DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-083/S-040, S-041, S-044

Johnson & Johnson Pharmaceutical Research and Development
Attention: Melissa L. Gannon
Associate Director, Global Regulatory Affairs
920 Route 202 South
P.O. Box 300
Raritan, New Jersey 08869-0602

Dear Ms. Gannon:

Please refer to the following supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SPORANOX® (itraconazole) Capsules, 100 mg.

Supplemental Number	**Date of Submission**	**Date Received**
S-040	June 22, 2006	June 22, 2006
S-041	August 24, 2007	August 25, 2007
S-044	January 17, 2008	January 17, 2008

We also acknowledge receipt of your submissions dated July 28, September 4, and October 30, 2008. Your submissions dated September 4, 2008, received on September 5, 2008, constituted a complete response to our approvable letters dated December 22, 2006 (S-040), February 28, 2007 (S-041), and July 17, 2008 (S-044).

These supplemental new drug applications provide for changes to the **DESCRIPTION, CLINICAL PHARMACOLOGY/Special Populations/Renal Insufficiency, CLINICAL PHARMACOLOGY/Special Populations/Hepatic Insufficiency, MICROBIOLOGY, CONTRAINDICATIONS/Drug Interactions, WARNINGS/Cardiac Disease, PRECAUTIONS/General, PRECAUTIONS/Information for Patients, PRECAUTIONS/Antiarrhythmics, PRECAUTIONS/Drug Interactions/Calcium Channel Blockers, PRECAUTIONS/Drug Interactions/Other, PRECAUTIONS/Geriatric Use, ADVERSE REACTIONS/Post-marketing Experience, DOSAGE AND ADMINISTRATION,** and **HOW SUPPLIED** section of the package insert (PI) and the **WHO SHOULD NOT TAKE SPORANOX** and **WHAT ARE THE POSSIBLE SIDE EFFECTS OF SPORANOX** sections of the patient package insert (PPI).

We have completed our review of these applications as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling submitted on September 4, 2008.

The revisions to the package insert (PI) and patient package insert (PPI) are as follow (additions are noted with underline and deletions with ~~strikethrough~~):

1. In the **DESCRIPTION** section, the last paragraph is revised as follows (S-040):

   SPORANOX® Capsules contain 100 mg of itraconazole coated on sugar spheres. Inactive ingredients are hard gelatin capsule, ~~hydroxypropyl methylcellulose~~ hypromellose, polyethylene glycol (PEG) 20,000, starch, sucrose, titanium dioxide, FD&C Blue No. 1, FD&C Blue No. 2, D&C Red No. 22 and D&C Red No. 28.

2. The **CLINICAL PHARMACOLOGY/Special Populations/Renal Insufficiency** subsection is revised as follows (S-041):

   Limited data are available on the use of oral itraconazole in patients with renal impairment. A pharmacokinetic study using a single 200-mg dose of itraconazole (four 50-mg capsules) was conducted in three groups of patients with renal impairment (uremia: n=7; hemodialysis: n=7; and continuous ambulatory peritoneal dialysis: n=5). In uremic subjects with a mean creatinine clearance of 13 mL/min. x 1.73 m^2, ~~the bioavailability~~ the exposure, based on AUC, was slightly reduced compared with normal population parameters. This study did not demonstrate any significant effect of hemodialysis or continuous ambulatory peritoneal dialysis on the pharmacokinetics of itraconazole (T_{max}, C_{max}, and AUC_{0-8}). Plasma concentration-versus-time profiles showed wide intersubject variation in all three groups. Caution should be exercised when the drug is administered in this patient population. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION.)

3. In the **CLINICAL PHARMACOLOGY/Special Populations/Hepatic Insufficiency** subsection, is revised as follows (S-041):

   Hepatic Insufficiency
   Itraconazole is predominantly metabolized in the liver. Patients with impaired hepatic function should be carefully monitored when taking itraconazole. A pharmacokinetic study using a single oral 100 mg capsule dose of itraconazole was conducted in 6 healthy and 12 cirrhotic subjects. ~~No statistically significant differences in AUC were seen between these two groups.~~ A statistically significant reduction in mean C_{max} (47%) and a twofold increase in the elimination half-life (37 ± 17 hours vs. 16 ± 5 hours) of itraconazole were noted in cirrhotic subjects compared with healthy subjects. However, overall exposure to itraconazole, based on AUC, was similar in cirrhotic patients and in healthy subjects. ~~Patients with impaired hepatic function should be carefully monitored when taking itraconazole.~~ The prolonged elimination half-life of itraconazole observed in the single oral dose clinical trial with itraconazole capsules in cirrhotic patients should be considered when deciding to initiate therapy with other medications metabolized by CYP3A4. Data are not available in cirrhotic patients during long-term use of itraconazole. (See BOX WARNING, CONTRAINDICATIONS, PRECAUTIONS: Drug Interactions and DOSAGE AND ADMINISTRATION.)

