CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: **20-966**

MICROBIOLOGY REVIEW(S)

REVIEW FOR HFD-580
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805

Microbiologist's Review #2 of NDA 20-966 Amendment
Response to Deficiencies
March 9, 1999

1. **APPLICATION NUMBER:** 20-966 Amendment

APPLICANT: Janssen Pharmaceutical
1125 Trenton-Harbourton Road
PO Box 200
Titusville, New Jersey 08560-0200

2. **PRODUCT NAMES:** Sporanox (itraconazole) Injection

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** 25 ml ampoules, 10 mg/ml itraconazole, 20 ml fill volume. The full content of the ample is to be diluted in 50 ml bag of Normal Saline and infusing 60 ml of the admixture.

4. **METHOD(S) OF STERILIZATION:** Terminal moist heat sterilization

5. **PHARMACOLOGICAL CATEGORY:** Treatment of histoplasmosis, blastomycosis, and aspergillosis in patients refractory to amphotericin B.

B. 1. **DATE OF INITIAL SUBMISSION:** April 27, 1998

2. **AMENDMENT:** January 27, 1999

3. **RELATED DOCUMENTS:** [redacted]

4. **ASSIGNED FOR REVIEW:**

5. **DATE OF CONSULT REQUEST:**

C. **REMARKS:**

This is the response to the deficiencies in Microbiology Review #1. It is filed as an amendment to [redacted] Container/Closure Validation-Contract Manufacturing.

D. CONCLUSIONS:

The response to the deficiencies was satisfactory. The submission is recommended for approval for issues concerning microbiology.

/S/ 3/9/99

Brenda Uratani, Ph.D.
Review Microbiologist

JAC 3/10/99

cc:

NDA 20-966
HFD-590/ Div. File
HFD-805/ Uratani
HFD-590/Holbert
HFD-590/Kimzey
drafted by: Brenda Uratani, 3/9/99
R/D initialed by P. Cooney, 3/9/99

12/31/98 finished
Rev. to Sponsor
ejk

MICROBIOLOGY REVIEW
DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS (HFD-590)

NDA #: 20-966

REVIEWER	: Shukal Bala
CORRESPONDENCE DATE	: 04-27-98
CDER RECEIPT DATE	: 05-22-98
REVIEW ASSIGN DATE	: 05-25-98
REVIEW COMPLETE DATE	: 10-05-98

SPONSOR: Janssen Pharmaceutica Research Foundation
1125 Trenton-Harbourton Road
Post Office Box 200
Titusville, NJ 08560

SUBMISSION REVIEWED: Original

DRUG CATEGORY: Anti-fungal

INDICATION: For the treatment of histoplasmosis, blastomycosis and aspergillosis in patients refractory to amphotericin B

DOSAGE FORM: New dosage (intravenous injection / infusion) form for individuals unable to take oral capsules

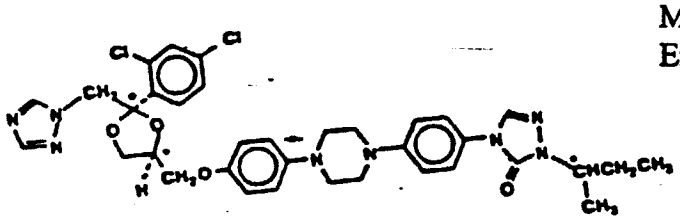
PRODUCT NAMES:

a. **PROPRIETARY:** Sporanox

b. **NONPROPRIETARY:** Itraconazole

c. **CHEMICAL:** (±)-cis-4[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one

STRUCTURAL FORMULA:



Molecular weight: 705.64
Empirical formula: $C_{35}H_{38}Cl_2N_8O_4$

SUPPORTING DOCUMENTS: NDA # 20-083, 20-657, 20-510;

BACKGROUND:

Itraconazole is an approved drug for the treatment of fungal infections. The capsule formulation is approved for treatment of Blastomycosis, Histoplasmosis, and Aspergillosis in both immunocompromised and nonimmunocompromised patients. The oral solution is approved for the treatment of oropharyngeal and esophageal candidiasis. In this submission the sponsor has requested approval of the intravenous formulation for the treatment of patients with histoplasmosis, blastomycosis and aspergillosis who are refractory to amphotericin B.

SUMMARY:

Itraconazole is an approved drug with activity *in vitro* and *in vivo* against a variety of fungi. It exhibits anti-fungal activity by inhibition of the cytochrome P-450 enzyme that is essential for the synthesis of ergosterol from lanosterol (a component of the fungal cell membrane). No additional preclinical Microbiology information has been included in this submission and nor is the microbiology section of the label altered.

