DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-966/S-006

Johnson and Johnson Pharmaceutical Research and Development. L.L.C.
Attention: Hanna Benze
Director, Regulatory Affairs
1125 Trenton-Harbourton Rd.
P. O. Box 200
Titusville, NJ 08560-0200

Dear Ms. Benze:

Please refer to your supplemental new drug application dated February 5, 2002, received February 14, 2002, 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 June 11, 2002 and June 27, 2002.

This supplemental new drug application provides for the following changes to the Sporanox® Injection label. Added text is double underlined and deleted text is in ~~strikethough.~~

1. WARNINGS

- The second paragraph is now bolded and revised to read:

> **Hepatic Effects**: **SPORANOX® has been associated with rare cases of serious hepatotoxicity, including liver failure and death. Some of these cases had neither pre-existing liver disease nor a serious underlying medical condition.** **and some of these cases developed within the first week of treatment. If clinical signs or symptoms develop that are consistent with liver disease,** ~~the risks and benefits of continued~~ **treatment should be discontinued and liver function testing performed. Continued SPORANOX® use** ~~should be reassessed.~~ **or reinstitution of treatment with SPORANOX® is strongly discouraged unless there is a serious or life threatening situation where the expected benefit exceeds the risk. (See PRECAUTIONS: Information for Patients and ADVERSE REACTIONS.)**

2. PRECAUTIONS

- In the **General** subsection, the first paragraph was completely revised and a neuropathy statement was added to read:

~~**General:** Hepatic enzyme test values should be monitored in patients with pre-existing hepatic function abnormalities or those who have experienced liver toxicity with other medications. Hepatic enzyme test values should be monitored periodically in all patients~~

~~receiving continuous treatment for more than 1 month, or at any time a patient develops signs or symptoms suggestive of liver dysfunction.~~

General: Rare cases of serious hepatotoxicity have been observed with Sporanox® treatment, including some cases within the first week. In patients with elevated or abnormal liver enzymes or active liver disease, or who have experienced liver toxicity with other drugs, treatment with Sporanox® is strongly discouraged unless there is a serious or life threatening situation where the expected benefit exceeds the risk. Liver function monitoring should be done in patients with pre-existing hepatic function abnormalities or those who have experienced liver toxicity with other medications and should be considered in all patients receiving Sporanox®. Treatment should be stopped immediately and liver function testing should be conducted in patients who develop signs and symptoms suggestive of liver dysfunction.

If neuropathy occurs that may be attributable to Sporanox® capsules, the treatment should be discontinued.

3. ADVERSE REACTIONS

- The third sentence in the first paragraph was revised to read:

If clinical signs or symptoms develop that are consistent with liver disease, ~~the~~ treatment should be discontinued and liver function testing performed. The risks and benefits of ~~continued~~ SPORANOX® use should be reassessed. (See WARNINGS: Hepatic Effects and PRECAUTIONS: General and Information for Patients.)

- The **Post-marketing Experience** subsection was completely revised to read:

~~In worldwide post-marketing experience with SPORANOX® Capsules in treatment of onychomycosis and/or systemic fungal infections, peripheral edema, allergic reactions, including rash, pruritus, urticaria, angioedema, and, in rare instances, anaphylaxis and Stevens-Johnson syndrome, have been reported. Post-marketing experiences have also included reports of elevated liver enzymes and rarely liver failure. Rare cases of congestive heart failure and pulmonary edema have been reported. Rare cases of alopecia, hypertriglyceridemia, menstrual disorders, and neutropenia, and isolated cases of neuropathy have also been reported, although the causal association with SPORANOX® is uncertain. (See CLINICAL PHARMACOLOGY: Special Populations, CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions for more information).~~

Worldwide post-marketing experiences with the use of SPORANOX® include adverse events of gastrointestinal origin, such as dyspepsia, nausea, vomiting, diarrhea, abdominal pain and constipation. Other reported adverse events include peripheral edema, congestive heart failure and pulmonary edema, headache, dizziness, peripheral neuropathy, menstrual disorders, reversible increases in hepatic enzymes, hepatitis, liver failure, hypokalemia, hypertriglyceridemia, alopecia, allergic reactions (such as pruritus, rash, urticaria, angioedema, anaphylaxis), Stevens-Johnson syndrome, and neutropenia. (See CLINICAL PHARMACOLOGY: Special Populations, CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions for more information).

We have completed the review of this supplemental application, 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, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted June 27, 2002).

Please submit the copies of final printed labeling (FPL) electronically 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, this submission should be designated "FPL for approved supplement NDA 20-966/S-006." Approval of this submission by FDA is not required before the labeling is used.

If a 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}

Renata Albrecht, M.D.
Acting Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Renata Albrecht

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