# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**22-484**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

**CLINICAL PHARMACOLOGY REVIEW – ADDENDUM**

| | |
|---|---|
| **Original NDA:** | **22-484** |
| **Brand Name:** | TBD |
| **Generic Name:** | Itraconazole 200 mg |
| **Dosage Form & Strength:** | Film-coated tablets |
| **Indication:** | Oral treatment of onychomycosis of the toenail (b) (4) |
| **Applicant:** | Stiefel Laboratories |
| **Submission:** | 505(b)(1), Standard |
| **Submission Dates:** | 03/31/2009 |
| **OND Division:** | Dermatological and Dental Products |
| **OCP Divisions:** | Clinical Pharmacology 3 |
| **Primary Reviewer:** | Seongeun Julia Cho, Ph.D. |
| **Team Leader:** | Dennis Bashaw, Pharm.D. |

## Introduction

This is an addendum to the original review of NDA 22-484, Itraconazole Tablet. During the review of the application and the sponsor's proposed label, the review team recognized that the list of drugs that has drug interaction potential with itraconazole was incomplete in the proposed label. The sponsor, having a "right of reference" from the original NDA holder, had copied the current DDI data from the SPORANOX label which is somewhat out-dated and not in PLR format. Following the Agency's request, the sponsor submitted additional drug interaction information, based on the literature search. The following is a review of submitted literature articles related to this issue and labeling recommendation by the clinical pharmacology review team. The labeling recommendation for each drug was also consulted by each therapeutic division and reflects their concurrences.

## Efavirenz

1. Andrade R.A.; Evans R.T.; Hamill R.J.; Zerai T.;Giodano T.P.; Clinical evidence of interaction between itraconazole and nonnucleoside reverse transcriptase inhibitors in HIV-infected patients with disseminated histoplasmosis. Annals of Pharmacotherapy. 2009;43:5:908-913.

This is a report of retrospective cohort study to evaluate whether itraconazole concentrations are affected by antiretroviral therapy. Ten patients were included in the analysis and all were prescribed 200 mg or 400 mg itraconazole. Among them, 4 patients were taking NNRTI (nonnucleoside reverse transciptase inhibitors), efavirenz or nevirapine, while the rest were taking either protease inhibitors (PI) or a combination of PI and NNRTI. All 4 patients on NNRTI had serum itraconazole concentrations below LOD (50 ng/ml), which is much lower than those from other patients and below a therapeutic range.

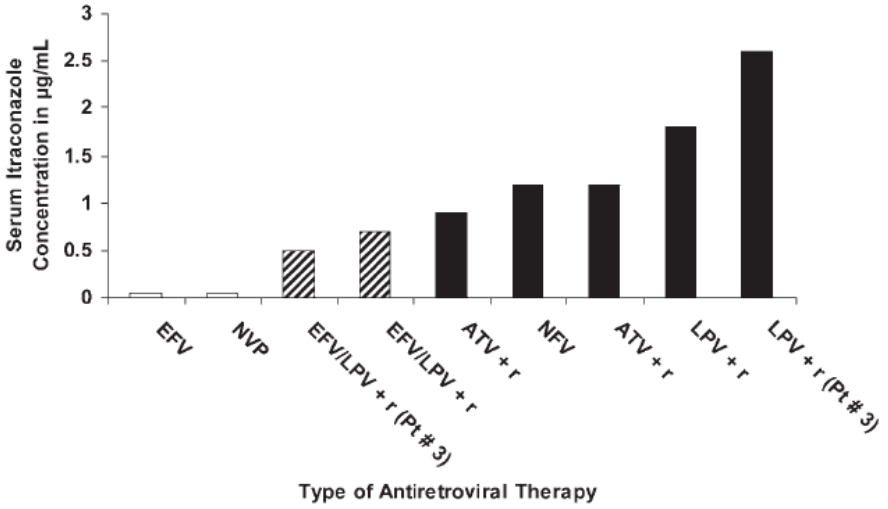



**Figure 1.** Serum itraconazole concentrations distributed by type of antiretroviral therapy. Open bars are itraconazole concentrations from patients on NNRTIs. Striped bars are concentrations from patients on both NNRTI and PI. Solid bars are concentrations from patients on PI. ATV = atazanavir; EFV = efavirenz; LPV = lopinavir; NFV = nelfinavir; NNRTI = nonnucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; r = ritonavir.

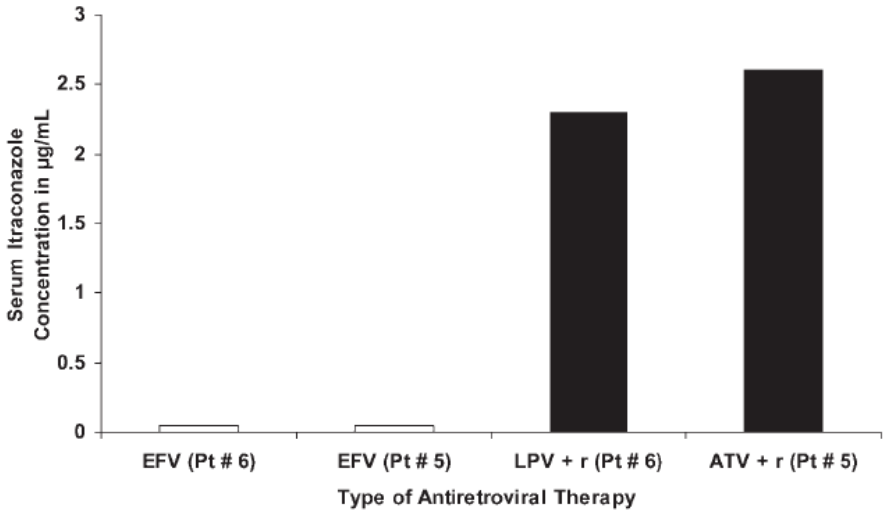



**Figure 2**. Serum itraconazole concentrations for patients switching from NNRTI- to PI-based antiretroviral therapy. Open bars are itraconazole concentrations while on NNRTI. Solid bars are concentrations from patients on PI. ATV = atazanavir; EFV = efavirenz; LPV = lopinavir; NNRTI = nonnucleoside reverse transcriptase inhibitor; PI = protease inhibitor; r = ritonavir.

## Reviewer's Comments

It is not clear how many patients (out of 4) are on efavirenz in this analysis. However, the data from patient #5 and 6 clearly suggest the reduction of serum itraconazole concentration due to efavirenz, which is an inducer of CYP3A4, which is consistent with the known pharmacologic interactions between these agents. The current Sporanox label contains the following dosage recommendation for nevirapine, another NNRT1, in the DDI section.

> Nevirapine is an inducer of CYP3A4. In vivo studies have shown that nevirapine induces the metabolism of ketoconazole, significantly reducing the bioavailability of ketoconazole. Studies involving nevirapine and itraconazole have not been conducted. However, because of the similarities

between ketoconazole and itraconazole, concomitant administration of SPORANOX® and nevirapine is not recommended.

Therefore, we recommend including the efavirenz study to the label of itraconazole tablet and indicate a concomitant use of efavirenz and itraconazole is not recommended.