4. In the **MICROBIOLOGY/Activity in Vitro and In Vivo** subsection, the first paragraph is revised as follows (S-041)

   Itraconazole exhibits *in vitro* activity against *Blastomyces dermatitidis, Histoplasma capsulatum, Histoplasma duboisii, Aspergillus flavus, Aspergillus fumigatus, Candida albicans,* and *Cryptococcus neoformans*. Itraconazole also exhibits varying *in vitro* activity against *Sporothrix schenckii, Trichophyton* species, *Candida krusei,* and other *Candida* species. ~~The bioactive metabolite, hydroxyitraconazole, has not been evaluated against *Histoplasma capsulatum, Blastomyces dermatitidis.* Correlation between minium inhibitory concentration (MIC) results in vitro and clinical outcome has yet to be established for azole antifungal agents.~~

5. In the **MICROBIOLOGY/Activity in Vitro and In Vivo** subsection, a second paragraph is added as follows (S-041)

   Candida krusei, Candida glabrata and *Candida tropicalis* are generally the least susceptible *Candida* species, with some isolates showing unequivocal resistance to itraconazole *in vitro*. Itraconazole is not active against *Zygomycetes* (e.g., *Rhizopus* spp., *Rhizomucor* spp., *Mucor* spp. and *Absidia* spp.), *Fusarium* spp., *Scedosporium* spp. and *Scopulariopsis* spp.

6. In the **MICROBIOLOGY/Activity in Vitro and In Vivo** subsection, the last sentence of the first paragraph becomes the third paragraph as follows (S-041)

   The bioactive metabolite, hydroxyitraconazole, has not been evaluated against *Histoplasma capsulatum, Blastomyces dermatitidis, Zygomycete, Fusarium* spp., *Scedosporium* spp. and *Scopulariopsis* spp. Correlation between minimum inhibitory concentration (MIC) results *in vitro* and clinical outcome has yet to be established for azole antifungal agents.

7. In the **MICROBIOLOGY/Resistance** subsection, a third and fourth paragraphs are added as follows (S-041):

   Candida krusei, Candida glabrata and *Candida tropicalis* are generally the least susceptible *Candida* species, with some isolates showing unequivocal resistance to itraconazole *in vitro*.

   Itraconazole is not active against *Zygomycetes* (e.g., *Rhizopus* spp., *Rhizomucor* spp., *Mucor* spp. and *Absidia* spp.), *Fusarium* spp., *Scedosporium* spp. and *Scopulariopsis* spp.

8. In the **CONTRAINDICATION/Drug Interactions** subsection the second sentence is revised as follows (S-040):

   Cisapride, oral midazolam, nisoldipine, pimozide, quinidine, dofetilide, triazolam and levacetylmethadol (levomethadyl) are contraindicated with SPORANOX®.

9. In the **WARNINGS/Cardiac Disease** subsection, the third paragraph is revised as follows (S-041):

   Itraconazole has been shown to have a negative inotropic effect. When itraconazole was administered intravenously to anesthetized dogs, a dose-related negative inotropic effect was documented. In a healthy volunteer study of SPORANOX® Injection (intravenous infusion),

transient, asymptomatic decreases in left ventricular ejection fraction were observed using gated SPECT imaging; these resolved before the next infusion, 12 hours later.

10. In the **WARNINGS/Cardiac Disease** subsection, a fourth and fifth paragraphs are added as follows (S-040):

    SPORANOX® has been associated with reports of congestive heart failure. In post-marketing experience, heart failure was more frequently reported in patients receiving a total daily dose of 400 mg although there were also cases reported among those receiving lower total daily doses.

