DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-966/S-017, S-018, S-020

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) Injection, 10 mg/mL.

Supplemental Number	**Date of Submission**	**Date Received**
S-017	June 21, 2006	June 22, 2006
S-018	August 24, 2006	August 25, 2006
S-020	January 17, 2008	January 17, 2008

We also acknowledge receipt of your submissions dated July 28, September 4, and October 30, 2008. Your submission dated September 4, 2008 received September 5, 2008, constituted a complete response to our approvable letters dated December 22, 2006 (S-017), February 24, 2007 (S-018), and July 17, 2008 (S-020).

These supplemental new drug applications provide for changes to the **CLINICAL PHARMACOLOGY/ Pharmacokinetics and Metabolism, CLINICAL PHARMACOLOGY/Special Populations/Renal Insufficiency, CLINICAL PHARMACOLOGY/Special Population/Hepatic Insufficiency, MICROBIOLOGY, CONTRAINDICATIONS/Drug Interactions, WARNINGS/Cardiac Disease, PRECAUTIONS, PRECAUTIONS/Drug Interactions/Calcium Channel Blockers, PRECAUTIONS/Geriatric Use, ADVERSE REACTIONS/Post-marketing Experience, DOSAGE AND ADMINISTRATION,** and **HOW SUPPLIED** sections of the package insert.

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 text submitted on September 4, 2008.

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

1. In the **CLINICAL PHARMACOLOGY/Pharmacokinetics and Metabolism** subsection, the third paragraph is revised as follows: (S-018)

   The estimated mean ±SD half-life at steady-state of itraconazole after intravenous infusion was 35.4 ± 29.4 hours. In previous studies, the mean elimination half-life for itraconazole at steady-state after daily oral administration of 100 to 400 mg was 30-40 hours. ~~Approximately 93-101% of hydroxypropyl-β-cyclodextrin was excreted unchanged in the urine within 12 hours after dosing.~~

2. In the **CLINICAL PHARMACOLOGY/Pharmacokinetics and Metabolism** subsection, a fifth paragraph is added as follows: (S-018)

   Each intravenous dose of 200 mg itraconazole contains 8g hydroxypropyl-β-cyclodextrin to increase the solubility of itraconazole. The pharmacokinetic profiles of each are described below. (See Special Populations−Renal Insufficiency.)

3. In the **CLINICAL PHARMACOLOGY/Pharmacokinetics and Metabolism** subsection, the sixth (last) paragraph is revised as follows (S-018):

   Itraconazole is metabolized predominately by the cytochrome P450 3A4 isoenzyme system (CYP3A4), resulting in the formation of several metabolites, ~~including~~ .~~h~~Hydroxyitraconazole, the major metabolite, has *in vitro* antifungal activity comparable to itraconazole. Results of a pharmacokinetics study suggest that itraconazole may undergo saturable metabolism with multiple dosing. Based on an oral dose, fecal excretion of the parent drug varies between 3-18% of the dose. Renal excretion of ~~the parent drug is~~ itraconazole and the active metabolite hydroxyitraconazole account for less than ~~0.03% of the dose~~ 1% of an intravenous dose. Itraconazole is excreted mainly as inactive metabolites in ~~the~~ urine (35%) and feces (54%) within one week of an oral dose. ~~About 40% of the dose is excreted as inactive metabolites in the urine.~~ No single excreted metabolite represents more than 5% of a dose. Itraconazole mean total plasma clearance ~~average 381 ± 95 mL/min~~ is 278 ± 79 mL/min following intravenous administration. ~~Approximately 80-90% of hydroxypropyl-β-cyclodextrin is eliminated through the kidneys.~~ A mean of 89.2% of the administered intravenous dose of hydroxypropyl-β-cyclodextrin is excreted in urine. (See CONTRAINDICATIONS and PRECAUTIONS: Drug Interactions for more information.)

4. The **CLINICAL PHARMACOLOGY/Special Populations/Renal Insufficiency** subsection, is revised as follows (S-017 and S-018):

   ~~Plasma concentration of itraconazole in patients with mild to moderate renal insufficiency were comparable to those obtained in healthy subjects. The majority of the 8-gram dose of hydroxypropyl-β-cyclodextrin was eliminated in the urine during the 120-hour collection period in normal subjects and in patients with mild to severe renal insufficiency. Following a single intravenous dose of 200 mg to subjects with severe renal impairment (creatinine clearance ≤ 19 mL/minute), clearance of hydrxypropyl-β-cyclodextrin was reduced six-fold~~

~~compared with subjects with normal renal function. SPORANOX Injection should not be used in patients with creatinine clearance <30 mL/min.~~

A small fraction (<1%) of an intravenous dose of itraconazole is excreted unchanged in urine.