7. Huet E; Hadji C.; Hulin A.; Botterel F., Bretagne S.; Lévy Y. Therapeutic monitoring is necessary for the association itraconazole and efavirenz in a patient with AIDS and disseminated histoplasmosis. AIDS. 2008;Sep:12;22(14):1885-6.

In a 59-year-old woman from French Guiana with disseminated histoplasmosis and a HIV-1 infection, efavirenz decreased Cmin and AUC0-10 of itraconazole by 50 %, and increased Cmin and AUC0-10 of hydroxyitraconazole by 250%, following 6 days of itraconazole (600 mg daily). The authors noted that the levels hydroxyitraconazole, a major metabolite, should also be monitored, in addition to itraconazole, as it is an active metabolite.

**Reviewer's Comments**
The results of increased of hydroxyitraconazole reported in the paper is inconsistent to the information in the label of efavirenz (SUSTIVA). Efavirenz statements in itraconazole label are to be based on current efavirenz label and other previous studies. See above for labeling recommendation.

**Meloxicam**
3. Hynninen V.V.; Olkkola K.T.; Bertilsson L.; Kurkinen K.J.; Korhonen T.; Neuvonen P.J.; Laine K. Voriconazole increases while itraconazole decreases plasma meloxicam concentrations. Antimicrobial Agents and Chemotherapy. 2009;53:2:587-592.

This study investigated the effect of itraconazole on the pharmacokinetics and pharmacodynamics of meloxicam. Twelve healthy volunteers in a crossover study ingested 15 mg of meloxicam with or without itraconazole pretreatment. Compared to the control phase, itraconazole decreased the mean AUC0-72 and *C*max of meloxicam by 37% ($P < 0.001$) and by 64% ($P < 0.001$), respectively, and prolonged its $t1/2$ and time to *C*max. Lowered plasma meloxicam concentrations during the itraconazole phase were associated with decreased pharmacodymic effects of meloxicam, as observed by weaker inhibition of TxB2 synthesis.

**Reviewer's Comments**
While itraconazole is CYP3A4 inhibitor, it appears that itraconazole decreased the exposure to meloxicam by impairing its GI absorption. It is an unexpected finding, especially considering its 3A4 inhibition, and this information should be included in the label.

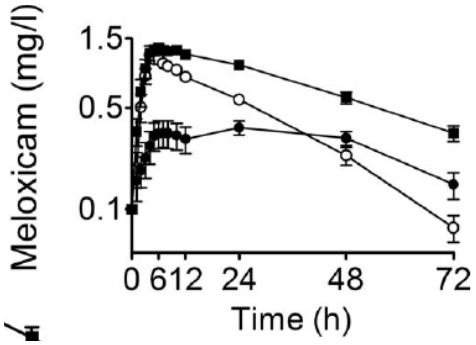



FIG. 1. Plasma concentrations (mean ± the standard error of the mean) of meloxicam after a single 15-mg oral dose in 12 healthy male subjects in control phase (○) or after pretreatment with voriconazole (■) or after pretreatment with itraconazole (●). The inset depicts the same data on a semilogarithmic scale.

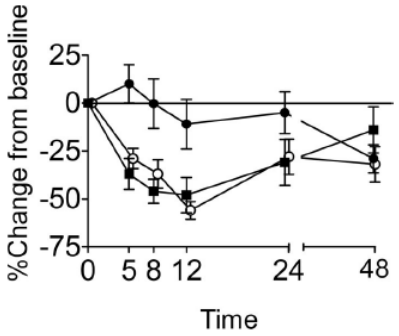



FIG. 3. Mean percent inhibition of $TxB_2$ generation from baseline by 15 mg of meloxicam either given alone (○) or after pretreatment with voriconazole (■) or after pretreatment with itraconazole (●).

**Labeling Recommendation**

(b) (4)

(b) (4)

Coadministration of itraconazole with meloxicam decreased peak plasma concentrations and the exposure of meloxicam by 64% and 37%,, respectively. Monitor patients for responses to meloxicam when itraconazole is concomitantly administered and dose adjustment should be considered if warranted.

**Morphine**

4. Heiskanen T.; Backman J.T.; Neuvonen M.; Kontinen V.K.; Neuvonen P.J.; Kalso E. Itraconazole, a potent inhibitor of P-glycoprotein, moderately increases plasma concentrations of oral morphine. Acta Anaesthesiologica Scandinavica.2008;52:10:1319-1326.

This study evaluated whether itraconazole would change the pharmacokinetics or the pharmacodynamics of oral morphine. Twelve healthy male volunteers ingested, in a randomized crossover study, once daily 200mg itraconazole or placebo for 4 days. On day 4, 1 h after the last pretreatment dose, the subjects ingested 0.3 mg/kg morphine. Pharmacodynamic effects were evaluated using a questionnaire, visual analogue scales, a reaction time test, the Digit Symbol Substitution Test and the Critical Flicker Fusion Test. Itraconazole increased AUC (0–9) of morphine by 29% (P=0.002), AUC (0–48) by 22% (P=0.013) and Cmax by 28% (P=0.035). Itraconazole did not significantly affect the pharmacodynamic effects of morphine. The mechanism of itraconazole-mediated

increased plasma concentrations of morphine is postulated to be via inhibition of Pgp in GI wall.

**Recommendation**
The changes in the exposure reported in this study are within the variability range known for this drug. Per consultation with DAARP, no clinical implication is anticipated from these data and, as such, no addition of such findings would be needed in the itraconazole label.

**Fexofenadine**
5. Tateishi T.; Miura M.; Suzuki T.; Uno T. The different effects of itraconazole on the pharmacokinetics of fexofenadine enantiomers. British Journal of Clinical Pharmacology. 2008;65:5:693-700.

This study was to determine the inhibitory effect of itraconazole on P-gp on the stereoselective pharmacokinetics of fexofenadine. A two-way double-blind, placebo-controlled crossover study was performed. Twelve healthy volunteers received either itraconazole 200 mg or placebo with a single oral dose of fexofenadine 60 mg. After placebo administration, mean plasma concentrations of *R*-fexofenadine were higher than those of *S*-fexofenadine. Itraconazole co-administration increased plasma concentrations of both enantiomers of fexofenadine (3-4 fold increases in AUC and C max). The authors noted that the stereoselective pharmacokinetics of fexofenadine are due to P-gp-mediated transport and the inhibition of the P-gp efflux by itraconazole increased fexofenadine absorption and reduced the stereoselectivity in fexofenadine enantiomers.

