CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **20-966**

CORRESPONDENCE

JANSSEN • PHARMACEUTICA • RESEARCH FOUNDATION •

March 26, 1999

Mark J. Goldberger, M.D., M.P.H., Director
Division of Special Pathogens and Immunologic
Drug Products/HFD-590
Food and Drug Administration, CDER
Central Document Room
9201 Corporate Blvd.
Rockville, MD 20850

Subject: **NDA 20-966**
SPORANOX® (itraconazole) Injection

Phase IV Commitments

Dear Dr. Goldberger:

Please refer to our pending New Drug Application (NDA 20-966) for SPORANOX (itraconazole) Injection and your electronic transmission of March 25, 1999 regarding an additional Phase IV commitment. We wish to inform you of our agreement to the following Phase IV commitment for the subject application.

- We commit to file a labeling supplement to NDA 20-966 by June 30, 1999, requesting addition of saquinavir and clarithromycin to the Drug Interactions subsection of the labeling. In this regard, we agree to provide available information on these compounds and macrolides as a class.

If you have any questions, please contact me at (609) 730-3486.

Sincerely,

Edward G. Brann
Assistant Director, Regulatory Affairs

g:\regulato\itra iv\fda032699

JANSSEN AT WASHINGTON CROSSING
1125 TRENTON-HARBOURTON ROAD
POST OFFICE BOX 200
TITUSVILLE, NEW JERSEY 08560-0200

JANSSEN • PHARMACEUTICA • • RESEARCH FOUNDATION •

March 24, 1999

Mark J. Goldberger, M.D., M.Ph., Director
Division of Special Pathogens and Immunologic
Drug Products/HFD-590
Food and Drug Administration, CDER
Central Document Room
9201 Corporate Blvd.
Rockville, MD 20850

Subject: **NDA 20-966**
SPORANOX® (itraconazole) Injection

Phase IV Commitments

Dear Dr. Goldberger:

Please refer to our pending New Drug Application (NDA 20-966) for SPORANOX (itraconazole) Injection and to facsimile transmissions of March 18 and 23, 1999 regarding two Phase IV commitments. We wish to inform you of our agreement to the following Phase IV commitments for the subject application.

- We commit to study the pharmacokinetics and safety of SPORANOX (itraconazole) Injection in patients with renal dysfunction, including a cohort of patients with a glomerular filtration rate of <30 mL/min. We project initiating this study in 4Q99 with a final report submitted in 4Q2001.

- We commit to conduct a study in non-anesthetized dogs to investigate the potential for cardiotoxicity. We project initiating this study in 3Q99 with a final report submitted in 2Q2000.

We recommend meeting with appropriate members of the division shortly to review the study design for both Phase IV commitments.

If you have any questions, please contact me at (609) 730-3486.

Sincerely,

Edward G. Brann
Assistant Director, Regulatory Affairs

g:\regulato\itra iv\fda032399

JANSSEN AT WASHINGTON CROSSING
1125 TRENTON-HARBOURTON ROAD
POST OFFICE BOX 200
TITUSVILLE, NEW JERSEY 08560-0200

HFD-590/KIMZEY

Copy

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Rockville MD 20857

Date: March 8, 1999

To: Ned Brann
Janssen Research Foundation
Phone (609) 730-3486
Fax (609) 730-3091

From: Rene Kimzey RK
Project Manager, DSPIDP
Phone (301) 827-2196
Fax (301) 827-2326

Subject: Proposed labeling for NDA 20-966

Referencing our internal meeting of March 5, 1999 and our subsequent informal discussion with you, we are providing the attached suggestions for your labeling submission. As you know, additional issues are still pending and are not, therefore, included in this draft.

This information is being provided by telephone facsimile and should not be considered official correspondence. Please feel free to contact me at the above numbers for any questions or concerns.

HFD-590 Kimzey

JAN 8 1999

[redacted]

Abbott Laboratories
Attention: Thomas F. Willer, Ph.D.
Assistant Director, Regulatory Affairs
Hospital Products Division
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, IL 60064-3537

Dear Dr. Willer:

Your letter dated April 6, 1998, authorizes us to reference Drug Master File (DMF) [redacted] "Container/Closure Validation – Contract Manufacturing" in support Janssen Research Foundation's NDA 20-966.

Your communication dated April 6, 1998, was reviewed in support of Janssen Research Foundation's NDA 20-966 and the following additional information is requested:

1. Pertaining to endotoxin removal from the glass ampoules.

[redacted]

1. Pertaining to microbiological efficacy of the sterilization cycle.

   a. Details for the microbiological efficacy validation should be provided. Information on the number of thermocouples (heat distribution and penetration) used, the placement of the BIs in the load, and parameters for validation (specifications for temperature, time and F_o) should be included.
   b. It is not sufficient to submit validation data of only one run. Please submit validation data on at least 3 runs for review.

1. Pertaining to container-closure integrity.

   a. The glass ampoules used in the container-closure integrity test should be processed in the same manner as in a production run, including [redacted]

b. Please provide a description on how the container-closure integrity test is being conducted.
c. Please provide the sensitivity of the leak test.

These issues must be addressed prior to approval of Janssen's NDA 20-966.

This information should be provided as an amendment to your Drug Master File. Please forward two (2) copies to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12229 Parklawn Drive
Rockville, Maryland 20852

Janssen Research Foundation will be notified that the information in your DMF is inadequate to support their NDA. When you amend your DMF [redacted] please notify Janssen Research Foundation in accordance with 21 CFR 314.420(c) and notify the review chemist at the address below that your DMF has been amended. Do not provide a copy of the amendment to the review chemist.

Gene W. Holbert, Ph.D.
Center for Drug Evaluation and Research
Division of Special Pathogen and Immunologic Drug Products
Attention: DOCUMENT CONTROL ROOM, HFD-590
5600 Fishers Lane
Rockville, Maryland 20857

Since approval of Janssen Research Foundation's NDA 20-966 is contingent upon adequate information being provided in a supporting DMF, please submit the requested information.

