DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20-657/S-026

SUPPLEMENT APPROVAL

Ortho-McNeil-Janssen Pharmaceuticals
c/o Johnson & Johnson Pharmaceutical Research
Attention: Melissa Gannon
Director, Global Regulatory Affairs
920 Route 202 South
P O Box 300
Raritan, New Jersey 08869-0602

Dear Ms. Gannon:

Please refer to your Supplemental New Drug Application (sNDA) dated and received October 25, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Sporanox® (itraconazole) Oral Solution.

We also acknowledge receipt of your amendments dated February 4, March 11, and April 8, 2011.

This supplemental new drug application provides for revisions to the Sporanox® labeling for the Oral Solution to remove all reference to the Injection product because that product is no longer marketed. These revisions to the labeling for Sporanox (itraconazole) Oral Solution are shown below (additions are noted with underline and deletions are noted with ~~strikethrough~~):

1. In the **BOXED WARNINGS** section, the second paragraph is revised as follows:

> **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. The **CLINICAL PHARMACOLOGY/ Special Populations: Decreased Cardiac Contractility** subsection is revised as follows:

When itraconazole was administered intravenously to anesthetized dogs, a dose-related negative inotropic effect was documented. In a healthy volunteer study of ~~SPORANOX® injection~~ itraconazole 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. If signs or symptoms of congestive heart failure appear during administration of SPORANOX® Oral Solution, monitor carefully and consider other treatment alternatives which may include discontinuation of SPORANOX® Oral Solution administration. (See WARNINGS, PRECAUTIONS: Drug Interactions and ADVERSE REACTIONS: Post-marketing Experience for more information.)

3. The **CLINICAL STUDIES** section, the entire subsection titled **"Empiric Therapy in Febrile Neutropenic Patients**" is deleted as follows:

~~**Empiric Therapy in Febrile Neutropenic Patients:**~~
~~An open randomized trial compared the efficacy and safety of itraconazole (intravenous followed by oral solution) with amphotericin B for empiric therapy in 384 febrile, neutropenic patients with hematologic malignancies who had suspected fungal infections. Patients received either itraconazole (injection, 200 mg b.i.d. for 2 days followed by 200 mg once daily for up to 14 days, followed by oral solution, 200 mg b.i.d.) or amphotericin B (total daily dose of 0.7-1.0 mg/kg body weight). The longest treatment duration was 28 days. An outcome assignment of "success" required (a) patient survival with resolution of fever and neutropenia within 28 days of treatment, (b) absence of emergent fungal infections, (c) no discontinuation of therapy due to toxicity or lack of efficacy, and (d) treatment for three or more days. The success rate using an intent-to-treat analysis was 47% for the itraconazole group and 38% for the amphotericin B arm.~~

~~**Overview of Efficacy**~~
~~**(Intent-to-Treat Population)**~~

~~**Efficacy Parameters**~~	~~**SPORANOX® N=179 (%)**~~	~~**Amphotericin B N=181 (%)**~~
~~**Success**~~	~~84 (47%)~~	~~68 (38%)~~
~~**Unevaluable***~~	~~24 (13%)~~	~~44 (24%)~~
~~**Failure**~~	~~71 (40%)~~	~~69 (38%)~~
~~**Reason for Failure**~~	~~-~~	~~-~~
~~- Intolerance after > 3 days of antifungal medication~~	~~12~~	~~37~~
~~- Persistent fever~~	~~20~~	~~7~~
~~- Change in antifungal medication due to fever~~	~~13~~	~~1~~
~~- Emergent fungal infection~~	~~10~~	~~9~~

Overview of Efficacy
(Intent-to-Treat Population)

Efficacy Parameters	**SPORANOX®** **N=179 (%)**	**Amphotericin B** **N=181 (%)**
- Documented bacterial or viral infection	7	8
- Insufficient response	6	5
- Deterioration of signs and symptoms	2	0
- Death after > 3 days antifungal medication	1	2
Resolution of fever	131 (73%)	127 (70%)
Survival	161 (90%)	156 (86%)

*Treatment duration ≤ 3 days (including patients who died within 3 days, withdrew because of adverse events or were deemed ineligible due to a confirmed pre-treatment infection).

4. The **INDICATIONS AND USAGE** section, is revised to remove information regarding Sporanox® injection as follows:

SPORANOX® (itraconazole) Injection/Oral Solution is indicated for empiric therapy of febrile neutropenic patients with suspected fungal infections. (NOTE: In a comparative trial, the overall response rate for itraconazole-treated subjects was higher than for amphotericin B treated subjects. However, compared to amphotericin B-treated subjects, a larger number of itraconazole-treated subjects discontinued treatment due to persistent fever and a change in antifungal medication due to fever. Whereas, a larger number of amphotericin B-treated subjects discontinued due to drug intolerance. (See CLINICAL STUDIES section.)

SPORANOX® (itraconazole) Oral Solution is also indicated for the treatment of oropharyngeal and esophageal candidiasis.

(See CLINICAL PHARMACOLOGY: Special Populations, WARNINGS, and ADVERSE REACTIONS: Post-marketing Experience for more information.)

5. In the **CONTRAINDICATIONS/Drug Interactions** subsection, the first paragraph is revised as follows:

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.)

6. In the **WARNINGS/Cardiac Disease** subsection, the second paragraph is revised as follows:

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 (~~ itraconazole intravenous infusion~~)~~[1], transient, asymptomatic decreases in left ventricular ejection fraction were observed using gated SPECT imaging; these resolved before the next infusion, 12 hours later.