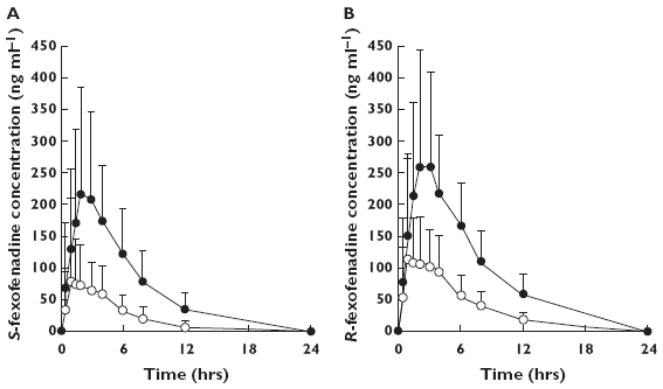



**Figure 1**
(A) Mean (+SD) plasma concentration–time curves of *S*-fexofenadine following a single oral administration of 60 mg fexofenadine hydrochloride in 12 healthy volunteers treated with placebo (open circles) or itraconazole (closed circles). (B) Mean (+SD) plasma concentration–time curves of *R*-fexofenadine following a single oral administration of 60 mg fexofenadine hydrochloride in 12 healthy volunteers treated with placebo (open circles) or itraconazole (closed circles)

12. Shon J. H.; Yoon Y.R.; Hong W.S.; Phuc M.N.; Lee S.S; Choi Y.G, Cha I.J.; Shin J.G. Effect of itraconazole on the pharmacokinetics and pharmacodynamics of fexofenadine in relation to the MDR1 genetic polymorphism. Clinical Pharmacology and Therapeutics. 2005;78:2:191-201.

The study was a double-blinded, randomized, crossover study to evaluate the effect of itraconazole on the pharmacokinetics and pharmacodynamics of fexofenadine, a P-glycoprotein substrate, in relation to the multidrug resistance 1 gene (*MDR1*) G2677T/C3435T haplotype. A single oral dose of 180 mg fexofenadine was administered to 7 healthy subjects with the 2677GG/3435CC (G/C) haplotype and 7 with the 2677TT/3435TT (T/T) haplotype. One hour before the fexofenadine dose, either 200 mg itraconazole or placebo was administered. In the placebo phase, pharmacokinetic parameters of fexofenadine or itraconazole were not different between 2 *MDR1* haplotypes. Itraconazole increased Cmax and AUC of fexofenadine more than a 3-fold and the mean fexofenadine AUC in the T/T group became significantly higher than that in the G/C group (15,630.6 vs. 9252.9 ng/mL · h). This increase was associated with a significantly higher antihistamine effect of fexofenadine in the itraconazole pretreatment phase.

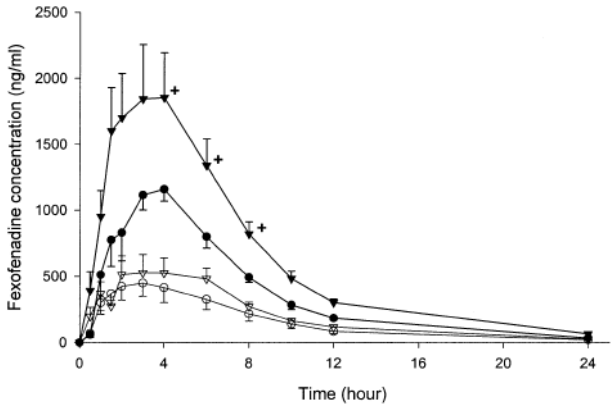



**Fig 2.** Mean plasma concentration (±SE) of fexofenadine after oral administration of 180-mg single dose when pretreated with placebo (*open symbols*) or 200 mg itraconazole (*solid symbols*) in multidrug resistance 1 gene (*MDR1*) 2677G/3435C (*circles*) and 2677T/3435T (*triangles*) haplotype groups. *Plus sign*, $P < .05$, rank sum test between *MDR1* haplotype groups.

**Reviewer's Comments**

Fexofenadine labeling indicates approximately 5 % of fexofenadine is metabolized and the pharmacokinetics of fexofenadine in patients with hepatic impairment did not differ substantially from that observed in healthy patients. However, the following information is included in the case for renally impaired patients.

> *Renally Impaired*: In subjects with mild to moderate (creatinine clearance 41-80 mL/min) and severe (creatinine clearance 11-40 mL/min) renal impairment, peak plasma concentrations of fexofenadine were 87% and 111% greater, respectively, and mean elimination half-lives were 59% and 72% longer, respectively, than observed in healthy subjects. Peak plasma concentrations in subjects on dialysis (creatinine clearance ≤10 mL/min) were 82% greater and half-life was 31% longer than observed in healthy subjects. Based on increases in bioavailability and half-life, a dose of 60 mg once daily is recommended as the starting dose in adult patients with decreased renal function. For pediatric patients with decreased renal function, the recommended starting dose of fexofenadine is 30 mg once daily for patients 2 to 11 years of age and 15 mg once daily for patients 6 months to less than 2 years of age.

The changes in Cmax of fexofenadine observed in the two referenced papers in this review (5 and 12) are much greater than those in the current fexofenadine label, cited above.

**Labeling Recommendation**

Results of the drug interaction studies need to be added. Dose adjustment recommendation is not made at the current time and will be pending on further assessment of the safety database and adverse event profiles such as drowsiness.

**Imidafenacin**

6. Ohno T.; Nakayama K.; Nakade S.; Kitagawa J.; Ueda S.; Miyabe H.; Miyata Y.; Ohnishi A. Effect of itraconazole on the pharmacokinetics of imidafenacin in healthy subjects. Journal of Clinical Pharmacology. 2008;48:3:330-334.

The study evaluated the effect of itraconazole on the pharmacokinetics of imidafenacin, a novel synthetic muscarinic receptor antagonist in 12 healthy subjects. In period I, subjects received a single oral dose of 0.1 mg imidafenacin. In period II, they received multiple oral doses of 200 mg itraconazole for 9 days and a single oral dose of 0.1 mg midafenacin on day 8. Following coadministration with itraconazole, Cmax of imidafenacin increased 1.32-fold and AUC0-∞ increased 1.78-fold. The article states no adverse events were reported after coadministration of imidafenacin with itraconazole (day 8 to day 10 in period II).

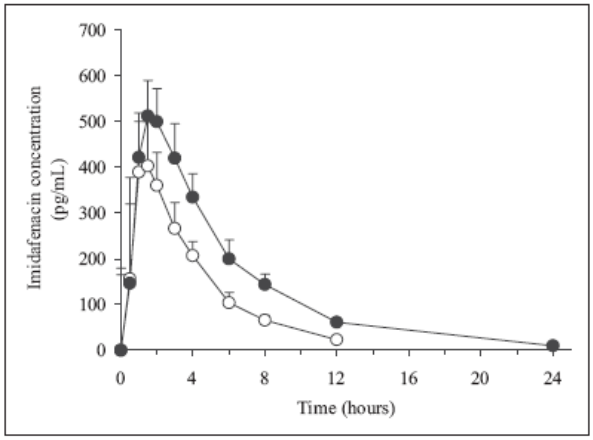



*Figure 1. Mean plasma concentration–time profiles of imidafenacin after administration of 0.1 mg imidafenacin alone (open circles) or coadministration with 200 mg itraconazole (filled circles) in 10 healthy subjects.*

**Reviewer's Comments**

It is a drug not marketed in US.

**Maraviroc**

8. Sayana S.; Khanlou H. Maraviroc: A new CCR5 antagonist. Expert Review of Anti-

Infective Therapy. 2009;7:1: 9-19.

9. Yost R.; Pasquale T.R.; Sahloff E.G. Maraviroc: A coreceptor CCR5 antagonist for management of HIV infection. American Journal of Health-System Pharmacy. 2009; 66:8:715-726.