If you have any questions you may contact Ms. Rene Kimzey at (301) 827-2127

Sincerely,

/S/

Norman R. Schmuff, Ph.D.
Division of Special Pathogen and
Immunologic Drug Products (HFD-590)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Rockville MD 20857

MEMORANDUM OF TELEPHONE FACSIMILE

Date: December 31, 1998

To: Ned Brann
Janssen Research Foundation
Phone (609) 730-3486
Fax (609) 730-3091

From: Rene Kimzey
Project Manager, DSPIDP
Phone (301) 827-2196
Fax (301) 827-2326

IND: 20-966
Sporanox (itraconazole) injection

Subject: Labeling comments

The following comments from the microbiology and clinical reviewers are being provided for your consideration:

CLINICAL

Proposed Dosage and Administration: "200 mg IV BID (2 one-hour infusions) for 2 days, followed by 200 mg IV QD (one one-hour infusion)"

In order to maintain consistency across the different labels it is recommended that the information describing resistance on lines 1 to 15, page 42 of volume 1, be provided under a separate subheading of "Resistance" in the Microbiology section of the label. Also, it would be appropriate to add a sentence to the existing text stating that like other azoles, treatment with itraconazole, can induce resistance. Finally, it would also be worthwhile to describe the drug interaction between the azoles and the polyenes in the "drug interaction" section (pages 47 – 51, volume 1) in addition to the discussion that appears under 'Microbiology'.

Based on the studies reviewed, the following changes in the 'Resistance' subsection of the label (lines 1 to 15, page 42, volume 1) and 'Drug Interaction' section (pages 47 – 51, volume 1) are recommended (the recommended changes are double-underlined):

The Label:

MICROBIOLOGY

Mechanism of Action:
No change.

Activity *in vitro* and *in vivo*:
No change.

Resistance:

Isolates from several fungal species with decreased susceptibility to itraconazole have been isolated *in vitro* and from patients receiving prolonged therapy.

~~*In vivo*~~ Studies *in vitro* and *in vivo* suggest that the activity of amphotericin B may be suppressed by prior azole antifungal therapy. As with other azoles, itraconazole inhibits the ^{14}C-demethylation step in the synthesis of ergosterol, a cell wall component of fungi. Ergosterol is the active site for amphotericin B. In one study the antifungal activity of amphotericin B against *Aspergillus fumigatus* infections in mice was inhibited by ketoconazole therapy. The clinical significance of test results obtained in this study is unknown.

Several *in vitro* studies have reported that some fungal clinical isolates, including *Candida* species, with reduced susceptibility to one azole antifungal agent may also be less susceptible to other azole derivatives. The finding of cross-resistance is dependent upon a number of factors, including the species evaluated, its clinical history, the particular azole compounds compared and the type of susceptibility test that is performed. The relevance of these *in vitro* susceptibility data to clinical outcome remains to be elucidated.

Drug Interaction

Polyenes: Prior treatment with itraconazole, like other azoles, may reduce or inhibit the activity of polyenes such as amphotericin B. However, the clinical significance of this drug effect has not been clearly defined.

HFD 590 Kimzey

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

NDA 20-966

Food and Drug Administration
Rockville MD 20857

DEC 29 1998

Janssen Research Foundation
Attention: Sheila M. Alexander
Asst. Director, Technical Regulatory Affairs
Janssen at Washington Crossing
1125 Trenton-Harbourton Road, P.O. Box 200
Titusville, NJ 80560-0200

Dear Ms. Alexander:

Please refer to your pending April 27, 1998 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sporanox (itraconazole) Injection.

We also refer to your submissions dated August 24, 1998 and October 1, 1998.

We have completed our review of the CMC section(s) of your submission and have the following comments and information requests:

1. With regard to controls for hydroxypropyl-β-cyclodextrin please:

   a. Provide information concerning the distribution of the hydroxypropyl groups.
   b. Delete the note concerning reduced sampling and testing (Vol. 1.2, p. 00050). Since this is not a compendial material, strict quality controls should be maintained.
   c. Tighten the specifications for Assay of β-CD, pH and Molar Degree of Substitution. Please provide batch analysis data from other batches of HP-β-CD to justify the limits for the tests. Please provide a numerical value for the results of the Heavy Metals test.
   d. Add an assay specification and test for HP-β-CD.
   e. Specify the flow rate used in the HPLC method for assay of β-cyclodextrin (Method E/A/0001/01).
   f. Explain why the Certificate of Analysis provided appears to have been issued by Janssen. [redacted] If so, the Certificate of Analysis should so state.
   g. Submit a letter of authorization for DMF [redacted] since it is referenced on Form 356H.
   h. Compare and evaluate the suitability of the specifications you propose for HP-β-CD with those proposed in Pharmacopeial Forum, 1998, 24(6), 7284-7289, and Stratten, C.E., "2-Hydroxypropyl-β-Cyclodextrin, Part II: Safety and Manufacturing Issues," Pharmaceutical Technology, Februarv 1992, 52-58.
   i. Provide method identification codes for all methods in Report No. SPR-EXC 97-019. The term "method appended" should not be used.

j. Provide a RSD value for the IR Method for Determination of Molar Substitution Degree of HP-β-CD.

2. With regard to manufacture of the drug product please:

a. Provide lot numbers and COAs for itraconazole and HP-β-CD used to manufacture the lots of drug product described in the batch records.
b. Provide numerical values in the Certificate of Analysis where appropriate, instead of the word "complies".

3. With regard to the Proposed Finished Product Specifications and Methods:
a. Please provide specific USP references. Please specify the number of samples for the Volume in Container control.
b. Please provide the RSD value for Accuracy of the HPLC method.
c. None of the batches show R057348 present near the 1.0% level. The limit should be reduced to 0.3%.
d. No batch exceeded 0.8% total impurities except in photostability studies. In view of the stability results, the specification for total impurities should be tightened from not more than 3% to not more than 1.0%.

4. With regard to the Container/Closure System:

a. The finished product specifications list the volume in the container [redacted] The size of the ampoule is specified as 25 mL. Rough calculations based on the dimensions from the drawing suggest that the ampoule size is 50 mL. Please clarify.
b. Please describe the siliconizing process.

5. With regard to Drug Product Stability:

a. Please identify any degradation products of HP-β-CD.
b. Please explain the changes in the assay procedures for itraconazole as stability studies progressed.
c. Please clarify the statement concerning the "switch to colorless ampoules...based on the new ICH guideline for photostability testing" which appears on page 45, Volume 1.3 and repeated on page 53 of the amendment of October 1, 1998.

6. With regard to the Marketed Stability Protocol: Testing should be performed quarterly for the first year. A nine-month test point should be added.