    Calcium channel blockers can have negative inotropic effects which may be additive to those of itraconazole. In addition, itraconazole can inhibit the metabolism of calcium channel blockers. Therefore, caution should be used when co-administering itraconazole and calcium channel blockers due to an increased risk of CHF. Concomitant administration of SPORANOX® and nisoldipine is contraindicated.

11. The information contained in the **PRECAUTIONS** section is rearranged and formatted with the following subheadings (S-044).

    General
    SPORANOX® (itraconazole) Capsules should be administered after a full meal.
    (See CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism.)
    Under fasted conditions, itraconazole absorption was decreased in the presence of decreased gastric acidity. The absorption of itraconazole may be decreased with the concomitant administration of antacids or gastric acid secretion suppressors. Studies conducted under fasted conditions demonstrated that administration with 8 ounces of a cola beverage resulted in increased absorption of itraconazole in AIDS patients with relative or absolute achlorhydria. This increase relative to the effects of a full meal is unknown. (See CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism.)

    Hepatotoxicity
    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.

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

12. In the **PRECAUTIONS** section, a new subsection titled **Hearing Loss** is added as follows (S-044):

Hearing Loss

Transient or permanent hearing loss has been reported in patients receiving treatment with itraconazole. Several of these reports included concurrent administration of quinidine which is contraindicated (see BOX WARNING: Drug Interactions; CONTRAINDICATIONS: Drug Interactions and PRECAUTIONS: Drug Interactions). The hearing loss usually resolves when treatment is stopped, but can persist in some patients.

13. In the **PRECAUTIONS/Information for Patients** subsection, a new bullet is added (S-044):

- Instruct patients that hearing loss can occur with the use of itraconazole. The hearing loss usually resolves when treatment is stopped, but can persist in some patients. Advise patients to discontinue therapy and inform their physicians if any hearing loss symptoms occur.

14. In the **PRECAUTIONS/Drug Interactions** subsection, the following changes were made to Table 1 (S-040 and S-044).

Table 1. Selected Drugs that Are Predicted to Alter the Plasma Concentration of Itraconazole or Have Their Plasma Concentration Altered by SPORANOX®[1]

Drug plasma concentration increased by itraconazole	
Antiarrhythmics	digoxin, dofetilide,[2] quinidine,[2] disopyramide
Anticonvulsants	carbamazepine
Antimycobacterials	rifabutin
Antineoplastics	busulfan, docetaxel, vinca alkaloids
Antipsychotics	pimozide[2]
Benzodiazepines	alprazolam, diazepam, midazolam,[2,3] triazolam[2]
Calcium Channel Blockers	dihydropyridines (including nisoldipine[2]), verapamil
Gastrointestinal Motility Agents	cisapride[2]
HMG CoA-Reductase Inhibitors	atorvastatin, cerivastatin, lovastatin,[2] simvastatin[2]
Immunosuppressants	cyclosporine, tacrolimus, sirolimus
Oral Hypoglycemics	oral hypoglycemics
Protease Inhibitors	indinavir, ritonavir, saquinavir
Other	levacetylmethadol (levomethadyl),[2] ergot alkaloids,[2] halofantrine, alfentanil, buspirone, methylprednisolone, budesonide, dexamethasone, fluticasone, trimetrexate, warfarin, cilostazol, eletriptan, fentanyl
Decrease plasma concentration of itraconazole	
Anticonvulsants	carbamazepine, phenobarbital, phenytoin
Antimycobacterials	isoniazid, rifabutin, rifampin
Gastric Acid Suppressors/Neutralizers	antacids, H_2-receptor antagonists, proton pump inhibitors
Non-nucleoside Reverse Transcriptase Inhibitors	nevirapine
Increase plasma concentration of itraconazole	
Macrolide Antibiotics	clarithromycin, erythromycin
Protease Inhibitors	indinavir, ritonavir

15. In the **PRECAUTIONS/Antiarrhythmics** subsection, the third paragraph is modified as follows (S-041):

    Concomitant administration of digoxin and SPORANOX® has led to increased plasma concentrations of digoxin via inhibition of P-glycoprotein.

