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APPLICATION NUMBER:

20-966/S-001, S-003, S-004

20-657/S-004, S-005

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	20-966
Generic	Itraconazole
(Brand®)	Sporanox®
Submission Date:	April 28, 2000
Sponsor:	Janssen
Type of Submission:	Efficacy Supplement
Reviewer:	Houda Mahayni

Background

This is an efficacy supplement to NDA 20-966 to provide for an additional indication: empiric therapy in febrile neutropenic patients with suspected fungal infections. The dosing regimen provides for treatment with Sporanox injection followed by Sponranox oral solution until resolution of the clinically significant neutropenia. The recommended dosage regimen for this indication is Sporanox injection 200 mg b.i.d. for four doses, followed by 200 mg once daily for up to 14 days. Treatment should be continued with Sporanox oral solution 200 mg (20 mL) b.i.d. until resolution of the clinically significant neutropenia.

Mean itraconazole levels during the intravenous treatment in study ITR-INT-62 were 768, 854, and 1337 ng/mL on day 3, 8, and 15, respectively. These levels remained approximately stable after switching to follow-up treatment with the oral solution: mean concentration were 1133 and 975 ng/mL on day 15 and 22 of the oral treatment, respectively. The average ratio of hydroxy-itraconazole/itraconazole was 1.54±0.73 during the intravenous phase and 1.61±0.58 during the oral follow-up phase. On day 3 of the intravenous itraconazole treatment, 96% of the subjects had pre-dose plasma concentrations that were higher than 250 ng/mL. After one week of treatment, these levels were maintained or slightly increased. For subjects who stopped during the intravenous phase, the concentration averaged 976±565 ng/mL. For 95% of the subjects, these values were > 250 ng/mL. For the oral follow-up phase, the mean end of treatment concentration was 1608±867 ng/mL. For 95% of the subjects these values were >250 ng/mL.

The efficacy data supporting this supplemental NDA are derived from one clinical study (ITR-INT-62), a multicenter, open randomized trial comparing the efficacy and safety of intravenous itraconazole followed by oral itraconazole (192 patients) with intravenous amphotericin B (192 patients) in febrile neutropenic patients with hematologic malignancy.

Safety data are derived from 11 studies: ITR-INT-62, ITR-INT-60 (an uncontrolled aspergillosis study of intravenous followed by oral itraconazole), four pharmacokinetic studies which initiated therapy with IV itraconazole, and five prophylaxis studies with the oral solution formulation of itraconazole. These data provide a safety database of over 300 patients who received IV itraconazole and a total of approximately 1200 patient who received itraconazole in any formulation in these studies.

Findings

There are no labeling changes to the clinical pharmacology section of the product package insert. Sporanox oral solution is currently approved at a dose of 200 mg (20 mL) daily in single dose or divided doses for up to 2 weeks for oropharyngeal candidiasis and at a dose of 100 mg (10 mL) daily for a minimum of three weeks for esophageal candidiasis. For the treatment of blastomycosis, histoplasmosis and aspergillosis, the recommended intravenous dose is 200 mg b.i.d. for 4 doses, followed by 200 mg q.d.

Recommendation
Following a review of this supplemental application to NDA 20-966, there is adequate data in support of the proposed dosage regimen from a clinical pharmacology/biopharmaceutics view point

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CC: NDA 20-966(orig., 1 copy), HFD-590(Leissa, Kimzey), HFD-880(Ajayi, Mahayni).