7. With regard to the Static/Dynamic Compatibility Studies please:

   a. Identify the chemical composition of particulate matter.
   b. Explain why an assay for HP-β-CD was not performed on the solution in these studies.

6. With regard to the draft Labeling please:

   a. Add the warning "NOT FOR IV BOLUS INJECTION" to the package insert.
   b. Note that the established name on the kit (outer) carton is not at least half as large of the proprietary name as required by 21 CFR § 201.10 (g) (2).
   c. Emphasize the statement "NOT FOR IV BOLUS INJECTION" on the vial labels and carton, perhaps by bolding.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee re-authorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee re-authorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Rene Kimzey, Project Manager, at (301) 827-2127.

Sincerely,

/S/ 12/23/98

Norman R. Schmuff, Ph.D.
Chemistry Team Leader for the
Division of Special Pathogen and Immunologic Drug Products, (HFD-590)
DNDC III, Office of New Drug Chemistry
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DATE: November 16, 1998

TO: Ned Brann
Janssen Research Foundation
1125 Trenton-Harbourton Road
Titusvile, N J 08560-0200
Phone (609) 730-3486
FAX (609) 730-3091

FROM: Rene Kimzey OK
DSPIDP/CDER/FDA
Phone (301) 827-2196
FAX (301) 827-2326

DRUG: Sporanox (itraconazole)

NDA: 20-966

The following comments on the above NDA are provided from the chemistry reviewer:

1. Please respond to the issues concerning HPBCD that were raised in FDA's IND letter dated January 26, 1966.

2. The molecular degree of substitution is stated to be 0.58-0.73. On the average, to how many hydroxypropyl groups per molecule does this value correspond?

3. How many possible isomers exist for this degree of substitution?

4. Is any information available concerning the distribution of the hydroxypropyl groups?

5. Please explain why the COA that was submitted in the NDA [redacted]

6. Please submit COA's for additional lots of HPBCD.

7. Please submit an LOA for DMF [redacted] since you reference it on Form 356H.

This information is being provided for your convenience by telephone facsimile and should not be considered official correspondence. Please feel free to contact me at the above numbers for any questions.

JANSSEN • PHARMACEUTICA • • RESEARCH FOUNDATION •

December 4, 1998

Mark J. Goldberger, M.D., M.Ph., Director
Division of Special Pathogens and Immunologic
Drug Products/HFD-590
Food and Drug Administration, CDER
Central Document Room
9201 Corporate Blvd.
Rockville, MD 20850

Subject: **NDA 20-966**
SPORANOX® (itraconazole) Injection
Addendum to Six-Month Safety Update

Dear Dr. Goldberger:

Please refer to our pending New Drug Application (NDA 20-966) for SPORANOX (itraconazole) Injection and to the amended six-month safety update submitted November 23, 1998.

On November 20, 1998, the undersigned and Dr. Suzanne Travers of the Janssen Research Foundation spoke with Dr. Regina Alivisatos to inform her of two points regarding the Integrated Summary or Safety (ISS). The first was that an amended six-month safety update would be submitted on November 23rd. The second was that we were preparing an addendum to the ISS reporting on cardiovascular safety data from a study in dogs. We reported that at the highest dose administered (10 mg/kg), a decrease in cardiac contractile performance and relaxation, an increase in peripheral vascular resistance and an increase in heart rate were noted. Although these findings may represent a species specific finding, the adverse event database was examined for any evidence of similar itraconazole-related cardiovascular events, including congestive heart failure as a clinical manifestation of decreased cardiac contractile performance. The addendum is enclosed.

A diskette formatted in Word 6.0 with the summary report from the addendum is also enclosed.

If you have any questions, please contact me at (609) 730-3486.

Sincerely,

Edward G. Brann
Manager, Regulatory Affairs

Enclosures
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Cardiovascular safety data on itraconazole HP-β-CD (hydroxypropyl-beta-cyclodextrin) intravenous solution in dogs and relevance for man

This study was conducted and the report submitted to Kyowa in Japan subsequent to the filing of NDA #20-966 and is provided in the six-month safety update to the NDA because of its relevance to itraconazole injection.

Findings in dogs

The cardiovascular safety (ECG, heart rate and blood pressure) of itraconazole (HP-β-CD) was evaluated in dogs dosed at 5, 7.5 and 10 mg/kg by intravenous infusion lasting 20 or 30 min./day for a period of one month in 2 repeated dose toxicity studies.[1-4] The infusion was done with a peripheral catheter placed into either the vena saphena or vena cephalica. As mentioned in the Integrated Nonclinical Summary[1], the dose of 10mg/kg resulted in one fatality, salivation, vomiting and decubitus, whereas the 5 mg/kg dose was well tolerated and the 7.5 mg/kg dose resulted in slight to moderate toxicity. No adverse effects on ECG, heart rate and blood pressure were observed when measured at the end of infusion at day 25 of the experiment at any of the doses tested.

Recently, at the occasion of the cardiovascular safety evaluation of another intravenous itraconazole formulation, comparative pharmacology trials with itraconazole HP-β-CD were initiated in anaesthetised dogs.

The results of these cardiovascular safety experiments are described in detail in Addendum 1 (Cardiovascular and pulmonary effects in anaesthetised dogs of 2.5 and 10 mg/kg intravenously of an itraconazole hydroxypropyl-β-cyclodextrin formulation; N133746). In summary, no adverse effects were noted with the vehicle (HP-β-CD) or with itraconazole IV dosed at 2.5 mg/kg over a period of one hour. At the toxic dose of 10 mg/kg given over a period of 1, 2 or 3 hours, a number of effects became evident, mainly consisting of a decrease in cardiac contractile performance and relaxation, an increase in peripheral vascular resistance and an increase in heart rate. These effects became apparent during the dosing period and were more expanded in time and less pronounced when a longer infusion period was used. As soon as the infusion was ended, a recovery was seen with normalisation to pre-dosing conditions. In this respect, the adverse effects are considered to be related to the high plasma concentration of itraconazole as measured in the blood compartment of these dogs. These effects were absent at the proportionally lower plasma concentrations of itraconazole at 2.5 mg/kg, indicating a threshold.

