CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-966/S-001, S-003, S-004

20-657/S-004, S-005

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

NDA 20-966/S-001, S-003, S-004

Janssen Research Foundation
Attention: Edward G. Brann
Asst. Director, Regulatory Affairs
1125 Trenton-Harbourton Rd.
P. O. Box 200
Titusville, NJ 08560-0200

Dear Mr. Brann:

Please refer also to your supplemental new drug application (S-001) dated July 9, 1999, received July 14, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sporanox® (itraconazole) Injection, 10 mg/mL.

We acknowledge receipt of your submissions dated October 9, 2000, October 26, 2000, January 19, 2001, April 2, 2001, April 16, 2001 and May 4, 2001.

This supplemental new drug application provides for two of the three commitments acknowledged in our March 30, 1999 approval letter as follows:

2. Conduct a study of intravenous itraconazole in non-anesthetized dogs to investigate the potential for cardiotoxicity.

3. File a labeling supplement to NDA 20-966 by June 30, 1999, requesting the addition of saquinavir and clarithromycin to the Drug Interactions subsection of the labeling, and provide available information on these compounds and macrolides as a class.

We have reviewed your submissions and conclude that the above commitments were fulfilled.

A **Macrolide Antibiotics** statement has been added to **PRECAUTIONS/Drug Interactions**, and clarithromycin and erythromycin are included in that statement. A **Protease Inhibitor** statement including saquinavir, indinavir and ritonavir has also been added to **PRECAUTIONS/Drug Interactions**.

We agreed that based on the results of the dog study, labeling revisions were necessary to address cardiotoxicity.

The following commitment acknowledged in our March 30, 1999 approval letter is still pending:

1. 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 less than 30 mL/min., to be initiated in 4Q99 with a final report submitted 4Q01.

Please refer also to your supplemental new drug application (S-003) dated January 19, 2000, received January 21, 2000.

We acknowledge receipt of your submissions dated October 9, 2000, October 26, 2000, January 19, 2001, April 2, 2001, April 16, 2001 and May 4, 2001.

This supplemental new drug application provides for changes to the Sporanox® Injection label as summarized below:

1. Information concerning congestive heart failure in patients receiving Sporanox® has been added to the **Boxed Warning, CLINICAL PHARMACOLOGY/Special Populations/Decreased Cardiac Contractility, CONTRAINDICATIONS/Congestive Heart Failure, WARNINGS/Cardiac Dysrythmias, WARNINGS/Cardiac Disease,** and **ADVERSE REACTIONS/Post-marketing Experience.**

2. Dofetilide has been added to the list of **Drug Interactions** in the **Boxed Warning, CONTRAINDICATIONS/Drug Interactions,** and **PRECAUTIONS/ Drug Interactions/Antiarrythmics**. Astemizole has been deleted from these sections of the label and the **PRECAUTIONS/Drug Interactions/Antihistamine** statement regarding astemizole has also been deleted.

3. Information describing Sporanox® as a CYP3A4 inhibitor causing increased plasma concentration levels of certain co-administered drugs has been added to the **Boxed Warning, CONTRAINDICATIONS/Drug Interactions** and **PRECAUTIONS/ Drug Interactions.** This information has also been added to the following drug classes in **PRECAUTIONS/ Drug Interactions: Anticonvulsants, Antimycobacterials, Antipsychotics, Macrolide Antibiotics, Non-nucleoside Reverse Transcriptase Inhibitors, Protease Inhibitors** and alfentanil and trimetrexate listed in the **"Other"** category.

4. Information concerning hepatotoxicity in patients receiving Sporanox® has been added to **CLINICAL PHARMACOLOGY/Special Populations/Hepatic Insufficiency, CONTRAINDICATIONS/Hepatitis, WARNINGS/Hepatic Effects, ADVERSE REACTIONS** and **ADVERSE REACTIONS/Post-marketing Experience.**

5. Information concerning the negative inotropic effect of dihydropyridine calcium channel blockers in patients receiving Sporanox® has been added to **PRECAUTIONS/Calcium Channel Blockers**.

6. The following drugs have been added to **PRECAUTIONS/Drug Interactions:**

   - alfentanil
   - alprazolam
   - atorvastatin
   - buspirone
   - cerivastatin
   - clarithromycin
   - docetaxel
   - dofetilide

- erythromycin
- nevirapine
- pimozide
- saquinavir
- sirolimus
- trimetrexate
- verapamil

Additionally, this section has been reorganized to include new class names.

7. Menstrual disorders was added to rare cases described in **ADVERSE REACTIONS/Post-marketing Experience.**

Please refer also to your supplemental new drug application (S-004) dated April 28, 2000, received May 1, 2000.

We acknowledge receipt of your submissions dated March 2, 2001, April 2, 2001, April 16, 2001 and May 4, 2001. Your submission of April 16, 2001 constituted a complete response to our March 1, 2001 action letter.

This supplemental new drug application provides for the use of Sporanox® Injection for empiric therapy in febrile neutropenic patients with suspected fungal infections (ETFN). This information has been added to **CLINICAL STUDIES, INDICATION AND USAGE,** and **DOSAGE AND ADMINISTRATION**.

We have completed the review of these supplemental applications, as amended, 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 agreed upon enclosed labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (package insert submitted May 4, 2001).