16. In the **PRECAUTIONS/Drug Interactions/Calcium Channel Blockers** subsection, the second paragraph is revised as follows (S-040):

    Calcium channel blockers can have a negative inotropic effect which may be additive to those of itraconazole; itraconazole can inhibit the metabolism of calcium channel blockers such as dihydropyridines (e.g., nifedipine and felodipine) and verapamil. Therefore, caution should be

used when co-administering itraconazole and calcium channel blockers due to an increased risk of CHF. Concomitant administration of SPORANOX® and nisoldipine results in clinically significant increases in nisoldipine plasma concentrations, which cannot be managed by dosage reduction, therefore the concomitant administration of SPORANOX® and nisoldipine is contraindicated. (See CLINICAL PHARMACOLOGY: Special Populations, CONTRAINDICATIONS, WARNINGS, and ADVERSE REACTIONS: Post-marketing Experience for more information).

17. In the **PRECAUTIONS/Drug Interactions/Other** subsection, the sixth bullet is revised as follows (S-044):

    - SPORANOX® may inhibit the metabolism of certain glucocorticosteroids such as budesonide, dexamethasone, fluticasone and methylprednisolone.

18. In the **PRECAUTIONS/Drug Interactions/Other** subsection, a tenth bullet is added as follows (S-040):

    - Fentanyl plasma concentrations could be increased or prolonged by concomitant use of SPORANOX® and may cause potentially fatal respiratory depression.

19. In the **PRECAUTIONS** section, a new **Geriatric Use** subsection is added as follows (S-044):

    Geriatric Use
    Transient or permanent hearing loss has been reported in elderly patients receiving treatment with itraconazole. Several of these reports included concurrent administration of quinidine which is contraindicated (see BOX WARNING: Drug Interactions, CONTRAINDICATIONS: Drug Interactions and PRECAUTIONS: Drug Interactions). Itraconazole should be used with care in elderly patients (see PRECAUTIONS).

20. In the **PRECAUTIONS** section, two new subsections titled **Renal Impairment** and **Hepatic Impairment** are added as follows (S-040):

    Renal Impairment
    Limited data are available on the use of oral itraconazole in patients with renal impairment. Caution should be exercised when this drug is administered in this patient population. (See CLINICAL PHARMACOLOGY: Special Populations and DOSAGE AND ADMINISTRATION.)

    Hepatic Impairment
    Limited data are available on the use of oral itraconazole in patients with hepatic impairment. Caution should be exercised when this drug is administered in this patient population. (See CLINICAL PHARMACOLOGY: Special Populations and DOSAGE AND ADMINISTRATION.)

21. The **ADVERSE REACTIONS/Post-Marketing Experience** subsection is revised as follows (S-044):

    Post-marketing Experience
    ~~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, anaphylactic, anaphylactoid and allergic reactions, photosensitivity and neutropenia.~~

Adverse drug reactions that have been identified during post-approval use of SPORANOX (all formulations) are listed in the table below. Because these reactions are reported voluntarily from a population of uncertain size, reliably estimating their frequency or establishing a causal relationship to drug exposure is not always possible.

Postmarketing Reports of Adverse Drug Reactions	
Blood and lymphatic system disorders:	Leukopenia, neutropenia, thrombocytopenia
Immune system disorders:	Anaphylaxis; anaphylactic, anaphylactoid and allergic reactions; serum sickness; angioneurotic edema
Metabolism and nutrition disorders:	Hypertriglyceridemia, hypokalemia
Nervous system disorders:	Peripheral neuropathy, paresthesia, hypoesthesia, headache, dizziness
Eye disorders:	Visual disturbances, including vision blurred and diplopia
Ear and labyrinth disorders:	Transient or permanent hearing loss, tinnitus
Cardiac disorders:	Congestive heart failure
Respiratory, thoracic and mediastinal disorders:	Pulmonary edema
Gastrointestinal disorders:	Abdominal pain, vomiting, dyspepsia, nausea, diarrhea, constipation, dysgeusia
Hepato-biliary disorders:	Serious hepatotoxicity (including some cases of fatal acute liver failure), hepatitis, reversible increases in hepatic enzymes
Skin and subcutaneous tissue disorders:	Toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, leukocytoclastic vasculitis, erythema multiforme, alopecia, photosensitivity, rash, urticaria, pruritus
Musculoskeletal and connective tissue disorders:	Myalgia, arthralgia
Renal and urinary disorders:	Urinary incontinence, pollakiuria
Reproductive system and breast disorders:	Menstrual disorders, erectile dysfunction
General disorders and administration site conditions:	Peripheral edema

There is limited information on the use of SPORANOX® during pregnancy. Cases of congenital abnormalities including skeletal, genitourinary tract, cardiovascular and ophthalmic malformations as well as chromosomal and multiple malformations have been reported during post-marketing experience. A causal relationship with SPORANOX® has not been established. (See CLINICAL PHARMACOLOGY: Special Populations, CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions for more information.)