Venous and arterial plasma concentrations measured in the CPF189 study and their pharmacokinetic analysis are presented in Addendum 2 (Plasma concentration itraconazole (R051211) and of hydroxy-itraconazole (R063373) in anaesthetised beagle dogs after single

intravenous infusion of an HP-β-CD formulation of itraconazole at 2.5 and 10 mg/kg; N133747). Peak venous plasma concentrations of itraconazole averaged 1.25 (2.5 mg/kg in 1 hour), 4.77 (10 mg/kg in 2 hours) and 6.77 µg/ml (10 mg/kg/h). There was a prominent arterio-venous plasma concentration difference during the infusion, which increased with increasing infusion rates. The mean arterial plasma concentration of itraconazole when cardiovascular effects because apparent at 10 mg/kg given over a period of 1 hour is estimated to be about 5.6 µg/ml.

Safety data in humans

The cardiovascular safety of itraconazole IV was also discussed in the Integrated Summary of Safety.[4] As described in this summary, for study ITR-BEL-57, blood pressure and heart rate were monitored in four healthy volunteers during and after a 1-hour lasting infusion of 200 mg itraconazole (dosing schedule: 200 mg b.i.d.) for 2 days or approximately 2.5 mg/kg body weight per dose. No adverse effects on heart rate and blood pressure were noticed. The arterial mean plasma levels were estimated to be 4.2 µg/ml.

In another trial, ITR-BEL-77, twelve healthy volunteers received a single intravenous dose up to 200 mg during a 1 hour infusion period. Cardiovascular safety was monitored before and at 1 and 24 hours after the start of the infusion. No clinically relevant changes in heart rate, systolic and diastolic blood pressure or ECG intervals were observed.

The safety evaluation in 255 itraconazole treated patients did not reveal relevant adverse effects on cardiovascular parameters. The higher incidence of hypotension and cardiac failure in the intravenous itraconazole group required individual patient evaluation. None of these events, however, were considered to be related to the trial medication. It should be noted that the target patient population for this indication are patients at risk for deep fungal infections i.e., AIDS patients, patients with haematological malignancies and intensive care unit (ICU) patients.

In patients at steady-state for the recommended dosage scheme (1-hour infusions of itraconazole 200 mg b.i.d. on days 1-2, followed by 200 mg o.d.), the highest mean peak venous plasma concentrations of itraconazole averaged 2.86-3.12 µg/ml. The estimated mean maximal arterial plasma concentration is 4.2 µg/ml.

Discussion and conclusion

Adverse effects on cardiovascular parameters were seen in dogs dosed intravenously with itraconazole HP-β-CD formulation at a dose of 10 mg/kg (given either during a 1, 2 or 3 hour infusion period) whereas the dose of 2.5 mg/kg showed no effects. These new observations are not in conflict with the available documentation of itraconazole IV which

shows that in humans, at the therapeutic dose level, these high, toxic-dose-related findings in dogs were not observed. Therefore, these findings are not classified as a non-clinical ADE (Adverse Drug Effect) but, nevertheless, an update of the previous report is being prepared. The trigger at which the effects are induced in dogs is calculated to be around 5.6 µg/ml (arterial samples). In humans, the estimated mean maximal arterial plasma concentration at steady state of the proposed therapeutic dosage scheme is 4.2 µg/ml. The threshold for adverse cardiovascular effects, as seen in dogs, is not reached in humans. This is evidenced by the clinical safety data obtained up to now, suggesting an interspecies difference.

1. NDA 20-966, Item 5, Pharmaco-Toxicological Integrated Summary (Vol. 5, p 113). Van Cauteren H, et al. Pharmaco-Toxicological Integrated Summary on itraconazole-HP-β-CD intravenous solution (Expert Report). N129353

2. NDA 20-966, Item 5, (Vol. 12, p 18). Verstraeten A, et al.: Itraconazole (HP-β-CD). One-month subchronic toxicity study in Beagle dogs. N71078

3. NDA 20-966, Item 5, (Vol. 13, p 1). Borghys H, et al.: Itraconazole (HP-β-CD). One-month toxicity study in Beagle dogs. N112407

4. NDA 20-966, Item 8, (Vol. 59, p 1). Travers S, et al.: Integrated summary of information on the safety of itraconazole intravenous solution (itraconazole injection) in the treatment of systemic fungal infections. N133523/1

Summary of cardiac adverse event data in NDA #20-966

Since becoming aware of the cardiac findings in the dog studies, we initiated a review of the clinical trial safety database filed to NDA #20-966 on November 10, 199. A review of only those adverse events coded to "cardiac failure" and "left cardiac failure" occurring during the intravenous infusion period or within 14 days of completing the intravenous phase from the 360 patient itraconazole database is summarized in Table 1. Ten of the 360 patients (2.8%) treated with itraconazole injection in controlled, uncontrolled or pharmacokinetic trials had an adverse event coded to one of these two terms. Nine of these 10 patients were treated with itraconazole injection in controlled clinical trials. One event was considered by the investigator to be possibly related to test medication. There were no reports of cardiac failure in the 32 fluconazole patients. Two intravenous amphotericin B-treated patients had adverse events coded to congestive heart failure (2/202 amphotericin B patients; 1.0%). Summaries are presented for those itraconazole patients for whom Case Record Forms or adverse event forms were available. If an adverse event of any nature was reported as a Serious Adverse Event, that is noted in the summary.

Table 1: Summary of itraconazole injection-treated patients with an adverse event of cardiac failure during or within 14 days of completing therapy