Both of the articles are review papers, summarizing pharmacology, PK, clinical efficacy, drug interaction, adverse events, and dosage administration of maraviroc. While there are no data presented for co-administration of maraviroc and itraconazole, both papers describe the effect of concomitant use of CYP3A4 inhibitors on PK of maraviroc and the necessity of dose adjustment from 300 mg BID to 150 mg BID.

**Labeling Recommendation**
Add maraviroc to the anti-HIV category. Language indicating Maraviroc dose should be decreased when concomitantly administered with itraconazole should be added to cross-label with the Maraviroc label (in consult with anti-viral product clin pharm division).

**Propoxyphene (opiate analgesics)**

11. Armstrong S.C.; Wynn G.H.; Sandson N.B. Pharmacokinetic drug interactions of synthetic opiate analgesics. Psychosomatis. 2009;50:2:169-176.

This is a review on pharmacokinetic drug interactions of synthetic opiate analgesics. It is noted that the use of propoxyphen has been associated with QTc prolongation and use of 3A4 inhibitors may increase the risk. Description of drug interaction relating to CYP3A4, however, is a mechanism-based prediction.

**Reviewer's Comments**
Information from Darvon (propoxyphen) label:

> **Drug Interactions**
> The metabolism of propoxyphene may be altered by strong CYP3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazadone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil) leading to enhanced propoxyphene plasma levels.

The evidence of propoxyphen inducing QTc prolongation is not concrete at this moment and warrants further assessment. An inclusion into the label is not recommended as per consult with DAARP.

**Telithromycin**

13. Shi J.; Montay G.; Leroy B.; Bhargava V.O. Effects of itraconazole or grapefruit juice on the pharmacokinetics of telithromycin. Pharmacotherapy. 2005;25:1:42-51.

To determine if itraconazole modified the PK profile of telithromycin, an open-label, nonrandomized, sequential, multiple dose study was conducted. Seventeen healthy,

nonsmoking male volunteers aged 18–45 years participated in the study and subjects received placebo on day -1, telithromycin 800 mg/day on days 1–4, no drug on days 5–6, itraconazole 200 mg/day on days 7–20, and itraconazole plus telithromycin on days 21–24. Itraconazole increased the steady-state AUC0–24h of telithromycin by 53.8% ($p<0.0001$). Mean Cmax-ss was higher with concomitant itraconazole but the difference was not significant. Authors noted that concomitant administration of telithromycin and itraconazole was well tolerated and not serious or severe adverse effects were reported.

Table 2. Mean Pharmacokinetic Parameters of Telithromycin After Oral Telithromycin 800 mg/day Alone (n=17) or with Concomitant Itraconazole 200 mg (n=17)

| | | | | | Pairwise Comparisons (TEL + ITR/TEL Alone) | | |
|---|---|---|---|---|---|---|---|
| Parameter | Treatment | Mean | % CV | Adjusted Mean[a] | Ratio[a] (%) | (90% CI[a]) | p Value |
| $AUC_{(0-24)-ss}$ (mg/L•hr) | TEL | 13.40 | 36.00 | 12.65 | | | |
| | TEL + ITR | 20.56 | 34.32 | 19.46 | 153.82 | (135.64–174.44) | <0.0001 |
| $AUC_{(0-\infty)-ss}$ (mg/L•hr) | TEL | 14.37 | 36.09 | 13.57 | | | |
| | TEL + ITR | 23.24 | 38.99 | 21.69 | 158.86 | (140.97–181.27) | <0.0001 |
| $C_{max-ss}$ (mg/L) | TEL | 2.53 | 29.72 | 2.42 | | | |
| | TEL + ITR | 3.05 | 25.74 | 2.95 | 121.71 | (103.37–143.30) | 0.0520 |
| $C_{min-ss}$ (mg/L) | TEL | 0.04 | 57.89 | 0.04 | | | |
| | TEL + ITR | 0.10 | 72.16 | 0.08 | 219.30 | (168.73–285.02) | <0.0001 |
| $T_{1/2-ss}$ (hrs) | TEL | 13.32 | 42.53 | 11.25 | | | |
| | TEL + ITR | 14.13 | 65.70 | 11.30 | 100.39 | (88.90–113.36) | 0.9566 |

16. Lorenz J. Telithromycin: The first ketolide antibacterial for the treatment of community-acquired respiratory tract infections. International Journal of Clinical Practice. 2003;57:6:519-529.

It is a review paper summarizing antibacterial activities, PK, clinical efficacy and drug interactions of telithromycin. It states that co-administration of itraconazole or ketoconazole with telithromycin resulted in an increase in the telithromycin exposure by 1.5-fold and 2-fold, respectively, referring to an abstract presented at American Society for Microbiology in 2002. No additional information was provided.

**Reviewer's Comment**

The labeling for telithromycin indicates that 37 % of the dose is metabolized by the liver. In the drug interaction section of the label, it is stated that "A multiple-dose interaction study with itraconazole showed that Cmax of telithromycin was increased by 22% and AUC by 54%", without any mention on prescribing recommendation.

As per communications with anti-infective clinical pharmacology team, the increase seen in this paper is likely not clinically relevant and a dose adjustment is not recommended in the absence of severe renal impairment. The increase in telithromycin concentrations in this paper is similar to that observed in elderly patients in which the AUC was 2.0-fold higher among healthy subjects in Phase 1 and 1.4-fold higher among patients >65 yrs of age in Phase 3. No dose adjustment is recommended for elderly patients in the current telithromycin label. Therefore, no dose adjustment recommended for concomitant use with itraconazole.

**Brotizolam**

14. Osanai T.; Ohkubo T.; Yasui N.; Kondo T.; Kaneko S. Effect of itraconazole on the pharmacokinetics and pharmacodynamics of a single oral dose of brotizolam. British Journal of Clinical Pharmacology. 2004;58:5:476-481.

The aim of the study was to assess the effect of itraconazole on the single oral dose pharmacokinetics and pharmacodynamics of briotizolam. It was a randomized, double-blind, cross-over trial design. Ten healthy male subjects received either itraconazole 200 mg or placebo once daily for 4 days. On day 4, a single 0.5 mg dose of brotizolam was administered orally. Brotizolam PK and psychomotor function were assessed. Itraconazole significantly decreased the apparent oral clearance (CL/*F*) and increased AUC (2.6 fold) of brotizolam. The AUC(0,24 h) of the DSST (digit symbol substitution test) and the item 'sleepiness' of UKU side-effect rating scale were significantly decreased, while VAS (thinking speed) and VAS (Spacy) scores were not different between two groups.

**Reviewer's Comments**

It is a drug not marketed in US.

**Cimetidine**

15. Karyekar C.S.; Eddington N.D.; Briglia A.; Gubbins P.O.; Dowling T.C. Renal interaction between itraconazole and cimetidine. Journal of Clinical Pharmacology. 2004;44:8:919-927.

