(For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric subgroups. Further information is not required.

___ 2. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. The applicant has committed to doing such studies as will be required.
- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, explain the status of discussions on the back of this form.

___ c. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 3. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in children. Explain, on the back of this form, why pediatric studies are not needed. → Onychomycosis is unusual before puberty JW 11/5/96

___ 4. **EXPLAIN.** If none of the above apply, explain, as necessary, on the back of this form.

EXPLAIN, AS NECESSARY, ANY OF THE FOREGOING ITEMS ON THE BACK OF THIS FORM.

JB Hood, MA, CDR, Project Manager 10/22/96

Signature of Preparer and Title (PM, CSO, MO, other) Date

cc: Orig NDA/PLA # 20-694
HFD-540 /Div File
NDA/PLA Action Package
HFD-510/GTroendle (plus, for CDER APs and AEs, copy of action letter and labeling)

Jennifer Willis 12/5/96

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

5/95

NOV 25 1996

Medical Officer's Review of NDA 20-694

1. General Information

NDA #20-694
Original

Submission date: December 13, 1995
Received date: December 14, 1995
Assigned date: February 27, 1996
Review completed: September 12, 1996
Review revised: September 23 & 27, November 1 and 20, 1996.

Drug name: Sporanox®

Generic name: Itraconazole

Proposed trade name: Sporanox®

Chemical name : (±)-1-[(RS)-sec-Butyl]-4-[p-[4-[p-[[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-l-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one, with molecular formula $C_{35}H_{38}Cl_2N_8O_4$

Applicant: Janssen Pharmaceutica
1125 Trenton-Harbourton Road
Titusville, NJ 08560

Pharmacologic Category: Antifungal

Proposed Indication(s): for the treatment of onychomycosis of fingernail

Dosage Form(s) and Route(s) of Administration: Capsule, 100 mg

NDA Drug Classification: 6 S

Related NDAs:
NDA 20-083 Sporanox® for treatment of systemic mycosis (approved)
NDA 20-510 Sporanox® for treatment of onychomycosis (approved)
NDA 20-657, itraconazole oral solution, has not been approved.

U.S. studies for NDA , 20-510 and 20-694 were conducted under IND . It is the understanding of the Applicant that upon approval, this NDA will become an Efficacy Supplement of NDA 20-083.

Related Reviews: **Statistical Review dated:** 10/31/96
Biopharm Review dated: 6/11/96

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3. Material Reviewed

This review is based on vols 1.1-1.3 of the original submission and subsequent amendments vol 2.1, 3.1-3.2, 4.1-4.2, 5.1 and 7.1 for requested material.

4. Chemistry/Manufacturing Controls See review by Chemist

5. Animal Pharmacology/Toxicology See review by Pharmacologist/toxicologist

6. Clinical Background

6.1 Relevant human experience

Onychomycosis represents about 30% of mycotic infections of the skin and is often caused by dermatophytes. Fingernail infection is less common than toenail infection. In distal subungual onychomycosis, the most common type of onychomycosis, the pathophysiology starts with invasion of the nail unit by dermatophyte involving the hyponychium and distal nail bed, with subsequent hyperkeratosis and onycholysis.

Itraconazole was first marketed in Mexico for superficial and systemic mycosis in 1987 and has since been approved in 63 additional countries for systemic mycosis and 33 for superficial mycosis. It is marketed for onychomycosis in 22 countries. In the U.S., itraconazole is currently marketed under NDA 20-083 (9/11/92) for the treatment of a) pulmonary and extrapulmonary blastomycosis, b) histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis, and c) (since April, 1994) pulmonary and extrapulmonary aspergillosis, in patients who are intolerant of or who are refractory to amphotericin B therapy. It was approved for the indication of onychomycosis of toenails with or without fingernail involvement (under NDA 20-510, September 28, 1995). Premarketing human experience was gained through the following commercial INDs :

. Studies for superficial dermatophytosis were originally initiated under IND and subsequently transferred to IND in 1989 when these indications were separated from systemic mycosis. There were numerous investigator-originated INDs for the treatment of systemic mycosis and one (IND for studying itraconazole interaction with rifabutin.

The mechanism of action of itraconazole, like that of other azole antifungals, is based on its relatively selective effects on fungal cytochrome P-450 IIIA. It disturbs sterol synthesis in fungal membranes leading to inhibition of cell growth and possibly cell death. Animal and human studies have shown its high affinity for tissue and this may provide therapeutic advantage in onychomycosis and superficial dermatophytosis due to its retention in nails and stratum corneum, although nail bed would be the compartment of greatest interest for retention in onychomycosis.

6.2 Important information from related INDs and NDAs

See above under "Related NDAs" and Section 6.1. In the Advisory Committee

for Dermatologic Drug Products meeting held in September, 1994, it was agreed that efficacy for toenail onychomycosis would confer efficacy for fingernails in the presence of toenail disease, but a proper dosing regimen must be established for fingernail onychomycosis without concomitant toenail onychomycosis. When itraconazole was approved for the treatment of toenail onychomycosis (NDA 20-510) in 1995, a recommendation was made to the Applicant to conduct a study "to evaluate the dosage regimen that would most effectively be used to treat onychomycosis of the fingernail in patients without concomitant onychomycosis of the toenail." This NDA attempts to address this recommendation.

6.3 Foreign Experience

See Section 6.1. In addition, the following new information is noted:

Significant Marketing Developments given in 1996 Annual Report of IND

Indications	superficial mycoses	onychomycosis	systemic mycoses
Countries and approval dates	Australia 2/96 Canada 1/96 Germany 5/96 Norway 12/95	Greece 10/95 Portugal 6/95 South Africa 10/95 Sweden 2/96 U.S.A. 9/95	Greece 10/95

Itraconazole has not been withdrawn from marketing in any country.

6.4 Human pharmacology, pharmacokinetics and pharmacodynamics

See Biopharm review.

Itraconazole is well absorbed after oral administration. Optimal bioavailability is obtained when it is taken immediately after a meal. Concomitant rifampin affects itraconazole bioavailability by reducing its plasma concentration. Itraconazole shows drug interactions with the following medications, primarily due to its effects on hepatic cytochrome P450 3A4 enzyme system: cyclosporine, digoxin, sulfonylureas, terfenadine, warfarin, H_2-antagonists, isoniazid and phenytoin.

Uptake of itraconazole in tissues such as the stratum corneum and its retention results in tissue levels higher than the corresponding plasma levels and persistence after therapy. In one report, it was noted that inhibitory levels persisted in stratum corneum for 2-4 weeks after the end of a 4-week course of daily itraconazole 100 mg. Pharmacodynamic studies in humans revealed no adverse effects on body functions including cholesterol biosynthesis or in a broad spectrum of endocrine, immunological and cardiovascular parameters. In addition, eye toxicity or photosensitizing potential were not demonstrated. However, rare cases of idiosyncratic hepatitis have been reported and cholestatic hepatitis may occur in itraconazole-treated patients. In the current label, the Applicant states that in premarketing studies involving over 2500 patients, 3 cases of reversible idiosyncratic hepatitis have been observed. It is hard to estimate the true incidence as the adverse event may have been reported under different terms, and in postmarketing experience, the denominator is often ill defined. Effects on human reproduction are unknown.

6.5 Other relevant background information

This current NDA stems from studies conducted under IND which was originally submitted on 6/8/89.

6.6 Directions for Use

The directions for use in the treatment of onychomycosis of toenails in the current label are: "The recommended dose is 200 mg once daily for 12 consecutive weeks." It is recommended to be taken with a full meal to enhance absorption.

The Applicant is requesting a change in the dosing directions to include treatment of fingernails as follows: "Toenails with or without fingernail involvement: The recommended dose is 200 mg (2 capsules) daily for 12 consecutive weeks. Fingernails: The recommended dosing regimen is two treatment pulses, each consisting of 200 mg twice daily (2 x 2 capsules) for 7 days. The pulses are separated by a 21-day drug-free period."

7. Description of Clinical Data Sources

This review is based primarily on the data submitted for the two clinical trials summarized in the Table below:

Table 7 Data Source for NDA 20-694

Trial	Trial Design	Trial Arms	Patient no. Sex (M/F) Age Range
USA-71	Randomized, multicenter, double-blind, placebo-controlled, comparative trial with two 7-day treatment phases separated by a 3-wk interval & preceding a 19-wk follow-up period for the treatment of onychomycosis of **Fingernails**.	Placebo bid	29/7
		Itraconazole 200 mg bid	34/3
ITR-FIN-1	Randomized, multicenter, double-blind, comparative trial with 12 wks of treatment phase preceding a 36-wk follow-up period for the treatment of onychomycosis of **Toenails**	Continuous 200 mg/d of itraconazole	36/29
		Pulse 200 mg bid (3 7-day itraconazole treatments, each followed by 21-days of Placebo bid)	36/28

8. Clinical Studies

8.1 Indication#1. Onychomycosis of Fingernails

8.1.1 Trial #1. Applicant's protocol Study#ITR-USA-71: Randomized, multicenter placebo-controlled, double-blind study of itraconazole capsules intermittent therapy for the treatment of onychomycosis of the fingernail.

8.1.1.1 Objective/Rationale to evaluate the safety and efficacy of itraconazole capsules, 200 mg twice daily during the first week of each month for 2 months compared with a placebo, for the treatment of onychomycosis of the fingernails.

8.1.1.2 Design Randomized (1:1), multicenter, double-blind, placebo-controlled, comparative 24-week trial, with enrollment of 10-15 per site to obtain a total of 70 evaluable subjects.

8.1.1.3 Protocol

8.1.1.3.1 Population/Procedures

Patient Selection

a) Inclusion: Anyone aged 18-70 with onychomycosis of fingernail(s) caused by dermatophyte(s), confirmed by KOH and culture (within 3 weeks of entry; if > 3 weeks but <6 weeks, a positive repeat KOH was required; not acceptable if >6 weeks) and having ≥25% involvement of one fingernail's whole surface (including a possibly destroyed and missing part of a nail plate).

b) Exclusion:

1. Use of investigational drug concurrently or within one month of entry.
2. Pregnancy or lactation or child-bearing potential without effective contraception.
3. Hypersensitivity to imidazole or azole compounds.
4. Liver function enzyme tests of over 2 times upper normal limit.
5. Need for H2 blockers, omeprazole or antacid use, which may impair itraconazole absorption.
6. Use of rifampin, phenobarbital, phenytoin, carbamazepine, astemizole, terfenadine or digoxin.
7. Serious concurrent disease such as HIV infection.
8. Unreliability.
9. Current or past history of psoriasis.
10. Systemic antifungal therapy (e.g. itraconazole, griseofulvin, ketoconazole) within 2 months of entry.
11. Use of topical antifungals on fingernails within 2 weeks of entry.
12. Onychomycosis not due to dermatophyte (e.g. by molds, *Candida spp* or bacteria).
13. Participation in onychomycosis study with systemic agent(s) within 6 months of entry.

Procedures The following flow chart gives the procedures in this study:

Schedule of Visits

Weeks of study	-2	0	1	4	5***	12	24
Inclusion/exclusion criteria	x						
Consent form	x						
history/physical exam			x			x	
choose affected nail	x						
% affected nail plate	x	x			x	x	x
signs of onychomycosis		x			x	x	x
length of unaffected part of target nail		x			x	x	x
global assessment					x	x	x
culture	x				x	x	x
KOH	x				x	x	x
Laboratory tests*		x	x		x		
pregnancy test**		x			x		
Subjects start 7 day therapy		x		x			

*CBC with differential and platelets, SMAC22 and urinalysis

**Females of childbearing age must have negative urine pregnancy test before start of treatment.

***Same procedures to be followed for premature termination of study.

For the treatment phase, the subjects were randomized (1:1) to take two capsules of itraconazole 100 mg or placebo twice daily (morning and evening) during the first week of each month for 2 months. The test drug was to be taken with food to ensure maximal absorption. Subjects having "unchanged" or better scores at the end of treatment phase

were enrolled into the follow-up period for observation until the 24th week.

8.1.1.3.2 Endpoints and Parameters Evaluated The study endpoint was week-24. Parameters evaluated were -

1. Percent of nail involvement for each nail.
2. In an appropriate "target" fingernail (appropriateness took into account thickness, ability to culture and get KOH and ability to measure the distance between proximal nailfold edge and the border of onychomycosis), the following would be assessed:

- KOH,
- dermatophyte culture (using Mycosel),

  The Investigator cleaned the target nail with ether and, using a curette, clipped a part of the damaged nail or subungual debris or both with as much material as possible from the border between the healthy area and the affected part of the nail.
- the distance between proximal nailfold edge and the border of onychomycosis and is a measure of the healthy part of the nail, and
- onycholysis, hyperkeratosis and discoloration, the scores being:

Score	Onycholysis	Hyperkeratosis	Nail Plate Discoloration
0	No nail plate separation from nail bed	No subungual thickening	No discoloration
1	≤50% separation	≤50% thickening under nail plate	≤50% discoloration
2	>50% to ≤75% separation	>50% to ≤75% thickening	>50% to ≤75% discolored
3	>75% separation	>75% thickening	>75% discolored

3. Global evaluation by Investigator, scored as:

   cleared=clearance of all signs±residual malformation and no need of further therapy
   markedly improved=minimal extent of nail involvement ***and*** significant ↓ in signs
   slightly-moderately improved=slight-moderate ↓ in extent of involvement ***and*** signs
   unchanged=no change in extent of involvement ***and/or*** signs
   deteriorated=worsening in extent of involvement ***or*** increase in signs.

Using the data collected at evaluation visits, the following are defined:

1. Clinical success=global as cleared or markedly improved, any time during study (for first time).
2. Time to clinical success=no. of weeks until clinical success occurs.
3. Mycological success=negative KOH **and** culture, any time during study (for the first time).
4. Time to mycological success=no. of weeks until mycological success occurs.
5. Overall success=clinical and mycological success, anytime during study (for the first time).
6. Time to overall success=no. of weeks until mycological success occurs.
7. Clinical relapse=global evaluation becomes worse anytime after being a clinical success (excluding worsening after clinical success at week-24).
8. Time to clinical relapse=no. of weeks until clinical relapse occurs.
9. Mycological relapse=positive KOH or culture after achieving mycological success.
10. Time to mycological relapse=no. of weeks until mycological relapse occurs.
11. Overall relapse=positive KOH or culture or worsening of global after achieving overall success (excluding worsening after clinical success at week-24).
12. Time to overall relapse=no. of weeks until overall relapse occurs.

For 1, 3 and 5, anyone discontinuing with global of "deteriorated" and with positive mycology is considered a failure.

Comment Clinical and overall success should be based on a global of "cleared".

8.1.1.3.3 Statistical Considerations

The applicant stated that the objective was to show superiority of itraconazole over placebo for overall response rate. The assumption was that placebo response would be ≤20% and itraconazole ≥60%. Significance at α=0.05 and β=0.2 required 27 subjects per arm. Allowing for dropouts, 35 per arm were enrolled. Three analyses were done with the following criteria, with #1 (intent-to-treat) being the ***primary analysis for efficacy***:

	eligibility criteria	≥1 dose	≥1 postbaseline visit	≥ 5 wks of therapy phase
1. Intent-to-treat	+	+	+	±
2. Compliant-patient	+	+	+	+
3. All-patient	±	+	+	±

Efficacy analysis methodology.

- Comparability of treatment groups (for age, weight, sex, race and pre-treatment vital signs) was evaluated by 2-way ANOVA for continuous variables and by Cochran-Mantel-Haenszel test for categorical variables.
- The primary variable was overall success rate of nail clearing.
- The following parameters were also analyzed: percent involvement of each affected nail, each clinical sign on the "target" nail and length of unaffected nail part of "target" nail -
  a) within treatment comparisons of the change from baseline to week-5, week-12 and week-24 via the Wilcoxon signed rank test
  b) between treatment comparisons of the change from baseline to week-5, week-12 and week-24 via a 2-way ANOVA, with effects due to treatments, center and treatment x center in the model.
- For all parameters involving "time to" an event, between treatment comparisons were to be made via Gehan-Wilcoxon procedure (Gehan EA. Biometrika 52: 203-223, 1965). Survival distributions were to be compared via Kaplan-Meier method (Kaplan EL and Meier PJ. American Statistical Association 53: 457-481, 1958).
- Cochran-Mantel-Haenszel test stratified by center were done at each visit for -
  clinical success, mycological success, overall success, clinical relapse, mycological relapse, overall relapse and each global rating.
- The timepoint used for analysis of success was the first visit at which success occurred. For sample sizes of 15 or less, (in each treatment group), p values recommended by Hollander and Wolfe were used. Otherwise, a normal approximation to the binomial distribution was used.
- Separately for each variable, between group comparisons of changes from baseline to weeks-5, -12 and -24 and endpoint were done using a two way ANOVA on the rank-transformed data with effects due to treatment, center and treatment-by-center interaction in the model. The treatment-by-center interaction was tested to assess the suitability of pooling. Only descriptive statistics were to be given when investigator had no patient from a treatment group to be included in analysis (week-24 - Dr. Elewski's site had no placebo patients).

8.1.1.4 Results

8.1.1.4.1 Patient Disposition, Comparability

Investigators

Nardo Zaias, M.D. Miami Beach, FL 33140	Richard K. Scher, M.D. New York, NY 10032	Richard Odom, M.D. San Francisco, CA 94143
Boni E. Elewski, M.D. Cleveland, OH 44106	Ralph Daniel, M.D. Jackson, MS 39216	Richard Devillez, M.D. San Antonio, TX 78284

Investigator	No. of Subjects Itraconazole	Placebo
Zaias	4	4
Elewski	5	5
Scher	8	8
Daniel	5	5
Odom	7	6
Devillez	8	8
	37	36

Patient Disposition

	Itraconazole	Placebo
Enrolled	37	36
Fit entry criteria and took medication	37	36
ITT analysis (entry criteria +, medication + & Postbaseline data +)	**36**	**35**
completed treatment phase	35	34
entered follow-up phase	30	23
completed follow-up phase	27	17
Compliant patient analysis (correct timing/dosing of medication)	**22**	**24**
Non-compliant patients	**15**	**12**
Premature discontinuation in treatment phase*	**2**	**2**
Premature discontinuation in follow-up phase**	**3**	**6**
symptom deterioration	0	2
relapse	0	2
"other"	1	1
lost	2	1

*One from each treatment group having no posttbaseline data discontinued for adverse events (pruritus and rash [itraconazole, [redacted]) and poor compliance [placebo, [redacted] and the other two patients discontinued on the basis of abnormal lab data (↑ triglycerides [itraconazole, [redacted] and ↑ GGT [placebo, [redacted]).

**"Relapse" at follow-up phase was not according to the protocol definitions given above and was a clinical judgment. For "other", one itraconazole patient restarted Sporanox and one placebo patient did not fit F/U criteria.

Patients excluded from Analysis

One patient from each treatment group was excluded from intent-to-treat analysis because of lack of postbaseline data. Twenty-seven patients (15/36 itraconazole, 12/35 placebo) were excluded from the secondary, compliant-patients analysis as follows:

	Itraconazole*	Placebo*
<12 days on medication	2	2
>16 days on medication	3	2
<16 days between treatment phases	2	1
>26 days between treatment phases	7	8
Incorrect dosing	6	4

*Total patient numbers exceed 27 due to overlap of the protocol violations.

Baseline Demographic Data (all patients)

	Itraconazole	Placebo
Patients entered (M/F)	37 (34/3)	36 (29/7)
Race		
white	27 (73%)	24 (67%)
black	2 (5%)	3 (8%)
Hispanic	8 (22%)	9 (25%)
Age in yrs: median (min-max)	49 (26-66)	48 (24-70)
Duration of present infection in years:		
mean (min-max)	12 (0.3-42)	12 (0.3-47)
Previous antifungal medication	26 (70%)	29 (81%)

Baseline Demographic Data (compliant patients)

	Itraconazole	Placebo
Patients entered (M/F)	22 (19/3)	24 (19/5)
Race		
white	19 (86%)	20 (83%)
black	1 (5%)	1 (4%)
Hispanic	2 (9%)	3 (13%)
Age in yrs: median (min-max)	51 (28-65)	46 (24-70)
Duration of present infection in years:		
mean (min-max)	11 (0.3-42)	11 (0.3-47)
Previous antifungal medication	15 (68%)	20 (83%)

T. rubrum was identified in the baseline cultures in all enrolled patients. The commonest antifungal agent used previously was griseofulvin (9 itraconazole and 13 placebo patients). Concurrent allowed medications were used in 15/37 (41%) of itraconazole patients and 16/36 (44%) of the placebo patients. The most commonly used medications were acetylsalicylic acid (itraconazole 2, placebo 3) and ibuprofen (placebo 5).

Comment

1. None of the differences in demographic data between the 2 treatment groups were statistically significant (p>0.05) in either analysis.
2. Both treatment arms had disproportionately high male:female ratios (92% in itraconazole group and 81% in placebo group were males).

8.1.1.4.2 Efficacy Endpoint Outcomes

8.1.1.4.2.1 Intent-to-treat Analysis

Table 8.1.1.4.2.1A "Success" and "Relapse" Rates

	Itraconazole	Placebo	p values
"Success" Rates			
Clinical	27/36=75%	0/35=0	<0.001
Mycological	22/36=61%	4/35=11%	<0.001
Overall	20/36=56%	0/35=0	<0.001
"Relapse" Rates			
Clinical	0/27=0	---	---
Mycological	0/22=0	1/4=25%	0.157
Overall	0/20=0	---	---

Comments The primary parameter should have been an overall success rate based on (1) clinical success as defined by a clear nail (2) mycological cure and (3) no relapse. The Applicant should reanalyze the data with these criteria. It can be shown that 18/36 subjects in the itraconazole group and 0/35 in the placebo group fit these criteria (p< 0.001). Such data would indicate superiority of itraconazole over placebo.

Table 8.1.1.4.2.1B Growth of Unaffected Part of Target Nail

Length of Unaffected	Itraconazole			Placebo			Between treatment
Part in mm	n	mean±SE	p (vs BL)	n	mean±SE	p (vs BL)	p values
baseline length	36	2.04±0.33		35	1.94±0.34		0.638
·ble-blind wk-5	36	2.92±0.48	<0.001	35	1.27±0.36	0.004	<0.001
w-up wk-12	27	6.50±0.41	<0.001	21	1.14±0.49	0.036	<0.001*
..ow-up wk-24	26	10.29±0.69	<0.001	17	0.94±0.37	0.042	ND
endpoint	36	8.50±0.74	<0.001	35	1.36±0.37	0.002	<0.001*

*p values for treatment-center interactions were all not significant (>0.05) except for these 2 timepoints for length of unaffected part of target nail (0.014 for wk-12 and 0.003 for endpoint).

Table 8.1.1.4.2.1C Global Evaluations

cleared-markedly improved-slightly improved-unchanged-worse

	Itraconazole		Placebo		
	n	Scores	n	Scores	p values
double-blind wk-5	36	0- 6-22- 4- 4	35	0- 0-12-12-11	<0.001
follow-up wk-12	27	5-17- 5- 0- 0	21	0- 0- 7- 9- 5	<0.001
follow-up wk-24	27	21- 5- 1- 0- 0	17	0- 0- 5-12- 0	<0.001
endpoint	36	21- 6- 4- 1- 4	35	0- 0- 7-13-15	<0.001

Table 8.1.1.4.2.1D Negative mycology

	Itraconazole	Placebo	p values
KOH			
double-blind wk-5	11/36=31%	3/35=11%	0.037
follow-up wk-12	14/27=52%	2/21=9%	<0.001
follow-up wk-24	22/26=85%	4/17=23%	<0.001
Culture			
double-blind wk-5	19/36=53%	11/35=31%	0.070
follow-up wk-12	22/27=81%	7/21=33%	<0.001
follow-up wk-24	21/26=81%	6/17=35%	0.007

Table 8.1.1.4.2.1E Changes of Clinical Parameters from Baseline*

	Itraconazole			Placebo			Between treatment
anges from BL	n	mean±SE	p (vs BL)	n	mean±SE	p (vs BL)	p values
Onycholysis scores							
baseline	36	(1.83±0.15)		35	(1.49±0.17)		0.061
double-blind wk-5	36	-0.56±0.14	<0.001	35	-0.03±0.06	0.812	<0.001
follow-up wk-12	27	-1.30±0.17	<0.001	21	-0.10±0.12	0.562	<0.001
follow-up wk-24	27	-1.78±0.19	<0.001	17	-0.12±0.08	ND	ND
endpoint	36	-1.39±0.19	<0.001	35	-0.09±0.08	0.376	<0.001
Hyperkeratosis scores							
baseline	36	(1.94±0.15)		35	(1.71±0.15)		0.249
double-blind wk-5	36	-0.50±0.14	<0.001	35	-0.11±0.09	0.299	0.024
follow-up wk-12	27	-1.26±0.20	<0.001	21	-0.29±0.17	0.161	<0.001
follow-up wk-24	27	-1.78±0.18	<0.001	17	-0.06±0.18	0.844	ND
endpoint	36	-1.39±0.19	<0.001	35	-0.06±0.11	0.669	<0.001
Discoloration scores							
baseline	36	(2.22±0.13)		35	(1.97±0.17)		0.432
double-blind wk-5	36	-0.64±0.13	<0.001	35	-0.06±0.08	0.593	<0.001
follow-up wk-12	27	-1.44±0.14	<0.001	21	-0.10±0.22	0.570	<0.001
follow-up wk-24	27	-2.11±0.17	<0.001	17	0.00±0.19	>0.999	ND
endpoint	36	-1.67±0.19	<0.001	35	-0.06±0.11	0.669	<0.001
Percent involvement of target nail							
baseline	36	(76.47±3.54)		35	(71.37±4.40)		0.760
double-blind wk-5	36	-18.36±3.89	<0.001	35	0.43±1.46	0.855	<0.001
follow-up wk-12	27	-59.56±4.20	<0.001	21	-4.48±2.05	0.042	<0.001
follow-up wk-24	27	-74.63±3.93	<0.001	17	-5.59±2.56	0.054	ND
ᵗpoint	36	-58.69±6.19	<0.001	35	0.00±1.93	0.796	<0.001

lues for treatment-center interactions were all not significant (>0.05).