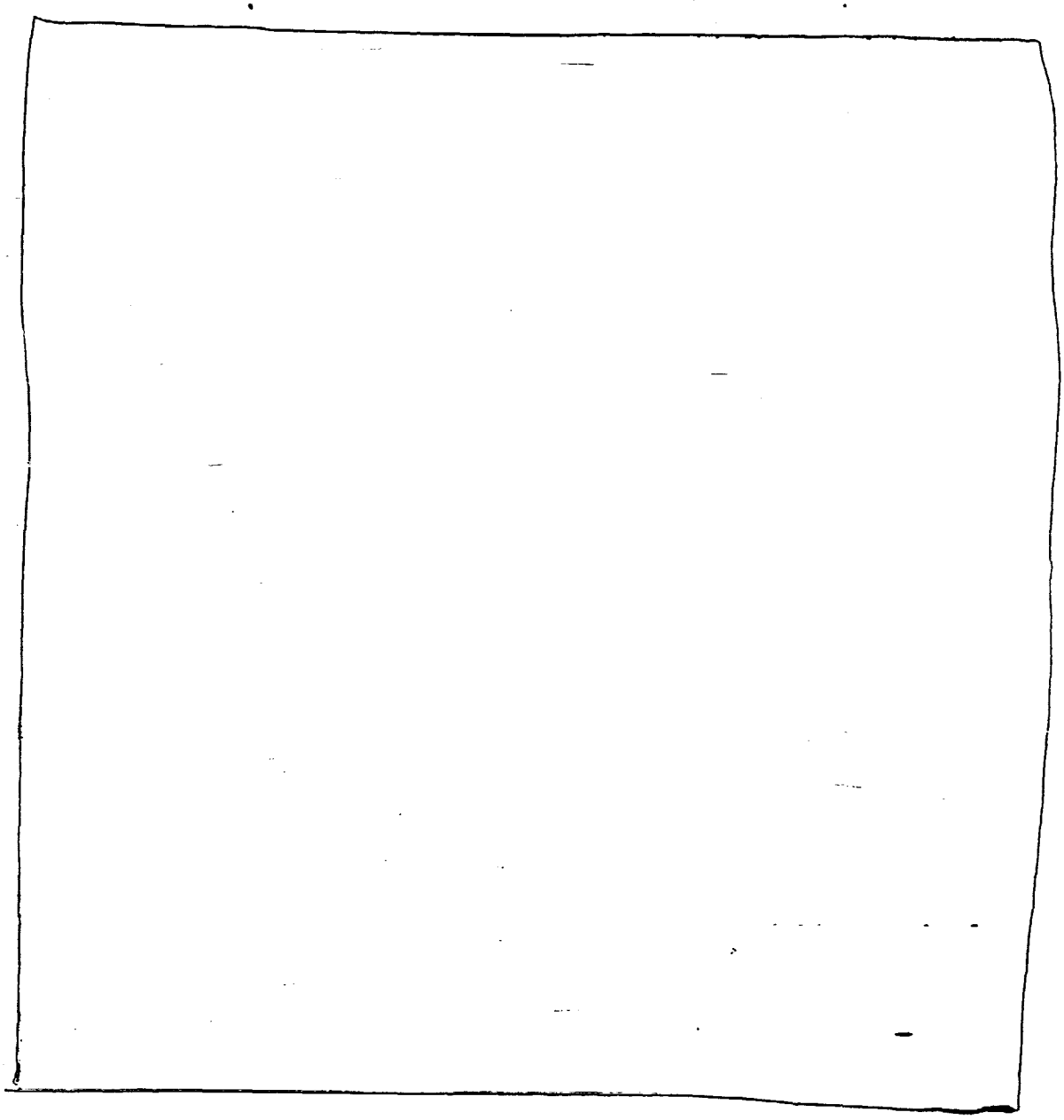
Trial	Subject	Gender[1]/Race[2]/Age	Adverse event	Dose	Days to onset	Severity	Relationship to drug (Investigator)	Outcome from AE
ITR-INT-58	0012	F/C/53	Refractory cardiac insufficiency	400	1	--	None	Died
ITR-INT-62	3218	M/C/55	Cardiac decompensation	400	3	Severe	None	Not recovered*
	3339	M/C/29	Cardiac decompensation	400	1	Moderate	None	Recovered
	3434	F/C/37	Congestive heart failure	200	5	Severe	None	Died
	3444	M/C/32	Cardiac insufficiency	400	3	Severe	None	Died
	3520	M/C/27	Pericardial rub	200	1	Moderate	None	Recovered
	3558	M/C/71	Cardiac toxicity	200	4	Severe	None	Died
	3423	M/O/61	Cardiogenic pulmonary edema	200	7	Moderate	None	Not recovered

[1]Gender: M=male, F=female

[2]Race: C=Caucasian, B=Black, O=Other

[3]Adverse event began in a no-treatment phase but within 14 days of the end of treatment

*Erratum: Case Record Form for Patient 3218 indicated that the patient did not recover from the adverse event, whereas, the adverse event listings in final database indicated that the patient recovered

