



NDA 20-657/S-025

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 dated and received on September 24-2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Sporanox[®] (itraconazole) Oral Solution.

We also acknowledge your amendment dated December 17, 2010.

This supplemental new drug application provides for the following revisions to the labeling for Sporanox (additions are noted with underline and deletions are noted with ~~strikethrough~~):

The **MICROBIOLOGY** section is revised as follow:

Mechanism of Action:

In vitro studies have demonstrated that itraconazole inhibits the cytochrome P450-dependent synthesis of ergosterol, which is a vital component of fungal cell membranes.

Activity *In Vitro* and *In Vivo*

~~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.~~

Itraconazole has been shown to be active against most strains of the following microorganisms, **both *in vitro* and in clinical infections.**

Aspergillus flavus
Aspergillus fumigatus
Blastomyces dermatitidis
Candida albicans

*Histoplasma capsulatum**Histoplasma duboisii*

~~*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., *Seedosporium* spp. and *Scopulariopsis* spp.~~

The bioactive metabolite, hydroxyitraconazole, has not been evaluated against *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Zygomycete*, *Fusarium* spp., *Seedosporium* 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.

Susceptibility Testing Methods

(Applicable to *Candida* isolates from patients with oropharyngeal or esophageal candidiasis)

Candida albicans

The interpretive criteria and breakpoints for itraconazole against *Candida albicans* are applicable to tests performed using Clinical Laboratory and Standards Institute (CLSI) microbroth dilution reference method M27A for MIC (partial inhibition endpoint) read at 48 hours.

Broth Microdilution Techniques

Quantitative methods are used to determine antifungal minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of *Candida* spp. to antifungal agents. MICs should be determined using a standardized procedure at 48 hours. Standardized procedures are based on a microdilution method (broth) with standardized inoculum concentrations and standardized concentrations of itraconazole powder. The MIC values should be interpreted according to the criteria provided in Table below:

Susceptibility Interpretive Criteria for Itraconazole			
<u>Pathogen</u>	<u>Broth Microdilution MIC* (µg/mL) at 48 Hours</u>		
	<u>S</u>	<u>I</u>	<u>R</u>
<u><i>Candida albicans</i></u>	<u>≤ 0.125</u>	<u>0.25 – 0.5</u>	<u>≥ 1</u>

*A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. The *intermediate* category implies that an infection due to the isolate may be appropriately treated in body sites where the drugs are physiologically concentrated or when a high dosage of drug is used. The *resistant* category implies that isolates are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies. The *intermediate* category is sometimes called *Susceptible-Dose Dependent* (SDD) and both categories are equivalent for itraconazole.

Quality Control

Standardized susceptibility test procedures require the use of quality control organisms to control the technical aspects of the test procedures. Standard itraconazole powder should provide the following range of values noted in the table below.

NOTE: Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within fungi; the specific strains used for microbiological control are not clinically significant.

<u>Acceptable Quality Control Ranges for Itraconazole to be used in Validation of Susceptibility Test Results</u>	
<u>QC Strain</u>	<u>Broth Microdilution MIC (µg/mL) at 48 Hours</u>
<u><i>Candida parapsilosis</i> ATCC† 22019</u>	<u>0.06-0.25</u>
<u><i>Candida krusei</i> ATCC 6258</u>	<u>0.12-0.5</u>

† ATCC is a registered trademark of the American Type Culture Collection.

Activity in Animal Models

Itraconazole administered orally was active in a variety of animal models of fungal infection using standard laboratory strains of fungi. Fungistatic activity has been demonstrated against disseminated fungal infections caused by *Blastomyces dermatitidis*, *Histoplasma duboisii*, *Aspergillus fumigatus*, *Coccidioides immitis*, *Cryptococcus neoformans*, *Paracoccidioides brasiliensis*, *Sporothrix schenckii*, *Trichophyton rubrum*, and *Trichophyton mentagrophytes*.

Itraconazole administered at 2.5 mg/kg and 5 mg/kg via the oral and parenteral routes increased survival rates and sterilized organ systems in normal and immunosuppressed guinea pigs with disseminated *Aspergillus fumigatus* infections. Oral itraconazole administered daily at 40 mg/kg and 80 mg/kg increased survival rates in normal rabbits with disseminated disease and in immunosuppressed rats with pulmonary *Aspergillus fumigatus* infection, respectively.

Itraconazole has demonstrated antifungal activity in a variety of animal models infected with *Candida albicans* and other *Candida* species.

Resistance

Isolates from several fungal species with decreased susceptibility to itraconazole have been isolated *in vitro* and from patients receiving prolonged therapy. Several *in vitro* studies have reported that some fungal clinical isolates, including *Candida* species, with reduced susceptibility to one azole antifungal agent may also be less susceptible to other azole derivatives. The finding of cross-resistance is dependent on a number of factors, including the species evaluated, its clinical history, the particular azole compounds compared, and the type of susceptibility test that is performed. The relevance of these *in vitro* susceptibility data to clinical outcome remains to be elucidated.

Candida krusei, *Candida glabrata* and *Candida tropicalis* are generally the least susceptible to *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.

Studies (both *in vitro* and *in vivo*) suggest that the activity of amphotericin B may be suppressed by prior azole antifungal therapy. As with other azoles, itraconazole inhibits the ¹⁴C-demethylation step in the synthesis of ergosterol, a cell wall component of fungi. Ergosterol is the active site for amphotericin B. In one study the antifungal activity of amphotericin B against *Aspergillus fumigatus* infections in mice was inhibited by ketoconazole therapy. The clinical significance of test results obtained in this study is unknown.

We have completed our review of this supplemental application, as amended. This supplement is approved, effective on the date of this letter, for use as recommended in the package insert attached to this letter, which is identical to the package insert submitted on December 17, 2010.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>, that is identical to the enclosed labeling (text for the package insert) and include the labeling changes proposed in any pending “Changes Being Effected” (CBE) supplements. 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 pending “Changes Being Effected” (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.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

LETTERS TO HEALTH CARE PROFESSIONALS

If you decide to issue a letter communicating important safety-related information about this drug product (i.e., a “Dear Health Care Professional” letter), we request that you submit, at least 24 hours prior to issuing the letter, an electronic copy of the letter to this NDA to the following address:

MedWatch Program
Office of Special Health Issues
Food and Drug Administration
10903 New Hampshire Ave
Building 32, Mail Stop 5353
Silver Spring, MD 20993

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, 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/

RENATA ALBRECHT
01/04/2011