Comment Secondary parameters also support the efficacy of itraconazole.

8.1.1.4.2.2 Compliant Patient Analysis

Table 8.1.1.4.2.2A "Success" and "Relapse" Rates

	Itraconazole	Placebo	p values
"Success" Rates			
Clinical	17/22=77%	0/24=0	<0.001
Mycological	16/22=73%	3/24=13%	<0.001
Overall	15/22=68%	0/24=0	<0.001
"Relapse" Rates			
Clinical	0/27=0	—	—
Mycological	0/22=0	0/3=0	—
Overall	0/20=0	—	—

Table 8.1.1.4.2.2B Growth of Unaffected Part of Target Nail

Length of Unaffected Part in mm	Itraconazole n	Itraconazole mean±SE	Itraconazole p (vs BL)	Placebo n	Placebo mean±SE	Placebo p (vs BL)	Between treatment p values
baseline length	22	2.18±0.32		24	2.25±0.42		0.849
double-blind wk-5	22	2.20±0.41	<0.001	24	0.90±0.37	0.033	0.017
follow-up wk-12	18	6.75±0.51	<0.001	15	0.87±0.36	0.054	<0.001
follow-up wk-24	17	10.44±0.56	<0.001	13	1.00±0.38	0.047	ND
ɔoint	22	8.89±0.82	<0.001	24	0.90±0.39	0.050	<0.001*

.lues for treatment-center interactions were all not significant (>0.05) except for this timepoint: (0.017 for endpoint).

Table 8.1.1.4.2.2C Global Evaluations

	Itraconazole n	Itraconazole Pt nos giving Globals C- MI- SI - UN- W*	Placebo n	Placebo Pt nos giving Globals C- MI- SI - UN- W*	p
double-blind wk-5	22	0- 3-12- 4- 3	24	0- 0- 5- 9-10	<0.001
follow-up wk-12	18	4- 9- 5- 0- 0	15	0- 0- 5- 8- 2	<0.001
follow-up wk-24	18	15- 2- 1- 0- 0	13	0- 0- 4- 9- 0	<0.001
endpoint	22	15- 2- 1- 1- 3	24	0- 0- 4- 9-11	<0.001

*C=cleared, MI=markedly improved, SI=slightly improved, UN=unchanged and W=worse.

Table 8.1.1.4.2.2D Negative mycology

	Itraconazole	Placebo	p values
KOH			
double-blind wk-5	8/22=36%	2/24=8%	0.039
follow-up wk-12	11/18=61%	2/15=13%	0.005
follow-up wk-24	15/17=88%	3/13=23%	0.002
endpoint	17/22=77%	4/24=17%	<0.001
Culture			
double-blind wk-5	11/22=50%	8/24=33%	0.271
follow-up wk-12	16/18=89%	5/15=33%	<0.001
follow-up wk-24	15/17=88%	4/13=31%	0.008
ɔoint	18/22=82%	6/24=25%	<0.001

Table 8.1.1.4.2.2E Changes of Clinical Parameters from Baseline

Changes from BL	Itraconazole n	Itraconazole mean±SE	Itraconazole p (vs BL)	Placebo n	Placebo mean±SE	Placebo p (vs BL)	Between treatment p values
Onycholysis scores							
baseline	22	(1.77±0.19)		24	(1.63±0.19)		0.351
double-blind wk-5	22	-0.41±0.16	0.028	24	-0.04±0.09	0.812	0.015
follow-up wk-12	18	-1.33±0.21	<0.001	15	-0.07±0.12	0.562	<0.001
follow-up wk-24	18	-1.72±0.24	<0.001	13	-0.15±0.10	ND	ND
endpoint	22	-1.36±0.26	<0.001	24	-0.08±0.08	0.376	<0.001
Hyperkeratosis scores							
baseline	22	(1.91±0.19)		24	(1.71±0.18)		0.508
double-blind wk-5	22	-0.41±0.16	0.028	24	-0.08±0.10	0.562	0.137
follow-up wk-12	18	-1.22±0.27	<0.001	15	-0.33±0.21	0.196	0.004*
follow-up wk-24	18	-1.72±0.23	<0.001	13	-0.15±0.19	0.625	ND
endpoint	22	-1.36±0.25	<0.001	24	-0.13±0.13	0.438	<0.001
Discoloration scores							
baseline	22	(2.36±0.14)		24	(2.13±0.19)		0.802
double-blind wk-5	22	-0.59±0.13	<0.001	24	-0.08±0.10	0.562	<0.001
follow-up wk-12	18	-1.56±0.20	<0.001	15	-0.13±0.27	0.624	<0.001
follow-up wk-24	18	-2.22±0.21	<0.001	13	0.00±0.23	>0.999	ND
endpoint	22	-1.82±0.25	<0.001	24	0.08±0.13	0.633	<0.001
Percent involvement of target nail							
baseline	22	(73.41±4.03)		24	(67.71±5.48)		0.982
double-blind wk-5	22	-13.18±3.32	0.002	24	1.04±1.53	0.494	<0.001*
w-up wk-12	18	-58.33±5.86	<0.001	15	-5.33±2.10	0.032	<0.001*
w-up wk-24	18	-72.50±4.95	<0.001	13	-5.77±2.71	0.046	ND
endpoint	22	-58.41±7.68	<0.001	24	0.21±2.03	0.804	<0.001

*p values for treatment-center interactions were all not significant (>0.05) except for these 3 timepoints: hyperkeratosis (0.030 for wk-12), and percent involvement of target nail (0.039 for wk-5 and 0.047 for wk-12).

Comment Compliant patient analysis supports the intent-to-treat analysis.

8.1.1.4.3 Safety Comparisons

8.1.1.4.3.1 Adverse Events Profile

Table 8.1.1.4.3.1 Adverse Events in Study ITR-USA-71

	Patient number (Percent of patients)			
	Itraconazole		Placebo	
	All	Treatment-related	All	Treatment-related
Total patient numbers	**37 (100)**		**36 (100)**	
Total # with Adv Events	**11 (30)**		**9 (25)**	
Gastrointestinal	5 (14)		4 (11)	
nausea	2 (5)	2 (5)		
constipation	1 (3)	1 (3)	1 (3)	1 (3)
abdominal pain	1 (3)		1 (3)	1 (3)
dyspepsia	1 (3)	1 (3)	2 (6)	2 (6)
ulcerative stomatitis	1 (3)	1 (3)		
gingivitis	1 (3)			
diarrhea			2 (6)	2 (6)
discolored feces			2 (6)	2 (6)
Body as a whole	4 (11)		4 (11)	

Table 8.1.1.4.3.1 (Cont'd) Adverse Events in Study ITR-USA-71

	Patient number (Percent of patients)			
	Itraconazole		Placebo	
	All	Treatment-related	All	Treatment-related
fatigue	1 (3)	1 (3)		
malaise		1 (3)		
pain	1 (3)	1 (3)	1 (3)	
injury	1 (3)		2 (6)	
back pain			1 (3)	
Nervous system	3 (8)		3 (8)	
headache	3 (8)	2 (6)	3 (8)	
migraine				1 (3)
Respiratory system	3 (8)		2 (6)	
rhinitis	2 (5)		1 (3)	
sinusitis	1 (3)		1 (3)	
Skin and appendages	2 (5)		1 (3)	
pruritus	2 (5)	1 (3)		
rash	1 (3)	1 (3)		
erythematous rash			1 (3)	
skin exfoliation			1 (3)	
Musculoskeletal system	1 (3)		1 (3)	
bursitis	1 (3)			
tendinitis			1 (3)	
Psychiatric	1 (3)		1 (3)	
anxiety	1 (3)	1 (3)		
depression	1 (3)	1 (3)		
nervousness		1 (3)	1 (3)	1 (3)
Metabolic and nutritional	1 (3)		0	
hypertriglyceridemia	1 (3)	1 (3)		
Special senses	0		1 (3)	
taste perversion			1 (3)	1 (3)
Liver and biliary system	0		1 (3)	
gamma-GT elevation			1 (3)	1 (3)
Resistance mechanism	0		1 (3)	
infection			1 (3)	

Adverse Events Leading to Discontinuation See under Patient Disposition in 8.1.1.4.1.

Serious Adverse Events None reported.

8.1.1.4.3.2 Clinical Laboratory Abnormalities

There were no consistent clinically significant laboratory abnormalities. Two patients discontinued because of laboratory findings:

(59/M, itraconazole): hypertriglyceridemia (520, 449, 318, 774 and 510 mg/dl for screening, baseline, day-1, day-23 and day-28 values respectively).

(43/M, placebo): GGT elevation (70, 100 and 81 U/L for baseline, day-37 and day-49 values respectively).

8.1.1.5 Comments/Conclusions

1. This is an acceptable study demonstrating efficacy and safety of a 2-cycle pulse regimen with itraconazole in the treatment of onychomycosis of fingernails.
2. This study has not compared different dosing schemes and therefore fails to establish the

best treatment regimen of itraconazole for fingernail onychomycosis.
3. In order to have accurate labeling of this product for the treatment of fingernail onychomycosis, the Applicant should reanalyze the data and reassess efficacy using a clear nail with negative mycology and no relapse as primary parameter.

8.1.2 Trial #2. Applicant's protocol Study#ITR-FIN-1: Effect of itraconazole in the treatment of onychomycosis of toenails. A randomized, double-blind trial comparing continuous treatment with pulse therapy. Part I: Efficacy and safety.

Comment The Sponsor should supply all parts of this study for review. If there are no additional sections, the Applicant should modify the title.

8.1.2.1 Objective/Rationale to evaluate the safety and efficacy of pulse (intermittent) therapy of itraconazole capsules 200 mg twice daily one week per month for 3 months compared with continuous treatment of itraconazole 200 mg daily for 3 months (12 weeks) in the treatment of onychomycosis of toenails.

8.1.2.2 Design Randomized (1:1), multicenter, double-blind, parallel-group, comparative 48-week study, with a 12-week treatment period and a 36-week follow-up period.

8.1.2.3 Protocol

8.1.2.3.1 Population/Procedures

Patient Selection

a) Inclusion: Anyone aged 18-60 with onychomycosis of toenails with clinical diagnosis confirmed by KOH and culture (positive for a dermatophyte) and having ≥30% involvement of one toenail's whole surface (including a possibly destroyed and missing part of a nail plate). Presence of onychomycosis of fingernail, tinea pedis or tinea corporis is optional and not an inclusion criterion.

b) Exclusion:

1. Onychomycosis not due to dermatophyte (e.g. by molds or *Candida spp*)
2. Liver function abnormality at the start of trial.
3. Psoriasis.
4. Systemic antifungal therapy within 6 months of entry.
5. Use of topical antifungals within 2 weeks of entry.
6. Concurrent use of digoxin, oral anticoagulants, terfenadine, cyclosporine A, H2-receptor blockers and/or enzyme-inducing drugs like rifampin and phenytoin.
7. Serious concurrent disease that might prevent completion of the trial.
8. Unreliability.
9. Hypersensitivity to azole antifungals.
10. (Possible) pregnancy or lactation.

c) Withdrawal:

1. Serious adverse event (including transaminase >3x upper normal limit).
2. Investigator or subject deciding termination.
3. Ineligibility due to selection criteria violation.
4. Broken randomization code

Procedures The following flow sheet gives the procedures in this study:

Schedule of Visits

	Double-Blind Treatment				Follow-up		
Months	**0**	**1**	**2**	**3**	**6**	**9**	**12**
History, patient and disease characteristics	x						
Efficacy							
Global				x	x	x	x
Mycological evaluation (KOH/culture)	x	x	x	x	x	x	x
Signs and symptoms	x	x	x	x	x	x	x
Safety							
Overall tolerability				x			
Adverse events		x	x	x	x	x	x
Laboratory tests							
Hematology	x			x	(x)*		
Biochemistry: -							
Liver function	x	x	(x)	x	(x)		
Others	x			x	(x)		

*(x) refers to repeating test if previous visit data showed abnormality.

During the 12-week double-blind treatment phase, the subjects were randomized (1:1) to take the test medication as follows:-

Continuous - 2 capsules of placebo od in morning and 2 capsules of itraconazole 100 mg od in evening.

Pulse therapy - 2 capsules of itraconazole 100 mg bid during the first week of a 4-week cycle and 2 capsules of placebo bid in the remaining 3 weeks of the cycle.

Prohibited medications were those under exclusion criteria and topical corticosteroids.

Comment In the original protocol, both plasma and nail levels of itraconazole were assessed. In the final report of this study, neither have been mentioned in the procedures or results sections. The title of this study mentions that this is "Part I" of a larger study. Details of all procedures and data that have been obtained as a result of the protocol must be submitted for review.

8.1.2.3.2 Endpoints and Parameters Evaluated The study endpoint was month-12 or the last visit of the patient.

Parameters evaluated were from affected nails, but excluding the outermost (5th) toenail:

1. Percent of nail involvement for each nail (including fingernails); involvement being interpreted to include destroyed and missing parts of the nail.
2. In a "target" toenail (the most severely affected one), the following would be assessed -
   - KOH (performed under Prof Havu of Laaketieteellinen Sienilaboratorio), dermatophyte culture,
   - the distance between proximal nailfold edge and the border of onychomycosis and is a measure of the healthy part of the nail, &
   - onycholysis, hyperkeratosis, paronychial inflammation and/or discoloration, the scores being: 0=none, 1=mild, 2=moderate and 3=severe.
3. Global evaluation by Investigator, scored as:
   1=cured with no malformation, 2=cured with residual malformation, 3=markedly improved (>50% improvement), 4=moderately improved (<50% improvement), 5=no change and 6=deteriorated.

Comment Although evaluation included percent nail involvement of fingernails, since mycology was taken only from a target toenail, the success status of fingernails cannot be interpreted. Moreover, the data on percent nail involvement were not presented in such a manner as to enable distinction between results of fingernails vs toenails. A separate analysis of fingernail data has not been made.

8.1.2.3.3 Statistical Considerations

The applicant stated that to detect a 25% difference (π_1=90% and π_2=65%) in response between the trial groups at a 2-sided 5% significance level with 80% power, 43 subjects per group were needed. To allow for dropouts, 75 per arm were planned. The ***primary analysis for efficacy*** was to be an **intent-to-treat analysis** including all randomized patients with postbaseline data.

Comparability of the treatment groups (for age, weight, sex, race and pre-treatment vital signs) was evaluated by the Mann-Whitney U-test for continuous variables and by the Fisher exact test for categorical variables.

Efficacy analysis.

- The primary variables were:

1. Clinical response, defined as global evaluation of 3 or better and
2. Mycological cure, defined as negative KOH and culture.

In the **"observed case" analysis**, missing values were not imputed. However, to get full data on all, missing values were imputed in a **"worst case" analysis** with the worst possible score. Patients without data were considered nonresponders. An additional analysis was done with separate subsets of patients: those having baseline affected nail part involvement of ≥75% and those with <75% involvement.

Comments
1. These two parameters: clinical response and mycological response cannot be used as primary parameters when analyzed separately. The primary parameter should be a clear nail with mycological cure and no relapse.
2. By "affected nail part", it is unclear whether this involvement referred to all affected nails or just the target nail.

- The secondary variables were:

1. Overall response, defined as mycological cure plus clinical response.
2. Percent affected part of big toenail and of all toenails.
3. Length of the unaffected part of the target toenail.
4. Number of affected toenails.
5. Signs and symptoms of the target nail: onycholysis, hyperkeratosis, paronychial inflammation, discoloration and total scores of these.
6. Time to first clinical relapse, defined as the number of days between the day the patient was clinically responding and the first day the patient was not responding.
7. Clinical relapse, mycological relapse and overall relapse at the end of follow-up.

Responses were also evaluated by the Mann-Whitney U-test for continuous

variables and by the Fisher exact test for categorical variables. Kaplan-Meire Product Limit Estimate and the Gehan's Generalized Wilcoxon test were used for time to first clinical relapse.

Subsequently, the Applicant contended that an equivalence hypothesis was more appropriate and a 2-sided 5% significance level was applied, with a 15% difference deemed clinically acceptable. The Blackwelder equivalence test was used for the primary variables. A first p-value was calculated for the null hypothesis that the response under continuous treatment was larger than the response under pulse therapy (p<2-sided significance level would indicate that response under continuous treatment was not larger than under pulse). A second p-value was calculated for the null hypothesis that the response under pulse treatment was larger than the response under continuous therapy (p<2-sided significance level would indicate that response under pulse treatment was not larger than under continuous treatment). If both p-values were <2-sided significance level, equivalence between the 2 groups was said to be proven. If only one p-value was significant, one treatment was at least equivalent (or better) than the other.

Comments
1. "Overall response" is a combination of the two primary parameters. As discussed above, clinical response and mycological cure should not have been separate primary variables.
2. It is not proper to change hypotheses to fit experimental findings.

8.1.2.4 Results

8.1.2.4.1 Patient Disposition, Comparability

Investigators

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	200 mg continuous	400 mg pulse
Brandt	5	4
Heikkilae	8	8
Hollmen	5	5
Oksman	5	5
Rantanen	10	10
Saari	13	12
Stubb	7	7
Turjanmaa	12	13
	65	64

Dropouts (defined as premature termination of study, but not including those with

premature termination of treatment and yet being followed up)

	200 mg continuous		400 mg pulse	
Phase:	Double-blind	Follow-up	Double-blind	Follow-up
Adverse event*	1	1**	3	0
Lack of efficacy	0	1	0	1
Treatment deviation	0	0	1	0

*Details - see under 8.1.2.4.3.1.
**Due to abnormal lab value.

One patient in each treatment group violated protocol for failing entry criteria.

Baseline Demographic Data (all patients)

	200 mg continuous	400 mg pulse
Patients entered (M/F)	65 (36/29)	64 (36/28)
Age in yrs: median (min-max)	45 (25-59)	41 (21-61)
Duration of present infection in months: median (min-max)	72 (6-384)	54 (6-360)
Present infection being a relapse	11 (17%)	8 (13%)
KOH positive	56 (86%)	55 (86%)
Culture positive	64 (98%)	60 (94%)
Previous antifungal medication	38 (58%)	33 (52%)
topical antifungals	29 (45%)	28 (44%)
systemic antifungals	15 (23%)	9 (14%)
Concurrent dermatophytosis		
tinea pedis	26 (40%)	22 (34%)
tinea manus	1 (2%)	0

None of the differences between the 2 treatment groups were statistically significant ($p>0.05$). All subjects were Caucasians and *T. rubrum* was identified in the baseline cultures in 84% of the patients (50/65= 77% of the continuous therapy group and 46/64=72% of the pulse group). Three patients used concomitant antifungal therapy during the study without specification as to the study phase (treatment or follow-up period) or duration of use:

200 mg/d continuous group	used topical econazole bid
200 mg bid pulse group	used the antifungal "Focusan" and
200 mg bid pulse group	used "topical antifungal".

Comment

1. Not all patients were both KOH and culture positive at baseline. However, the study report noted only one patient in each group as being protocol deviants on the basis of negative culture for dermatophyte. This is incorrect, since two subjects in the continuous group and 4 in the pulse group were classified as "cured" mycologically at baseline.
2. The patients given antifungals during study were also protocol deviants.
3. The intent-to-treat analysis should have been based on all patients with postbaseline data, as dictated by the original protocol.

8.1.2.4.2 Efficacy Endpoint Outcomes

Primary parameters

Table 8.1.2.4.2A Primary Parameters - Clinical Response and Mycological Cure

		200 mg continuous (n=65)	400 mg pulse (n=64)	p values
1. Clinical response (global of ≤3)				
observed case analysis	month-3	31/63 (49%)	32/61 (52%)	0.724
	month-6	57/63 (90%)	55/61 (90%)	1.000
	month-9	48/64 (75%)	52/61 (85%)	0.183
	month-12	43/62 (69%)	48/59 (81%)	0.145
	endpoint	44/64 (69%)	49/61 (80%)	0.156
worst case analysis	endpoint*	44/65 (68%)	49/64 (77%)	0.327
2. Mycological cure (Negative KOH/Culture)				
DB phase	start	1/65 (2%)	2/64 (52%)	0.365
	month-1	20/63 (32%)	25/62 (52%)	0.355
	month-2	20/63 (32%)	28/60 (52%)	0.100
	month-3	34/63 (54%)	26/61 (43%)	0.215
FU phase	month-6	36/64 (56%)	30/58 (52%)	0.716
	month-9	39/64 (61%)	41/61 (52%)	0.576
	month-12	41/62 (66%)	40/58 (52%)	0.846
	endpoint**	41/65 (63%)	42/64 (66%)	0.855

*Pulse therapy at least equivalent to continuous treatment (95% C.I. -26.7%; 3.5%)
**A trend towards equivalence of the 2 treatment groups (95% C.I. -19.1%; 14%)

Comment These two parameters: clinical response and mycological response cannot be used as primary parameters when analyzed separately. The primary parameter should be a clear nail with mycological cure and no relapse. The Applicant needs to reanalyze the data. Since there is no placebo arm for comparison, it is difficult to establish efficacy for either dosing scheme. Efficacy is only inferred from historical data in the previously approved NDA 20-510 (Studies #1601, 1602 and 1603).

Secondary Parameters

Table 8.1.2.4.2B Changes of Clinical Parameters from Baseline

	200 mg continuous		400 mg pulse		
Changes from BL	n	mean±SE	n	mean±SE	p values
Onycholysis scores					
baseline	65	(1.2±0.1)	64	(1.5±0.1)	0.035*
double-blind mo-3	63	-0.2±0.1	61	-0.4±0.1	0.139
follow-up mo-12	62	-0.9±0.1	59	-1.2±0.1	0.058
endpoint	65	-0.9±0.1	64	-1.2±0.1	0.074
Hyperkeratosis scores					
baseline	65	(2.2±0.1)	64	(2.3±0.1)	0.348
double-blind mo-3	63	-0.7±0.1	61	-0.8±0.1	0.517
follow-up mo-12	62	-1.5±0.1	59	-1.7±0.1	0.266
endpoint	65	-1.5±0.1	64	-1.7±0.1	0.317
Discoloration scores					
baseline	65	(2.2±0.1)	64	(2.4±0.1)	0.178
ble-blind mo-3	63	-0.6±0.1	61	-0.7±0.1	0.692
w-up mo-12	62	-1.4±0.1	59	-1.7±0.1	0.191
endpoint	65	-1.4±0.1	64	-1.6±0.1	0.362

Table 8.1.2.4.2B (Cont'd) Changes of Clinical Parameters from Baseline

Changes from BL	200 mg continuous n	200 mg continuous mean±SE	400 mg pulse n	400 mg pulse mean±SE	p values
Paronychial inflammation scores					
baseline	65	(0.2±0.1)	64	(0.2±0.1)	0.295
double-blind mo-3	63	-0.3±0.1	61	-0.2±0.1	0.213
follow-up mo-12	61	-0.2±0.1	59	-0.2±0.1	0.298
endpoint	65	-0.2±0.1	64	-0.2±0.1	0.281
Total scores					
baseline	65	(5.8±0.2)	64	(6.3±0.2)	0.086
double-blind mo-3	63	-1.7±0.2	61	-2.0±0.2	0.692
follow-up mo-12	62	-4.0±0.3	59	-4.8±0.3	0.124
endpoint	65	-3.9±0.3	64	-4.6±0.3	0.187

*statistically significant difference at baseline.

Table 8.1.2.4.2C Extent of Nail Disease

	200 mg continuous n	200 mg continuous mean±SE	400 mg pulse n	400 mg pulse mean±SE	p values
Percent involvement					
All toenails					
baseline	65	66±3	64	60±3	0.162
double-blind mo-3	63	38±3	61	33±3	0.110
follow-up mo-12	62	14±3	59	13±3	0.727
endpoint	65	15±2	64	14±3	0.836
Big toenails					
·line	58	63±4	58	60±4	0.512
ɔle-blind mo-3	56	38±3	55	37±3	0.855
follow-up mo-12	52	21±4	46	20±4	0.781
endpoint	58	20±4	58	19±3	0.623
Length of unaffected part of target nail (mm)					
baseline	64	1.0±0.3	63	1.0±0.2	0.958
double-blind mo-3	62	6.1±0.3	61	5.7±0.3	0.329
follow-up mo-12	20	8.2±1.2	19	9.7±1.4	0.490
endpoint	65	8.3±0.5	64	8.7±0.5	0.716

Comments

1. It is not clear what is being referred to as the "big toenail" data: whether this was an average of two diseased big toes or whether one was chosen for reference. In the protocol, there was no provision that the target nail had to come from a big toe.
2. In ITR-USA-71, the data on percentage of affected nail at any given timepoint was expressed as ***change from baseline***, i.e., as the difference between the two percentages. The data here are given as the ***actual percentage involvement***. Such difference in presentation is confusing. Data must be presented and analyzed in a consistent manner using proper statistical methodology.

Table 8.1.2.4.2D Global Evaluations

	200 mg continuous n	200 mg continuous Pt nos giving Globals C-CM-MI-MDI-UN-W*	400 mg pulse n	400 mg pulse Pt nos giving Globals C-CM-MI-MDI-UN-W	p
double-blind mo-3	63	0- 2-29-31- 1- 0	61	0- 1-31-28- 1- 0	0.001
follow-up mo-6	63	7- 1-49- 5- 1- 0	61	5- 2-48- 4- 2- 0	0.014
follow-up mo-9	64	12- 1-35- 9- 1- 6	61	12- 4-36- 5- 1- 3	0.208
follow-up mo-12	62	25- 2-16- 8- 1-10	59	24- 2-22- 5- 1- 5	0.459
endpoint	64	25- 2-17- 8- 1-11	61	24- 2-23- 6- 1- 5	0.434

*C=cured, CM=cured with malformation, MI=markedly improved, MDI=moderately improved, UN=unchanged and W=worse.