22. In the **DOSAGE and ADMINISTRATION** section, two new subsections titled **Use in Patients with Renal Impairment** and **Use in Patients with Hepatic Impairment** are added as follows (S-041):

Use in Patients with Renal Impairment
Limited data are available on the use of oral itraconazole in patients with renal impairment. Caution should be exercised when this drug is administered in this patient population. (See CLINICAL PHARMACOLOGY: Special Populations and PRECAUTIONS for further information.)

Use in Patients with Hepatic Impairment
Limited data are available on the use of oral itraconazole in patients with hepatic impairment. Caution should be exercised when this drug is administered in this patient population. (See CLINICAL PHARMACOLOGY: Special Populations, WARNINGS, and PRECAUTIONS.)

REVISIONS TO THE PATIENT PACKAGE INSERT:

23. In the **WHO SHOULD NOT TAKE SPORANOX** section, under the "**Never** take SPORANOX if you" heading, a 13th bullet is added as follows (S-040):

- Nisoldipine (such as Sular®**)**

24. In the **WHO SHOULD NOT TAKE SPORANOX** section, a last paragraph is added as follows (S-040):

Taking SPORANOX® with certain other medicines could lead to serious or life-threatening medical problems. For example, taking fentanyl, a strong opioid narcotic pain medicine, with SPORANOX® could cause serious side effects, including trouble breathing, that may be life-threatening. Tell your doctor and pharmacist the name of all the prescription and non-prescription medicines you are taking. Your doctor will decide if SPORANOX® is the right treatment for you.

25. The **WHAT ARE THE POSSIBLE SIDE EFFECTS OF SPORANOX** section was revised as follows (S-040 and S-044):

The most common side effects that cause people to stop treatment either for a short time or completely include: skin rash, high triglyceride test results, high liver test results, and digestive system problems (such as nausea, bloating, and diarrhea).

Stop SPORANOX® and call your doctor or get medical assistance right away if you have a severe allergic reaction. Symptoms of an allergic reaction may include skin rash, itching, hives, shortness of breath or difficulty breathing, and/or swelling of the face. Very rarely, an oversensitivity to sunlight, a tingling sensation in the limbs or a severe skin disorder can occur. If any of these symptoms occur, stop taking SPORANOX® and contact your doctor.

Stop SPORANOX® and call your doctor right away if you develop shortness of breath; have unusual swelling of your feet, ankles or legs; suddenly gain weight; are unusually tired; cough up white or pink phlegm; ~~or~~ have unusual fast heartbeats; or begin to wake up at night. In rare cases, patients taking SPORANOX® could develop serious heart problems, and these could be warning signs of heart failure.

Stop SPORANOX® and call your doctor right away if you become unusually tired; lose your appetite; or develop nausea, abdominal pain, or vomiting, a yellow color to your skin or eyes, or dark colored urine or pale stools (bowel movements). In rare cases, patients taking SPORANOX® could develop serious liver problems and these could be warning signs.

Stop SPORANOX® and call your doctor right away if you experience any hearing loss symptoms. In very rare cases, patients taking SPORANOX® have reported temporary or permanent hearing loss.

Call your doctor right away if you develop tingling or numbness in your extremities (hands or feet), if your vision gets blurry or you see double, if you hear a ringing in your ears, if you lose the ability to control your urine or urinate much more than usual.

Additional possible side effects include upset stomach, vomiting, abdominal pain, constipation, headache, menstrual disorders, erectile dysfunction, dizziness, muscle weakness or pain, painful joints, unpleasant taste, or hair loss. These are not all the side effects of SPORANOX®. Your doctor or pharmacist can give you a more complete list.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling text for the package insert and patient package insert. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate these submissions, "**SPL for approved supplements NDA 20-083 S-040, S-041, and S-044.**

Marketing the product with FPL that is not identical to the approved labeling text and in the required format may render the product misbranded and an unapproved new drug.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call June Germain, Regulatory Health Project Manager, at (301) 796-4024.

Sincerely,
{See appended electronic signature page}

Renata Albrecht, MD
Director
Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Research and Evaluation

Enclosure: package insert and patient package insert

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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