DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-083/S-034, S035

Johnson & Johnson Pharmaceutical Research and Development, L.L.C.
Attention: Kathleen F. Dusek, R. Ph., RAC
Associate Director, Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

Dear Ms. Dusek:

Please refer to your supplemental new drug applications dated January 14, 2004 and January 23, 2004 received January 15, 2004 and January 26, 2004, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sporanox® (itraconazole) Capsules, 100 mg.

We acknowledge receipt of your submissions dated January 21, 2004, March 24, 2004, and July 1, 2004.

These "Changes Being Effected in 30 days" supplemental new drug applications provide for the following revisions to the Sporanox® Capsule package insert (PI) and patient package insert (PPI):

Added text = double underline and Deleted text = ~~strikethrough~~

1. BOX WARNING

- Levacetylmethadol is added as a contraindicated drug with Sporanox® in the **Drug Interactions** subsection to read:

  Drug Interactions: Coadministration of cisapride, pimozide, quinidine, dofetilide, or levacetylmethadol (levomethadyl) with SPORANOX® (itraconazole) Capsules, Injection or Oral Solution is contraindicated. SPORANOX®, a potent cytochrome P450 3A4 isoenzyme system (CYP3A4) inhibitor, may increase plasma concentrations of drugs metabolized by this pathway. Serious cardiovascular events, including QT prolongation, torsades de pointes, ventricular tachycardia, cardiac arrest, and/or sudden death have occurred in patients using cisapride, pimozide, levacetylmethadol (levomethadyl), or quinidine concomitantly with SPORANOX® and/or other CYP3A4 inhibitors. See **CONTRAINDICATIONS**, **WARNINGS**, and **PRECAUTIONS: Drug Interactions** for more information.

2. CONTRAINDICATIONS

- Levacetylmethadol and ergot alkaloids are added as contraindicated drugs with Sporanox® in the **Drug Interactions** subsection to read:

Drug Interactions: 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, 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**.)

3. WARNINGS

- Levacetylmethadol is added as a contraindicated drug with Sporanox® in the **Cardiac Dysrhythmias** subsection to read:

  Cardiac Dysrhythmias: Life-threatening cardiac dysrhythmias and/or sudden death have occurred in patients using cisapride, pimozide, levacetylmethadol (levomethadyl), or quinidine concomitantly with SPORANOX® and/or other CYP3A4 inhibitors.

4. PRECAUTIONS

- Addition of disopyramide, halofantrine, budesonide, dexamethasone, cilostazol and eletriptan to **Table 1** in the **Drug Interactions**:

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
Anticoagulants	warfarin
Anticonvulsants	carbamazepine
Antimycobacterials	rifabutin
Antineoplastics	busulfan, docetaxel, vinca alkaloids
Antipsychotics	pimozide[2],
Benzodiazepines	alprazolam, diazepam, midazolam,[2,3] triazolam[2]
Calcium Channel Blockers	dihydropyridines, 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), ergot alkaloids, halofantrine, alfentanil, buspirone, methylprednisolone, budesonide, dexamethasone, trimetrexate, warfarin, cilostazol, eletriptan

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

- The following statement regarding concomitant use of disopyramide with Sporanox is added to **Antiarrhythmics** subsection:

  The class IA antiarrhythmic disopyramide has the potential to increase the QT interval at high plasma concentrations. Caution is advised when SPORANOX® and disopyramide are administered concomitantly.

- New information is added in the **PRECAUTIONS: Other** subsection to read:

  Other:
  - Levacetylmethadol (levomethadyl) is known to prolong the QT interval and is

metabolized by CYP3A4. Co-administration of levacetylmethadol with SPORANOX® could result in serious cardiovascular events.Therefore, concomitant administration of SPORANOX® and levacetylmethadol is contraindicated.