Table 8.1.2.4.2E Negative Mycology

	200 mg continuous (N=65)	400 mg pulse (N=64)	p
KOH			
double-blind mo-1	35/63=56%	37/62=60%	ND
double-blind mo-3	46/63=73%	38/61=62%	ND
follow-up mo-6	41/64=64%	37/58=64%	ND
follow-up mo-12	51/62=82%	46/58=79%	ND
Culture			
double-blind mo-1	27/63=43%	30/62=48%	ND
double-blind mo-3	43/63=68%	41/61=67%	ND
follow-up mo-6	55/64=86%	49/58=84%	ND
follow-up mo-12	45/62=73%	49/58=84%	ND

Table 8.1.2.4.2F "Response" and "Relapse" Rates

	200 mg continuous	400 mg pulse	p
"Overall Response" Rates			
month-3	17/63=27%	14/61=23%	0.680
endpoint	32/65=49%	33/64=52%	0.861
"Relapse" Rates			
Clinical	19/63=30%	9/58=16%	0.083
Mycological	22/63=35%	18/60=30%	0.571
Overall	25/57=44%	15/48=31%	0.228

Comments

1. The relapse rates should have been based on the number of patients who have achieved a "response" or "cure" and not on the total number of patients having available data.
2. Based on the "Clinical Relapse" data from data listings (Vol 4.2, p. 90) the relapse rates were 30/57=53% and 19/48=40% for the 200 mg/d and 400 mg/d groups respectively. The discrepancy with the data shown above (Vol 1.3, p. 67 - display 26) needs to be reconciled.
3. Even if one uses the data from the above Table, the relapse rates in this study are still high.

Table 8.1.2.4.2F Tolerability*

	200 mg continuous (n=65)			400 mg pulse (n=64)			p values
	very good	good	poor	very good	good	poor	
investigator's	58(92%)	5(8%)	0	53(87%)	7(12%)	1(2%)	0.337
patient's	55(87%)	8(13%)	0	48(79%)	12(20%)	1(2%)	0.193

*Defined as very good, good or poor as shown in Table.

Comment Although not significant, the 400 mg/d dose appears to be less tolerable.

8.1.2.4.3 Safety Comparison

8.1.2.4.3.1 Adverse Events Profile

Table 8.1.2.4.3.1 Adverse Events in Study ITR-FIN-1

Phase of Study	200 mg qd continuous			200 mg bid pulse		
	Double-blind		Follow-up**	Double-blind		Follow-up**
Total number of patients	65		64	63		61
Total with ≥1 adverse event	17 (26%)	11 (17%)	5 (8%)	23 (36%)	9 (15%)	4 (7%)
Body as a whole	3			3		
Allergic reaction				1		
Fatigue	1			1		
Influenza-like symptoms	2			1		
Cardiovascular				1	1*	
Heart disorder				1	1	
Nervous system				4	2	
Headache				1	1	
Vertigo				3	1	
Gastrointestinal	7	5*	2	9	6	
Abdominal pain	2					
Diarrhea	1	1		1		
Dyspepsia	1	1	1	1	1	
Flatulence	1	1		3	3	
"GI disorder"	1	1	1			
Gastroenteritis				1		
Hematemesis				1		
Melena				1		
Nausea	1	1		2	2	
Esophagitis				1		
Liver and biliary system	4	3		3		
Gamma-GT increase	1	1				
SGOT increase	1	1		3		
SGPT increase	4	3				
Metabolic and nutritional				1		
NPN increased				1		
Musculoskeletal			1	1		
Pathological fracture			1	1		
Psychiatric				2	1	
Impotence				1	1	
Paranoid reaction				1		
Erythrocyte	2		1			
Anemia	2		1			
Reproductive (female)				2		
Breast pain				1		
Menstrual disorder				1		
Resistance mechanism	1		1	2		1
Fungal infection				1		
Viral infection						1
Otitis media	1		1	1		
Respiratory system	2		1	4		1
Asthma	1					
Bronchitis			1	2		1
Sinusitis	2			1		
Upper respiratory infection				2		
Skin and appendages	2	2	2	2	2	2
Dermatitis	1	1				
Fungal dermatitis			1			2
Nail disorder				1	1	
Paronychia			1			
Pruritus				1	1	
Rash	1	1				
Urinary tract	1	1		1	1	
Frequency				1	1	
Abnormal urine	1	1				
White Cell and RES				1		
"WBC abnormal"				1		

*Shaded figures represent numbers of subjects having adverse events considered possibly, probably or definitely related to treatment.
**None of the adverse events in follow-up phase were considered to be treatment-related.

Adverse Events Leading to Discontinuation of Treatment

Continuous 200 mg/d Group

38/F/W moderate dermatitis (possibly drug-related) during treatment period.

31/M/W SGPT and GGT elevation (possibly drug-related) during treatment period, but the investigator believed these were probably related to influenza, since the enzyme levels had decreased one day after cessation of treatment (day-34):

		Double-blind period	Follow-up		
	Baseline	day29	day35	day49	day56
AST (normal 10-35 U/L)	25	59	21	35	29
ALT (normal 10-35 U/L)	18	149	47	55	44
Alkaline phosphatase (normal 50-270 U/L)	101	367	275	153	122

Pulse 400 mg/d Group

30/W/M paranoid reaction considered not drug-related.

46/W/M impotence considered possibly drug-related.

39/W/M esophagitis, hematemesis, melena and elevated NPN believed to be related to excess alcohol intake.

35/W/F gastroenteritis considered not drug-related.

Serious Adverse Events

400 mg/d pulse group 39/W/M esophagitis, hematemesis, melena and elevated NPN believed to be related to excess alcohol intake.

8.1.2.4.3.2 Laboratory Findings

There were no consistent changes in laboratory parameters. In one subject continuous itraconazole group), AST and ALT elevation was noted during double-blind treatment period despite normal alkaline phosphatase levels:

		Double-blind period			Follow-up
	Baseline	1 mo	2 mo	3 mo	6 mo
AST (normal 10-35 U/L)	21	22	46	133	27
ALT (normal 10-35 U/L)	19	22	77	196	28

Comment The enzyme elevations in this patient were probably drug-related.

8.1.2.5 Conclusions

1. Both dosing regimens, 200 mg/d continuously or 200 mg bid x 7 consecutive days in 3 cycles over 3 months appear to be safe and effective in treating toenail onychomycosis. However, a high relapse rate is noted in patients treated with either regimen. The 400 mg/d dose appears to be slightly less tolerable than the 200 mg/d dose.
2. Since this study is primarily for comparing two dosage regimens for toenail onychomycosis, even though some patients had fingernail involvement, the data have not been analyzed to provide adequate information on the effect of itraconazole on onychomycosis of fingernails. Therefore this study may serve as support for the efficacy and safety of the 3-cycle pulse regimen, but not for the requested label change for adding a 2- cycle pulse regimen for the treatment of fingernail onychomycosis.
3. The primary parameter should have been a clear nail with negative mycology and no

relapse. The Applicant should reanalyze the data. In addition, subgroup analyses of individuals with clinical data on fingernail disease should be done despite lack of mycological data for their fingernails.
4. The Applicant has not submitted data from all parts of this study for review, including data on plasma or nail itraconazole levels, which would have been studied according to the original protocol.

9. Overview of Efficacy

This NDA requests the indication for the treatment of onychomycosis of the **fingernail**. One study (ITR-USA-71) was submitted in which onychomycosis of fingernails was treated with itraconazole. Another study (ITR-FIN-1) was a comparative trial of two dosage regimens for the treatment of onychomycosis of the **toenail**. The data of these two studies are not comparable or poolable.

Tables 9A and 9B list reports where fingernails have been treated with different dosing regimens of itraconazole for onychomycosis. Data for Table 9A are from original NDA 20-510 and those for Table 9B from vol 3.1 of NDA 20-694.

In the original onychomycosis NDA (#20-510), there were no controlled studies presented involving treatment of fingernail onychomycosis with less than 18 Gm of itraconazole exposure (current dose regimen for onychomycosis of toenails). For uncontrolled studies, the following used possibly less than 18 Gm itraconazole per patient *in toto*:

Table 9 A Studies with Possible Use of ≤18 Grams of Itraconazole in Fingernail Onychomycosis

Investigator	Dosing Regimen	Exposure (Gm)	Patient No.	Outcome
Svejgaard	50-100 mg/d x 3-6 mo	4.5-9		1/5 global "cure"
Meisel (ITR-GER-9)	50 mg/d x 3-6 mo	4.5-9		93% mycological cure
Willemsen	100 mg/d x 3 mo	9		3/3 clinical and mycological cure
Dinotta	100 mg/d x 3 mo	9		82% clinical and mycological cure
Jen	100 mg/d x 3 mo	9		"Signs of definite improvement"
Andre	100 mg/d x 14 wk	9.8		Rapid regrowth of healthy nail; no relapse
Lasagni	100 mg/d x 4 mo	12	not reported	Clinical/mycological "recovery" in 2-4 mo
Rongioletti	100 mg/d x 4 mo	12		5/10 "cure" for Candida infection but not for dermatophytes
Hay	100 mg/d x 4 mo; then 200 mg/d till recovery	≥12		94% fingernails had clinical/mycological remission; 3% of these relapsed
Shrenker	50 mg/d x 6 wk; then 100 mg/d x 20 wks	16.1		All fingernails cured at wk-20
Marcano	50-400 mg/d up to 12 months	up to 18-144		2/3 clinical response "cure"
Kim	100 mg/d x ≤12 mo	up to 36		82% clinical and mycological cure
Hay	100-200 mg/d x ? duration	?		100% "cure rate"
Meisel	50 mg/d x 1d-10 mo	0.05-15	fingernails) not reported	Not interpretable (fingernails+toenails)

Investigator	Dosing Regimen	Exposure (Gm)	Patient No.	Outcome
Reinel (ITR-GER-10)	50 mg/d x 3-12 mo	4.5-18		Not interpretable (fingernails+toenails)
Degreef	100 mg/d x 3-21 mo	9-63		Not interpretable (fingernails+toenails)
Montoya	50-100 mg/d x 8 mo	12-24		Not interpretable (fingernails+toenails)
Glowania (ITR-GER-8)	50-100 mg/d x ≤73 wks	up to 26-51		Not interpretable (fingernails+toenails)
Alcantara	100 mg/d x up to 11 mo	up to 33		Not interpretable (fingernails+toenails)

Table 9 B Updated Reports on the Use of Itraconazole for Onychomycosis

Investigator/Country	Type of Trial	Area treated	Dosing Regimen	Patient No.
Hann/Korea	Open	Toenail	100 mg/d x 116 days	
Palva/Finland	Open	not specified	100 mg/d "followed by" 200 mg/d Not specified	
Palva/Finland	Open	not specified	100 mg/d for unspecified time period 200 mg/d x 1 week	
DePadova-Elder/U.S.	Open	Toenails and fingernails (Candida infection)	100 mg/d x 24 weeks. Pause for 4.5 mo and maintenance at 100 mg/d x 7d every 4 weeks for 2 mo.	
eck/Germany	Open	Toenails	100 mg/d x 14d. After 3rd relapse, 100 mg 2x/wk	
Rosen/U.S.	Open	Toenails ***Fingernails***	100 mg bid x 6 weeks ***100 mg bid x 12 days***	
Lopez-Martinez/Mexico	Open	Toenails	200 mg/d x 12 wks	
Kim/Korea	Open	***Fingernails***	***200 mg qd x 6 weeks***	
DeDoncker/Belgium	Open	Toenails	200 mg bid x 7d/mo for 3 mo 200 mg bid x 7d/mo for 4 mo	
Goedadi/Indonesia	Open	***Fingernails***	***200 mg/d x 7d/mo for 3 mo***	
Arenas/Mexico	Open	Toenails	200 mg/d x 3 mo Terbinafine 250 mg/d x 3 mo	
Heremans/Belgium	Open & double-blind	Not specified	200 mg/d x 3 mo Miconazole or placebo	

Three of these 12 studies in Table 9B involved non-candidal onychomycosis of the fingernails. None used a dosage more than 200 mg/d and one was a pulse therapy study:

Investigator	Dose Regimen	Pt No	Outcome
Rosen	100 mg bid x 12 days	1	Itraconazole-induced edema leading to withdrawal
Kim	200 mg qd x 6 weeks	21	Mycological cure 19/21. Clinical plus mycological cure 17/21 (90%) (81%)
Goedadi	200 mg/d (7d/mo x 3 mo)	21	Mycological cure 20/21. Clinical plus mycological cure 19/21 (95%) (90%)

In ITR-USA-71, mycological success (negative KOH and culture) was 61% (22/36) and clinical cure (cleared) was 58% (21/36), while "overall success" as defined by the Applicant (mycological success plus clinically markedly improved or cleared) was 56% (20/36). Although it is difficult to make historical comparisons, the pulsing dosage regimen 400 mg/d x 7d/month x 2 months used in ITR-USA-71 does not appear to offer advantage over schemes using <400 mg/d of itraconazole. Specifically, in the Goedadi study, in which 200 mg/d was given in monthly 7-consecutive-day pulses over 3 months, the cure rates were superior while the exposure to itraconazole was only 4.2 gm (vs 5.6 gm in ITR-USA-71).

Comment The Applicant should have tried a full dose-ranging trial in order to assess the optimal dose. Smaller daily doses or lower total itraconazole exposure, as suggested by the results in Table 9B, may be able to achieve comparable rates of success in the treatment of fingernail onychomycosis. This should be addressed.

Subset Analysis

Subset analyses for age, sex and race have not been performed for efficacy in studies involving itraconazole treatment of fingernail onychomycosis, as the number of itraconazole-treated patients in each trial has been small (21 in the studies by Kim and by Goedadi, and 37 in ITR-USA-71).

10. Overview of Safety

Safety data for itraconazole in the treatment of onychomycosis have been analyzed in the Medical Officer Review in NDA 20-510 and the combined data for onychomycosis and dermatophyte skin infection/tinea versicolor have been analyzed in the Medical Officer Review in NDA The current NDA provides for the treatment of onychomycosis of fingernails but no separate analysis of an integrated database for fingernail onychomycosis has been provided by the Applicant. Instead, upon request for an integrated summary of safety for this NDA, a safety update for NDA 20-510 dated 4/7/95 with data cutoff date of 1/1/95 was submitted. This review is done with the full database, with onychomycosis of toenails and fingernails combined.

Comment This is unacceptable. An integrated summary of safety should have been submitted updating information to 1996.

The following account is based on the material submitted with 1/1/95 cutoff date. This database includes information from original NDA 20-510 and from the two trials in Section 8 of this review, together with another pulse regimen study, ITR-BEL-43, the

details of which was not given in NDA 20-510 or presented in the original submission of NDA 20-694. The Applicant also included data from studies for dermatophytosis/tinea versicolor in the safety section of the original NDA 20-510, but as there were no new data, none was provided in the safety update of 4/7/95. Safety data for dermatophytosis/tinea versicolor have been reviewed under NDA and will not be combined here with onychomycosis data, as it will be misleading to lower the incidence of adverse events due to the much lower exposure to itraconazole in the treatment of these conditions. Table 10 summarizes the onychomycosis database.

Table 10 Database for Safety Analysis of Itraconazole in Treatment of Onychomycosis

	NDA 20-510			New Data			Combined Data			
	Controlled Trials		Open	Controlled Trials		Open	Controlled Trials		Open	Total
Trial location	Itra*	Placebo	Itra	Itra	Placebo	Itra	Itra	Placebo	Itra	Itra
U.S.	112	109	2	37	36	0	149	145	2	151
Non-U.S.	500	524	1131	129	0	50	629	524	1181	1810
							778	669	1183	1961

*Itra=itraconazole

In addition, postmarketing experience with "Serious Adverse Events" have been received up to a cutoff date of 1/31/96. Review of these documents have not yielded additional information with respect to safety.

10.1 Significant/Potentially Significant Events

10.1.1 Deaths

10.1.2 Other Significant/Potentially Significant Events

10.1.3 Overdosage exposure

There were no deaths or overdose reports in the new material submitted. U.S. post-marketing "serious adverse events" are listed below. There was one patient in Study ITR-FIN-1 given itraconazole 400 mg/d aged 39, W/M) who developed serious adverse events: esophagitis, hematemesis, melena and elevated creatinine level, considered to be related to his excess alcohol intake.

10.2 Other Safety Findings

10.2.1 ADR Incidence Tables

10.2.1.1 An updated ADR incidence Table is attached to this review as Appendix I. This Table includes all data from U.S. onychomycosis trials in NDA 20-510 plus data of the two studies in this NDA (ITR-USA-71 and ITR-FIN-1) and Study ITR-BEL-43. As the subjects in these studies had total exposure to itraconazole similar to or less than those in the original NDA 20-510, little new information has been gained by including the 252 patients (216 itraconazole and 36 placebo) in the safety database.

Comment The Applicant has not integrated the new data into an analysis of adverse events from worldwide onychomycosis trials. Instead, summary Tables analyzing an integrated worldwide database of onychomycosis and dermatophyte skin infections/tinea versicolor were presented. This is unacceptable, as the exposure to itraconazole in the treatment of dermatophyte skin infections/tinea versicolor is substantially lower than that in onychomycosis, and the incidences of adverse events were lowered by this data manipulation. A resubmission with data from worldwide onychomycosis trials would be required.

10.2.1.2 Discontinuations due to adverse events in the two studies in this NDA are:

Study/subject	Age/sex/Race	Adverse Event	Dose	Time to Onset
ITR-USA-71	62/M/W	diffuse pruritus and diffuse rash*	400 mg/d	8 d
ITR-USA-71	43/M/W	gamma-GT elevation	Placebo	8 d
ITR-USA-71	59/M/W	abnormal lab result (↑ triglyceride level)	400 mg/d	23 d
ITR-FIN-1	30/M/W	paranoid reaction	400 mg/d	65 d
ITR-FIN-1	39/M/W	esophagitis/hematemesis/melena/↑ creatinine	400 mg/d	24 d
ITR-FIN-1	46/M/W	impotence*	400 mg/d	4 d
ITR-FIN-1	38/F/W	dermatitis*	200 mg/d	35 d
ITR-FIN-1	35/F/W	gastroenteritis	400 mg/d	84
ITR-FIN-1	31/M/W	gamma-GT and SGPT elevation*	200 mg/d	34 d

*considered possibly related to test medication

10.2.2 Laboratory Findings, Vital Signs, ECGs

There is no significant new information with respect to laboratory findings, or vital signs in the trials presented. ECGs were not part of the studies although there is the possibility of interaction between itraconazole and some antihistamines (e.g. terfenadine and astemizole) resulting in ECG abnormalities.

10.2.3 Special Studies

The following two special studies in 10.2.3.1 and 10.2.3.2 were presented in support of the pulse dosing regimen, both in the form of published articles.

10.2.3.1 Posttreatment itraconazole levels in the nail. *New implications for treatment in onychomycosis.* Willemsen M; DeDoncker P; Willems J; Woestenborghs R; Van deVelde V; Heykants J; Van Cutsem J; Cauwenbergh G; Roseeuw D. *J Am Acad Dermatol* 1992; 26: 731-5.

This study was designed to investigate itraconazole nail kinetics in 39 patients with onychomycosis in relation to their therapeutic outcome. METHODS: All patients received itraconazole for 3 months at a dose of 100 or 200 mg daily. Itraconazole levels of distal nail clippings were determined during a 6-month posttherapy period. RESULTS: Therapeutic itraconazole concentrations were found in the nail plates of fingernails and toenails for up to 6 months after treatment (Fig.1). Cure of the toenails was observed in 79% of the patients treated with the 200 mg dosage and in 26% of those treated with 100 mg at 6 months after therapy. CONCLUSION: The data suggest that the drug reaches the nail via incorporation into the matrix and by diffusion from the nail bed and is eliminated with regrowth of the nail after discontinuation of treatment.

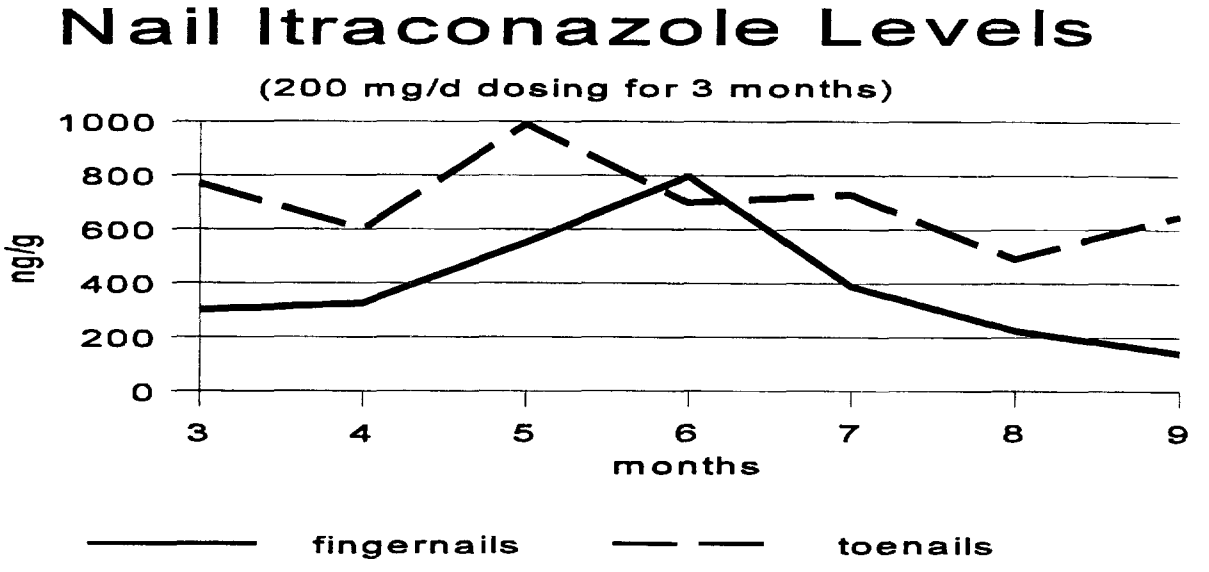


Fig 1 Nail Clipping Itraconazole Levels following 3 Months of 200 mg/d Treatment

Comments

1. This study does not use pulse dosing. The relevance of this information with regard to pulse regimens needs to be substantiated with further studies.
2. The therapeutic level of itraconazole in nails has not been defined. In fact, in the current label, it is stated that the "Correlation between *in vitro* minimum inhibitory concentration results and clinical outcome has yet to be established for azole antifungal agents". Although the investigators noted direct correlation between cure rates and dose, they have failed to present data relating the outcome of individual nails to the itraconazole levels in the nail clippings.
3. The validation of the methodologies for nail collection and itraconazole extraction/assay has not been presented.
4. Ultimately it is the level of drug in the nail bed (not nail plate) that is most relevant.

10.2.3.2 New approaches to the treatment of onychomycosis. Roseeuw D; DeDoncker P. *J Am Acad Dermatol* 1993; 29: S45-50.

The purpose of this article was to review the pharmacologic properties of two newer agents, itraconazole and terbinafine, and to assess their clinical efficacy in onychomycosis. The improved effectiveness of these agents was probably related to their rapid penetration into the nails and prolonged bioavailability at the site of infection. For itraconazole, data were presented for nail itraconazole levels upon pulse dosing with 200 mg bid 1 week/month for 3 or 4 cycles (Fig. 2).

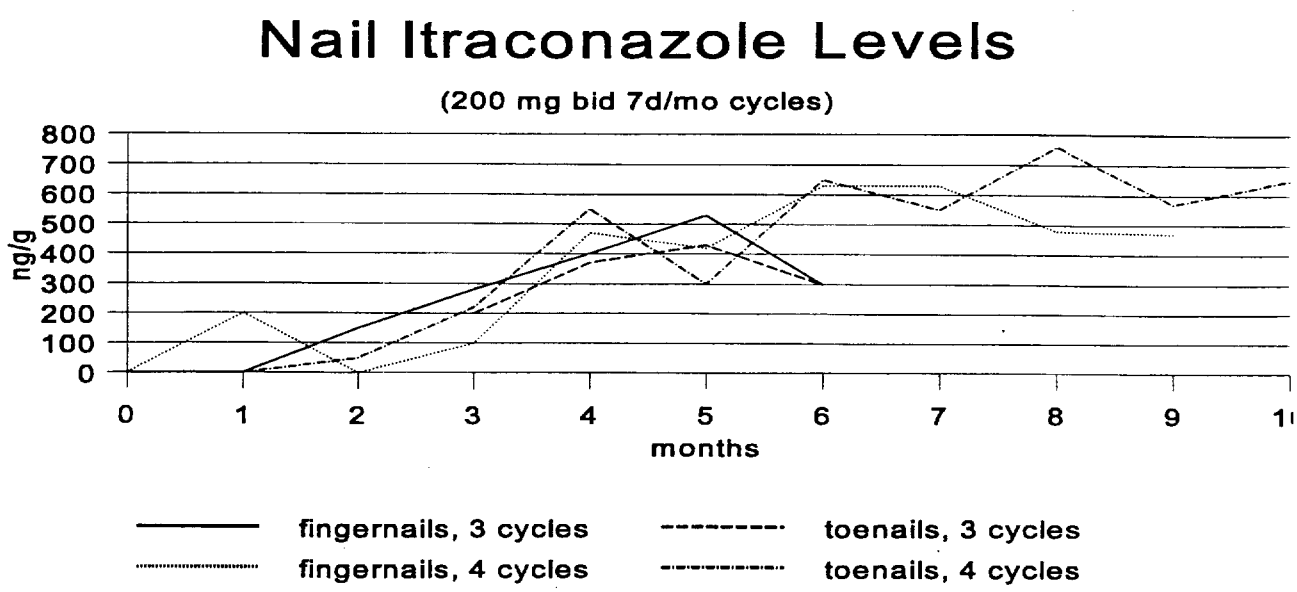


Fig 2 Nail Clipping Itraconazole Levels following 3 or 4 Cycles of 400 mg/d Treatment

Comments

1. The validation of the methodologies for nail collection and itraconazole extraction/assay has not been presented.
2. The proposed dosing regimen for fingernail onychomycosis is two pulses of 200 mg bid x 7 days, separated by 21 days of no itraconazole. The data for this study with 3 or 4 pulses do not address the nail itraconazole levels to be attained with the proposed regimen.
3. Plasma levels were not measured in this study. As the proposed dosing regimen involves a daily dose during the pulse phase higher than the currently approved dose for onychomycosis, the plasma pharmacokinetics for this pulse regimen should be studied.
4. As discussed above, ultimately it is the level of drug in the nail bed (not nail plate) that is most relevant.