This study evaluated the effect of itraconazole on the renal tubular secretion of cimetidine in healthy volunteers. On day 1, subjects received cimetidine infusion over 4 hours. Following discontinuation of the infusions, subjects received itraconazole 200 mg twice a day for 4 days with standardized meal. On day 5, immediately following the itraconazole dose, cimetidine infusions were initiated. GFR was measured using iothalamate clearance. Renal tubular secretion (CLsec) of cimetidine was calculated as the difference between renal clearance (CLr) and GFR (CLioth). Cimetidine AUC0-240 min increased by itraconazole by 25% (NS). The GFR and Vd remained unchanged, but significant reductions in CLt and CLsec were observed. The increased systemic exposure of cimetidine during coadministration with itraconazole was likely due to inhibition of P-gp mediated renal tubular secretion.

**Recommendation**

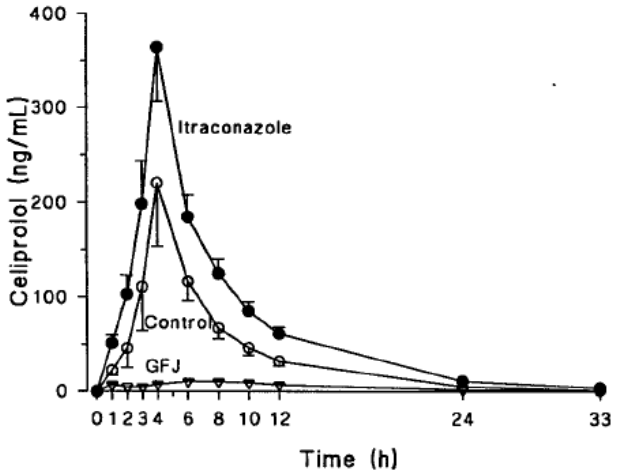
Twenty five percent increase in cimetidine AUC is not deemed to be clinically significant, per consultation with DGP, and not to be included in itraconazole label.

**Celiprolol**

17. Lilja J.J.; Backman J.T.; Laitila J.; Luurila H.; Neuvonen P.J. Itraconazole increases but grapefruit juice greatly decreases plasma concentrations of celiprolol. Clinical

Pharmacology and Therapeutics. 2003;73:3:192-198.

The study evaluated the effects of itraconazole (and grapefruit juice) on the pharmacokinetics of the alpha–adrenergic receptor–blocking agent celiprolol in healthy volunteers. In a randomized 3-phase crossover study, 12 healthy volunteers took itraconazole 200 mg orally or placebo twice a day. On the morning of day 3, 1 hour after ingestion of itraconazole or placebo, each subject ingested 100 mg celiprolol. Following itraconazole, AUC(0-33) of celiprolol was 80% greater. The cumulative excretion into urine of celiprolol was increased by 59% by itraconazole. The itraconazole-celiprolol interaction most likely resulted from increased absorption of celiprolol due to P-glycoprotein inhibition in the intestine. However, hemodynamic variables (BP, HR) did not differ between the phases.




**Reviewer's Comments**
It is a drug not marketed in US.

**Bromperidol, haloperidol, risperidone**
18. Furukori H.; Kondo T.; Yasui N.; Otani K.; Tokinaga N.; Nagashima U.; Kaneko S.; Inoue Y. Effects of itraconazole on the steady-state plasma concentrations of bromperidol and reduced bromperidol in schizophrenic patients. Psychopharmacology. 1999;145:2:189-192.

The study investigated pharmacokinetic interaction between bromperidol and itraconazole. Itraconazole 200 mg/day for 7 days was coadministered to eight schizophrenic patients treated with a fixed dose of bromperidol 12 or 24 mg/day for at least 2 weeks. Plasma concentrations of bromperidol during itraconazole coadministration were 1.9-fold higher ($P$<0.01) than before itraconazole coadministration. Plasma concentrations of reduced bromperidol during itraconazole coadministration were also higher ($P$<0.01) than before itraconazole coadministration. No changes were observed in Brief Psychiatric Rating Scale (BPRS) and the Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale scores.

**Table 1** Changes in plasma concentrations of bromperidol and reduced bromperidol and the concentration ratios of reduced bromperidol to bromperidol before and during itraconazole treatment and after its discontinuation

| Case no. | Bromperidol concentration (ng/ml) | | | Reduced bromperidol concentration (ng/ml) | | | Reduced bromperidol/ bromperidol | | |
|---|---|---|---|---|---|---|---|---|---|
| | Before | During | After | Before | During | After | Before | During | After |
| 1 | 10.7 | 11.9 | 9.4 | 2.1 | 3.5 | 2.8 | 0.2 | 0.3 | 0.3 |
| 2 | 15.7 | 21.1 | 18.1 | 3.9 | 7.9 | 4.8 | 0.2 | 0.4 | 0.3 |
| 3 | 13.9 | 17.2 | 13.9 | 3.4 | 6.0 | 5.3 | 0.2 | 0.3 | 0.4 |
| 4 | 9.3 | 12.4 | 9.7 | 1.3 | 6.7 | 1.9 | 0.1 | 0.5 | 0.2 |
| 5 | 3.8 | 14.1 | 8.2 | 0.6 | 0.7 | 0.5 | 0.2 | 0.0 | 0.1 |
| 6 | 4.8 | 19.3 | 7.5 | 0.6 | 0.7 | 0.7 | 0.1 | 0.0 | 0.1 |
| 7 | 4.9 | 12.1 | 4.2 | 0.6 | 0.6 | 0.5 | 0.1 | 0.0 | 0.1 |
| 8 | 8.2 | 25.4 | 8.1 | 1.8 | 2.8 | 2.0 | 0.2 | 0.1 | 0.2 |
| Mean±SD | 8.9±4.4 | 16.7±4.9[a] | 9.9±4.3 | 1.8±1.3 | 3.6±2.9[b] | 2.3±1.9 | 0.2±0.1 | 0.2±0.2 | 0.2±0.1 |

19. Yasui N.; Kondo T.; Otani K.; Furukori H.; Mihara K.; Suzuki A.; Kaneko S.; Inoue Y. Effects of itraconazole on the steady-state plasma concentrations of haloperidol and its reduced metabolite in schizophrenic patients: In vivo evidence of the involvement of CYP3A4 for haloperidol metabolism. Journal of Clinical Psychopharmacology. 1999;19:2:149-154.

The effects of itraconazole on the steady-state plasma concentrations of haloperidol and reduced haloperidol were examined. Thirteen schizophrenic patients treated with haloperidol 12 or 24 mg/day received 200 mg/day of itraconazole for 7 days. Plasma concentrations of haloperidol and reduced haloperidol during the itraconazole treatment were 2-fold ($p < 0.01$) higher than those observed before itraconazole treatment. No change was found in clinical symptoms assessed by BPRS, whereas neurologic side effects were increased during itraconazole coadministration.

2. Bruggemann R.J.M.: Alffenaar J.W.C.; Blijlevens N.M.A.; Billaud E.M.; Kosterink J.G.W., Verweij P.E.; Burger D.M. Clinical relevance of the pharmacokinetic interactions of azole antifungal drugs with other co-administered agents. Clinical Infectious Diseases. 2009;48:10:1441-1458.