After a single intravenous dose, the mean terminal half-lives of itraconazole in patients with mild (CrCl 50-79 mL/min), moderate (CrCl 20-49 mL/min), and severe renal impairment (CrCl <20 mL/min) were similar to that in healthy subjects (range of means 42-49 hr vs 48 hr in renally impaired patients and healthy subjects, respectively). Overall exposure to itraconazole, based on AUC, was decreased in patients with moderate and severe renal impairment by approximately 30% and 40%, respectively, as compared with subjects with normal renal function.

Data are not available in renally impaired patients during long-term use of itraconazole. Dialysis has no effect on the half-life or clearance of itraconazole or hydroxyitraconazole. (See CONTRAINDICATIONS, PRECAUTIONS and DOSAGE AND ADMINISTRATION.)

In patients with normal renal function, the pharmacokinetic profile of hydroxypropyl-β-cyclodextrin, an ingredient of SPORANOX® intravenous formulation, has a short half-life of 1 to 2 hours, and demonstrates no accumulation following successive daily doses. In healthy subjects and in patients with mild to severe renal insufficiency, the majority of an 8 g dose of hydroxypropyl-β-cyclodextrin (per 200 mg itraconazole) is eliminated in the urine. Following a single intravenous dose of itraconazole 200 mg, clearance of hydroxypropyl-β-cyclodextrin was reduced in subjects with mild, moderate, and severe renal impairment, resulting in higher exposure to hydroxypropyl-β-cyclodextrin; in these subjects, half-life values were increased over normal values by approximately two-, four-, and six-fold, respectively. In these patients, successive infusions may result in accumulation of hydroxypropyl-β-cyclodextrin until steady state is reached. Hydroxypropyl-β-cyclodextrin is removed by hemodialysis.

In patients with mild (creatinine clearance 50-80 mL/min) to moderate (creatinine clearance 30-49 mL/min) renal impairment, SPORANOX® Injection should be used with caution. Serum creatinine levels should be closely monitored and, if renal toxicity is suspected, consideration should be given to changing to SPORANOX® Capsules, if clinically indicated and consistent with approved indications. SPORANOX® Injection is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min). (See CONTRAINDICATIONS, PRECAUTIONS, and DOSAGE AND ADMINISTRATION.)

5. The **CLINICAL PHARMACOLOGY/Special Populations/Hepatic Insufficiency** subsection is revised as follows (S-018):

Studies have not been conducted with intravenous itraconazole in patients with hepatic impairment. 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 dose of itraconazole (one 100-mg capsule) was conducted in 6 healthy and 12 cirrhotic subjects. 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. The

prolonged elimination half-life of itraconazole observed in the single oral dose ~~a~~ 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.)

6. In the **MICROBIOLOGY/Activity in Vitro and In Vivo** subsection, the first paragraph is revised as follows (S-018):

   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. T~~he 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.~~

7. In the **MICROBIOLOGY/Activity in Vitro and in Vivo** subsection, a second paragraph is added as follows (S-018):

   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 **MICROBIOLOGY/Activity in Vitro and in Vivo** subsection, the last sentence of the first paragraph becomes the third paragraph as follows:

   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.

9. In the **MICROBIOLOGY/Resistance** subsection, a third and fourth paragraph are added as follows (S-018):

   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.

10. The **CONTRAINDICATIONS/Drug Interactions** subsection the first paragraph is revised as follows (S-018):

    Concomitant administration of SPORANOX® (itraconazole) Capsules, Injection, or Oral Solution and certain drugs metabolized by the cytochrome P450 3A4 isoenzyme system (CYP3A4) may result in increased plasma concentrations of those drugs, leading to potentially serious and/or life-threatening adverse events. Cisapride, oral midazolam, nisoldipine, pimozide, quinidine, dofetilide, triazolam and levacetylmethadol (levomethadyl) are contraindicated with SPORANOX®. HMG CoA-reductase inhibitors metabolized by CYP3A4, such as lovastatin and simvastatin, are also contraindicated with SPORANOX®. Ergot alkaloids metabolized by CYP3A4 such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine) are contraindicated with SPORANOX®. (See BOX WARNING and PRECAUTIONS: Drug Interactions.)

11. In the **CONTRAINDICATIONS/Drug Interactions** subsection, a third and fourth paragraphs are added as follows (S-018):

    SPORANOX IV cannot be used when administration of Sodium Chloride Injection is contraindicated.

    The excipient hydroxypropyl-β-cyclodextrin is eliminated through glomerular filtration. Therefore, SPORANOX IV is contraindicated in patients with severe renal impairment (defined as creatinine clearance below 30 mL/min). (See CLINICAL PHARMACOLOGY: Special Populations, PRECAUTIONS, and DOSAGE and ADMINISTRATION.)