10.2.3.3 Other Studies Although the Applicant has not submitted data from earlier onychomycosis studies where dosing with 400 mg/d has been used, some pertinent information may be gained from the approved label (in CLINICAL PHARMACOLOGY section, under *Pharmacokinetics and Metabolism):*

1. The pharmacokinetics of itraconazole was studied using six healthy male volunteers who received 50 mg or 200 mg with a full meal. ***Doubling the SPORANOX dose resulted in approximately a 3-fold increase in the itraconazole plasma levels.***

2. Steady-state concentrations were reached within 15 days following oral doses of 50-400 mg daily. Values given in Table 10.2.3.3 are data at steady-state from a pharmacokinetics study in which 27 healthy male volunteers took 200 mg SPORANOX b.i.d. (with a full meal) for 15 days. Results of this study suggested that itraconazole might undergo saturation metabolism with multiple dosing.

Table 10.2.3.3 Steady State PK Parameters in Healthy Males Taking Itraconazole 200 mg/d

	Itraconazole	Hydroxyitraconazole
C_{max} (ng/mL)	2282 ± 514	3488 ± 742
C_{min} (ng/mL)	1855 ± 535	3349 ± 761
T_{max} (hours)	4.6 ± 1.8	3.4 ± 3.4
$AUC_{0-12\,h}$(ng.h/mL)	22569 ± 5375	38572 ± 8450
$t_{1/2}$ (hours)	64 ± 32	56 ± 24

Values are means ± standard deviation

Comments

1. A dose of 200 mg bid for 15 consecutive days has been tolerated by 27 healthy male volunteers with the pharmacokinetic parameters collected shown above.
2. A dose of 200 mg bid has been approved for certain systemic mycoses. In the current label, it is stated under DOSAGE AND ADMINISTRATION -

> "**Treatment of blastomycosis and histoplasmosis:** The recommended dose is 200 mg once daily (2 capsules). ***If there is no obvious improvement or there is evidence of progressive fungal disease, the dose should be increased in 100 mg increments to a maximum of 400 mg daily. Doses above 200 mg per day should be given in two divided doses.*** **Treatment of aspergillosis:** ***A daily dose of 200 to 400 mg of itraconazole is recommended.***
>
> **In life-threatening situations:** Although these studies did not provide for a loading dose, it is recommended, based on pharmacokinetic data, that ***a loading dose of 200 mg (2 capsules) t.i.d. (600 mg/day)*** be given for the first three days."

3. The Applicant has not addressed the issue of saturation metabolism with a pulse regimen and whether the higher daily dose may greatly enhance systemic exposure in patients with compromised organ function, especially when the increase in plasma level in association with doubling dose may not necessarily be linear. It is the opinion of the Biopharm Group that since (a) itraconazole has a relatively wide therapeutic range and (b) the current label does recommend careful monitoring in patients with liver impairment, no additional studies are necessary at this time.

10.2.4 Drug-Demographic Interactions

The number of patients added to the onychomycosis clinical trial database is small as compared to that in the original NDA 20-510, especially when split into subset populations (Table 10.2.4). Differences between the sexes, races and ages in the incidence of adverse events were consistent between itraconazole- and placebo-treated subjects and did not suggest an increased risk in any special subset.

Table 10.2.4 Patient Numbers in Demographic Subsets in Onychomycosis Trials

Subset	U.S.				WORLDWIDE			
	itraconazole		Placebo		itraconazole		Placebo	
	NDA 20-510 (n=112)	New Data (n=37)	NDA 20-510 (n=109)	New Data (n=36)	NDA 20-510 (n=612)	New Data (n=166)	NDA 20-510 (n=633)	New Data (n=36)
Male	81 (72%)	34 (92%)	77 (71%)	29 (81%)	342(56%)	106(64%)	348(55%)	29 (81%)
Female	31 (28%)	3 (8%)	32 (29%)	7 (19%)	270(44%)	60 (36%)	285(45%)	7 (19%)
White	87 (78%)	27 (73%)	81 (74%)	24 (67%)	536(88%)	155(93%)	546(86%)	24 (67%)
Black	7 (6%)	2 (5%)	5 (5%)	3 (8%)	7 (1%)	2 (1%)	5 (1%)	3 (8%)
Hispanic	16 (14%)	8 (22%)	19 (17%)	9 (25%)	17 (3%)	8 (5%)	20 (3%)	9 (25%)
Other	2 (2%)	0	4 (4%)	0	4 (1%)	0	10 (2%)	0
? Race	0	0	0	0	48 (8%)	1 (1%)	52 (8%)	0
≤12	0	0	0	0	0	0	0	0
13-64	102(91%)	35 (95%)	95 (87%)	31 (86%)	546(89%)	164(99%)	559(88%)	31 (86%)
≥65	10 (9%)	2 (5%)	14 (13%)	5 (14%)	22 (4%)	2 (1%)	27 (4%)	5 (14%)
? Age	0	0	0	0	44 (7%)	0	47 (7%)	0

10.2.5 Drug-Disease Interactions

10.2.6 Drug-Drug Interactions

10.2.7 Withdrawal Phenomena/Abuse Potential

10.2.8 Human Reproduction Data

There is no new information for 10.2.5 through 10.2.8

11. Labeling Review

Comments

1. The INDICATIONS section should state the number of patients treated with itraconazole (37) rather than the total number of patients. In addition, the rate should be replaced by an rate as an endpoint to be described. Thus, this part should read as follows:

2. The dosing regimen in the proposed change is acceptable, in lieu of better data. The Applicant has failed to fulfill an earlier agreement to find the best dosage regimen for the treatment of onychomycosis of fingernails in order to gain approval for NDA 20-510. Approval for this 400 mg/d two-pulse dose

to gain approval for NDA 20-510. Approval for this 400 mg/d two-pulse dose regimen may need to be modified following the availability of dose-ranging data.
3. The Table on adverse events leading to discontinuation combines data from different dosing regimens and is, therefore, unacceptable. The Applicant should give separate Tables for data from 200 mg/d continuous dosing in the treatment of toenail onychomycosis vs 400 mg/d pulse dosing for fingernail disease. In addition, a Table or statement on adverse events with ≥1% incidence should be presented for the dosing regimen for fingernail onychomycosis.

12. Conclusions

Although it appears evident that efficacy for toenail onychomycosis would confer efficacy for fingernails, a proper dosing regimen must be established to minimize drug exposure. When itraconazole was approved for the treatment of toenail onychomycosis, a recommendation was made to the Applicant to conduct a study "to evaluate the dosage regimen that would most effectively be used to treat onychomycosis of the finger nail in patients without concomitant onychomycosis of the toenail." This NDA is an attempt to address this recommendation for phase 4 study.

However, the studies presented in this NDA were done prior to the Applicant's agreement to conduct the recommended study. Thus, although these studies have demonstrated the merits of a pulse dosing regimen, the Applicant has yet to establish the optimal dosing scheme. Therefore, submission of this NDA is not a substitute for conducting the studies agreed to previously. Moreover, protocol ITN-FIN1 studied a dosing regimen with 3 pulses of itraconazole in the treatment of toenail onychomycosis and is not relevant to the Applicant's proposed regimen with 2 pulses of itraconazole for fingernail onychomycosis.

Nevertheless, since the proposed dosing regimen with 2 pulses of 200 mg bid for 7 days separated by 21 days of no itraconazole is safe and effective in the treatment of onychomycosis of fingernails as shown in Study ITR-USA-71, this application is approvable. The Applicant, however, is to be reminded that it must commit to conduct proper phase 4 studies to find the best dosing regimen in the treatment of onychomycosis of fingernails.

13. Recommendations

13.1 Regulatory Recommendation: The proposed pulse regimen of itraconazole in the treatment of onychomycosis of fingernails presented in this NDA is approvable.

13.2 Phase 4 Recommendations:
1. The Applicant must conduct proper studies to find the best dosing regimen for itraconazole in the treatment of onychomycosis of fingernails and change the recommended dosing regimen when this optimal dose is found. Such studies should include sufficient numbers of both males and females for analysis.
2. The therapeutic level of itraconazole in nails has not been defined. In fact, in the

current label, it is stated that the "Correlation between *in vitro* minimum inhibitory concentration results and clinical outcome has yet to be established for azole antifungal agents." Although the studies by Willemsen *et al* presented in this NDA noted direct correlation between cure rates and dose, they have failed to

current label, it is stated that the "Correlation between *in vitro* minimum inhibitory concentration results and clinical outcome has yet to be established for azole antifungal agents." Although the studies by Willemsen *et al* presented in this NDA noted direct correlation between cure rates and dose, they have failed to present data relating the outcome of individual nails to the itraconazole levels in the nail clippings. Studies should be done to establish itraconazole therapeutic levels in nails, especially in the nail bed, which is the area most relevant in onychomycosis therapy.

13.3 Labeling: Labeling should be modified as per comments given in Section 11.

13.4 Other: The Applicant should address the following deficiencies: - put in letter
1. The Applicant has not integrated the new safety data into an analysis of adverse events from worldwide onychomycosis trials. Instead, summary Tables analyzing an integrated worldwide database of onychomycosis and dermatophyte skin infections/tinea versicolor were presented. This is unacceptable, as the exposure to itraconazole in the treatment of dermatophyte skin infections/tinea versicolor is substantially lower than that in onychomycosis, and the incidences of adverse events were lowered by this data manipulation. A resubmission with data from worldwide onychomycosis trials is required. Update of foreign marketing experience including details of approved dosing regimens for onychomycosis of toenails as well as fingernails would also be required.
2. A complete report of Study ITR-FIN-1 in addition to Part I must be submitted. The Applicant should indicate whether one or both big toes were analyzed for the data on percentage of nail involvement. The validation of the methodologies for nail collection and itraconazole extraction/assay in this study should be presented.
3. The Applicant needs to reanalyze data of fingernail studies using as primary parameter for success a global of "cleared" plus mycological cure and no relapse. ???

#3 Addressed via new labeling per Dr. Ko conversation 12/2/96

H. S. Ko 11-21-96.
Hon-Sum Ko, M.D.
11/25/96
cc: Original NDA 20-694
HFD-540
HFD-340
HFD-540/CSO/Cross
HFD-540/CHEM/Higgins
HFD-540/PHARM/Mainigi
HFD-520/MICRO/Sheldon
HFD-715/BIOMETRICS/Thomson
HFD-540/MO/Ko

Appendix I

Adverse Events in Clinical Trials of Itraconazole in the Treatment of Onychomycosis*

	Itraconazole			Placebo		
	NDA 20-510 Pt no (%)	NEW DATA Pt no (%)	COMBINED Pt no (%)	NDA 20-510 Pt no (%)	NEW DATA Pt no (%)	COMBINED Pt no (%)
Total Patients	117	37	151	109	36	145
Pts With Events	71 (63)	10 (27)	81 (54)	60 (55)	9 (25)	69 (48)
System/Event						
Gastrointestinal	**21 (18)**	**4 (11)**	**25 (17)**	**15 (14)**	**4 (11)**	**19 (13)**
diarrhea	5 (4)	0 (0)	5 (3)	4 (4)	2 (6)	6 (4)
dyspepsia	5 (4)	1 (3)	6 (4)	3 (3)	2 (6)	5 (3)
flatulence	5 (4)	0 (0)	5 (3)	2 (2)	0 (0)	2 (1)
abdominal pain	4 (4)	0 (0)	4 (3)	3 (3)	1 (3)	4 (3)
nausea	3 (3)	2 (5)	5 (3)	6 (6)	0 (0)	6 (4)
appetite increase	2 (2)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)
constipation	2 (2)	1 (3)	3 (2)	1 (1)	1 (3)	2 (1)
gastritis	2 (2)	0 (0)	2 (1)	1 (1)	0 (0)	1 (1)
gastroenteritis	2 (2)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)
dry mouth	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
tooth disorder	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
tooth ache	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
feces discolored	0 (0)	0 (0)	0 (0)	0 (0)	2 (6)	2 (1)
ulcerative stomatitis	0 (0)	1 (3)	1 (1)	0 (0)	0 (0)	0 (0)
gingivitis	0 (0)	1 (3)	1 (1)	0 (0)	0 (0)	0 (0)
Respiratory	**20 (18)**	**2 (5)**	**22 (15)**	**19 (17)**	**2 (6)**	**21 (15)**
[illegible]is	10 (9)	1 (3)	11 (7)	11 (10)	1 (3)	12 (8)
[illegible]sitis	8 (7)	1 (3)	9 (6)	5 (5)	1 (3)	6 (4)
pharyngitis	2 (2)	0 (0)	2 (1)	3 (3)	0 (0)	3 (2)
coughing	1 (1)	0 (0)	1 (1)	4 (4)	0 (0)	4 (3)
pleurisy	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
bronchitis	1 (1)	0 (0)	1 (1)	1 (4)	0 (0)	1 (1)
Body as a whole	**20 (18)**	**4 (11)**	**24 (16)**	**21 (19)**	**4 (11)**	**25 (17)**
injury	8 (7)	0 (0)	8 (5)	11 (10)	2 (6)	13 (9)
asthenia	2 (2)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)
fever	2 (2)	0 (0)	2 (1)	3 (3)	0 (0)	3 (2)
pain	2 (2)	1 (3)	3 (2)	1 (1)	1 (3)	2 (1)
allergic reaction	1 (1)	0 (0)	1 (1)	1 (1)	0 (0)	1 (1)
chest pain	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
fatigue	1 (1)	1 (3)	2 (1)	1 (1)	0 (0)	1 (1)
malaise	1 (1)	1 (3)	2 (1)	3 (3)	0 (0)	3 (2)
"edema of legs"	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
allergy	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
influenza-like symptoms	1 (1)	0 (0)	1 (1)	1 (1)	0 (0)	1 (1)
abnormal lab results	0 (0)	1 (3)	1 (1)	0 (0)	0 (0)	0 (0)
back pain	0 (0)	0 (0)	0 (0)	2 (2)	1 (3)	3 (2)
rigors	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
Nervous	**17 (15)**	**3 (8)**	**20 (13)**	**19 (17)**	**3 (8)**	**22 (15)**
headache	11 (10)	3 (8)	14 (10)	17 (16)	3 (8)	20 (14)
dizziness	4 (4)	0 (0)	4 (3)	3 (3)	0 (0)	3 (2)
tremor	2 (2)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)
hypoesthesia	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
vertigo	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
leg cramps	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
[illegible]raine	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
[illegible]tis	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)

	Itraconazole			Placebo		
	NDA 20-510 Pt no (%)	NEW DATA Pt no (%)	COMBINED Pt no (%)	NDA 20-510 Pt no (%)	NEW DATA Pt no (%)	COMBINED Pt no (%)
Resistance disorders	**16 (14)**	**0 (0)**	**16 (11)**	**7 (6)**	**1 (3)**	**8 (6)**
URI	9 (8)	0 (0)	9 (6)	6 (6)	0 (0)	6 (4)
herpes zoster	2 (2)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)
infection	1 (1)	0 (0)	1 (1)	1 (1)	1 (3)	2 (1)
bacterial infection	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
viral infection	1 (1)	0 (0)	1 (1)	1 (1)	0 (0)	1 (1)
otitis media	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
herpes simplex	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
abscess	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Skin and appendages	**8 (7)**	**2 (5)**	**10 (7)**	**7 (6)**	**1 (3)**	**8 (6)**
rash	4 (4)	1 (3)	5 (3)	3 (3)	0 (0)	3 (2)
acne	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
nail disorder	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
pruritus	1 (1)	2 (5)	3 (2)	1 (1)	0 (0)	1 (1)
skin hypertrophy	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
rash, erythematous	0 (0)	0 (0)	0 (0)	2 (2)	1 (3)	3 (2)
"skin disorder"	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
dry skin	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
skin exfoliation	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	1 (3)
basal cell carcinoma	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (3)
Urinary	**6 (5)**	**0 (0)**	**6 (4)**	**2 (2)**	**0 (0)**	**2 (1)**
cystitis	3 (3)	0 (0)	3 (2)	0 (0)	0 (0)	0 (0)
urinary tract infection	3 (3)	0 (0)	3 (2)	1 (1)	0 (0)	1 (1)
nephrosis	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
Liver and biliary	**5 (4)**	**0 (0)**	**5 (3)**	**3 (3)**	**1 (3)**	**4 (3)**
·ormal liver function	3 (3)	0 (0)	3 (2)	0 (0)	0 (0)	0 (0)
)T increase	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
⌋PT increase	1 (1)	0 (0)	1 (1)	2 (2)	0 (0)	2 (1)
hepatic enzymes increase	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
bilirubinemia	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
GGT increase	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	1 (1)
Cardiovascular	**5 (4)**	**0 (0)**	**5 (3)**	**1 (1)**	**0 (0)**	**1 (1)**
hypertension	4 (4)	0 (0)	4 (3)	1 (1)	0 (0)	1 (1)
hypotension, postural	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
hypotension	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Musculoskeletal	**4 (4)**	**1 (3)**	**5 (3)**	**6 (6)**	**1 (3)**	**7 (5)**
myalgia	3 (3)	0 (0)	3 (2)	2 (2)	0 (0)	2 (1)
tendinitis	1 (1)	0 (0)	1 (1)	1 (1)	1 (3)	2 (1)
arthralgia	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
myopathy	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
torticollis	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
skeletal pain	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
bursitis	0 (0)	1 (3)	1 (1)	0 (0)	0 (0)	0 (0)
Psychiatric disorders	**3 (3)**	**1 (3)**	**4 (3)**	**2 (2)**	**1 (3)**	**3 (2)**
abnormal dreams	2 (2)	0 (0)	2 (1)	0 (0)	0 (0)	0 (0)
anxiety	1 (1)	1 (3)	2 (1)	0 (0)	0 (0)	0 (0)
nervousness	1 (1)	0 (0)	1 (1)	0 (0)	1 (3)	1 (1)
depression	0 (0)	1 (3)	1 (1)	0 (0)	0 (0)	0 (0)
insomnia	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	2 (1)
Vision disorders	**1 (1)**	**0 (0)**	**1 (1)**	**2 (2)**	**0 (0)**	**2 (1)**
glaucoma	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
conjunctivitis	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
abnormal vision	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
⌊earing/vestibular Disorders	**0 (0)**	**0 (0)**	**0 (0)**	**2 (2)**	**0 (0)**	**2 (1)**
ɜche	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
disorder, nos	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)

	Itraconazole			Placebo		
	NDA 20-510 Pt no (%)	NEW DATA Pt no (%)	COMBINED Pt no (%)	NDA 20-510 Pt no (%)	NEW DATA Pt no (%)	COMBINED Pt no (%)
Other special senses disorders	**1 (1)**	**0 (0)**	**1 (1)**	**0 (0)**	**1 (3)**	**1 (1)**
taste perversion	1 (1)	0 (0)	1 (1)	0 (0)	1 (3)	1 (1)
Metabolic/Nutritional	**1 (0)**	**0 (0)**	**1 (1)**	**2 (2)**	**0 (0)**	**2 (1)**
hyperglycemia	1 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
electrolyte abnormality	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
gout	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
hypokelemia	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
hyponatremia	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
Vascular (Extracardiac) Disorders	**1 (1)**	**0 (0)**	**1 (1)**	**0 (0)**	**0 (0)**	**0 (0)**
vasculitis	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Reproductive (male)	**1 (1)**	**0 (0)**	**1 (1)**	**2 (2)**	**0 (0)**	**2 (1)**
orchitis	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
prostatic disorder	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	2 (1)
Reproductive (female)	**0 (0)**	**0 (0)**	**0 (0)**	**3 (3)**	**0 (0)**	**3 (2)**
leukorrhea	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	2 (1)
menstrual disorder	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
Bleeding disorders	**0 (0)**	**0 (0)**	**0 (0)**	**2 (2)**	**0 (0)**	**2 (1)**
purpura	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	2 (1)

*Data derived from Tables 5C in vol 3.1 of NDA 20-694.

Addendum to Medical Officer's Review of NDA 20-694

Background: Since completion of this review (9/12/96), the Applicant has submitted on 10/31/96 new labeling based on a label soon to be approved by HFD-530 for SPORANOX Capsules. There are four areas in this label that relate to the proposed changes for toenail and fingernail onychomycosis.

Proposed Changes for Onychomycosis in the 10/31/96 label:

1. Indications and Usage Section:

SPORANOX Capsules are also indicated for the treatment of the following fungal infections in non-immunocompromised patients:

1. Onychomycosis of the toenail or fingernail due to dermatophytes (tinea unguium).

Comment Toenail and Fingernail indications should be separated. This should be changed to read:

2. *Descriptions of Clinical Studies* in Indications and Usage Section:

Comment Toenail studies should precede fingernail studies in the description. It should read as follows:

1 Page

Deleted

Labeling

Revisions

Comments
1. As discussed in my original review, this presentation is deficient. My comments were as follows:

4. Dosage and Administration Section

Comment This should be modified for clarification as follows:

Regulatory Recommendations
1. The Applicant should modify the label with sections relating to onychomycosis changed as recommended above.
2. It is recommended that the remainder of the label follow agreements reached between the Applicant and HFD-530.

H-S. Ko. 11-11-96.

Hon-Sum Ko, M.D.
11/25/96
cc: Original NDA 20-694
HFD-540
HFD-340
HFD-540/CSO/Cross
HFD-540/CHEM/Higgins
HFD-540/PHARM/Mainigi
HFD-520/MICRO/Sheldon
HFD-715/BIOMETRICS/Thomson
HFD-540/MO/Ko

11/25/96

NOV 27 1996

Second Addendum to Medical Officer's Review of NDA 20-694

Background: The Applicant has submitted a revised label with all the suggested changes from the Agency incorporated. A copy is attached here as Appendix I.

Regulatory Recommendations

1. It is recommended that the proposed pulse dosing regimen of SPORANOX® in the treatment of onychomycosis of fingernails, together with the revised label in Appendix I be approved.
2. The Applicant should notify this Division of any further changes in labeling to be reached between itself and HFD-530.
3. The Applicant should also commit to perform the phase 4 studies suggested in my original review of this NDA.

H. S. Ko 11-26-96

Hon-Sum Ko, M.D.

cc: Original NDA 20-694
HFD-540
HFD-340
HFD-540/CSO/Cross
HFD-540/CHEM/Higgins
HFD-540/PHARM/Mainigi
HFD-520/MICRO/Sheldon
HFD-715/BIOMETRICS/Thomson
HFD-540/MO/Ko

G Will 11/27/96

Stat/Clin

Statistical / Clinical Review and Evaluation

NDA/ Drug Class:	20-694 / 6S
Name of Drug:	Sporanox® (Itraconazole) 100mg Capsules,
Applicant:	Janssen Research Foundation 1125 Trenton-Harbourton Road Titusville, NJ 08560-0200
Type of Report:	Clinical/Statistical
Indication:	Onychomycosis of the fingernail
Documents Reviewed:	Volumes 1.1-1.3, with a report on study ITR-RSA-2, and diskettes containing SAS data sets from the sponsor
Medical Officer:	Dr. Hon S. Ko (HFD-540)

1. Introduction

According to the sponsor: "Onychomycosis represents 30 percent of the mycotic infections of the skin and 18-40 percent of all nail diseases. Fingernails are affected in 20 percent of the cases, but rarely are involved concurrently with onychomycosis of the toenail. Fingernails take approximately six months to grow out, compared to toenails which take 12-18 months to grow out completely. This difference in rate of nail growth is reflected in the length of treatment with available therapy: The course of treatment of treatment with [the competitor] griseofulvin is generally one year for fingernails and 18 months for toenails."

Both pharamacokinetic and phase II studies have shown that itraconazole has a high affinity for keratinous tissue. According to the published literature included by the sponsor (e.g. Roseeuw & Donker, 1993, Willemsen et al, 1992) itraconazole diffuses rapidly into the nail via the nail bed, and from there to the nail matrix. "The penetration route into the nail and persistent concentrations of itraconazole provide a rationale for using intermittent dosing to achieve efficacy comparable to continuous dosing. ... Intermittent administration of itraconazole, 200 mg twice daily for seven days the first week of each month for two consecutive months, offers a lower dose than continuous dosing with 200 mg daily for three to four months." The sponsor claims this pulse dosing offers "an improved safety profile while maintaining the efficacy of treatment."

Previously, in NDA 20-510, the agency requested that the Sporanox INDICATIONS AND USAGE insert contains the provision that sporanox is appropriate for "Onychomycosis due to dermatophytes (tinea unguium) of the toenail with or without fingernail involvement." This supplemental NDA is intended to support the change of this provision

to "Onychomycosis of the toenail or fingernail due to dermatophytes (tinea unguium)." In addition the sponsor wishes to change the label to reflect the pulse dosing regimen, as described above, for fingernail involvement.

The primary support for the sponsor's claims is provided by a randomized, double-blind, placebo-controlled, multicenter trial, labeled ITR-USA-71, for the treatment of onychomycosis of the fingernail. The sponsor included other data sets, though generally poorly documented, from a number of other studies in various countries across the world. Two reports were included, ITR-RSA-2 and ITR-FIN-1. These studies primarily involved onychomycosis of the toenails, apparently under various dosing regimens. The Medical Officer expressed the opinion that these were of limited relevance, and hence are only slightly mentioned in the following.