Information on the potential emergence of resistance and cross resistance is provided in the Microbiology section of the label under the subheading '*Activity in vitro and in vivo*'. In order to promote consistency across different labels a separate subheading of 'Resistance' should be considered. It should be noted that the existing label states that pretreatment with azoles can reduce the activity of amphotericin B. The label also describes the potential for development of cross resistance among azoles. However, it doesn't state outright that treatment with itraconazole can cause resistance.

There are many reports published in recent years showing the development of resistance to itraconazole *in vitro* and *in vivo*. Some of this information is summarized below:

In a surveillance study by Pfaller *et al.*, 1998 (J. Clin. Microbiol. 36: 1886), the *in vitro* drug susceptibility of isolates from patients with blood stream infections was measured. The results showed that 37% of *Candida glabrata* and 67% of the *C. krusei* isolates tested were resistant to itraconazole. In another study (Chryssanthou, E. 1997: Scand. J. Inf. Dis. 29: 509), isolates of *Aspergillus fumigatus* from 3 of 80 patients with respiratory tract infections showed reduced *in vitro* susceptibility to itraconazole (i.e., a 128 to 256 -fold increase in minimum inhibitory concentration, MIC, values) after prolonged therapy (200 to 400 mg/day for 5 months to 3 years).

Studies *in vitro* also support the development of resistance by various fungal species to itraconazole. In addition, prior exposure of *C. albicans* to itraconazole (2ug/ml) or fluconazole (50ug/ml) for 16 hours, was shown to decrease susceptibility to amphotericin B. While several other non-albicans

Candida species were not able to grow in culture after pre-exposure to an azole, the viability was not reduced. This observation also suggests some degree of cross resistance between azoles and polyenes such as amphotericin B (Vazquez, J. A. *et al.*, 1998, J. Clin. Microbiol. 36: 2690).

It is also of note that breakpoints have been established by the NCCLS for some antifungals, including itraconazole against *Candida* isolates from patients with oropharyngeal candidiasis (NCCLS guidelines entitled 'Reference method for broth dilution antifungal susceptibility testing of yeasts; approved standard' June, 1997, vol. 17, No. 9). These guidelines were also published by Lewis *et al.*, 1998 (Pharmacotherapy 18: 509). However, the relevance of these breakpoints for other indications is not clear at the present time. Also, it should be noted that these breakpoints are based on methods recommended by NCCLS and may vary if other methods are used for the measurement of *in vitro* susceptibility.

CONCLUSIONS:

The sponsor has submitted an NDA for a new formulation of itraconazole, an approved antifungal agent. No new preclinical microbiology information is included in this submission and the microbiology section of the label is not altered.

In order to maintain consistency across the different labels it is recommended that the information describing resistance on lines 1 to 15, page 42 of volume 1, be provided under a separate subheading of "Resistance" in the Microbiology section of the label. Also, it would be appropriate to add a sentence to the existing text stating that like other azoles, treatment with itraconazole, can induce resistance. Finally, it would also be worthwhile to describe the drug interaction between the azoles and the polyenes in the "drug interaction" section (pages 47 – 51, volume 1) in addition to the discussion that appears under 'Microbiology'.

Based on the studies reviewed, the following changes in the 'Resistance' subsection of the label (lines 1 to 15, page 42, volume 1) and 'Drug Interaction' section (pages 47 – 51, volume 1) are recommended (the recommended changes are double-underlined):

The Label:

MICROBIOLOGY

Mechanism of Action:
No change.

Activity *in vitro* and *in vivo*:
No change.

Resistance:

Isolates from several fungal species with decreased susceptibility to itraconazole have been isolated *in vitro* and from patients receiving prolonged therapy.

~~*In vivo*~~ Studies *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 ^{14}C-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.

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 upon 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.

Drug Interaction

Polyenes: Prior treatment with itraconazole, like other azoles, may reduce or inhibit the activity of polyenes such as amphotericin B. However, the clinical significance of this drug effect has not been clearly defined.

RECOMMENDATIONS:

This NDA is approvable with respect to microbiology pending an accepted version of the label.

/S/

Shukal Bala
Microbiologist, HFD-590

CONCURRENCES:

HFD-590/Deputy Dir. /S/ Signature 12/23/98 Date
HFD-590/Micro TL Signature 12/14/98 Date
CC: /S/