7. In the **WARNINGS/Treatment of Severely Neutropenic Patients** subsection, the second paragraph is deleted as follows:

~~In febrile neutropenic subjects in whom the likelihood of systemic candidiasis is considered high, therapy should be initiated with Sporanox Intravenous formulation.~~[1]

8. In The **ADVERSE REACTIONS** section, the entire subsection titled "**Adverse Events Reported in Empiric Therapy in Febrile Neutropenic (ETFN) Patients**" subsection, is deleted as follows:

~~**Adverse Events Reported in Empiric Therapy in Febrile Neutropenic (ETFN) Patients**~~

~~Adverse events considered at least possibly drug related in a clinical trial of empiric therapy in 384 febrile, neutropenic patients (192 treated with SPORANOX® and 192 with amphotericin B) with suspected fungal infections are listed in Table 2 below. Patients received a regimen of SPORANOX® Injection followed by SPORANOX® Oral Solution. The dose of SPORANOX® Injection was 200 mg twice daily for the first two days followed by a single daily dose of 200 mg for the remainder of the intravenous treatment period. The majority of patients received between 7 and 14 days of SPORANOX® Injection. The dose of SPORANOX® Oral Solution was 200 mg (20 mL) b.i.d. for the remainder of therapy.~~

~~**Table 2: Summary of Possibly or Definitely Drug-Related Adverse Events Reported in ≥ 2% of Subjects (Empiric Therapy Trial in Febrile Neutropenic Patients)**~~

~~**Adverse Event**~~	~~**SPORANOX® (N=192) %**~~	~~**Amphotericin B (N=192) %**~~
~~**Gastrointestinal system disorders**~~	-	-
~~Nausea~~	~~11~~	~~15~~
~~Diarrhea~~	~~10~~	~~9~~
~~Vomiting~~	~~7~~	~~10~~
~~Abdominal pain~~	~~3~~	~~3~~

Table 2: Summary of Possibly or Definitely Drug-Related Adverse Events Reported in ≥ 2% of Subjects (Empiric Therapy Trial in Febrile Neutropenic Patients)

Adverse Event	SPORANOX® (N=192) %	Amphotericin B (N=192) %
Metabolic and nutritional disorders	-	-
Hypokalemia	9	28
Serum creatinine increased	3	25
LDH increased	2	0
Alkaline phosphatase increased	2	2
Hypomagnesemia	2	4
Blood urea nitrogen increased	1	6
Fluid overload	1	3
Hypocalcemia	1	2
Liver and biliary system disorders	-	-
Bilirubinemia	6	3
Hepatic function abnormal	3	2
SGPT/ALT increased	3	1
Jaundice	2	1
SGOT/AST increased	2	1
Skin and appendage disorders	-	-
Rash	5	3
Sweating increased	2	1
CNS and peripheral nervous system	-	-
Headache	2	2
Body as a whole	-	-
Edema	2	2
Rigors	1	34
Fever	0	7
Respiratory system disorder	-	-
Dyspnea	1	3
Urinary system disorder	-	-
Renal function abnormal	1	12
Cardiovascular disorders, general	-	-
Hypotension	1	3
Hypertension	0	2
Heart rate and rhythm disorders	-	-

~~**Table 2: Summary of Possibly or Definitely Drug-Related Adverse Events Reported in ≥ 2% of Subjects (Empiric Therapy Trial in Febrile Neutropenic Patients)**~~

~~**Adverse Event**~~	~~**SPORANOX® (N=192) %**~~	~~**Amphotericin B (N=192) %**~~
~~Tachycardia~~	~~1~~	~~3~~

~~The following additional adverse events considered at least possibly related occurred in between 1 and 2% of patients who received SPORANOX® Injection and Oral Solution: constipation, hypophosphatemia, gamma-GT increased, erythematous rash, pruritus, dizziness, tremor, and pulmonary infiltration.~~

9. In the **ADVERSE REACTIONS** section, a new subsection titled "**Adverse Events Reported from Other Clinical Trials**" is added at the end of the section as follows:

Adverse Events Reported from Other Clinical Trials
A comparative clinical trial in patients who received intravenous itraconazole followed by SPORANOX® Oral Solution or received amphotericin B reported the following adverse events in the itraconazole intravenous/SPORANOX® Oral Solution treatment arm which are not listed above in the subsection "Adverse Events Oropharyngeal or Esophageal Candidiasis Trials" or listed below as postmarketing reports of adverse drug reactions: serum creatinine increased, blood urea nitrogen increased, renal function abnormal, hypocalcemia, hypomagnesemia, hypophosphatemia, hypotension, tachycardia, tremor, and pulmonary infiltration.

10. In the **DOSAGE AND ADMINISTRATION** section, the entire subsection titled "**Empiric Therapy in Febrile, Neutropenic Patients with Suspected Fungal Infections (ETFN)**" is deleted as follows:

~~The recommended dose of SPORANOX® Injection is 200 mg b.i.d. for four doses, followed by 200 mg once daily for up to 14 days. Each intravenous dose should be infused over 1 hour. Treatment should be continued with SPORANOX® Oral Solution 200 mg (20 mL) b.i.d. until resolution of clinically significant neutropenia. The safety and efficacy of SPORANOX® use exceeding 28 days in ETFN is not known.~~

~~SPORANOX® Oral solution is a different preparation that SPORANOX® Capsules and should not be used interchangeably.~~

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text, which is identical to the labeling submitted April 8, 2011

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA

automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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 Ms. June Germain, MS Regulatory Health Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

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

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/

JUNE GERMAIN
04/15/2011

RENATA ALBRECHT
04/15/2011