2. Experimental Design

The primary support for the sponsor's claims is provided by a randomized, double-blind, placebo-controlled, multicenter trial, labeled ITR-USA-71, for the treatment of onychomycosis of the fingernail. In this study, seventy-three patients with clinically diagnosed fingernail onychomycosis were in the study at six sites in the U.S., apparently chosen to be reasonably demographically diverse. In addition to these six sites, one further investigator was dropped from the study, apparently since he was unable to enroll any subjects. Potential subjects were included if they had onychomycosis of the fingernail, confirmed by a positive KOH examination and a culture positive for dermatophytes, as well as having at least 25% nail involvement of the nail surface. Patients were excluded if, among other criteria, the onychomycosis was caused by molds, bacteria, or *Candida spp.* without the presence of a dermatophyte.

Patients were treated with itraconazole or placebo twice daily during the first seven days of each month, for two consecutive months. "Seventy-one patients (35 placebo, 36 itraconozole) who received trial drug and returned after the baseline visit were included in the primary analysis of effectiveness. Investigators assessed onycholysis, hyperkeratosis, discoloration, and nail growth and performed a KOH examination and culture at baseline and week 5, and, if the patient's condition had not deteriorated, at post-treatment weeks 12 and 24. Patients' conditions were globally evaluated at week 5." If appropriate, follow-up assessments were made at weeks 12 and 24 (for those patients with a global assessment of at least "unchanged" or better, i.e. patients who deteriorated were deleted.).

i. Response Measures:

The extent of signs of onychomycosis was rated at baseline, week 5, and, for patients who had not deteriorated by week 5, at post-treatment follow-up visits weeks 12 and 24. The following scales were used:

Onycholysis

0=absence of separation of nail plate from the nail bed,
1=separation of nail plate≤50%, from the nail bed,
2=50%<separation of nail plate≤75%,
3=>75% separation of nail plate.

Hyperkeratosis

0=absence of subungual thickening,
1=thickening of ≤50% of the subungual region,
2=50%<thickening of subungual region≤75%,
3=>75% subungual thickening.

Discoloration

0=absence of any unusual coloration (white, yellow, etc.) of the nail plate,
1=discoloration extending to ≤50% of the nail plate,
2=50%<discoloration≤75% of nail plate,
3=>75% discoloration of nail plate.

At week 5 or upon discontinuation of treatment, the investigator globally evaluated the patient's condition based on the reduction in extent of nail involvement and the improvement in signs compared to baseline.

Investigators' global evaluation

0=Cleared of all signs with or without residual nail malformation,
1= Markedly improved, i.e., minimal nail involvement with significantly decreased signs ,
2=Slight to moderate improvement, i.e., slight to moderate reduction in extent of nail, plus slight to moderate decrease in signs,
3=Unchanged, i.e., no change in extent of nail involvement or no change in signs,
4=Deteriorated, i.e., worsening of nail involvement or increase in signs.

Patients who completed treatment (week 5) with a global assessment of "unchanged" through "cleared" were scheduled for follow-up visits at weeks 12 and 24 to measure the various signs and symptoms.

Clinical success was defined by the sponsor as any global evaluation of "cleared" or "markedly improved." **Mycological success** was defined as the occurrence of negative KOH and culture. The Sponsor defined **Overall success** as simultaneous clinical and mycological success. For this review the Medical Officer defined **Complete Cure** as a global evaluation of "cleared" and mycological success. This variable is defined to be the primary response variable, supported by the signs and symptoms scores. Other response measures are considered primarily supportive.

In addition nail growth of a target nail, initially chosen at baseline or screening to be the "worst" fingernail (more severely affected than the others), was measured by two variables:

a. The **length of the unaffected nail part**: At baseline, week 5, and if appropriate weeks 12 and 24, a superficial cut with a scalpel or file was made on the normal nail plate, adjacent to

the border of the infection. "Measurements were taken(in mm) from this point to the proximal nail fold's edge."

b. The **percentage of nail affected**: Progression or regression of infection was monitored by reassessing the percentage of each nail infected at the end of treatment week 5, and when appropriate, at follow-up visits on weeks 12 and 24. For this analysis attention was restricted to the target nail.

Adverse events that occurred during the trial and follow-up period were noted by the investigator. The scheduled of operations in the experiment are summarized in the following table:

Table 1. Operations of Experiment

Visit-weeks	History & Con-sent	Physical Exam	Preg-nancy Test	KOH exam & culture	% nail involve-ment & length unaffect ed nail	Global Evalua-tion (relative to base-line)	Signs of Onychomy-cosis	Laboratory Safety tests
Screen -3				x				
Baseline -2	x	x	x	x[1]	x		x	x
Treatment Week								
0								
1								x
5		x	x	x	x	x	x	x
Follow-up Phase								
12 week-12				x	x	x	x	
24 week-24				x	x	x	x	

[1]Repeated at baseline only if more than three weeks had elapsed since screening for percentage of nail involvement and KOH, or more than six weeks for culture.

The primary analysis population was based on an intent-to-treat definition. In this study, all patients randomized to treatment had their infection confirmed by both KOH and culture. So there is no difference between the so-called intent-to-treat and "modified intent-to-treat" populations. Note that the protocol called for dropping treatment failures from the study at week 5, where "failure" was assessed by a deterioration in the physician's global evaluation. That suggests that one should depend primarily upon the "last-observation-carried-forward" (LOCF) analysis, where each subject's score on a response variable is their last measurement. Within each treatment group this should give a conservative estimate of efficacy.

In addition, the sponsor and to some extent this reviewer, performed a per protocol analysis on the set of compliant patients, defined as those who satisfied the intent-to-treat criteria, took 12-16 days of medication, had 16-26 days between dose pulses, and took the correct dosage. Some 22 patients in the Itraconazole group and 24 in the placebo group fit these criteria. However results from using this group are virtually identical to those from using the intent-to-treat group, and the intent-to-treat sample has the advantage of a larger sample size, and thus the distribution of test statistics would be closer to its asymptotic distribution. For

more information please see the statistical note on page 7.

ii. Patient Demographics:

The following table summarizes the demographics of the subjects.

Table 2. Demographics

		Sporanox	Placebo
Age (Yrs) (Mean ± Std. Dev.)		49±11	48±14
% Target Nail Involvement		76±22	70±27
Sex	M	34	27
	F	3	7
Race	White	27	22
	Hispanic	8	9
	Black	2	3
Total no. patients		37	34

There were no statistically significant differences among treatments with respect to age. Percent of target nail involvement, sex, races (white versus other). The first two descriptive variables were evaluated using ANOVA with center effects, the latter two using CMH (Cochrane-Matel-Haenzsel) tests stratified on center as well as loglinear models (treating center as random).

iii. Patient Disposition

Table 3. Patient Disposition

	Itraconazole	Placebo	Total
Enrolled	37	36	73
Intent-to-treat Analysis			
Data beyond baseline visit	36	35	71
Completed treatment phase	34	34	69
Entered follow-up phase	30	23	53
Completed follow-up phase	27	17	44

As noted above, a per protocol analysis on the set of compliant patients was also performed, but will not be covered here. Results again were virtually identical to those from the intent-to-treat population.

2. Efficacy Results:

Again the "intent-to-treat" subset of patients is used in these analyses. Further, recall that those patients' whose investigator global evaluations at week 5 were scored as "deteriorated" were completely dropped form the study, i.e., deleted from the analysis set. To be conservative, those patients should be carried forward, presumably as "failure." One way of implementing this criterion is to use a "last-observation-carried-forward" (LOCF) analysis. For each of the endpoints above, scores are provided in the following tables 4-8 for screening or baseline (if appropriate), week 5 (end of treatment), weeks 12 and 24, and the corresponding LOCF value.

The primary endpoint was defined by the Medical Officer as complete cure, tabulated in table 4 below (the sponsor defined overall success is included for comparison).:

Table 4. Complete Cure / Sponsor Defined Overall Success

		Visit Week 5		12		24		LOCF	
		Itracon-azole	placebo	Itracon-azole	placebo	Itracon-azole	placebo	Itracon-azole	placebo
Complete Cure:									
Cured	n	.	.	4	.	17	.	17	.
	%			14.8%		65.4%		47.2%	
Not cured	n	36	35	23	21	9	17	19	35
	%	100%	100%	85.2%	100%	34.6%	100%	52.8%	100%
Total	n	36	35	27	21	26	17	36	35
MH p-value		.*		0.068▮		0.001		0.001	
Sponsor Defined Overall Success:									
cured	n	3	.	9	.	19	.	20	.
not cured	n	33	35	18	21	7	17	16	35
Total		36	35	27	21	26	17	36	35
MH p-value		0.087▮		0.004▮		0.001		0.001	

*-Since there is only one response, the MH test is not defined.
▮-Mantel-Fleiss(1980) criterion indicates the sample is too small for asymptotic p-value to be accurate.

As noted above, complete cure is defined as an investigator global evaluation of "cleared," with or without residual nail malformation, and a negative KOH and culture. This variable is defined to be the primary response variable, supported by the signs and symptoms scores. The sponsor defined overall success is simultaneous clinical and mycological success with an investigator global evaluation of "markedly improved" or "cleared." From the LOCF analysis it seems that Itraconazole (Sporanox) with pulse dosing is associated with a roughly 50% complete cure rate, while placebo has a 0% cure rate. These differences are statistically highly significant. Note that two or three subjects, all protocol violators, did not have valid responses in the data sets for some of these measures or factors. Thus, they are dropped from the analyses. Deletion of these subjects has no impact upon conclusions.

One problem with the usual implementation of Mantel-Haenszel test, as used above to give the p-values, is that the p-values are based on asymptotic approximations. The Mantel-Fleiss criterion (1980) essentially computes minimum expected cell size requirements for the one degree of freedom chi-square approximation. The p-values in table 4 above are flagged as to whether the table layout meets the criterion. When it does not, the exact p-values in the table are suspect. Note that the LOCF analyses, upon which we are placing primary reliance, are associated with layouts that easily exceed the criterion. This seems to generalize to the Cochrane-Mantel-Haenszel (CMH) tests used for the other response variables in tables 5 and 6 below.

The physicians' global evaluation of response to treatment is displayed in the table below:

Table 5. Physicians' Global Evaluation

		Visit Week 5		12		24		LOCF	
GLOBAL EVALUATION		itracon-azole	placebo	itracon-azole	placebo	itracon-azole	placebo	itracon-azole	placebo
Cleared	n	.	.	5	.	21	.	21	.
	%			18.5%		77.8%		58.3%	
Markedly improved	n	6	.	17	.	5	.	6	.
	%	16.7%		63.0%		18.5%		16.7%	
Slightly/ moderately improved	n	22	12	5	7	1	5	4	7
	%	61.1%	34.3%	18.5%	33.3%	3.7%	29.4%	11.1%	20.0%
Unchanged	n	4	12	.	9	.	12	1	13
	%	11.1%	34.3%		42.9%		70.6%	2.8%	37.1%
Deteriorated	n	4	11	.	5	.	.	4	15
	%	11.1%	31.4%		23.8%			11.1%	42.9%
Total	n	36	35	27	21	27	17	36	35
CMH p-value		0.001		0.001		0.001		0.001	

Again, by inspecting the Cochrane-Mantel-Haenszel mean comparison p-values in table 5. above we see that the pulse dose of Sporanox (itraconazole) shows a statistically significantly better score for global response to treatment at all weeks by the fifth week.

Statistical Note:

The p-values above are computed from asymptotic approximations that are questionable in at least one case above. The CMH tests of interest are based on sums, over investigators, of scores computed by summing over levels within each investigator. So Central Limit Theorems tend to apply, and asymptotic approximations should tend to be appropriate. This reviewer is not aware of any published criterion like the Mantel-Fleiss criterion above to indicate if the Cochrane-Mantel-Haenszel tests are appropriate, although this reviewer is working to develop such a criterion. However, in this case these observations are basically moot, since in each of these tests the results are so extreme that the true p-values are of little interest (i.e., whether the "true" p-value is .0001 or .0000001 is of little interest).

For signs and symptoms, i.e., onycholysis, hyperkeratosis, and discoloration, we have the following table 6:

Table 6. Signs and Symptoms (Onycholysis, Hyperkeratosis, and Discoloration)

Week:		Baseline		5		12		24		LOCF	
Onycholysis		itracon-azole	placebo	itracon-azole	placebo	itracon-azole	placebo	itracon-azole	placebo	itracon-azole	placebo
0= none	n	3	5	4	5	12	5	24	4	26	6
	%	8.1%	13.9%	11.1%	14.3%	44.4%	23.8%	88.9%	23.5%	72.2%	16.7%
1= ≤50%	n	9	15	21	14	15	7	3	7	6	14
	%	24.3%	41.7%	58.3%	40.0%	55.6%	33.3%	11.1%	41.2%	16.7%	38.9%
2= ≤75%, >50%	n	16	9	8	11	.	6	.	4	2	11
	%	43.2%	25.0%	22.2%	31.4%		28.6%		23.5%	5.6%	30.6%
3= >75%	n	9	7	3	5	.	3	.	2	2	5
	%	24.3%	19.4%	8.3%	14.3%		14.3%		11.8%	5.6%	13.9%
Total		37	36	36	35	27	21	27	17	36	36
CMH p-value		0.087		0.334		0.001		0.001		0.001	

Week:		Baseline		5		12		24		LOCF	
Hyperkeratosis		itracon-azole	placebo	itracon-azole	placebo	itracon-azole	placebo	itracon-azole	placebo	itracon-azole	placebo
0=none	n	1	1	3	1	9	2	22	.	24	.
	%	2.7%	2.8%	8.3%	2.9%	33.3%	9.5%	81.5%		66.7%	
1= ≤50%	n	12	17	20	18	18	11	5	9	7	17
	%	32.4%	47.2%	55.6%	51.4%	66.7%	52.4%	18.5%	52.9%	19.4%	47.2%
2= ≤75%, >50%	n	12	8	7	10	.	4	.	7	2	13
	%	32.4%	22.2%	19.4%	28.6%		19.0%		41.2%	5.6%	36.1%
3= >75%	n	12	10	6	6	.	4	.	1	3	6
	%	32.4%	27.8%	16.7%	17.1%		19.0%		5.9%	8.3%	16.7%
Total		37	36	36	35	27	21	27	17	36	36
CMH p-value		0.291		0.422		0.001		0.001		0.001	

Week:		Baseline		5		12		24		LOCF	
Discoloration		itracon-azole	placebo	itracon-azole	placebo	itracon-azole	placebo	itracon-azole	placebo	itracon-azole	placebo
0= none	n	1	2	2	2	7	2	23	1	25	2
	%	2.7%	5.6%	5.6%	5.7%	25.9%	9.5%	85.2%	5.9%	69.4%	5.6%
1= ≤50%	n	5	11	17	10	20	4	4	4	5	9
	%	13.5%	30.6%	47.2%	28.6%	74.1%	19.0%	14.8%	23.5%	13.9%	25.0%
2= ≤75%, >50%	n	16	8	11	12	.	8	.	7	3	10
	%	43.2%	22.2%	30.6%	34.3%		38.1%		41.2%	8.3%	27.8%
3= >75%	n	15	15	6	11	.	7	.	5	3	15
	%	40.5%	41.7%	16.7%	31.4%		33.3%		29.4%	8.3%	41.7%
Total		37	36	36	35	27	21	27	17	36	36
CMH p-value		0.266		0.061		0.001		0.001		0.001	

Note that at baseline, there is no statistically significant difference between treatment groups for each of the three signs: onycholysis, hyperkeratosis, and discoloration of the nail. In fact, for each measure the placebo group at baseline would have a smaller (i.e., better) mean score than the Sporanox treatment group. By week 12, the scores for each sign are statistically significantly better in the itraconazole group than in the placebo group. The same conclusions hold for the LOCF population.

For the mean scores of the unaffected nail length in mm and the percent of nail we get the following means across treatments:

Table 7. Length of the Unaffected Nail Part (in mm) For Target Nail

	Visit week									
	Screening/ Baseline		5		12		24		LOCF	
Target Fingernail	itracon- azole	placebo	itracon- azole	placebo	itracon- azole	placebo	itracon- azole	placebo	itracon- azole	placebo
n	37	34	36	33	27	20	26	17	35	34
mean	2.0	1.9	5.0	3.4	8.3	2.7	12.0	2.9	10.6	3.4
std dev	2.0	2.1	3.3	2.2	2.2	1.9	3.2	2.0	4.2	2.3
ANOVA P-value‖	0.7823		0.0032		0.0001		0.0001		0.0001	

‖From an type III sums of squares of an Analysis of Variance using treatment, investigator, and interaction as factors.

Again, at baseline note that there is no statistically significant difference over treatment groups for the length of the unaffected nail in the target nail as well as the proportion of unaffected nail part (below). However, by the fifth week, i.e., the end of treatment both measures show statistically significant differences, with the Sporanox group having the better score. This difference, and the associated statistical significance become greater with time.

Statistical Note:

The p-values above are computed from an analysis of variance at each time point. The original response scores were used, despite the fact they are not close to normal. Transformed values were also used and gave similar results.

Table 8. Percent of Unaffected Nail Part of Target Nail

% Affected in Target Nail	Visit week											
	Screening		Baseline		5		12		24		LOCF	
Target Fingernail	itra-cona-zole	plac-ebo	itra-cona-zole	plac-ebo	itra-cona-zole	plac-ebo	itra-cona-zole	plac-ebo	itra-cona-zole	plac-ebo	itra-cona-zole	plac-ebo
n	37	34	12	12	36	33	27	20	27	17	36	33
mean	76.3	70.2	77.9	73.8	58.1	69.8	17.6	71.8	2.6	69.7	17.8	69.3
std dev	21.2	26.2	18.9	17.1	24.6	23.6	13.1	21.7	5.8	24.9	30.7	24.8
ANOVA p-value‖	0.4502		0.8380		0.0032		0.0001		0.0001		0.0001	

‖From an type III sums of squares of an Analysis of Variance using treatment, investigator, and interaction as factors.

So, at the end of the study, the mean percent of affected target nail can be conservatively estimated at roughly 18% in the Sporanox group, versus 70% in the placebo group.

Finally, note that by week 12, all response measures show a statistically significant superiority of itraconazole (Sporanox) over placebo. Again, however, this result is conditional upon the subject's condition not deteriorating, at least as measured by the physician's global evaluation, since such subjects are dropped from the study. Thus, for each treatment, the individual LOCF groups should provide conservative measures of efficacy. But even for the LOCF samples, Sporanox is statistically significantly better than placebo ($p \leq 0.001$ or $p \leq 0.0001$) for each of the response measures in table 8 above.

3. Subset Analyses

To investigate the possible differential effects among demographic subsets, subgroups of patients were formed by gender, race (Caucasian versus Other), and age (split at the median age 48). Note that the small sample sizes associated with the subgroups do suggest even more problems with the asymptotic approximation to the distribution of the Mantel-Haenszel test statistic restricted to the subsets. However, as before the extreme nature of the outcomes do mitigate against these problems. For all subgroups, Sporanox is statistically significantly better than placebo. Given the small sample sizes, results for males and females are similar, as are results for the two race groups.

Table 9. Complete Cure broken down by Gender and Race

Complete Cure Subgroup		5		12		24		LOCF	
Sex		itracon-azole	placebo	itracon-azole	placebo	itracon-azole	placebo	itracon-azole	placebo
Female cured	n	.	.	.	.	3	.	3	.
not cured	n	3	7	3	5	.	4	.	7
Total	n	3	7	3	5	3	4	3	7
CMH p-value		NA*		NA*		0.014▮		0.003▮	
Male cured	n	.	.	4	.	14	.	14	.
	%			16.7%		60.9%		42.4%	
not cured	n	33	28	20	16	9	13	19	28
	%			83.3%	100%	39.1%	100%	57.6%	100%
Total	n	33	28	24	16	23	13	33	28
CMH p-value		NA*		0.089▮		0.001		0.001	
ANOVA p-value		NA		0.2225		0.2112		0.0787	
Race									
Caucasian cured	n	.	.	3	.	14	.	14	.
	%			14.3%		70.0%		53.8%	
not cured	n	26	24	18	15	6	12	12	24
	%			85.7%	100%	30.0%	100%	46.2%	100%
Total	n	26	24	21	15	20	12	26	24
CMH p-value		NA*		0.132▮		0.001		0.001	
Other cured	n	.	.	1	.	3	.	3	.
	%			16.7%		50.0%		30.0%	
not cured	n	10	11	5	6	3	5	7	11
	%			83.3%	100%	50.0%	100%	70.0%	100%
Total	n	10	11	6	6	6	5	10	11
CMH p-value		NA*		0.317▮		0.077▮		0.046▮	
ANOVA p-value		NA*		0.6066		0.7282		0.9487	

*-Since there is only one level of response, the CMH (or ANOVA) test is not defined.
▮-Mantel-Fleiss(1977) criterion indicates the sample is too small for asymptotic p-value to be accurate.
▮-From an F-ratio of testing interaction of race or gender with treatment in an Analysis of Variance model using treatment, investigator, and interaction, with race or gender, and the respective interaction with treatment. This is only a rough analysis due to the binary nature of the response.

Note the observed proportions for each gender or level of race are quite similar. These observations were confirmed by an analysis of variance, treating the binary response as a continuous variable, i.e., using an ANOVA there were no statistically significant differences across levels of gender or levels of race.

Statistical Note:

For the situations in table 9 above first glance it might appear that a logistic or loglinear model would be a more appropriate method of analysis for comparing strata. However, given the large number of levels of factors, the relatively small number of observations, and the extreme differential effect of treatment, there is certainly "separation of factors," i.e., maximum likelihood estimates will not exist. For logistic models weighted least squares techniques may not even converge to the correct parameters. So one is left with either using unweighted least squares, e.g., ANOVA like techniques or perhaps to use exact logistic regression. Exact logistic regression is available with LogXact, a new program soon to be installed, but it was felt that the exact rather than the rough approximate p-values were not of sufficient interest to justify the extra effort.

These results for gender and race generalize to the other response measures as well. That is, at least for the LOCF analysis, using an ANOVA model, there are no statistically significant differences between gender and race for any of the other response variables.

However, there is some evidence of a differential effect of age. While Sporanox is statistically significantly better than placebo in both age groups, there is some evidence that it may be more effective in younger patients than in older patients. Note the differential cure rates in the age groups below. Again, in the following table 10, due to the small size of this experiment, age was split into only two groups, at the sample median age, 48.

Table 10. Complete Cure Broken Down by Age Group

Complete Cure Subgroup		5		12		24		LOCF	
Age Group		itracon-azole	placebo	itracon-azole	placebo	itracon-azole	placebo	itracon-azole	placebo
24-48 cured	n	.	.	4	.	11	.	11	.
	%			30.8%		84.6%		61.1%	
not cured	n	18	20	9	10	2	8	7	20
	%			69.2	100%	15.4%	100%	38.9%	100%
Total	n	18	20	13	10	13	8	18	20
CMH p-value		NA*		0.059‖		0.001‖		0.001	
49-70 cured	n	.	.	.	.	6	.	6	.
	%					46.2%		33.3%	
not cured	n	18	15	14	11	7	9	12	15
	%					53.8%	100%	66.7	100%
Total	n	18	15	14	11	13	9	18	15
CMH p-value		NA*		NA*		0.020‖		0.018‖	
ANOVA p-value‖		NA*		0.4873		0.2986		0.0409	

*-Since there is only one level of response, the CMH (or ANOVA) test is not defined.
‖-Mantel-Fleiss(1977) criterion indicates the sample is too small for asymptotic p-value to be accurate.
‖-From an F-ratio of testing homogeneity of age over treatment in an Analysis of Variance model using treatment, investigator, and interaction, with age as a covariate, and age by treatment as the homogeneity term. This is only a rough analysis due to the binary nature of the response.

The results for each of the tables above (from the presumably conservative LOCF subgroup) all seem to suggest that for each demographic subgroup, itraconazole is statistically significantly better than placebo, with complete cure rates at least 30% or more in the Sporanox

groups, versus 0% in the placebo group. Note that table 10 above suggests that there is some differential effect due to age. A test of a difference in the effect of age on complete cure rate is roughly provided by the ANOVA test above. Again this is provided by a test of homogeneity of the age covariate across levels of treatment, in a model that includes these factors, as well as treatment, investigator and interaction ($p \leq 0.0409$).

When other response measures, either noted above or below, were broken down by gender or race, they also often showed statistically significant differences between the Sporanox treatment group and placebo in each subgroup. Again, there are often problems with the asymptotic approximations used to derive p-values, which in turn are largely mitigated by the extreme nature of the results. In the corresponding ANOVA, they almost never showed an interaction of treatment and gender or race.

Table 11. Physician's Global Evaluation of Efficacy Broken Down by Age Group

			Visit Week 5		12		24		LOCF	
Age Group	GLOBAL EVALUATION		itracon-azole	placebo	itracon-azole	placebo	itracon-azole	placebo	itracon-azole	placebo
24-48	Cleared	n	.	.	5	.	13	.	13	.
		%			38.5%		92.9%		72.2%	
	Markedly improved	n	6	.	6	.	1	.	1	.
		%	33.3%		46.2%		7.1%		5.6%	
	Slightly/ moderately improved	n	7	7	2	3	.	3	2	5
		%	38.9%	35.0%	15.4%	30.0%		37.5%	11.1%	25.0%
	Unchanged	n	3	7	.	4	.	5	.	6
		%	16.7%	35.0%		40.0%		62.5%		30.0%
	Deteriorated	n	2	6	.	3	.	.	2	9
		%	11.1%	30.0%		30.0%			11.1%	45.0%
49-70	Cleared	n	.	.	.	.	8	.	8	.
		%					61.5%		44.4%	
	Markedly Improved	n	.	.	11	.	4	.	5	.
		%			78.6%		30.8%		27.8%	
	Slightly / moderately Improved	n	15	5	3	4	1	2	2	2
		%	83.3%	33.3%	21.4%	36.4%	7.7%	22.2%	11.1%	13.3%
	Unchanged	n	1	5	.	5	.	7	1	7
		%	5.6%	33.3%		45.5%		77.8%	5.6%	46.7%
	Deteriorated	n	2	5	.	2	.	.	2	6
		%	11.1%	33.3%		18.2%			11.1%	40.0%
	ANOVA p-value‖		0.0044		0.8978		0.0242		0.0067	

‖From an F-ratio of testing homogeneity of age over treatment in an Analysis of Variance model using treatment, investigator, and interaction, with age as a covariate, and age by treatment as the homogeneity term.