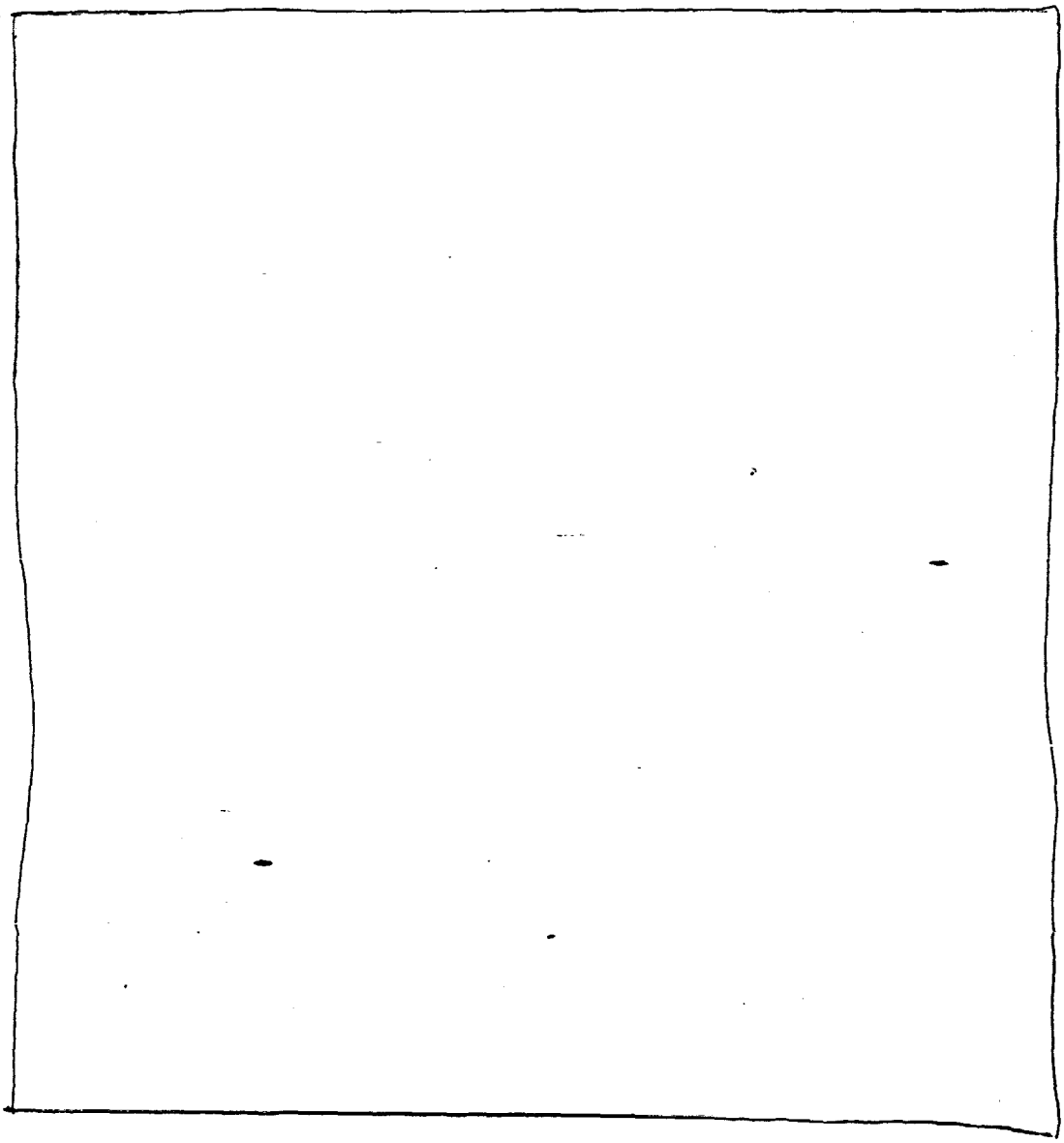


ITR-INT-58: A pharmacokinetic trial of itraconazole injection followed by itraconazole oral solution in intensive care unit patients.

Patient #0012, a 53-year-old Caucasian female, entered the trial on 15 March 1995. The patient was hospitalized in the intensive care unit in a coma following hypoglycemia-induced aspiration pneumonia. Her medical history included Addison's disease, insulin-dependent diabetes, and ischemic cardiomyopathy. Her initial clinical examination prior to receiving study medication was pertinent for left ventricular failure and cardiomyopathy. Upon admittance to the intensive care unit 1on 2 March 1995, the patient developed supraventricular tachycardia and three days later developed sudden

bradycardia followed by a cardiac arrest. She was successfully resuscitated and was started on an epinephrine continuous infusion. The patient's hemodynamic and pulmonary status stabilized but was vasodepressor-dependent. She developed renal insufficiency, possibly due to cardiac failure. On 17 March 1995 the patient was started on itraconazole injection. On the same day, she developed hypoxia, hypotension, and a cardiac arrest. She then developed cardiogenic shock and a left-sided pneumothorax due to ventilator-associated barotrauma. She died on 18 March 1995 from refractory hypoxia and shock.

This patient was reported as having a Serious Adverse Event.



ITR-INT-62: A randomized comparative multicenter trial of itraconazole injection followed by itraconazole oral solution versus intravenous amphotericin B for the empiric treatment of febrile neutropenic patients with hematological malignancy.

Patient #3218, a 55-year-old Caucasian male, entered the trial on 26 October 1996 with a history of acute lymphocytic leukemia. Initial clinical findings were significant for dyspnea, lung crepitations and lung infiltrates. The patient had undergone his first treatment for ALL on 2 October 1996 and subsequently received vincristine, isofosfamide, methotrexate, cyclophosphamide, cytarabine, and teniposide. Treatment with itraconazole injection was initiated on 26 October 1996. Therapy with itraconazole injection was discontinued after 4 days due to severe dyspnea not attributed by the investigator to itraconazole. Other adverse events reported included cardiac decompensation and fever.

This patient was reported as having a Serious Adverse Event.

Patient #3339: No further data are available as the adverse event was not serious and did not result in trial discontinuation.

Patient #3434, a 37-year-old Caucasian female, entered the trial on 21 January 1997 with a history of acute myelogenous leukemia and a fever of unknown origin. The patient had undergone her first treatment for AML on 14 January 1997 with cytarabine and hydroxyurea. Treatment with itraconazole was started on 21 January 1997. Admission physical examination revealed a pale, diaphoretic woman with right sided chest wheezes. On 25 January she was diagnosed with severe congestive heart failure reported by the investigator as serious but unrelated to trial medication. The patient was noted to be short of breath with a cough and rapid breathing during febrile episodes on 25 through 27 January 1997. Symptoms improved after diuresis but worsened over the night of 30 to 31 January 1997. A chest X-ray showed congestive heart failure. She became hypotensive and was intubated. She continued on study medication for a total of 15 days discontinuing therapy on 4 February 1997 with increased BUN, creatine phosphokinase, and liver enzymes. The patient died on 28 March 1997 of overwhelming sepsis, pancytopenia, AML, acute renal failure, and a dilated cardiomyopathy.

This patient was reported as having a Serious Adverse Event.

Patient #3444, a 32-year-old Caucasian male, entered the trial on 31 July 1996 with a history of a second relapse of lymphoma and fever of unknown origin. There was no past history of cardiac disease and physical examination on entry into the study revealed normal cardiac findings. The patient received chemotherapy treatment with etoposide, cyclophosphamide, and another medication, probably carmustine, beginning on 23 July 1996 with a peripheral stem cell transplant on 29 July 1996. Treatment with itraconazole injection was started on 1 August 1996 and was discontinued 5 August 1996 due to cardiac failure and respiratory insufficiency, neither of which were attributed by the investigator to study drug. The patient died on 6 August 1996. The Case Record Form revealed that the patient inadvertently received 200 mg itraconazole injection twice daily for the first four days, instead of the protocol specified two days.

This patient was reported as having a Serious Adverse Event.

Patient #3520: No further data are available as the adverse event was not serious and did not result in trial discontinuation.

Patient # 3558, a 71-year-old Caucasian male, with a history of acute myelogenous leukemia, was hospitalized on 15 August 1997 for chemotherapy. The patient had undergone his first treatment for AML on 15 August 1997 with idarubicin and cytarabine. During the hospitalization, he experienced neutropenic fevers with negative blood cultures. At initiation of treatment with intravenous itraconazole (20 August 1997), the patient was fluid overloaded with a concomitant medical history of pulmonary edema, hyponatremia, hypocalcemia, and hypophosphatemia. On physical examination the patient appeared ill with shortness of breath, tachycardia, and atrial fibrillation. An echocardiogram showed grossly diminished left ventricular function with probable left ventricular enlargement. The patient underwent a right heart catheterization and was diagnosed with fluid overload and sepsis. He was also hypotensive and diagnosed with acute renal failure. On 22 August 1997, the patient required intubation for respiratory distress. Treatment with study medicine was discontinued on 23 August 1997. On 24 August 1997, the patient was found to be hypotensive in atrial fibrillation with a rapid ventricular rate. The patient died that same day. The investigator attributed his death to cardiac toxicity from chemotherapy and a suspected, but undocumented, infection.