Please submit the copies of final printed labeling (FPL) electronically to each application according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no 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, these submissions should be designated "FPL for approved supplements NDA 20-966/S-001, S-003, S-004." Approval of these submissions by FDA is not required before the labeling is used.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632)(21 CFR 314.55 (or 601.27)). The Agency has not made a determination if a health benefit would be gained by studying Sporanox® Injection in pediatric patients for its approved indications. FDA is deferring submission of the pediatric assessments of safety and effectiveness that may be required under these regulations because pediatric studies should be delayed until additional safety or effectiveness data have been collected and reviewed. FDA will inform you

on or before September 30, 2002 whether pediatric studies are required under the rule. If FDA determines at that time that pediatric studies are necessary, FDA will also set a specific time at which you must submit the required assessments.

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

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If an additional letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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, call Robin Anderson, Labeling Reviewer at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Mark J. Goldberger, M.D., M.P.H.
Director
Division of Special Pathogen and Immunologic
Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

NDA 20-657/S-004, S-005

Janssen Research Foundation
Attention: Edward G. Brann
Asst. Director, Regulatory Affairs
1125 Trenton-Harbourton Rd.
P. O. Box 200
Titusville, NJ 08560-0200

Dear Mr. Brann:

Please refer to your supplemental new drug application (S-004) dated January 25, 1999, received January 27, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sporanox® (itraconazole) Oral Solution, 10mg/mL.

We acknowledge receipt of your submissions dated January 19, 2001, April 2, 2001, April 16, 2001 and May 4, 2001.

This supplemental new drug application provides for changes to the Sporanox® Oral Solution label as summarized below:

1. Information concerning congestive heart failure in patients receiving Sporanox® has been added to the **Boxed Warning, CLINICAL PHARMACOLOGY/Special Populations/Decreased Cardiac Contractility, CONTRAINDICATIONS/Congestive Heart Failure, WARNINGS/Cardiac Dysrythmias, WARNINGS/Cardiac Disease, PRECAUTIONS/Information for Patients** and **ADVERSE REACTIONS/Post-marketing Experience.**

2. Dofetilide has been added to the list of **Drug Interactions** in the **Boxed Warning, CONTRAINDICATIONS/Drug Interactions,** and **PRECAUTIONS/ Drug Interactions/Antiarrythmics**. Astemizole has been deleted from these sections of the label and the **PRECAUTIONS/Drug Interactions/Antihistamine** statement regarding astemizole has also been deleted.

3. Information describing Sporanox® as a CYP3A4 inhibitor causing increased plasma concentration levels of certain co-administered drugs has been added to the **Boxed Warning, CONTRAINDICATIONS/Drug Interactions** and **PRECAUTIONS/ Drug Interactions.** This information has also been added to the following drug classes in **PRECAUTIONS/ Drug Interactions: Anticonvulsants, Antimycobacterials, Antipsychotics, Macrolide Antibiotics, Non-nucleoside Reverse Transcriptase Inhibitors, Protease Inhibitors** and alfentanil and trimetrexate listed in the **"Other"** category.

4. Information concerning hepatotoxicity in patients receiving Sporanox® has been added to **CLINICAL PHARMACOLOGY/Special Populations/Hepatic Insufficiency, CONTRAINDICATIONS/Hepatitis, WARNINGS/Hepatic Effects, ADVERSE REACTIONS** and **ADVERSE REACTIONS/Post-marketing Experience.**

5. The **CLINICAL PHARMACOLOGY/Special Populations/Renal Insufficiency** subsection was revised to provide a description of a pharmacokinetic study of itraconazole capsules in renally impaired patients.

6. 6.Information concerning the negative inotropic effect of dihydropyridine calcium channel blockers in patients receiving Sporanox® has been added to **PRECAUTIONS/Calcium Channel Blockers**.

7. The following drugs have been added to **PRECAUTIONS/Drug Interactions:**

    - alfentanil
    - alprazolar
    - atorvastatin
    - bisulfan
    - buspirone
    - cerivastatin
    - clarithromycin
    - docetaxel
    - dofetilide
    - erythromycin
    - nevirapine
    - omeprazole
    - pimozide
    - saquinavir
    - sirolimus
    - trimetrexate
    - verapamil

    Additionally, this section has been reorganized to include new class names.

8. Menstrual disorders was added to rare cases described in **ADVERSE REACTIONS/Post-marketing Experience.**

Please refer also to your supplemental new drug application (S-005) dated April 28, 2000, received May 1, 2000.

We acknowledge receipt of your submissions dated March 2, 2001, April 2, 2001, April 16, 2001 and May 4, 2001. Your submission of April 16, 2001 constituted a complete response to our March 1, 2001 action letter.

This supplemental new drug application provides for the use of Sporanox® Injection for empiric therapy in febrile neutropenic patients with suspected fungal infections (ETFN). This information

has been added to **CLINICAL STUDIES, INDICATION AND USAGE,** and **DOSAGE AND ADMINISTRATION.**

We have completed the review of these supplemental applications, as amended, 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 agreed upon labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

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Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632)(21 CFR 314.55 (or 601.27)). The Agency has not made a determination if a health benefit would be gained by studying Sporanox® Oral Solution in pediatric patients for its approved indications. FDA is deferring submission of the pediatric assessments of safety and effectiveness that may be required under these regulations because pediatric studies should be delayed until additional safety or effectiveness data have been collected and reviewed. FDA will inform you on or before September 30, 2002 whether pediatric studies are required under the rule. If FDA determines at that time that pediatric studies are necessary, FDA will also set a specific time at which you must submit the required assessments.

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Sincerely,

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Mark J. Goldberger, M.D., M.P.H.
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