This is a review paper, summarizing drug interactions of azole drugs (including itraconazole) and a variety of other coadministered antipsychotic drugs (including bromperidol, haloperidol, risperidone, aripiprazole).

**Labeling Recommendation**
The clinical implications of these changes in psychiatric drug exposure need further evaluation by the therapeutic team and a consult is in place with DNP clinical pharmacology. As such, an inclusion of prescribing information in the label such as dose adjustment has not been determined at this time.

## Aripiprazole

10. Koue T.; Kubo M.; Funaki T.; Fukuda T.; Azuma J.; Takaai M.; Kayano Y.: Hashimoto Y. Nonlinear mixed effects model analysis of the pharmacokinetics of aripiprazole in healthy Japanese males. Biol Pharm Bull. 2007;Nov;30(11):2154-8.

**Reviewer's Comments**
This is a population pharmacokinetic analysis of aripiprazole. Coadministration of aripiprazole and itraconazole increased plasma aripiprazole concentrations. No quantitative changes were reported in the paper. Based on the aripiprazole label, however, the following information is recommended to be added to the itraconazole label.

**Labeling Recommendation**
Increases in plasma aripiprazole concentrations have been demonstrated in subjects concomitantly receiving ketoconazole, requiring a reduction of the aripiprazole dose. Because of the similarities between ketoconazole and itraconazole, a similar dose reduction for aripiprazole is recommended when patients concomitantly receive itraconazole and aripiprazole.

**Felodipine**
20. Jalava K.M.; Olkkola K.T.; Neuvonen P.J. Itraconazole greatly increases plasma concentrations and effects of felodipine. Clinical Pharmacology and Therapeutics. 1997;61:4:410-415.

A double-blind, randomized, two-phase crossover design was used to investigate the interaction between felodipine and itraconazole. Nine healthy volunteers received either 200 mg itraconazole or placebo orally once a day for 4 days. On day 4, each ingested a single 5 mg oral dose of felodipine. Itraconazole increased Cmax of felodipine ~8-fold, AUC(0-32) and AUC(0-inf)] about 6-fold, and the elimination half-life 2-fold. The decreases in blood pressure and the increases in heart rate were significantly greater during the itraconazole phase than during the placebo phase. However, the correlation between the PK changes of felodipine and the Cmax or AUC of itraconazole was not statistically significant.

**Comments**:
The following is DDI information in felodipine label, regarding the effect of CYP3A4 inhibitors on felopidine exposure and dosing precaution.

**Drug Interactions**
*CYP3A4 Inhibitors* — Felodipine is metabolized by CYP3A4. Coadministration of CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, erythromycin, grapefruit juice, cimetidine) with felodipine may lead to several-fold increases in the plasma levels of felodipine, either due to an increase in bioavailability or due to a decrease in metabolism. These increases in concentration may lead to increased effects, (lower blood pressure and increased heart rate). These effects have been observed with coadministration of itraconazole (a potent CYP3A4 inhibitor). Caution should be used when CYP3A4 inhibitors are coadministered with felodipine. A conservative approach to dosing felodipine should be taken. The following specific interactions have been reported:
*Itraconazole* — Coadministration of another extended release formulation of felodipine with itraconazole resulted in approximately 8-fold increase in the AUC, more than 6-fold increase in the $C_{max}$, and 2-fold prolongation in the half-life of felodipine.

**Labeling Recommendation**
Per consultation with cardio-renal clinical pharmacology and safety team, the clinical implication due to the elevated felodipine exposure, when concomitantly used with itraconazole, is not deemed to be any different from that of nisoldipine and the

prescribing information for felodipine should be consistent with that for nisoldipine. Therefore, felodipine is contraindicated with itraconazole.

**Didanosine**

Moreno F.; Hardin T.C.; Rinaldi M.G.; Graybill J.R. Itraconazole-didanosine excipient interaction [5]. Journal of the American Medical Association. 1993;269:12:1508.

This is a letter to the Editor, reporting a case suggestive of reduced itraconazole absorption due to didanosine. A patient was given itraconazole (Sporanox) 6 x 100 mg with or without didanosine. When itraconazole was taken concomitantly with didanosine tablets, itraconazole absorption was delayed and a peak itraconazole concentration was lower, compared to itraconazole only. However, the author stated that there were insufficient data points to calculate other PK parameters. The author commented that this may be caused by the excipient of didanosine, altering the gastrointestinal pH.

**Reviewer's Comments**

The report is based on data obtained from a single case and lacks details on the results and data analysis. In addition, as the author pointed out, there were insufficient data points to allow a comparison of full PK properties. Assuming the presumed drug interaction with itraconazole is due to the excipient rather than didanosine itself, as suggested by the study author, the interaction potential could be product-specific and not applied to all didanosine products.

**Labeling Recommendation**

Due to the nature of a single published case report and the quality/quantity of the data we cannot consider this for inclusion at this time.

**Methadone**

22. NoorZurani MH, Vicknasingam B, Narayanan S. Itraconazole-induced torsade de pointes in a patient receiving methadone substitution therapy. Drug Alcohol Rev. 2009 Nov;28(6):688-90.

This is a case report describing the risk of Torsade de Pointes, a life-threatening cardiac arrhythmia, in a heroin-dependent patient receiving methadone substitution therapy who was prescribed itraconazole for vaginal thrush. The patient experienced chest discomfort and an episode of syncope following two doses of itraconazole (200 mg). ECG monitoring showed QT prolonged. The patient presented with no other risk factors. The author cautions the physicians treating heroin-dependent patients on methadone substitution therapy for the potential risk of drug interactions that may lead to fatal cardiac arrhythmias.

**Comments**

Methadone-induced QTc prolongation has been reported in the literature.

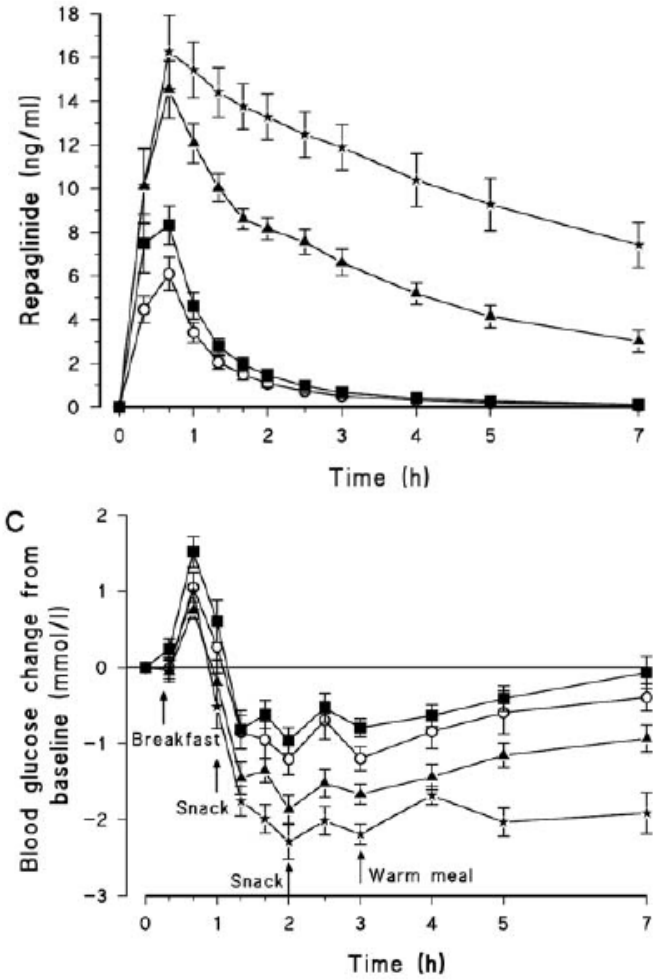
**Labeling Recommendation**

Methadone is known to prolong the QT interval and metabolized by CYP3A4. Co-administration of methadone with itraconazole may decrease clearance of methadone and increase or prolonge opioid effects. Thus, methadone-treated patients coadministered with itraconazole should be carefully monitored and dosage adjustment should be made if warranted (per consultation with DAARP clinical pharmacology).