The results in table 11 above confirm the overall efficacy of Sporanox (itraconazole) for both age groups, (for example, though p-values are not given above, both age groups show statistically significant differences between treatment groups). However, the statistically significant slope terms do suggest a differential effect of age, namely that, at least as measured by statistical significance, while sporanox is effective at all ages, that efficacy is inversely proportional to age.

To see if this effect remains in the other response measures, consider the following tables 12 and 13, displaying the signs and symptoms scores:

Table 12. Onycholysis and Hyperkeratosis Broken Down by Age Group

			Week of Visit									
			Baseline		5		12		24		LOCF	
Age Group	Onycholysis		itracon-azole	placebo	itracon-azole	placebo	itracon-azole	placebo	itracon-azole	placebo	itracon-azole	placebo
24-48	0	n	3	2	4	2	8	2	14	1	15	3
		%	16.7%	9.5%	22.2%	10.0%	61.5%	20.0%	100%	12.5%	83.3%	14.3%
	1	n	7	7	11	8	5	1	.	3	3	7
		%	38.9%	33.3%	61.1%	40.0%	38.5%	10.0%		37.5%	16.7%	33.3%
	2	n	2	6	2	6	.	4	.	2	.	7
		%	11.1%	28.6%	11.1%	30.0%		40.0%		25.0%		33.3%
	3	n	6	6	1	4	.	3	.	2	.	4
		%	33.3%	28.6%	5.6%	20.0%		30.0%		25.0%		19.0%
49-70	0	n	.	3	.	3	4	3	10	3	11	3
		%		20.0%		20.0%	28.6%	27.3%	76.9%	33.3%	61.1%	20.0%
	1	n	2	8	10	6	10	6	3	4	3	7
		%	10.5%	53.3%	55.6%	40.0%	71.4%	54.5%	23.1%	44.4%	16.7%	46.7%
	2	n	14	3	6	5	.	2	.	2	2	4
		%	73.7%	20.0%	33.3%	33.3%		18.2%		22.2%	11.1%	26.7%
	3	n	3	1	2	1	.	.	.	.	2	1
		%	15.8%	6.7%	11.1%	6.7%					11.1%	6.7%
ANOVA p-value‖			0.3709		0.1336		0.1335		0.3903		0.1535	

			Week of Visit									
			Baseline		5		12		24		LOCF	
Age Group	Hyperkeratosis		itracon-azole	placebo	itracon-azole	placebo	itracon-azole	placebo	itracon-azole	placebo	itracon-azole	placebo
24-48	0	n	1	1	2	.	7	1	13	.	14	.
		%	5.6%	4.8%	11.1%		53.8%	10.0%	92.9%		77.8%	
	1	n	7	9	9	11	6	4	1	6	3	11
		%	38.9%	42.9%	50.0%	55.0%	46.2%	40.0%	7.1%	75.0%	16.7%	52.4%
	2	n	3	4	5	4	.	2	.	1	1	5
		%	16.7%	19.0%	27.8%	20.0%		20.0%		12.5%	5.6%	23.8%
	3	n	7	7	2	5	.	3	.	1	.	5
		%	38.9%	33.3%	11.1%	25.0%		30.0%		12.5%		23.8%
49-70	0	n	.	.	1	1	2	1	9	.	10	.
		%			5.6%	6.7%	14.3%	9.1%	69.2%		55.6%	
	1	n	5	8	11	7	12	7	4	3	4	6
		%	26.3%	53.3%	61.1%	46.7%	85.7%	63.6%	30.8%	33.3%	22.2%	40.0%
	2	n	9	4	2	6	.	2	.	6	1	8
		%	47.4%	26.7%	11.1%	40.0		18.2%		66.7%	5.6%	53.3%
	3	n	5	3	4	1	.	1	.	.	3	1
		%	26.3%	20.0%	22.2%	6.7%		9.1%			16.7%	6.7%
ANOVA p-value‖			0.2268		0.5761		0.2063		0.4084		0.1249	

‖From an F-ratio of testing homogeneity of age over treatment in an Analysis of Variance model using treatment, investigator, and interaction, with age as a covariate, and age by treatment as the homogeneity term.

Table 13. Discoloration of the Nail Broken Down by Age Group

Age Group	Discoloration		Baseline itracon-azole	Baseline placebo	Week of Visit 5 itracon-azole	5 placebo	12 itracon-azole	12 placebo	24 itracon-azole	24 placebo	LOCF itracon-azole	LOCF placebo
24-48	0	n	1	1	2	1	6	1	14	.	15	1
		%	5.6%	4.8%	11.1%	5.0%	46.2%	10.0%	100%		83.3%	4.8%
	1	n	3	7	8	6	7	.	.	1	1	5
		%	16.7%	33.3%	44.4%	30.0%	53.8%			12.5%	5.6%	23.8%
	2	n	5	4	5	6	.	4	.	4	2	6
		%	27.8%	19.0%	27.8%	30.0%		40.0%		50.0%	11.1%	28.6%
	3	n	9	9	3	7	.	5	.	3	.	9
		%	50.0%	42.9%	16.7%	35.0%		50.0%		37.5%		42.9%
49-70	0	n	.	1	.	1	1	1	9	1	10	1
		%		6.7%		6.7%	7.1%	9.1%	69.2%	11.1%	55.6%	6.7%
	1	n	2	4	9	4	13	4	4	3	4	4
		%	10.5%	26.7%	50.0%	26.7%	92.9%	36.4%	30.8%	33.3%	22.2%	26.7%
	2	n	11	4	6	6	.	4	.	3	1	4
		%	57.9%	26.7%	33.3%	40.0%		36.4%		33.3%	5.6%	26.7%
	3	n	6	6	3	4	.	2	.	2	3	6
		%	31.6%	40.0%	16.7%	26.7%		18.2%		22.2%	16.7%	40.0%
ANOVA p-value‖			0.2720		0.6697		0.0852		0.1423		0.1340	

‖From an F-ratio of testing homogeneity of age over treatment in an Analysis of Variance model using treatment, investigator, and interaction, with age as a covariate, and age by treatment as the homogeneity term.

In the preceding tables 12 and 13, particularly using the LOCF samples, the differences across treatment group are statistically significant separately within each age group. However, while all three variables show mean differences across age groups, the ANCOVA tests suggests that those differences are not statistically significantly different across age ($p \leq 0.1535$, 0.1249, & 0.1340 respectively).

Table 14. Length of the Unaffected Nail Part (in mm) For Target Nail

Age Group	Length Target Fingernail		Visit week Screening/ Baseline itracon-azole	Screening/ Baseline placebo	5 itracon-azole	5 placebo	12 itracon-azole	12 placebo	24 itracon-azole	24 placebo	LOCF itracon-azole	LOCF placebo
24-48	n		18	19	18	18	13	14	13	13	17	18
	mean		2.3	1.5	6.2	3.4	8.8	2.0	12.3	2.3	11.3	3.2
	std dev		2.6	1.8	3.9	2.5	2.4	1.5	2.4	1.5	3.2	2.4
49-70	n		19	15	18	15	14	11	13	9	18	15
	mean		1.8	2.4	3.7	3.4	7.9	3.3	11.8	3.4	9.9	3.6
	std dev		1.2	2.3	2.0	1.9	2.0	2.1	4.0	2.4	5.0	2.1
ANOVA P-value‖			0.4335		0.0259		0.1614		0.0542		0.0063	

‖From an F-ratio of testing homogeneity of age over treatment in an Analysis of Variance model using treatment, investigator, and interaction, with age as a covered, and age by treatment as the homogeneity term.

Note that the differential effect of age still seems to be present ($p \leq 0.0063$).

Table 15. Percent of Affected Nail Part

		Visit week									
		Screening/ Baseline		5		12		24		LOCF	
Age Group	Percent Affected Fingernail	itracon-azole	placebo	itracon-azole	placebo	itracon-azole	placebo	itracon-azole	placebo	itracon-azole	placebo
24-48	n	18	19	18	18	13	14	14	13	18	18
	mean	75.8	70.7	52.6	70.0	14.6	70.6	0.7	70.0	13.1	69.3
	std dev	25.7	26.7	30.3	24.3	15.5	16.0	2.7	22.2	27.2	25.5
49-70	n	19	15	18	15	14	11	13	9	18	15
	mean	76.7	69.7	63.6	68.9	20.4	64.8	4.6	69.4	22.5	69.3
	std dev	16.6	26.5	16.3	23.4	10.3	23.9	7.5	28.4	33.9	24.9
ANOVA P-value‖		0.9215		0.0549		0.0663		0.0649		0.0881	

‖From an F-ratio of testing homogeneity of age over treatment in an Analysis of Variance model using treatment, investigator, and interaction, with age as a covered, and age by treatment as the homogeneity term.

As above, while the differential effect of age still seems to be present, it is not quite statistically significant, at least with this model.

Thus, overall, within each age group, for each response measure the difference across treatment means is statistically significant. Descriptively, there appears to be a generally quantitative interaction (i.e., the response variable increases or decreases with age similarly in both treatment groups, but at different rates). However this effect is statistically significant only for a complete cure ($p \leq 0.0409$), physicians' global evaluation ($p \leq 0.0067$), and the length of the unaffected nail part ($p \leq 0.0063$). However, studies are not typically designed to analyze population subsets, so when used for subset analysis, the study is essentially observational. That makes it more difficult to claim that an observed effect is not an artifact, and with a study this small it is quite conceivable that any such effect is purely artifactual. Still, it might be interesting. Again, even if there is a differential effect of age, note that it does not affect claims of overall efficacy.

4. Safety Data

Adverse Events

Table 16 below tabulates adverse events from the sponsor supplied data set. Note that none of them (including pruritus and nausea) would show statistically significant differences between the sporanox and placebo treatment groups.

Table 16. Frequency of Adverse Events

	# individuals		# events	
AE PREFERRED TERM	itracon-azole	placebo	itracon-azole	placebo
abdominal pain	1	1	1	2
anxiety	1	.	1	.
back pain	1	1	1	1
bursitis	1	.	1	.
constipation	1	1	1	1
depression	1	.	1	.
diarrhoea	.	2	.	2
dyspepsia	1	2	1	2
faeces discoloured	.	2	.	2
fatigue	1	.	2	.
gamma-gt increased	.	1	.	1
gingivitis	1	.	1	.
headache	3	3	5	4
hypertriglyceridaemia	1	.	1	.
infection	.	1	.	1
injury	1	2	1	2
malaise	1	.	1	.
migraine	.	1	.	1
nausea	2	.	3	.
nervousness	.	1	.	1
pain	1	1	1	1
pruritus	2	.	2	.
rash	1	.	1	.
rash erythematous	.	1	.	1
rhinitis	2	1	2	1
sinusitis	1	1	2	1
skin exfoliation	.	1	.	1
stomatitis ulcerative	1	.	1	.
taste perversion	.	1	.	1
tendinitis	.	1	.	1
Overall	25	25	30	27

Three patients discontinued early for reasons reported to be related to safety: "moderate rash and pruritus in one itraconazole patient, elevated triglyceride in one itraconazole patient, and elevated GET in one placebo patient.

Of the studies provided by the sponsor apparently only the Finnish study, ITR-FIN-1, had the pulse therapy, however, here primarily applied to toenails. In this study the profile of adverse events is similar to that given above, with apparently no statistically significant evidence of problems.

Reference:

1. Mantel, N., and Fleiss, J.: Minimum Expected Cell Size Requirements for the Mantel-Haenszel One-degree-of-freedom Chi-square Test and a Related Rapid Procedure. *American Journal of Epidemiology,* 112 (1980) 129-134.

2. Roseeuw, D., and De Doncker, P.: New Approaches to the Treatment of Onychomycosis. *Journal of the American Academy of Dermatology,* 29 (1993) S45-S50.

3. Willemsen, M, De Doncker, P., Willems, J., *et al.*: Posttreatment Itraconazole Levels in the Nail. *Journal of the American Academy of Dermatology,* 26 (1992) 731-735.

Conclusions (Which may be conveyed to the Sponsor):

1. The sponsor reports that itraconazole diffuses rapidly into the nail via the nail bed, and from there to the nail matrix, and then claims that: "The penetration route into the nail and persistent concentrations of itraconazole provide a rationale for using intermittent dosing to achieve efficacy comparable to continuous dosing. ... Intermittent administration of itraconazole, 200 mg twice daily for seven days the first week of each month for two consecutive months, offers a lower dose than continuous dosing with 200 mg daily for three to four months." The sponsor suggests that such "pulse" dosing offers "an improved safety profile while maintaining the efficacy of treatment."

2. Previously, in NDA 20-510, the agency requested that the Sporanox INDICATIONS AND USAGE insert contains the provision that sporanox is appropriate for "Onychomycosis due to dermatophytes (tinea unguium) of the toenail with or without fingernail involvement." This supplemental NDA is intended to support the change of this provision to "Onychomycosis of the toenail or fingernail due to dermatophytes (tinea unguium)." In addition the sponsor wishes to change the label to reflect the pulse dosing regimen, as described above, for fingernail involvement.

3. The primary support for the sponsor's claims is provided by a randomized, double-blind, placebo-controlled, multicenter trial, labeled ITR-USA-71, for the treatment of onychomycosis of the fingernail. The sponsor included data in a number of poorly documented datasets, from other studies outside of the U.S. These studies were almost completely for onychomycosis of the toenails, apparently under various dosing regimens. The Medical Officer expressed the opinion that these were of limited relevance for the current claim and hence were ignored.

4. The sponsor provided a number of efficacy measures. Among these were mycological success, defined as a negative KOH and culture, and a physician's global evaluation of treatment, ranked on a five point scale from "cleared of all signs" to "deteriorated," and signs and symptoms scores: onycholysis, hyperkeratosis, and discoloration were all ranked on four point scale: 0. none, 1. $\leq$50% of nail, 2. $>$50%, $\leq$75%of nail, 3. $>$75% of nail, for each condition. Complete cure was defined by the medical officer as a subject with a mycological cure whose physician's global evaluation was "cleared of all signs." This was chosen as the primary endpoint by the medical officer, to be supported by the signs and symptoms. In addition nail growth was measured by the length of the unaffected nail part and the percentage of nail affected were estimated at each visit.

5. One statistical problem with the design is that patients whose end of treatment, week 5, physician's global evaluation was "deteriorated" were dropped from the study. Thus, the follow-up values showing efficacy are primarily conditional upon dropping those subjects who were treatment failures. Hence it makes sense to use a "Last-Observation-Carried-Forward" (LOCF) subset for the primary analysis. At least within each treatment the LOCF samples should be conservative. For the LOCF samples, mean

differences for each of the response variables complete cure, signs and symptoms, physician's global evaluation, length of unaffected nail part and percentage of nail affected were all highly statistically significant (from tables 4-6, $p \leq 0.001$, or from tables 7 or 8, $p \leq .0001$). There is some evidence of a small quantitative interaction of treatment with age, with somewhat greater efficacy among younger patients. But this may be an artifact of the study, particularly since the study has a relatively small study sample size.

6. Thus, it is this reviewer's opinion that the sponsor has demonstrated that Sporanox® (Itraconazole) 100mg tablets using the "pulse" dosing of 200mg daily for one week at the first week for two months is statistically significantly more effective than placebo for the treatment of onychomycosis of the fingernails. While the sample is too small to observe a detailed adverse events profile, it does appear that there are no statistically significant differences between placebo and in any Sporanox in the occurrence of any particular adverse event.

Steve Thomson 10/31/96
Steve Thomson
Mathematical Statistician, Biometrics IV

10/31/96
concur: R. Srinivasan, Ph.D.
Acting Team Leader, Biometrics IV

cc:

Archival NDA: 20-694
HFD-540/Division File
HFD-540/Dr. Wilkin
HFD-540/Dr. Ko
HFD-540/Mr. Cross
HFD-725/Dr. Harkins
HFD-725/Dr. Srinivasan
HFD-725/Mr. Thomson
HFD-340/Dr. Lepay
This review has 20 pages.
Chron.

\Thomson\WP Text\x 7-2078\October 17, 1996\c:\wpfiles\nda20694.wp

Bio

NDA 20-694	**SUBMISSION DATE:** 2/29/96
PRODUCT: Itraconazole (caps)	
BRAND NAME: SPORANOX®	**REVIEWER:** Dan Wang, Ph.D.
SPONSOR: Janssen at Washington Crossing 1125 Trenton-Harbourton Road P.O. Box 200 Titusville, New Jersey 08560-0200	**TYPE OF SUBMISSION:** Amendment

The NDA 20-694 is submitted to response to the Agency's request of providing review copies for a subject NDA, originally submitted on Dec. 13, 1995 which is a supplemental NDA for NDA 20-083. In this supplemental NDA, reference is made to the Agency's approvable letter of July 25, 1995, for NDA 20-510, in which the sponsor was requested to evaluate the "dosage regimen that would most effectively be used to treat onychomycosis of the fingernail without concomitant onychomycosis of the toenail".

The sponsor provided data for changing the Sporanox INDICATIONS AND USAGE Section of the package insert from '

The PK study (N80552), which is used as supportive reference, was reviewed in NDA 20-510 submission.

Associated with the above INDICATION AND USAGE labeling change, the DOSAGE AND ADMINISTRATION Section is also changed from

. The pharmacokinetic profile of the new dosing regimen, 200 mg bid, has been already evaluated at the steady-state level in NDA 20-083 (Study 1001, submission date: 10/10/91). The study was reviewed by Dr. Ilisa B.G. Bernstein and found acceptable.

Please refer to the Drug File for above two PK reviews. No PK study needs to be reviewed in this submission.

6/6/96

Dan Wang
Division of Pharmaceutical Evaluation III

FT initialed by D. Bashaw, Pharm.D. 6/11/96

cc:
NDA 20-694 (Original)
HFD-540(Clinical, Cross)
HFD-870(Clarence Bott, Drug, Chron Files)
HFD-880(N. Fleischer, Bashaw, Wang)
HFD-860(Malinowski)
HFD-870(Mei-Ling Chen)
HFD-205(FOI)
HFD-344(Viswanathan)

Pharm/Tox

JUL 25 1996

CIES
540

REVIEW AND EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA
Division of Dermatologic and Dental Drug Products, HFD-540

NDA 20-694 (Original Submission 02-29-1996)

DRUG: Sporanox^{R} (itraconazole) capsules

SPONSOR: Jenssen Research Foundation
1125 Trenton-Harbourton Road
Titusville, NJ 08560
Cynthia Chianese: 609-730-3069

Number of Volumes: One (1)
Date CDER Received: 02-29-1996
Date Assigned: 03-08-1996
Date Review Started: 07-18-1996
Date Review Completed: 07-19-1996

Dosage and Route of Administration: Oral capsules, 100 mg
Category: Antifungal
Indication: Treatment of onychomycosis

Related Submissions:

INDs:

NDAs: 20-083 (itraconazole capsules)
20-510 (itraconazole capsules)

Background: This supplemental NDA was submitted in response to agency's request that the "dosage regimen that would most effectively be used to treat onychomycosis of the fingernail without concomitant onychomycosis of the toenail" should be established. Therefore, this submission is restricted to the relevant clinical issues. All the pharmacology / toxicology studies were reviewed under the above mentioned INDs and NDAs. The nonclinical portion of the label was approved under NDA 20-510 (ref: Dr. Chambers).

Regulatory Conclusion: I have no objection to the approval of this new drug application.

Kumar D. Mainigi, Ph.D., M.P.H., DABT
Toxicologist

CC: Original NDA 20-694
HFD-82
HFD-540
MO / KO
Pharm / Mainigi
Chem / Higgins
CSO / Cross
Pharm / Jacobs
Micro / King, HFD-520; Stinavage, HFD-160
Biopharm / Wang, HFD-880

Concurrence:
A.Jacobs,TL, HFD-540 7/19/96
J.Wilkin, Dir, HFD-540 7/25/96

Chem

NOV 26 1996

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 20-694 **CHEM.REVIEW #:** 01 **REVIEW DATE:** 25-NOV-96

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	13-DEC-95	14-DEC-95	12-MAR-96
AMENDMENT/BZ	29-FEB-96	01-MAR-96	12-MAR-96
AMENDMENT/BC	20-MAY-96	21-MAY-96	28-MAY-96
AMENDMENT/BC	27-AUG-96	28-AUG-96	11-SEPT-96
AMENDMENT/BC	10-SEPT-96	11-SEPT-96	18-SEPT-96
AMENDMENT/BC	28-OCT-96	31-OCT-96	04-NOV-96
AMENDMENT/BC	13-NOV-96	14-NOV-96	14-NOV-96

NAME & ADDRESS OF APPLICANT: Janssen Research Foundation
1125 Trenton-Harbourton Road
Titusville, NJ 08560

DRUG PRODUCT NAME

Proprietary:	Sporanox
Nonproprietary/USAN:	itraconazole
Code Names/#'s:	R 51,211
Chemical Type/ Therapeutic Class:	

PHARMACOLOGICAL CATEGORY/INDICATION: treatment of onychomycosis

DOSAGE FORM:	Capsules
STRENGTHS:	100 mg
ROUTE OF ADMINISTRATION:	oral
DISPENSED:	_____ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Refer to NDA 20-083 for more details

SUPPORTING DOCUMENTS:

NDA 20-083, Sporanox Capsules, Janssen Research Foundation; approved by Div. 530 on September 11, 1992.

CONSULTS:

Ms. Mary Ann Jarski was consulted on this application since she was the primary reviewer of the supporting NDA cited above. See section entitled, "Supporting Documents."

REMARKS/COMMENTS:

Since this NDA refers completely to NDA 20-083, the reviewer has referred to the approval of Division 530. NDA 20-083 was approved on September 11, 1992.

Ms. Jarski was contacted for an update on the CMC section of NDA 20-083. It was my understanding that no major CMC issues were in a pending status.

An EER request was filed and found acceptable by the Office of Compliance on August 27, 1996. Refer to the attached copy of the acceptable EER.

The draft labeling is acceptable. There have been no changes to the DESCRIPTION or HOW SUPPLIED sections of the label.

A EA review was completed and a FONSI was signed by the Team Leader of the Environmental Assessment Team, Nancy Sager on November 21, 1996.

CONCLUSIONS & RECOMMENDATIONS:

This application is recommended for an approval action from a chemistry point of view. The Office of Compliance rendered the facilities associated with this NDA to be acceptable on 8/27/96.

Janet G. Higgins 11/05/96

Janet G. Higgins, Chemist

cc: Orig. NDA 20-694
HFD-540/Division File
HFD-540/Higgins
HFD-540/MO/Ko
HFD-540/Pharm/Mainigi
HFD-540/CSO/Cross
R/D Init by: SUPERVISOR WJ 11/27/96

Filename:**N20694.r01**

JW 11/26/96

Clin. micro

CONSULTATIVE REVIEW FOR TOPICAL DRUG PRODUCTS
(HFD-540)

DIVISION OF ANTI-INFECTIVE DRUG PRODUCTS
Clinical Microbiological Review

NDA #: 20-694 **REVIEW #:** 1 **REVIEW DATE:** 26 Mar., 1996

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original NDA labeling	11 Mar.,1996	25 Mar.,1996	

NAME & ADDRESS OF APPLICANT: JANSSEN RESEARCH FOUNDATION
1125 Trenton-Harbourton Road
Titusville, NJ 08560

DRUG PRODUCT NAME

Proprietary:	SPORANOX
Nonproprietary/USAN:	Itraconazole
Code Names/#'s:	R 51,211
Chemical Type	
Therapeutic Class:	Antifungal

PHARMACOLOGICAL CATEGORY/INDICATION: Antifungal

DOSAGE FORM:	CAPSULES
STRENGTHS:	100 mg
ROUTE OF ADMINISTRATION:	ORAL
DISPENSED:	___X___ **Rx** _____ **OTC**

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

Chemical Name: (±)-1-[(RS)-sec-Butyl]-4-[p-[4-[p-[[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-Δ^2-1,2,4-triazolin-5-one

Molecular Formula: $C_{35}H_{38}Cl_2N_8O_4$

Molecular Weight: 705.64

REMARKS/COMMENTS:

This application is a supplement to NDA 20-083. When this application is approved, the requested labeling changes will revert to the NDA 20-083. Another NDA, NDA 20-510, similarly had its requested labeling changes revert to NDA 20-083. NDA 20-083 was approved by the Division of Antiviral Drug Products for treatment of systemic fungal infections, while NDA 20-510 was approved by the Division of Topical Drug Products for onychomycosis; microbiologically, *Trichophyton rubrum* was added to the Microbiology portion of the package insert. Meanwhile, NDA was being evaluated for

microbiologically, data were evaluated in a previous review of NDA for *Trichophyton rubrum, T. mentagrophytes,*

Microbiological activity was demonstrated for all of the species requested. This NDA requires no changes in the Microbiology section of the package insert.

CONCLUSIONS & RECOMMENDATIONS:

The microbiology section of this supplement is approvable. The approvable Microbiology section of the package insert is reprinted below.