This patient was reported as having a Serious Adverse Event.

Patient # 3423, a 61-year-old male was admitted with a fever of unknown origin and acute myelogenous. He also had a history of insulin dependent diabetes, stomatitis, and chemotherapy-related nausea and vomiting. The patient received study drug from 12 to 21 September 1997. From 11 through 20 September 1997, the patient also received daily platelet and/or red cell transfusions. The patient had undergone his first treatment for AML on 26 August 1997 with daunorubicin, ARA-C, and solumedrol. On 13 September adverse events of gastrointestinal bleeding, decreased air entry in both lungs and confusion were reported. On 14 September 1997, adverse events of an S3 gallop and irregular pulse of moderate severity were reported. The patient received his first dose of digoxin and Lasix® on 14 September 1997, with a diagnosis of fluid overload. The digoxin was continued daily for arrhythmia and chest pain. The patient had rigors on 16 September 1997, chest pain on 17 September and respiratory distress with a worsening chest examination diagnosed as cardiogenic pulmonary edema on 18 September 1997. None of these events were determined by the investigator to be related to study drug. On 19 September 1997, a right sided infiltrate was noted on chest X-ray which was reported as possibly related to trial medication. Amphotericin was initiated at this time. The patient was discontinued from itraconazole therapy on 22 September 1997 due to an insufficient response to therapy. The patient subsequently died on 29 September 1997 from pneumonia and underlying AML.

This patient was reported as having a Serious Adverse Event.

Other cardiac adverse events reported in clinical trials

The Sponsor reviewed the 234 patient itraconazole adverse event database for additional cardiovascular events from controlled clinical trials. The results of this review are summarized in Table 2. The small sample size of 32 fluconazole-treated patients makes treatment comparisons between fluconazole and itraconazole or amphotericin B of limited value.

Table 2: Number and incidence of patients with cardiovascular adverse events reported during or within 14 days of intravenous administration from controlled clinical trials

Adverse events	Controlled		
	ITR n=234	FLU n=32	AMB n=202
Cardiovascular disorders			
Heart murmur	4 (1.7)	0 (0.0)	2 (1.0)
ECG abnormal specific	1 (0.4)	0 (0.0)	0 (0.0)
Cyanosis	2 (0.9)	0 (0.0)	1 (0.5)
Circulatory failure	1 (0.4)	0 (0.0)	1 (0.5)
Cardiomegaly	2 (0.9)	0 (0.0)	2 (1.0)
Edema dependent	1 (0.4)	0 (0.0)	5 (2.5)
Hypotension, hypotension postural	23 (9.8)	4 (12.5)	24 (11.9)
Hypertension, aggravated hypertension	13 (5.6)	6 (18.8)	8 (4.0)
Heart rate and rhythm			
Cardiac arrest	0 (0.0)	3 (9.4)	2 (1.0)
Tachycardia, supraventricular tachycardia, and ventricular tachycardia	13 (5.6)	2 (6.3)	13 (6.4)
Palpitations	1 (0.4)	0 (0.0)	1 (0.5)
Extrasystoles	2 (0.9)	0 (0.0)	0 (0.0)
Bradycardia	4 (1.7)	2 (6.3)	0 (0.0)
Arrhythmia	3 (1.3)	0 (0.0)	3 (1.5)
Atrial fibrillation	7 (3.0)	0 (0.0)	3 (1.5)

Discussion and conclusions

A recently completed nonclinical cardiovascular safety study in dogs was conducted to investigate the safety of another itraconazole intravenous formulation (itraconzole nanocrystals). Itraconazole HP-β-CD was used as the comparator drug in that study. At the highest dose administered (10 mg/kg) and at estimated mean arterial concentrations of approximately 5.6 μg/ml, a decrease in cardiac contractile performance and relaxation, an increase in peripheral vascular resistance, and an increase in heart rate were noted. A normalization to predose conditions was observed after the infusion completed. Although these findings may represent a species specific finding, the adverse event database was examined for any evidence of similar itraconazole-related cardiovascular events, including congestive heart failure as a clinical manifestation of decreased cardiac contractile performance.

In the 360 patient itraconazole database, 10 patients (2.8%) experienced an adverse event coded to congestive heart failure during or within 14 days of completing treatment. In the 202 patient amphotericin B database, two patients (1.0%) had adverse events coded to congestive heart failure. If the database is restricted to only those patients participating in controlled trials, the incidence for itraconazole increases to 3.8% compared to 1.0% for amphotericin B.

Of the 10 cases of congestive heart failure in itraconazole-treated patients [redacted] a controlled trial in disseminated histoplasmosis and blastomycosis, one in ITR-INT-58, an open trial in patients in intensive care unit settings [redacted] and seven in ITR-INT-62, a controlled trials in patients with hematological malignancies, neutropenia, and fever of unknown origin. Of these 10 cases, one was determined by the investigator to be possibly related to itraconazole (Patient #0003). In the Sponsor's opinion, three additional cases raised a question of association between congestive heart failure and itraconazole (Patient #3444, #3423, and #3434). All three patients participated in ITR-INT-62 and had hematological malignancies treated with chemotherapeutic agents associated with multiple toxicities, including cardiovascular toxicity. Patient #3423, for example, was treated with daunorubicin, which carries a black box warning for

cardiac toxicity and congestive heart failure making a definitive conclusion of association difficult.

In the remaining six cases, two patients had a history of cardiac disease (Patient #0012, #1163) and one had signs and symptoms of ongoing cardiac disease at the time of initiation of itraconazole injection (Patient #3558). In other three cases there were insufficient data to determine a causal relationship between the adverse event and itraconazole injection (Patient #3218, #3339, and #3520).

The Sponsor further reviewed other cardiovascular adverse events from the 234 patient itraconazole database from controlled clinical trials. The incidence of other cardiovascular adverse events was comparable between itraconazole and amphotericin B with the following exceptions. Atrial fibrillation, hypertension, and bradycardia were observed with a slightly higher incidence in itraconazole-treated patients compared with the amphotericin B-treated patients. Dependent edema and hypotension were observed with a slightly higher incidence in amphotericin B-treated patients compared with itraconazole-treated patients.