**Repaglinide**

M. Niemi, J. T. Backman, M. Neuvonen, P. J. Neuvonen. Effects of gemfibrozil, itraconazole, and their combination on the pharmacokinetics and pharmacodynamics of repaglinide: potentially hazardous interaction between gemfibrozil and repaglinide Diabetologia (2003) 46:347–351

The study investigated drug interactions of itraconazole with repaglinide. In a randomized crossover study, 12 healthy volunteers received twice daily for 3 days 100 mg itraconazole (first dose 200 mg) or placebo. On day 3 they ingested a 0.25 mg dose of repaglinide. Itraconazole increased repaglinide AUC and Cmax by 1.4- and 1.45-folds, respectively ($p<0.001$).




Means plasma concentrations of repaglinide (**A**), and change in blood glucose concentrations (**C**) after a single oral dose of 0.25 mg repaglinide during placebo (open circles), itraconazole 100 mg bid (solid squares), gemfibrozil 600 mg bid (solid triangles), and combined itraconazole and gemfibrozil (solid stars) treatments

**Labeling Recommendation**

The extent of changes in repaglinide by itraconazole coadministration is not deemed to be clinically significant, warranting an adjustment of repaglinide doses (per consultation with DMEP clinical pharmacology). Study results will be stated in the label as follows.

> A human pharmacokinetic study showed that co-administration with itraconazole and a single dose of repaglinide (on the third day of a regimen of 200 mg initial dose, twice-daily 100 mg itraconazole) resulted in a 1.4-fold higher repaglinide AUC.

## Clinical Pharmacology Summary and Conclusions

The following is a summary table, including key findings and labeling recommendations based on the review of above mentioned articles.

| co-administered drug | subjects | Drug administration | results | AUC | Cmax | mechanism | labeling recommendation |
|---|---|---|---|---|---|---|---|
| efavirenz | 10 HIV | | significant reduction of itaconazole exposure | NA | BLOD | 3A4 induction | Concomitant use is not recommended (CR) |
| various | | | summary tables presented | | | | |
| meloxicam | 12 healthy | sporanox 200 mg QD, 4 days, meloxicam 10 mg oral | decrease maloxicam concentration and Tmax, may have reuiced GI absorption, decrease in PD (TxB2 inhibition) | 37% | 64% | 3A4 | dose adjusted as per patients responses to meloxicam |
| oral morphine | 12 healthy | sporanox 200 mg QD, 4 days, 0.3 mg/kg morphine oral | increased morphine conc, no effects on metabolites, no changes in PD effects | 22-29 % | 28% | Pgp inhib at GI | not to be included |
| fexofenadine | 12 healthy | 200 mg itraconazole & 60 mg fexofenadine | increase fexofenadine (steroselective), itraconzole under fasting | 3-4 fold | 3-4 fold | Pgp inhib at GI | PK results to be included |
| imidafenacin | 12 healthy | Itrizole 200 mg QD, 8 days, 0.1 mg imidafenacine oral | increase imidafenacin, no AE during day 8-10 | 75% | 30% | 3A4 | NA |
| efavirenz | 1 HIV | Itraconazole 600 mg | decrease itaconazole exposure; HO-itra increased | 50% red | | 3A4 induction | see above |
| maraviroc | | | no primary data, but commented mariviroc exposure was increased with itraconazole | NA | NA | 3A4 | New anti-HIV subsection (7): maraviroc dose should be decreased (CR) |
| maraviroc | | | | NA | NA | 3A4 | |
| aripiprazole | 27 healthy | itraconazole 100 mg QD, 21 days | | | | | dose adjustment (CR) |
| propoxyphene oral morphin | | | QTc prolongation potential may increase with 3A4 inhibitors | | | 3A4 | not to be included |
| fexofenadine | 14 healthy | 200 mg Sporanox &180 mg fexofenadine (both single oral) | increase fexofenadine (greater in TT mutant), greater PD effect, itraconzole under fasting | 2.3-3 fold | 2.7-3 fold | | PK results to be included (same as above) |
| telithromycin | 17 healthy | 200 mg itraconazole 14 days, w/ 800 mg telithromycin for additional 4 days | increased telithromycin, no SAE noted | 54% | 22% (p=0.052) | 3A4 | not to be included |
| brotizolam | 10 healthy | 200 mg Itrizole, 4 days, signle oral 0.5 mg brotizolam | increased brotizolam, 2 PD effects increased, itraconzole under fasting, t1/2 5-fold increase | 2.6 fold | NS | 3A4 | NA |
| cimetidine | 8 healthy | sporanox 200 mg BID 3 days, cimetidine 0.2 mg/kg and infusion 36 mg/h x4 hr | Total CL, renal CL decreased (24%), inhibition of renal tubular secretion | 25% (NS) | NA | Pgp inh in kidney | not to be included (statistically and clinically insignificant) |
| telithromycine | | | increased telithromycin exposure 1.5-2 fold (ref - abstract) | | | 3A4 | not to be included |
| celiprolol | 12 healthy | sporanox 100 mg BID, 2 days, celiprolo 100 mg oral on day 3 | no change in renal CL, BP, HR. cumulative excretion into urine increased by 59% | 80% | 33% | Pgp inh at GI/kidney | NA |
| bromperidol | 8 healthy (schizo) | bromperidol 12 or 24 mg/day + 200 mg itraconazole for 7 days | increased bromperidol, no changes in clinical effects, concommittant drugs - biperiden, flunitrazepam, sennoside | NA | Css 1.9 fold | 3A4 | not to be included at this time |
| haloperidol | 13 schizo | haloperidol 12 or 24 mg/day + 200 mg itraconazole for 7 days | increased haloperidol, no changes in clinical score (BPRS), but increased AE concommittant drugs - biperiden, flunitrazepam, sennoside | NA | Css 25% | 3A4 | not to be included at this time |
| felodipine | 9 healthy | sporanox 200 mg, 3 days, felodipine 5 mg oral on day 4 | increased felodipine, increased BP/HR effect of felodipine, trend of increased AE rates | 5-6 fold | 8 fold | 3A4 | Contraindicate |
| didanosine | | Sporanox 600 mg | decreased Cmax of itraconazole | NA | decrease | absorption interferenece | not to be included |
| methadone | | 200 mg oral itraconazole to a patient taking methadone | caused QT prolongation leading to Torsade de Pointes | NA | NA | | dose adjustment (CR) |
| Repaglinide | 12 healthy | 100 mg Sporanox for 3 days, single 0.25 mg dose of repaglinide on day 4 | increased repaglinide AUC and Cmax, no effect on minimum blood glc conc | 1.4 fold | 1.45 fold | 3A4 | describe change (CR) |
| loperamide | 12 healthy | 100 mg itraconazole, BID, 5 days | increased loperamide Cmax and AUC, no change in psychomotor test | 3.8 fold | 2.9 fold | 3A4 & Pgp | dose adjustment |
| Cabergoline | 2 pts | | cabergoline increased in 1 patient by itraconazole, also clinical improvement | | 3 fold | 3A4 | only a case, not to be included |
| Risperidol | 19 schizo | 200 mg/d itraconazole for 7days | increased risperidone no changes in clinical effects, concommittant drugs - biperiden, flunitrazepam, sennoside | NA | Css 82 % | 3A4 | not to be included at this time |
| CR: cross reference | | | | | | | |