James R. King
Review Microbiologist

cc: Orig. NDA 20-694, 20-510, 20-083
HFD-540/Division File
HFD-520/Micro/King
HFD-540/MO/Labib
HFD-520/Pharm/Manigi
HFD-540/Chem/JHiggins
HFD-540/CSO/Cross
HFD-520/SMicro/ASheldon TB 4/10/96
R/D Init by: RB 4/11/96

Printed for signatures on March 26, 1996

micro

MAY - 3 1996

C1055

540

REVIEW FOR HFD-540
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #1 OF NDA 20-694
30 April 1996

A. 1. NDA 20-694
APPLICANT: Janssen Research Foundation
1125 Trenton-Harbourton Road
P.O. Box 200
Titusville, NJ 08560-0200

2. PRODUCT NAMES: Sporanox® Capsules

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is an oral dosage form.

4. METHODS OF STERILIZATION:
The product is not a sterile preparation, but should conform to microbial limit specifications.

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product is used for treatment of onychomycosis due to dermatophytes of the toenail or fingernail.

B. 1. DATE OF INITIAL SUBMISSION: 13 December 1995

2. DATE OF AMENDMENT: BZ 2/29/96

3. RELATED DOCUMENTS: NDA's 20-083 and 20-510

4. ASSIGNED FOR REVIEW: 1 April 1996

C. REMARKS: The submission requests a labelling change in the *INDICATIONS AND USAGE* Section of the package insert to include

All Chemistry, Manufacturing, and Controls information for this application is cross-referenced to NDA 20-083. The CMC section of NDA 20-083 was requested and the attached review is based on information contained in the CMC section of NDA 20-083.

D. CONCLUSIONS: The application is recommended for approval based on the microbial limit specifications.

30 Apr 1 1996

Paul Stinavage, Ph.D.

FHC 5/3/96

cc: Original NDA 20-694
HFD-540/F. Cross
HFD-805/Consult File/Stinavage

Drafted by: P. Stinavage, 30 April 1996
R/D initialed by P. Cooney, 30 April 1996

EA and Fonsi

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Sporanox® Capsules

itraconazole capsules

100 mg

NDA 20-694

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF DERMATOLOGIC AND DENTAL DRUG PRODUCTS

(HFD-540)

FINDING OF NO SIGNIFICANT IMPACT

[NDA 20-694]

SPORANOX® CAPSULES, 100 mg

itraconazole capsules, 100 mg

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for Sporanox Capsules, Janssen Research Foundation has conducted a number of environmental studies and prepared an environmental assessment in accordance with 21 CFR 25.31a(a) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Itraconazole is a synthetic drug which is administered as a capsule in the treatment of blastomycosis, histoplasmosis, aspergillosis, and onychomycosis. The drug substance will be manufactured by Janssen Pharmaceutica, Beerse, Belgium. The finished drug product will be used in hospitals, clinics and/or by patients in their homes.

Disposal of the drug may result from out of specification lots, discarding of unused or expired product, and user disposal of empty or partly used product and packaging. Returned or out-of-specification drug substance and rejected or returned drug product will be disposed of at a licensed facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic regulations. From home use, empty or partially empty containers will typically be disposed of by a community's solid waste management system which may include landfills, incineration and recycling, while minimal quantities of unused drug may be disposed of in the sewer system.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

11/18/96
DATE

Janet G. Higgins
PREPARED BY
Janet G. Higgins
Review Chemist
Division of New Drug Chemistry III

1/19/96
DATE

Wilson H. De Camp, Ph.D.
DIVISION CONCURRENCE
Wilson De Camp, Ph.D.
Team Leader
Division of New Drug Chemistry III (HFD-540)

11/21/96
DATE

Nancy B. Sager
CONCURRED
Nancy B. Sager
Team Leader
Center for Drug Evaluation and Research

Attachments: Environmental Assessment
Material Safety Data Sheet

cc:

Original NDA 20-694
HFD-540/Higgins/8-29-96 rev.
HFD-540/De Camp
HFD-540/Cross
HFD-004/FONSI File **[NDA 20-694]**
HFD-004/Docket File
HFD-019/FOI COPY

1. DATE

May, 1996

2. NAME OF APPLICANT

Janssen Pharmaceutica N.V. on behalf of Janssen Research Foundation, Titusville, New Jersey.

3. ADDRESS

Janssen Pharmaceutica N.V.
Turnhoutseweg 30
2340 Beerse
Belgium

4. DESCRIPTION OF THE PROPOSED ACTION

a. Brief description of requested approval

Janssen Pharmaceutica N.V. has filed a type 6 NDA 20-694 for SPORANOX™ Capsules, containing 100 mg itraconazole, active drug substance, coated on sugar spheres. The capsules have a blue opaque cap and pink transparant body and are supplied in unit-dose blister packs of 3 x 10 capsules and bottles of 30 capsules.

This environmental assessment is prepared following 21 CFR § 25.31a(a).

b. Need for the action

Itraconazole is a broad spectrum, synthetic triazole antifungal agent. Itraconazole inhibits the cytochrome P-450-dependent synthesis of ergosterol, which is a vital component of fungal cell membranes.

SPORANOX™ (itraconazole capsules) is indicated for the treatment of the following fungal infections in immunocompromised and non-immunocompromised patients:

1. Blastomycosis, pulmonary and extrapulmonary;
2. Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, non-meningeal histoplasmosis;
3. Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are refractory to amphotericin B therapy; and
4. Onychomycosis of the toenail or fingernail due to dermatophytes (tinea unguium).

SPORANOX™ is already approved as 100 mg capsules (NDA 20-083). The present application concerns a new indication for pulse dosing for onychomycosis in fingernail.

The oral bioavailability of itraconazole is maximal when SPORANOX™ (itraconazole capsules) is taken with a full meal.

Treatment of blastomycosis and histoplasmosis: The recommended dose is 200 mg once daily. If there is no obvious improvement or there is evidence of progressive fungal disease, the dose should be increased in 100 mg increments to a maximum of 400 mg daily. Doses above 200 mg per day should be given in two divided doses.
Treatment of aspergillosis: A daily dose of 200-400 mg itraconazole is recommended.
In life-threatening situations: Although these studies did not provide for a loading dose, it is recommended, based on pharmacokinetic datam that a loading dose of 200 mg t.i.d. (600 mg/day) be given for the first three days.
Treatment should be continued for a minimum of three months and until clinical parameters and laboratory tests indicate that the active fungal infection has subsided.
Onychomycosis: Toenails with or without fingernail involvement: The recommended dose is 200 mg daily for 12 consecutive weeks. Fingernails: The recommended dosing regimen is two treatment pulses, each consisting of 200 mg twice daily for 7 days. The pulses are separated by a 21-day drug-free period.

c. Production locations

Itraconazole *drug substance* will be produced by:
Janssen Pharmaceutica
Turnhoutseweg 30
2340 Beerse, Belgium

Janssen Pharmaceutica
Janssen Pharmaceuticalaan 3
2240 Geel, Belgium

The *drug product*, SPORANOX™ Capsules, will be manufactured by:
Janssen Pharmaceutica
Turnhoutseweg 30
2340 Beerse, Belgium

Janssen Biotech N.V.
Lammerdries 55
2250 Olen, Belgium
(Itraconazole beads manufacture)

Manufacturing Sites

Janssen Pharmaceutica Beerse is located on a parcel of 148 acres. The site is surrounded with residential type housing and has its primary access from state road No. N 14 connecting Antwerp to Turnhout. The terrain is flat and the climate is temperate.

Janssen Pharmaceutica Geel is located on a parcel of 99 acres in the Geel industrial area. The industrial area is bounded to the north by the channel "Albertkanaal" and to the south by highway E313 connecting Antwerp to Köln. The terrain is flat and the climate is temperate.

is located on a parcel of 25 acres, dedicated for industrial use by the Puerto Rico Planning Board. The site is bounded on the west by State Road No. 933 and on the north by State Road No. 30. The facility has its primary access from State Road No. 933. The parcel is largely a flat area, with "Mamey Creek" flowing at a lower elevation along its eastern and southeastern boundary. The climate is temperate to tropical.

Prographarm is located on a parcel of about 300 acres in an industrial area. The site is situated about 1 km from the centre of Chateauneuf and is surrounded by a forest. Its primary access is from State road D 939 connecting Chartres to Verneuil. The terrain is flat and the climate is temperate.

Janssen Biotech is located on a parcel of 5 acres in the industrial area "De Heze", Olen. The site is bounded in the north by State Road No. 13 connecting Lier to Geel. The terrain is flat and the climate is temperate.

Location maps can be found in Appendix 2.

d. Locations of use

SPORANOX™ Capsules will be used in hospitals, clinics and private houses located throughout the USA. The drug product will be available for use only by prescription. The draft of the prescribing information is available in Appendix 1, along with Material Safety Data Sheet for itraconazole.

e. Disposal sites

* Waste resulting from manufacturing, testing and packaging or from rejected or outdated drug substance and drug product, will be transported from Beerse, Geel and Olen to the following licensed waste processor:

* Waste resulting from manufacturing in Olen will be transported by the following licensed waste transporter:

* Packaging material, from Beerse, Geel and Olen, not contaminated with pharmaceutical substances, is collected selectively and recycled by a specialized waste contractor.

* Waste solvents resulting from manufacturing in the Janssen Pharmaceutica plants in Beerse and Geel and in Janssen Biotech, Olen, can be hauled for recycling and reuse in relevant industries by the following licensed waste processors:

* Waste resulting from manufacturing the drug product in Gurabo, Puerto Rico, will be transported to the following licensed waste processor:

* Waste resulting from manufacturing, testing of the product or from rejected product will be transported from Chateauneuf, France, to the following licensed waste processor:

* Waste resulting from rejected, returned or outdated drug product in the U.S. will be transported to the following licensed waste processor:

* At US hospitals, pharmacies or clinics, empty or partially empty packages will be disposed of according to hospital, pharmacy or clinic procedures. In the home, empty or partially empty containers will typically be disposed of by community's solid waste management system which may include landfills, incineration and recycling.

Waste Processing Sites

is located on a parcel of about 100 acres in a rural environment. There is possibility both for incineration of the waste and landfilling. The terrain is flat and the climate is temperate.

Dapemo is located on a parcel of 150 acres in the industrial area of Olen, Belgium. The terrain is flat and the climate is temperate.

Beerse, Belgium is located in a rural environment on a parcel of about 14 acres, the terrain is flat and the climate is temperate.

, is located on a parcel of 200 acres in the industrial area of Belgium. The terrain is flat and the climate is temperate.

is located on a parcel of 160 acres in the industrial area of East Sussex, 3-5 miles from the nearest town, Rye. The terrain is flat and the climate is temperate oceanic.

is a domestic corporation, located at road no. 3, km 13.6, Canovanillas Industrial Park. The structure, equipment and machinery are established on approximately six (6) acres of land. The corporation is engaged in the business of incineration services to industrial, hospital and commercial customers and operates an incinerator for medical wastes and off-spec wastes. Wastes are picked up by their own fleet at different facilities in Puerto Rico. The climate is a normal tropical type of weather.

The climate is temperate. The site has received authorization from the French Authorities for incineration of solid waste.

is located on a parcel of about 250 acres in a rural environment. The site is located about one-half mile to the south of US Route 322, one-half mile to the west of US Route I-295, and one-half mile to the east of Bridgeport, NJ. The terrain is flat and the climate is temperate.

5. IDENTIFICATION OF CHEMICAL SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

5.1 Drug Substance: R 51211: Itraconazole
The complete specifications are amended to the Environmental Assessment of SPORANOX™ Oral Solution (NDA 20-657)

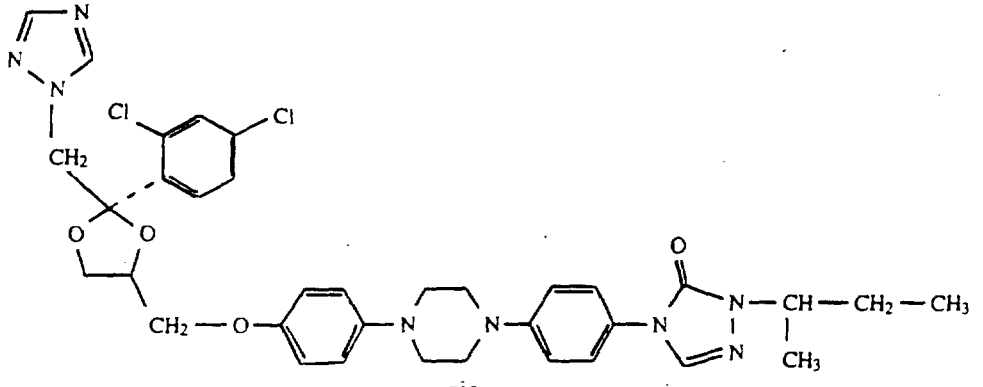
a. Complete nomenclature: (±)-cis-4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one

b. CAS Registration number: 84625-61-6

c. Molecular formula: $C_{35}H_{38}Cl_2N_8O_4$

d. Molecular weight: 705.64

e. Structural formula:



cis

f. Physical description: Itraconazole is a white to slightly yellowish powder

g. Additives: Not applicable

h. Impurities:

HPLC-purity:	Trans-isomer (R057348):	1% maximum
	Other impurities:	Total: 1% maximum
		Individual: 0.5 % maximum

5.2 Synthesis

A complete overview of the synthesis of intermediates T001330 and T001333, and itraconazole drug substance is appended in Confidential Appendix A.

5.3 Drug Product

See Confidential Appendix B.

Quantitative Composition and Batch Formula

Finished Goods Specifications: SPORANOX Capsules, 100 mg

Manufacturing Flow Scheme: SPORANOX™ 100 mg Capsules

How supplied
SPORANOX™ Capsules have a blue opaque cap and pink transparent body, imprinted with "JANSSEN" and "SPORANOX 100". The capsules are supplied in unit-dose blister packs of 3 x 10 capsules (NDC 50458-290-01) and bottles of 30 capsules (NDC 50458-290-04).
See also Appendix 1.

6. INTRODUCTION OF SUBSTANCES INTO THE ENVIRONMENT

I. Drug Substance
Janssen Pharmaceutica - Beerse - Belgium
Janssen Pharmaceutica - Geel - Belgium

d. Discussion of the Effect of Approval on Compliance with Current Emission Requirements

The synthesis of the drug substance itraconazole at the production facilities of Janssen Pharmaceutica N.V. in Beerse and Geel is not expected to have impact on compliance with current waste legislation or to violate the current permits.

Only a part of the synthesis of itraconazole is conducted at the site in Gurabo, starting from the Janssen intermediates T001207 (for T001333) and T001330.
See Confidential Appendix A.

a. List of substances to be emitted

Detailed information on the introduction of substances into the environment is available in Confidential Appendix C.

Waste water
All reactions are carried out in closed glass-lined or stainless steel jacketed vessels within a controlled temperature and pressure range.
The water layer originated from the synthesis process is lead to the waste water treatment plant. The aqueous layers with high BOD/COD content from "drug substance" production have a BOD (Biological Oxygen Demand) range of 2500-4000 mg/L and a COD (Chemical Oxygen Demand) range of 5000-9000 mg/L.

Air emissions
Ref. to Confidential Appendix C.

Solid waste
The filter cake generated after filtration, the off spec formulations, the dust filters and some packaging materials account for the majority of the solid waste that will be incinerated.
Packaging materials and process solvents will either be recuperated or incinerated depending on their composition.
The sludge obtained by the waste water treatment will be disposed of by landfilling.

b. The controls exercised

Waste water

The combined process waste waters from
come into two aerated tanks with a capacity of 30,000 gallons each.
Effluent from the equalization tanks is pumped to the pH adjustment tanks. After the pH adjustment tanks, the separation of solids (already flocculated and coagulated by the addition of polymers) takes place. The underflow from the clarifier is pumped to the sludge digester. The effluent from the primary clarifier is transferred to an equalization tank with a 167,000 gallons capacity and than to the bioreactor for the secondary biological treatment.
Powdered activated carbon is added at the entrance of the bioreactor to improve the BOD and COD removal efficiency. After biological treatment, the water flows to the secondary clarifiers to separate the sludge from the water effluent. The water effluent is pumped to a holding tank. The aerobic digester tank is designed to further stabilize the biological solids prior to dewatering and disposal.
The two stages biological waste water treatment system has a capacity of 900 kg BOD/day.

Air emissions

Air Emissions from *drug substance* production are discharged to the atmosphere through a two stage scrubber system.
In addition all reactors are equipped with an own cooler condensing system.
The emissions contain organic - Volatile Organic Compound (VOC) - and inorganic emissions.

Description of the scrubber

The chemical production units are provided with a two stage scrubber system. The first step consists of continuous addition of water to absorb the HCl. During the second step SO_2 is absorbed with NaOH.

Solid waste

No hazardous waste treatment is done at the site. Waste is temporarily stored in appropriate containers and at regular times hauled by a licensed transporter to a licensed high temperature waste incinerator.
A RCRA part B permit was obtained on August, 1986.

c. Citation of, and statement of compliance with, applicable emission requirements at Federal, State and local levels

Waste water

The effluent from the WWTP is discharged in compliance with the requirements set forth in the "Industrial Wastewater Bulk Discharge Permit #GDG-88-606-21" and the "Industrial Wastewater Discharge Permit #GDA-88-606-022", issued by "The Puerto Rico Aqueduct and Sewer Authority".
Ref. to Appendix 3.

Major requirements :

* *Bulk discharge into the Puerto Nuevo Treatment Plant*

- Flow rate	The permittee shall not discharge more than 13 tank-trucks (124,000 gallons) per day
- pH	6.5 - 9.0
- BOD	175 mg/L
- COD	300 mg/L
- Suspended Solids	125 mg/L

* *Discharge into the Gurabo WWTP*

- Flow rate	80,000 gpd
- pH	6.5 - 9.0
- B.O.D.	250 mg/L
- C.O.D.	425 mg/L

Air emissions

Air emissions are in compliance with the requirements set forth in the "Air emission permit #PFE 33-1291-1681-I-II-III-O". The permit is obtained from the Puerto Rico Environmental Quality Board.
Ref. to Appendix 3.

Solid waste

Hazardous and solid waste treatment, storage and disposal are done in compliance with the requirements set forth in the RCRA permit #PRD-980536049. Ref. to Appendix 3.

d. The effect of approval upon compliance with current emission requirements at the production site

The synthesis of the drug substance at the production site at Gurabo is not expected to have impact on compliance with current waste legislation or to violate the current permit.

II. Drug Product

Janssen Pharmaceutica - Beerse - Belgium

Information for Beerse and Gurabo:
1) on EA format item 6.II.a is described in the environmental assessment for SPORANOX™ Capsules (NDA 20-083), submitted November 16, 1990. *
2) on EA format items 6.II.b and 6.II.c: See above Item 6.I. Drug substance

Information on EA format item 6.II.a through 6.II.c for Chateauneuf-en-Thymerais is described in the environmental assessment for SPORANOX™ Capsules NDA 20-083 supplement SCM-005, submitted June 18, 1993. *

d. Discussion of the Effect of Approval on Compliance with Current Emission Requirements

The approval of the (total or partial) production of SPORANOX™ Capsules at the production facilities of Janssen Pharmaceutica N.V.,
is not expected to have impact on compliance with current waste legislation or to violate the current permits.

Janssen Biotech N.V. - Olen - Belgium

a. List of substances to be emitted

A full calculation of all substances expected to be emitted into the evironment is provided in the Confidential Appendix C.

b. The controls exercised

Waste water
The sanitary waste water and waste water from the offices are discharged into the public sewer system after passing a water quality control unit.
The industrial waste water from the laboratories and the manufacturing of the pellets may be discharged to the public sewer system if all emission requirements of the permit are fulfilled. Otherwise, the waste water is collected and transported to the licensed waste processor Indaver.

*Copy included in this section, for convenience of review.

Air emissions

The evaporated solvents from the Wurster coater are led to a recuperation unit. A closed loop system is present which prevents the emission of the major part of the solvents. The solvents are condensed from the nitrogen/solvent mixture and are reused.

Dust emissions from the pellets production are controlled with a two stages high efficiency, 99.97% removal dust filtration system.

Solid waste

Waste from manufacture of the pellets, filters and laboratory waste are incinerated by licensed waste processors.

Process solvents are recycled and/or incinerated.

c. Citation of, and statement of compliance with, applicable emission requirements at Federal, State and local levels

Air emissions and waste water discharge is in compliance with the requirements set forth in the environmental permit, dated July 29, 1993. This permit, obtained from the Permanent Deputation of the Provincial Council of Antwerp, is also the permit to operate.
Waste treatment is done in compliance with the Flemish regional waste legislation. Since no treatment takes place at the site, no special permit for treatment is necessary. However, yearly reports to the authorities are required.
Ref. to appendix 3.

d. The effect of approval upon compliance with current emission requirements at the production site

The approval of the production of Sporanox pellets will not have an impact on compliance with current emission requirements.

6.e. Expected Introduction Concentrations

6.e.1. Expected Introduction Concentration (EIC) for the aquatic environment from use of itraconazole

The Expected Introduction Concentration of itraconazole in waste water, asuming that all drug product is used and no depletion mechanisms are active, has been estimated based upon the mathematical formula provided in the Guidance for Industry for the Submission of an Environmental Assessment in Human Drug Applications and Supplements, CDER, November 1995. The corresponding calculation is provided in the Confidential Appendix D.

The EIC is based on certain assumptions, including dosing an estimate of the number of patients that would be prescribed the drug during the fifth year of marketing at the maximum therapeutic dose. In addition, although itraconazole is the administered drug, a portion of the dose is excreted as metabolites. This is not taken into account in the calculation in Appendix D. However, this has no significant bearing on the EIC calculation since the metabolites are of lower or almost the same molecular weight than itraconazole.
We may suppose that the calculated EIC represents a worst-case upper limit.

6.e.2. Expected Introduction Concentration (EIC) for the aquatic environment from disposal of itraconazole

No substances are expected to enter the aquatic environment from disposal because solid waste from manufacturing, packaging, labelling, quality control testing and distribution (i.e. waste resulting from rejected, returned or outdated substance/product) is disposed of by incineration or landfilling.

6.e.3. EIC for the terrestrial and atmospheric environment

No significant quantities of itraconazole from use or disposal are expected in the terrestrial or atmospheric compartment. The EIC_{ter} and the EIC_{atm} are not considered.

Co. Corres.

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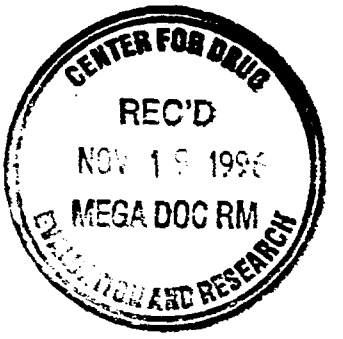

Sent Via Overnight Mail

November 18, 1996

Frank Cross
Project Manager
Division of Dermatologic and Dental Drug Products/HFD-540
Food and Drug Administration
Corporate Building
9201 Corporate Boulevard
Rockville, MD 20850

Subject: NDA 20-694
SPORANOX® (itraconazole capsules)
Revised proposed labeling

Dear Frank:

Per our discussion earlier today, attached please find revised proposed labeling for the above NDA. This version incorporates the comments faxed to us today and deletes all reference to Sporanox Oral Solution.

We have not incorporated comment #7 to add to the paragraph on postmarketing adverse experiences. As this change has serious implications worldwide, we can not agree to this change prior to further discussions with our colleagues in Belgium. We will inform you of our decision on this issue as quickly as possible.

A diskette containing the WordPerfect version of this labeling is provided.

Please call me at (609) 730-3069 if you have any questions.

Sincerely,

Cynthia Chianese
Manager, Regulatory Affairs

Enclosures
g:\regulato\wpdocs\1996\sporanox\20-694.pi3

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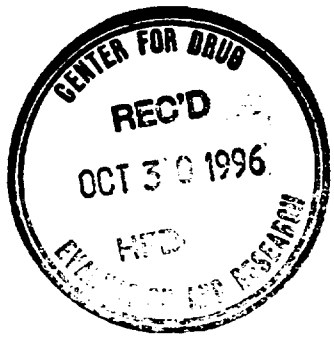
Sent Via Overnight Mail

October 29, 1996

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products/HFD-540
Food and Drug Administration
Corporate Building
9201 Corporate Boulevard
Rockville, MD 20850



Subject: NDA 20-694
SPORANOX® (itraconazole capsules)
Revised proposed labeling

Dear Dr. Wilkin:

In response to a request made by Frank Cross, Project Manager, attached please find the following revised labeling:

- A labeling supplement to NDA 20-083 was submitted to the Antiviral Division on June 13, 1996 and is currently under review. A revised version of the labeling for NDA 20-083, incorporating agreements made thus far with the Antiviral Division, is attached along with a list of outstanding issues. The Boxed Warning, Contraindications, Warnings and Precautions Sections have been revised extensively. The Microbiology Section has been revised significantly and relocated. Minor changes have been made to the Clinical Pharmacology Section and throughout the labeling. The formulation no longer appears as part of the established name based on discussions with Eric Sheinen, PhD, Director, New Drug Chemistry III, with agreement from the Antiviral Division.

- Revised draft labeling for NDA 20-694, incorporating the changes mentioned above, with additions specific to this NDA highlighted is also attached. Several revisions based on the recommended labeling issued with the action letter for NDA have been incorporated, including changes in the AE incidence tables based upon updated safety information. As discussed with Frank Cross, the safety update incorporating this new safety information will be submitted very shortly. We will discuss whether to update the adverse event incidence rates for systemic fungal infections with the Antiviral Division.

A diskette containing the WordPerfect versions of both of these versions is provided.

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Please call me at (609) 730-3069 if you have any questions.

Sincerely,

Cynthia Chianese

Cynthia Chianese
Manager, Regulatory Affairs

Enclosures

Desk copy: Frank Cross (hard copy plus diskette)

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REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Sent Via Overnight Mail

November 21, 1996

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products/HFD-540
Food and Drug Administration
Corporate Building
9201 Corporate Boulevard
Rockville, MD 20850

Subject: NDA 20-694
SPORANOX® (itraconazole) Capsules
Revised proposed labeling

Dear Dr. Wilkin:

Attached please find revised proposed labeling for the subject NDA, incorporating comments faxed to us on November 20, 1996.