The available information does not suggest that itraconazole intravenous solution has a negative effect on cardiac function in humans. In most of the clinical trial cases with an adverse event suggestive for cardiac failure the investigator did not attribute the event to the study drug, as other factors, such as previous chemotherapy, were more plausible explanations.

The only drugs currently available for intravenous use for the treatment of disseminated histoplasmosis, blastomycosis, and aspergillosis are amphotericin B and liposomal preparations of amphotericin B. Cardiovascular risks are not unique to the patient population being treated for systemic fungal infection and have been associated with amphotericin B preparations. The potential benefit from the use of itraconazole injection for its labeled indications outweighs potential risks of toxicity.

HFD-590 Kimzey

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM OF TELECONFERENCE

DATE: June 19, 1998

TO: Ned Brann

FROM: Rene Kimzey

NDA: 20-966 Sporanox (itraconazole)

SUBJECT: Proposal for four month Safety Update

FDA PARTICIPANTS

Regina Alivisatos MD
Brad Leissa, MD
Ellen Frank, PharmD
Rene Kimzey

JANSSEN PARTICIPANTS

Bruce Moskovitz, MD
Suzanne Travers, MD
Joe Guarnieri, PhD
Susan Christian
Ned Brann

Today's teleconference was held in response to your May 27, 1998 proposal for the four month safety update. In summary, the following four points were decided upon.

1. The 120 day safety update will include data on the initial 255 participants, 7 additional participants on the completed trial, and Serious Adverse Events from all trials through May 1, 1998.

2. On or before 10/31/98, the data on approximately 200 additional participants (~110 on itraconazole) will be supplied. This will include data through 5/1/98 from all closed trials or about 462 patients. The three uncompleted trials will not be included.

3. All information will be in the format used in the laptop database.

4. Janssen will submit proposed labeling revisions. This will include data sets and text supporting the changes.

We are providing the above information via telephone facsimile for your convenience. **This material should be viewed as unofficial correspondence.** Please feel free to contact me or Ellen Frank if you have any questions regarding the contents of this transmission.

/S/

Rene Kimzey
Project Manager
Division of Special Pathogens and Immunologic Drug Products

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-966

12/29/98

Janssen Research Foundation
Attention: Sheila M. Alexander
Asst. Director, Technical Regulatory Affairs
Janssen at Washington Crossing
1125 Trenton-Harbourton Road, P.O. Box 200
Titusville, NJ 80560-0200

Dear Ms. Alexander:

Please refer to your pending April 27, 1998 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sporanox (itraconazole) Injection.

We also refer to your submissions dated August 24, 1998 and October 1, 1998.

We have completed our review of the CMC section(s) of your submission and have the following comments and information requests:

1. With regard to controls for hydroxypropyl-β-cyclodextrin please:

   a. Provide information concerning the distribution of the hydroxypropyl groups.

   [redacted]

   c. Tighten the specifications for Assay of β-CD, pH and Molar Degree of Substitution. Please provide batch analysis data from other batches of HP-β-CD to justify the limits for the tests. Please provide a numerical value for the results of the Heavy Metals test.
   d. Add an assay specification and test for HP-β-CD.
   e. Specify the flow rate used in the HPLC method for assay of β-cyclodextrin (Method E/A/0001/01).
   f. Explain why the Certificate of Analysis provided appears to have been issued by Janssen. [redacted] so, the Certificate of Analysis should so state.
   g. Submit a letter of authorization for [redacted] since it is referenced on Form 356H.
   h. Compare and evaluate the suitability of the specifications you propose for HP-β-CD with those proposed in Pharmacopeial Forum, 1998, 24(6), 7284-7289, and Stratten, C.E., "2-Hydroxypropyl-β-Cyclodextrin, Part II: Safety and Manufacturing Issues," Pharmaceutical Technology, February 1992, 52-58.
   i. Provide method identification codes for all methods in Report No. SPR-EXC 97-019. The term "method appended" should not be used.

j. Provide a RSD value for the IR Method for Determination of Molar Substitution Degree of HP-β-CD.

2. With regard to manufacture of the drug product please:

a. Provide lot numbers and COAs for itraconazole and HP-β-CD used to manufacture the lots of drug product described in the batch records.
b. Provide numerical values in the Certificate of Analysis where appropriate, instead of the word "complies".

3. With regard to the Proposed Finished Product Specifications and Methods:
a. Please provide specific USP references. Please specify the number of samples for the Volume in Container control.
b. Please provide the RSD value for Accuracy of the HPLC method.
c. None of the batches show R057348 present near the 1.0% level. The limit should be reduced to 0.3%.
d. No batch exceeded 0.8% total impurities except in photostability studies. In view of the stability results, the specification for total impurities should be tightened from not more than 3% to not more than 1.0%.

4. With regard to the Container/Closure System:

a. The finished product specifications list the volume in the container [redacted]

b. Please describe the siliconizing process.

5. With regard to Drug Product Stability:

a. Please identify any degradation products of HP-β-CD.
b. Please explain the changes in the assay procedures for itraconazole as stability studies progressed.
c. Please clarify the statement concerning [redacted]

6. With regard to the Marketed Stability Protocol; Testing should be performed quarterly for the first year. A nine-month test point should be added.

7. With regard to the Static/Dynamic Compatibility Studies please:

   a. Identify the chemical composition of particulate matter.
   b. Explain why an assay for HP-β-CD was not performed on the solution in these studies.

6. With regard to the draft Labeling please:

   a. Add the warning "NOT FOR IV BOLUS INJECTION" to the package insert.
   b. Note that the established name on the kit (outer) carton is not at least half as large of the proprietary name as required by 21 CFR § 201.10 (g) (2).
   c. Emphasize the statement "NOT FOR IV BOLUS INJECTION" on the vial labels and carton, perhaps by bolding.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee re-authorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee re-authorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Rene Kimzey, Project Manager, at (301) 827-2127.

Sincerely,

/S/ 12/23/98

Norman R. Schmuff, Ph.D.
Chemistry Team Leader for the
Division of Special Pathogen and Immunologic Drug Products, (HFD-590)
DNDC III, Office of New Drug Chemistry
Center for Drug Evaluation and Research