- Elevated concentrations of ergot alkaloids can cause ergotism, ie. a risk for vasospasm potentially leading to cerebral ischemia and/or ischemia of the extremities. Concomitant administration of ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine) with SPORANOX® is contraindicated.
- Halofantrine has the potential to prolong the QT interval at high plasma concentrations. Caution is advised when SPORANOX® and halofantrine are administered concomitantly.
- In vitro data suggest that alfentanil is metabolized by CYP3A4. Administration with SPORANOX® may increase plasma concentrations of alfentanil.
- Human pharmacokinetic data suggest that concomitant administration of SPORANOX® and buspirone results in significant increases in plasma concentrations of buspirone.
- SPORANOX® may inhibit the metabolism of ~~methylprednisolone~~.certain glucocorticosteroids such as budesonide, dexamethasone and methylprednisolone.
- In vitro data suggest that trimetrexate is extensively metabolized by CYP3A4. In vitro animal models have demonstrated that ketoconazole potently inhibits the metabolism of trimetrexate. Although there are no data regarding the effect of itraconazole on trimetrexate metabolism, because of the similarities between ketoconazole and itraconazole, concomitant administration of SPORANOX® and trimetrexate may inhibit the metabolism of trimetrexate.
- SPORANOX® enhances the anticoagulant effect of coumarin-like drugs, such as warfarin.
- Cilostazol and eletriptan are CYP3A4 metabolized drugs that should be used with caution when co-administered with SPORANOX®.

- The following statement is added to the **Pregnancy: Teratogenic Effects. Pregnancy Category C** subsection:

  During post-marketing experience, cases of congenital abnormalities have been reported. (See **ADVERSE REACTIONS**, **Post-marketing Experience**.)

5. ADVERSE REACTIONS

- Addition of anaphylactic, anaphylactoid and allergic reactions and a statement regarding cases of congenital abnormalities to the **Post-marketing Experience** subsection to read:

  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. 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).

6. Patient Package Insert (PPI)

- The following sections of the PPI were revised to include levacetylmethadol and the ergot alkaloids as drugs contraindicated for use with Sporanox:

  Never take SPORANOX® if you:

  - are taking any of the medicines listed below. Dangerous or even life-threatening abnormal heartbeats could result:
    - quinidine (such as Cardioquin®, Quinaglute®, Quinidex®)
    - dofetilide (such as Tikosyn™)
    - cisapride (such as Propulsid®)
    - pimozide (such as Orap®)
    - levacetylmethadol (such as Orlaam®)

  - are taking any of the following medicines:
    - lovastatin (such as Mevacor®,Advicor™, Altocor™)
    - simvastatin (such as Zocor®)
    - triazolam (such as Halcion®)
    - midazolam (such as Versed®)
    - ergot alkaloids (such as Migranal®, Ergonovine, Cafergot®, Methergine®)

  The following are registered trademarks of their respective manufacturers: Mevacor® (Merck & Co., Inc.), Advicor™ (Kos Pharmaceuticals, Inc.), Altocor™ (Andrx Laboratories), Zocor® (Merck & Co., Inc.), Halcion® (Pharmacia), Versed® (Roche Pharmaceuticals), Cardioquin® (The Purdue Frederick Company), Quinaglute® (Berlex Laboratories), Quinidex® (A.H. Robins), Tikosyn™ (Pfizer, Inc.), Propulsid® (Janssen Pharmaceutica Products, L.P.), Orlaam® (Roxane Laboratories), Migranal® (Xcel Pharmaceuticals), Ergonovine (PDRX Pharmaceuticals), Cafergot® (Novartis Pharmaceuticals Corporation), Methergine®(Novartis Pharmaceuticals Corporation) and Orap® (Gate Pharmaceuticals)

We 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 enclosed labeling text. Accordingly, these supplemental applications are approved on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert submitted on January 21, 2004 and text for the patient package insert submitted on January 23, 2004).

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidances for industry regarding electronic submissions: ***Providing Regulatory Submissions in Electronic Format - NDAs*** (January 1999) and ***Providing Regulatory Submissions in Electronic Format – Content of Labeling*** (February 2004). The guidances specify that labeling to be submitted

in *pdf* format. To assist in our review of the FPL and future submission, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper. For administrative purposes, this submission should be designated "**FPL for approved supplements NDA 20-083/S-034, S-035**." Approval of this submission by FDA is not required before the labeling is used.

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, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

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 Yon Yu, Pharm D., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
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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