12. In the **WARNINGS/Cardiac Disease** subsection, the second paragraph is revised as follows (S-018):

    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.

13. In the **WARNINGS/Cardiac Disease** subsection, a third and fourth paragraph are added as follows (S-017):

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.

14. The information contained in the **PRECAUTIONS/General** subsection is reformatted with the addition of sub-headers as follows (S-020):

~~**General**~~ **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.

Renal Impairment:
As severe renal impairment prolongs the elimination rate of hydroxyl-β-cyclodextrin, SPORANOX® (itraconazole) Injection should not be used in patients with severe renal dysfunction (creatinine clearance <30 mL/min). (See CLINICAL PHARMACOLOGY: Special Populations.)

15. In the **PRECAUTIONS** section, a new subsection titled **Hearing Loss** is added as follows (S-020):

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.

16. In the **PRECAUTIONS/Information for Patients** subsection, a second paragraph is added as follows (S-020):

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 inform their physicians if any hearing loss symptoms occur.

17. In the **PRECAUTIONS/Drug Interactions** subsection, table 1 is revised as follows (S-017 and S-020):

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
Reverse Transcriptase Inhibitors	Nevirapine
Increase plasma concentration of itraconazole	
Macrolide Antibiotics	clarithromycin, erythromycin
Protease Inhibitors	indinavir, ritonavir

[1] This list is not all-inclusive.

[2] Contraindicated with SPORANOX® based on clinical and/or pharmacokinetics studies. (See WARNINGS and below.)

[3] For information on parenterally administered midazolam, see the Benzodiazepine paragraph below.

18. In the **PRECAUTIONS/Drug Interactions/Antiarrhythmics** subsection, the third paragraph is modified as follows (S-018):

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

19. In the **PRECAUTIONS/Drug Interactions/Calcium Channel Blockers** subsection, the second paragraph is revised as follows (S-017):

    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.)

20. In the **PRECAUTIONS/Drug Interactions/Other** subsection, the sixth bullet is revised as follows (S-020):

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

21. In the **PRECAUTIONS/Drug Interactions/Other** subsection, a tenth bullet is added to read as follows (S-017):

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

22. In the **PRECAUTIONS/Geriatric Use** subsection, a second paragraph is added as follows (S-020)*:*

    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).

23. In the **PRECAUTIONS** section two new subsections titled **Renal Impairment** and **Hepatic Impairment** are added as follows (S-017):

Renal Impairment:

Hydroxypropyl-β-cyclodextrin, when administered intravenously, is eliminated through glomerular filtration. Therefore, in patients with severe renal impairment defined as creatinine clearance below 30 mL/min, SPORANOX IV is contraindicated (see CONTRAINDICATIONS).

In patients with mild (defined as creatinine clearance 50-80 mL/min) and moderate (defined as creatinine clearance 30-49 mL/min) renal impairment, SPORANOX IV should be used with caution. Serum creatinine levels should be closely monitored and, if renal toxicity is suspected, consideration should be given to modifying the antifungal regimen to an alternate medication with similar antimycotic coverage. (See CLINICAL PHARMACOLOGY: Special Populations, CONTRAINDICATIONS, and DOSAGE and ADMINISTRATION for further information.)

Hepatic Impairment:

Studies have not been conducted with intravenous itraconazole 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 DOSAGE AND ADMINISTRATION.)

24. The **ADVERSE REACTIONS/Post-Marketing Experience** subsection is revised as follows. (S-017 and S-020):

~~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.)

25. 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-018):

Use in Patient with Renal Impairment
Limited data are available on the use of intravenous itraconazole in patients with renal impairment.

Hydroxypropyl-β-cyclodextrin, a required component of SPORANOX® intravenous formulation, is eliminated through glomerular filtration. Therefore, in patients with severe renal impairment (defined as creatinine clearance below 30 mL/min), the use of SPORANOX® IV is contraindicated. (See CONTRAINDICATIONS.)

In patients with mild (defined as creatinine clearance 50-80 mL/min) to moderate (defined as creatinine clearance 30-49 mL/min) renal impairment, SPORANOX® IV should be used with caution. Serum creatinine levels should be closely monitored and, if renal toxicity is suspected, consideration should be given to changing to SPORANOX® capsules. (See CLINICAL PHARMACOLOGY: Special Populations, CONTRAINDICATIONS, and PRECAUTIONS.)

Use on Patients with Hepatic Impairment:
Limited data are available on the use of 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).

26. In the **HOW SUPPLIED** section the following sentence is added (S-020)

Keep out of reach of children.

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 20-966 S-017, S-018, and S-020.**

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

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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