We have also provided a counterproposal for presentation of the Adverse Reactions. We would appreciate your review of our proposal, but only if this can be done without compromising timing of completion of the review process.

A diskette containing the WordPerfect version of this labeling is provided.

Please call me at (609) 730-3069 if you have any questions.

Sincerely,

Cynthia Chianese

Cynthia Chianese
Manager, Regulatory Affairs

Enclosures

Desk Copy: Frank Cross (hard copy plus diskette)

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Sent Via Overnight Mail

November 25, 1996

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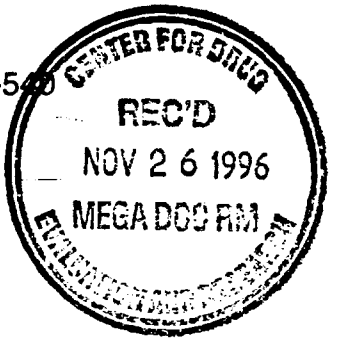

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products/HFD-5[illegible]
Food and Drug Administration
Corporate Building
9201 Corporate Boulevard
Rockville, MD 20850

Subject: NDA 20-694
SPORANOX® (itraconazole) Capsules
Revised proposed labeling

Dear Dr. Wilkin:

Attached please find revised proposed labeling for the subject NDA, incorporating comments discussed with Frank Cross, Project Manager, on November 25, 1996.

A diskette containing the WordPerfect version of this labeling is provided.

Please call me at (609) 730-3069 if you have any questions.

Sincerely,

Cynthia Chianese

Cynthia Chianese
Manager, Regulatory Affairs

Enclosures

Desk Copy: Frank Cross (hard copy plus diskette)

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REVIEWS COMPLETED:

CSO ACTION:
☐ LETTER ☐ N.A.I ☐ MEMO

CSO INITIALS DATE

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October 22, 1996

Jonathan Wilkin, M.D., Director
Division of Dermatologic and
Dental Drug Products/HFD-540
Food and Drug Administration
Corporate Building
9201 Corporate Boulevard
Rockville, MD 20850

Subject: SPORANOX® (itraconazole capsules)
ORIGINAL NEW DRUG APPLICATION CERTIFICATIONS
NDA 20-694

Dear Dr. Wilkin:

Janssen Research Foundation verifies the U.S. study, ITR-USA-71, submitted in this New Drug Application was conducted in compliance with the institutional review board regulations in 21 CFR Part 56 and the informed consent regulations in 21 CFR Part 50. The Finnish study, ITR-FIN-1, submitted in this application was performed in accordance with the declaration of Helsinki and its subsequent revisions.

Janssen Research Foundation also certifies it did not and will not use in any capacity the services of any person debarred under subsection 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this NDA.

Janssen Research Foundation assures that were not used in any analyses performed for this NDA.

Please call me at (609) 730-3069 if you have any questions.

Sincerely,

Cynthia Chianese

Cynthia Chianese
Manager, Regulatory Affairs

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Sent via Overnight Mail

April 15, 1996

Jonathan Wilkin, MD, Director
Division of Dermatologic and
Dental Drug Products/HFD-540
Food and Drug Administration
Building 2
9201 Corporate Boulevard
Rockville, MD 20850

Subject: NDA 20-694
SPORANOX® (itraconazole capsules)
Safety Update

Dear Dr. Wilkin:

We are submitting a safety update for the above referenced NDA. We have reviewed our worldwide safety database for any reports of serious adverse events, both pre-marketing and post-marketing, in patients treated for onychomycosis and dermatophytes. This review covers the time period from the cut-off of the safety update in the NDA (October 15, 1995) through January 31, 1996. Results of this review are attached.

Results of this safety update do not change the current safety profile and no changes to the proposed labeling are suggested.

Please call me at (609) 730-3069 if you have any questions.

Sincerely,

Cynthia Chianese

Cynthia Chianese
Manager, Regulatory Affairs

Desk copy: Frank Cross, Project Manager

Enclosure

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AMENDMENT

Sent Via Overnight Mail

March 28, 1996

Jonathan Wilkin, MD, Director
Division of Dermatologic and
Dental Drug Products/HFD-540
Food and Drug Administration
Corporate Building
9201 Corporate Boulevard
Rockville, MD 20850

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Subject: NDA 20-694
SPORANOX® (itraconazole capsules)
Response to Request

Dear Dr. Wilkin:

As requested by Frank Cross, Project Manager, we are providing two additional copies of the above mentioned NDA for the medical and statistical reviewers.

Safety information on the two studies comprising NDA 20-694 (ITR-USA-71 and ITR-FIN-1) is cross-referenced to the safety update submitted to NDA 20-510 on April 7, 1995. Two review copies of this safety update are provided per request. This safety update serves as the Integrated Safety Summary for NDA 20-694 and contains case record forms for patients who discontinued ITR-USA-71 or ITR-FIN-1 for an adverse event.

Additionally as requested, are five copies of the data listings for study ITR-FIN-1.

Responses to the remaining requests are in process and will be provided as quickly as possible.

Please call me at (609) 730-3069, if you have any questions or need anything further.

Sincerely,

Cynthia Chianese

Cynthia Chianese
Manager, Regulatory Affairs

Enclosures
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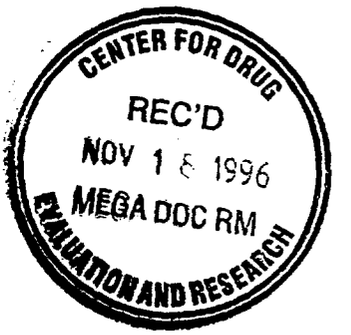

NEW CORRESPONDENCE

November 4, 1996

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products/HFD-540
Food and Drug Administration
Corporate Building
9201 Corporate Boulevard
Rockville, MD 20850

Subject: NDA 20-694
SPORANOX® (itraconazole capsules)
Safety Update

Dear Dr. Wilkin:

Reference is made to my conversation with Frank Cross, Project Manager, on November 4, 1996, regarding Janssen's response to the action letter for NDA submitted November 1, 1996, with cross-reference to the subject NDA.

Please be informed that safety information submitted in the November 1, 1996 submission to NDA serves as a safety update to NDA 20-694.

Please call me at (609) 730-3069 if you have any questions.

Sincerely,

Cynthia Chianese
Manager, Regulatory Affairs

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REVIEWS COMPLETED

CSO ACTION:
[ ] LETTER [ ] N A I [ ] MEMO

CSO INITIALS DATE

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April 5, 1996

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products/HFD-540
Food and Drug Administration
Corporate Building
9201 Corporate Boulevard
Rockville, Maryland 20850

SUBJECT: SPORANOX® (itraconazole) Capsules
NDA 20-694
Response to Request re: Manufacturing Sites Inspection Status

Dear Dr. Wilkin:

Per the Division's request, we confirm that the facilities listed in this NDA are ready for FDA inspection.

Please contact me at (609) 730-3079 if you have any questions.

Sincerely,

Jeffrey J. Blumenstein, Ph.D.
Director, Technical Regulatory Affairs

c: Frank Cross, Project Manager

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December 13, 1995

David Feigal, M.D., Director
Division of Antiviral Drug Products/HFD-530
Document Control Room #240
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: NDA 20-083
SPORANOX® (itraconazole capsules)
Supplemental NDA

Dear Dr. Feigal:

Reference is made to the Agency's approvable letter of July 25, 1995, for NDA 20-510, in which we were requested to evaluate the "dosage regimen that would most effectively be used to treat onychomycosis of the fingernail without concomitant onychomycosis of the toenail". A copy of the July 25 letter is attached.

This supplemental NDA responds to the above request and provides data for changing the Sporanox INDICATIONS AND USAGE Section of the package insert from **"Onychomycosis due to dermatophytes (tinea unguium) of the toenail with or without fingernail involvement"** to **"Onychomycosis of the toenail or fingernail due to dermatophytes (tinea unguium)."**

The following data are submitted in support of the labeling change:

Attachment 1) Background and overview, with supportive references (N80552 and N95381).

Attachment 2) Draft revised labeling.

Attachment 3) Report number N111467, A double-blind, placebo-controlled, multicenter trial for the treatment of onychomycosis of the fingernail, ITR-USA-71, conducted under IND demonstrating efficacy in onychomycosis of the fingernail with a pulse regimen.

Attachment 4) Report number N111311, Effect of itraconazole in the treatment of onychomycosis of the toenails. A randomized double-blind trial comparing continuous treatment with pulse therapy, ITR-FIN-1, conducted in Finland and demonstrating equivalence between continuous treatment and pulse therapy in onychomycosis of the toenail.

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Attachment 5) Safety update of serious adverse events from August 2, 1995, (the cut-off used for the last safety update) through October 15, 1995.

As you will remember from the Dermatologics Drugs Advisory Committee on onychomycosis on September 22 and 23, 1994, it was agreed that demonstration of efficacy for toenails confers efficacy for fingernails. Therefore, only the dosing regimen must be established. Please note that the study provided in Attachment 3, along with the study in Attachment 4 and the pharmacokinetic data in Attachment 1, support the use of pulse dosing for onychomycosis.

We will continue our Phase IV program to determine whether an altered dosage regimen would improve the efficacy/safety of Sporanox in the treatment of onychomycosis. As agreed, we will await preliminary data from the ongoing pulse dosing studies in onychomycosis of the toenail before designing the Phase IV study.

The use of itraconazole for the treatment of onychomycosis of the toenail, a continuous dosing for three months, radically decreased the length of treatment of previous therapies of up to 18 months. Pulse regimens could offer the same efficacy with an even lower total treatment dosage and revolutionize the treatment of onychomycosis. Short, fixed treatment regimens provide the promise of improved safety and better patient compliance while maintaining efficacy.

This submission is in response to the Division's recommendation, therefore we would appreciate an expedited review of this supplement. If you have any questions or comments regarding this submission, please contact me at 609-730-3396.

Sincerely,

Donna Castro Ohye

Donna Castro Ohye
Director, Regulatory Affairs

Enclosures
User Fee ID # 2897

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Sent Via Overnight Mail

February 29, 1996

Jonathan Wilkin, M.D., Director
Division of Dermatologic and
Ophthalmologic Drug Products/HFD-540
Food and Drug Administration
Corporate Building
9201 Corporate Boulevard
Rockville, MD 20850

Subject: NDA 20-694
SPORANOX® (itraconazole capsules)
Response to Request

Dear Dr. Wilkin:

As requested by Rosemary Cook and Frank Cross, we are providing review copies for the subject NDA, originally submitted December 13, 1995. Each review copy contains the cover letter, accompanying forms dated December 13, 1995, and proposed labeling, as well as additions noted below. Also, please note the following cross-references for each technical discipline:

Chemistry, Manufacturing, and Controls:	All information for this NDA is cross-referenced to NDA 20-083, including pending supplement 016 submitted February 8, 1996.
Pharmacology:	All information for this NDA is cross-referenced to NDAs 20-083 and 20-510.
Pharmacokinetics:	Review copy also contains background and overview with supportive references from December 13, 1995, submission. Additional information for this NDA is cross-referenced to NDAs 20-083 and 20-510 and to the supplement to NDA 20-083 dated October 23, 1995.

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Microbiology:	Review copy contains full copy of December 13, 1995, submission. Additional information for this NDA is cross-referenced to NDAs 20-083 and 20-510.
Clinical and Statistical:	Review copy contains proposed labeling only. Full copies for these disciplines were submitted December 13, 1995. Further safety information for this NDA is cross-referenced to the April 7, 1995, safety update to NDA 20-510.

Please call me at (609) 730-3069, if you have any questions.

Sincerely,

Cynthia Chianese

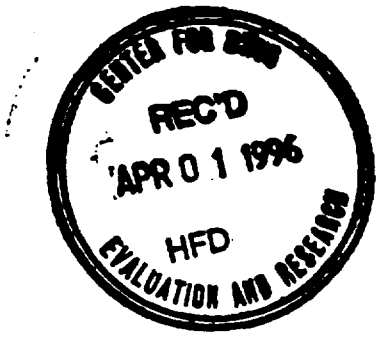
Cynthia Chianese
Manager, Regulatory Affairs

Enclosures

Desk Copy: Frank Cross (cover letter and proposed labeling in hard copy and WordPerfect diskette)
g:\regulato\wpdocs\1996\sporanox\fgrnail.sup

Sent Via Overnight Mail

March 29, 1996



Jonathan Wilkin, MD, Director
Division of Dermatologic and
Dental Drug Products/HFD-540
Food and Drug Administration
Corporate Building
9201 Corporate Boulevard
Rockville, MD 20850

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Subject: NDA 20-694
SPORANOX® (itraconazole capsules)
Response to Request

Dear Dr. Wilkin:

As requested by Frank Cross, Project Manager, enclosed are three diskettes containing the SAS datasets for studies ITR-USA-71 and ITR-FIN-1. The READ.ME file explains how to use the PKUNZIP program to inflate the *.ZIP files into PC SAS 6.10 datasets. It also describes the SAS formats.

Three hard copies of the SAS PROC contents of all the datasets are also provided.

Please call me at (609) 730-3069 if you have any questions.

Sincerely,

Cynthia Chianese

Cynthia Chianese
Manager, Regulatory Affairs

Enclosure

g:\regulato\wpdocs\1996\sporanox\response.fgr

JANSSEN AT WASHINGTON CROSSING
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Sent Via Overnight Mail

April 5, 1996

Jonathan Wilkin, MD, Director
Division of Dermatologic and
Dental Drug Products/HFD-540
Food and Drug Administration
Corporate Building
9201 Corporate Boulevard
Rockville, MD 20850

Subject: NDA 20-694
SPORANOX® (itraconazole capsules)
Response to Request

Dear Dr. Wilkin:

As requested by Frank Cross, Project Manager, enclosed are diskettes containing SAS programs for studies ITR-USA-71 and ITR-FIN-1. The diskette for ITR-USA-71 contains programs to generate all efficacy tables. The diskette for ITR-FIN-1 contains programs to generate the data displays as indicated on the diskette label, hard copies of which are also provided.

Please call me at (609) 730-3069 if you have any questions.

Sincerely,

Cynthia Chianese

Cynthia Chianese
Manager, Regulatory Affairs

Desk copy (letter only): Frank Cross

Enclosure

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Sent via Overnight Mail

April 15, 1996

Jonathan Wilkin, MD, Director
Division of Dermatologic and
Dental Drug Products/HFD-540
Food and Drug Administration
Building 2
9201 Corporate Boulevard
Rockville, MD 20850

Subject: NDA 20-694
SPORANOX® (itraconazole capsules)
Safety Update

Dear Dr. Wilkin:

We are submitting a safety update for the above referenced NDA. We have reviewed our worldwide safety database for any reports of serious adverse events, both pre-marketing and post-marketing, in patients treated for onychomycosis and dermatophytes. This review covers the time period from the cut-off of the safety update in the NDA (October 15, 1995) through January 31, 1996. Results of this review are attached.

Results of this safety update do not change the current safety profile and no changes to the proposed labeling are suggested.

Please call me at (609) 730-3069 if you have any questions.

Sincerely,

Cynthia Chianese

Cynthia Chianese
Manager, Regulatory Affairs

Desk copy: Frank Cross, Project Manager

Enclosure

g:\regulato\wpdocs\1996\sporanox\safetyup.fgr

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BM
NDA ORIG AMENDMENT

Sent Via Overnight Mail

April 19, 1996

Jonathan Wilkin, MD, Director
Division of Dermatologic and
Dental Drug Products/HFD-540
Food and Drug Administration
Corporate Building
9201 Corporate Boulevard
Rockville, MD 20850

Subject: NDA 20-694
SPORANOX® (itraconazole capsules)
Response to Request

Dear Dr. Wilkin:

As requested by Frank Cross, Project Manager, enclosed is an Integrated Summary of Effectiveness for the above referenced NDA.

Please call me at (609) 730-3069, if you have any questions.

Sincerely,

Cynthia Chianese

Cynthia Chianese
Manager, Regulatory Affairs

Desk copy: Frank Cross

Enclosure
g:\regulato\wpdocs\1996\sporanox\response.fgr

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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August 26, 1996

BS
NDA ORIG AMENDMENT

Jonathan Wilkin, MD, Director
Division of Dermatologic and
Dental Drug Products/HFD-540
Food and Drug Administration
Corporate Building
9201 Corporate Boulevard
Rockville, MD 20850

Subject: NDA 20-694
SPORANOX® (itraconazole capsules)
Response to Request

Dear Dr. Wilkin:

As requested by Dr. Srinivasan, enclosed is a copy of the reference for the Blackwelder equivalence test referred to in the clinical research report for study ITR-FIN-1.

Please call me at (609) 730-3069, if you have any questions.

Sincerely,

Cynthia Chianese

Cynthia Chianese
Manager, Regulatory Affairs

Desk copy: Dr. Srinivasan (Via Overnight Mail)

Enclosure
g:\regulato\wpdocs\1996\sporanox\response.ltr

REVIEWS COMPLETED

DSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

INITIALS DATE

JANSSEN AT WASHINGTON CROSSING
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September 10, 1996

Jonathan Wilkin, MD, Director
Division of Topical Drug Products
Document Control Room #12B-30
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

BM
NDA ORIG AMENDMENT

Subject: NDA 20-694
SPORANOX (itraconazole) Capsules

Dear Dr. Wilkin:

As requested during a telephone conversation with Frank Cross, we are providing the following information:

ITR-BEL-43 Dr. Ko requests the Clinical Research Report as well as the addendum. The addendum will be requested from the IR-Product Information Department.

Publications are enclosed, however, Clinical Research Reports do not exist.
N 106778 The study report for this publication was requested. Publication "Intermittent pulse treatment with itraconazole: a reality for onychomycosis" was presented for the 5th International Skin Therapy Symposium, Brussels, Belgium, May 25-28, 1994.

N 102987 "Efficacy and Tolerability of Itraconazole in patients with Fingernail Onychomycosis: a 6-week Pilot study." Current Therapeutic Research Vol. 56, No 10, October 1995.

N 106864 "Pulse Dose Regimen of Oral Itraconazole in the Therapy of Onychomycosis."

Please call me at (609) 730-3396 if you have any questions.

Sincerely,

Donna Ohye

Donna Ohye
Director, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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ORIGINAL
NEW CORRESP
NC

Sent Via Overnight Mail

September 20, 1996

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products/HFD-540
Food and Drug Administration
Corporate Building
9201 Corporate Boulevard
Rockville, MD 20850

Subject: NDA 20-694
SPORANOX® (itraconazole capsules)
Response To Request - Statistical

Dear Dr. Wilkin:

As requested by Dr. Steve Thompson, Statistical Reviewer, enclosed are the following:

- Clinical Research Report for study ITR-RSA-2
- SAS Codelist (on diskette) for ITR-USA-71
- Format Library

Please call me at 609-730-3069 if you have any questions.

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

Sincerely,

Cynthia Chianese

Cynthia Chianese
Manager, Regulatory Affairs

Enclosures
Desk Copy including diskette: Steve Thompson (submitted Sept. 19, 1996)

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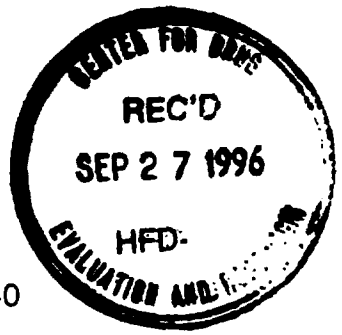
DUPLICATE

NC



September 23, 1996

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products/HFD-540
Food and Drug Administration
Corporate Building
9201 Corporate Boulevard
Rockville, MD 20850

Subject: NDA 20-694
SPORANOX® (itraconazole capsules)
Response To Request - Statistical

Dear Dr. Wilkin:

As requested by Dr. Steve Thompson, Statistical Reviewer, enclosed is a replacement diskette containing the format transport file for study ITR-USA-71.

Please call me at 609-730-3069 if you have any questions.

Sincerely,

Cynthia Chianese

Cynthia Chianese
Manager, Regulatory Affairs

Enclosures
Desk Copy including diskette: Steve Thompson (sent via overnight mail)

g:\regulato\wpdocs\1996\sporanox\corresp.fda

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Sent via overnight mail

October 22, 1996

NEW CORRESPONDENCE

Jonathan Wilkin, M.D., Director
Division of Dermatologic and
Dental Drug Products/HFD-540
Food and Drug Administration
Corporate Building
9201 Corporate Boulevard
Rockville, MD 20850

Subject: NDA 20-694
SPORANOX® (itraconazole capsules)
Response to request

Dear Dr. Wilkin:

In response to the request made by Frank Cross, Project Manager, enclosed please find the debarment statement and patent certification for the above NDA.

Please call me at (609) 730-3069 if you have any questions.

Sincerely,

Cynthia Chianese
Manager, Regulatory Affairs

Enclosure

Desk copy: Frank Cross (via facsimile)

g:\regulato\wpdocs\1996\sporanox\certify.fgr

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I ☐ MEMO

CSO INITIALS DATE

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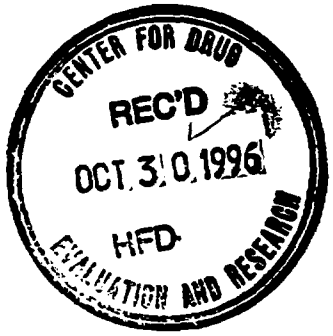
Sent Via Overnight Mail

October 29, 1996

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products/HFD-540
Food and Drug Administration
Corporate Building
9201 Corporate Boulevard
Rockville, MD 20850



Subject: NDA 20-694
SPORANOX® (itraconazole capsules)
Revised proposed labeling

Dear Dr. Wilkin:

esponse to a request made by Frank Cross, Project Manager, attached please find the following revised labeling:

- A labeling supplement to NDA 20-083 was submitted to the Antiviral Division on June 13, 1996 and is currently under review. A revised version of the labeling for NDA 20-083, incorporating agreements made thus far with the Antiviral Division, is attached along with a list of outstanding issues. The Boxed Warning, Contraindications, Warnings and Precautions Sections have been revised extensively. The Microbiology Section has been revised significantly and relocated. Minor changes have been made to the Clinical Pharmacology Section and throughout the labeling. The formulation no longer appears as part of the established name based on discussions with Eric Sheinen, PhD, Director, New Drug Chemistry III, with agreement from the Antiviral Division.

- Revised draft labeling for NDA 20-694, incorporating the changes mentioned above, with additions specific to this NDA highlighted is also attached. Several revisions based on the recommended labeling issued with the action letter for NDA 20-537 have been incorporated, including changes in the AE incidence tables based upon updated safety information. As discussed with Frank Cross, the safety update incorporating this new safety information will be submitted very shortly. We will discuss whether to update the adverse event incidence rates for systemic fungal infections with the Antiviral Division.

A diskette containing the WordPerfect versions of both of these versions is provided.

Please call me at (609) 730-3069 if you have any questions.

Sincerely,

Cynthia Chianese

Cynthia Chianese
Manager, Regulatory Affairs

Enclosures

Desk copy: Frank Cross (hard copy plus diskette)

g:\regulato\wpdocs\1996\sporanox\20-694.pi

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Sent Via Overnight Mail

October 31, 1996

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products/HFD-540
Food and Drug Administration
Corporate Building
9201 Corporate Boulevard
Rockville, MD 20850

Subject: NDA 20-694
SPORANOX® (itraconazole capsules)
Revised proposed labeling

Dear Dr. Wilkin:

In response to a request made by Frank Cross, Project Manager, attached please find revised proposed labeling for the above NDA. This version incorporates the changes agreed upon thus far with the Antiviral Division for NDA 20-083, without updated safety information for NDA 20-694.

A diskette containing the WordPerfect version of this labeling is provided.

Please call me at (609) 730-3069 if you have any questions.

Sincerely,

Cynthia Chianese
Manager, Regulatory Affairs

Enclosures

Desk copy: Frank Cross (hard copy plus diskette)

g:\regulato\wpdocs\1996\sporanox\20-694.pi2

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November 13, 1996

Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products, HFD-540
ATTN: Document Control Room
Food and Drug Administration, CDER, ODE V
5600 Fishers Lane
Rockville, Maryland 20857

SUBJECT: SPORANOX® (itraconazole) Capsules
NDA 20-694
Response to FDA Request re: Environmental Assessment

Dear Dr. Wilkin:

Reference a November 12, 1996 telephone conversation between Frank Cross (FDA) and Cindy Chianese (Janssen). In response to FDA's request, we hereby submit a revised EA for the subject NDA, removing all reference to SPORANOX® oral solution NDA 20-657. Please note that information extracted from referenced source documents, included herein for convenience of review, retain their original pagination.

We reiterate that Confidential Appendices A,B,C,D,E are considered proprietary trade secrets and may not be released without Janssen's prior authorization.

Please contact me at (609) 730-3079 if you have any questions.

Sincerely,

Jeffrey J. Blumenstein, Ph.D.
Director, Technical Regulatory Affairs

Desk copy: Frank Cross

g:\tra\itracon\dorado.sa\7

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Sent via Overnight Mail

December 3, 1996

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products/HFD-540
Food and Drug Administration
Corporate Building
9201 Corporate Boulevard
Rockville, MD 20850

Subject: NDA 20-694
SPORANOX® (itraconazole) Capsules
Final labeling and Phase IV commitment

Dear Dr. Wilkin:

As discussed with Frank Cross, Project Manager, this letter confirms that Janssen is in agreement with the labeling faxed to us on December 3, 1996.

Additionally, Janssen commitments to conduct proper study(ies) to find the best dosing regimen for itraconazole in the treatment of onychomycosis of the fingernails. This study will include sufficient numbers of both males and females for analysis. We will submit the draft protocol for your review within 6 months of approval of this NDA. We propose discussing the study design with Dr. Ko prior to submission of the draft protocol for further detail on the objective of the study.

Please call me at (609) 730-3069 if you have any questions.

Sincerely,

Cynthia Chianese

Cynthia Chianese
Manager, Regulatory Affairs

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