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22484 | ORIG-1 | STIEFEL LABORATORIES INC | HYPHANOX 200MG FILM-COATED TABLETS |

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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SEONGEUN CHO
03/02/2010

EDWARD D BASHAW
03/02/2010

Reviewer is to be congratulated for working across of the affected review teams within OCP in order to accomplish this undertaking. Final labeling comments will be shared with Division of Clinical Pharmacology-4 for revision of the itraconazole label for consistency across itraconazole labels. OGD should also be alerted to these changes as they occur.

**CLINICAL PHARMACOLOGY REVIEW**

| | |
|---|---|
| **NDA:** | **22-484** |
| **Brand Name:** | Hyphanox® |
| **Generic Name:** | Itraconazole |
| **Dosage Form & Strength:** | Film-coated tablets, 200 mg |
| **Indication:** | Oral treatment of onychomycosis of the toenail due to dermatophytes (Tinea Unguium) |
| **Applicant:** | Stiefel Laboratories |
| **Submission:** | 505(b)(1), Standard |
| **Submission Dates:** | 03/31/2009 |
| **OND Division:** | Dermatological and Dental Products |
| **OCP Divisions:** | Clinical Pharmacology 3 |
| **Primary Reviewer:** | Seongeun Julia Cho, Ph.D. |
| **Team Leader:** | Dennis Bashaw, Pharm.D. |

**Table of Contents**

# 1. EXECUTIVE SUMMARY

Itraconazole, an active ingredient in Hyphanox 200 mg film-coated tablets, is a broad spectrum oral antifungal belonging to the class of triazoles. It has been approved in the US in September 1992 as Sporanox, with a dosing regimen of once daily administration of two 100 mg capsules for the treatment of toenail onychomycosis. The current submission is for a new formulation/dosage form of itraconazole, which enables patients to take one 200 mg tablet, instead of two 100 mg capsules. The proposed rationale for this drug development is that it provides a simpler dosing regimen and thereby may enhance patient adherence and improve treatment outcomes, although it has not been empirically demonstrated.

## 1.1 Recommendation

The Office of Clinical Pharmacology has reviewed the clinical pharmacology section of NDA 22-484, submitted on March 31st, 2009, and found it acceptable.

## 1.2 Phase IV commitment

None

## 1.3 Summary of Clinical Pharmacology Findings

HYPHANOX is the itraconazole 200-mg film-coated tablet, being developed for the treatment of onychomycosis. Itraconazole is a broad spectrum oral antifungal agent, the same active ingredient in a previously approved drug, Sporanox 100-mg capsules. The proposed dosing regimen for Hyphanox is one 200 mg tablet once daily (QD) for 12 consecutive weeks, which is the same as the approved dosing regimen of Sporanox 100-mg capsule (two 100-mg itraconazole capsules once daily for 12 weeks) for the same indication.

Six clinical studies were conducted to support this application, among which are 3 bioequivalence/bioavailability studies and 2 pharmacokinetic studies. To evaluate if a 200-mg film-coated tablet is bioequivalent to two 100-mg Sporanox capsules, comparative PK studies were conducted using the to-be-marketed tablet product and commercially available capsules. Previous studies conducted to support the approval of Sporanox have shown that the absorption of itraconazole is affected by food and the label of Sporanox indicates that the drug is to be taken with food. Therefore comparative BE studies in this submission were conducted under both fasting and fed conditions.

All BE/BA studies were open label, randomized, cross-over, single-dose studies in healthy male and female subjects. In Study BT0300-BEL-005, the drugs were administered after a high-fat, high-calorie breakfast, in Study BT300-BEL-002, drugs

were administered with a sponsor-defined standard breakfast, and in Study BT300-BEL-006 drugs were administered under a fasting condition. It should be noted that a high-fat, high calorie meal that the sponsor refers to in this submission is essentially equivalent to the standard test meal recommended by FDA, which is different from the standard breakfast that was defined by the sponsor (see page 10 in QBR for details). Note that in this review, a standard breakfast refers to the one that the sponsor used, as in the study BT300-BEL-002, not the FDA breakfast.

The summary of mean PK parameters of itraconazole and BE statistics for each study is presented below.

**Study BT0300-BEL-005 (High-fat, high-calorie breakfast)**

| Parameter | | Itraconazole Capsule 2 x 100 mg - Reference - Mean ± STD | Itraconazole 200-mg film-coated tablet 1 x 200 mg - Test - Mean ± STD | Geometric Mean Ratio, % Test/Reference Ratio (90% CI) |
|---|---|---|---|---|
| **Itraconazole** | | | | |
| $T_{max}$ | (h) | 4.0 (2.0-8.0)[a] | 5.0 (2.5-8.0)[a] | 0.50 (0.00-0.75)[b] |
| $C_{max}$ | (ng/mL) | 227±106 | 185±112 | 80.4 (70.1-92.4) |
| $AUC_t$[c] | (µg·h/mL) | 3.22±1.83 | 2.28±152 | 69.6 (60.4 -80.2) |
| $AUC_\infty$ | (µg·h/mL) | 3.38±1.96 | 2.41±1.62 | 70.4 (61.4-80.6) |
| $t_{1/2term}$ | (h) | 24.9±6.2 | 23.9±7.6 | |
| **Hydroxy-itraconazole** | | | | |
| $T_{max}$ | (h) | 5.0 (2.5-12.0)[a] | 5.0 (3.5-8.0)[a] | 0.01 (-0.01-0.50)[b] |
| $C_{max}$ | (ng/mL) | 354±130 | 288±108 | 82.3 (73.5-92.0) |
| $AUC_t$[c] | (µg·h/mL) | 7.02±4.08 | 4.85±2.96 | 69.8 (60.3-80.8) |
| $AUC_\infty$ | (µg·h/mL) | 7.25±4.16 | 5.04±2.99 | 70.1 (60.9-80.8) |
| $t_{1/2term}$ | (h) | 9.8 ±2.9 | 8.7±2.7 | |

**Study BT0300-BEL-002 (Standard breakfast)**

| Parameter | | Itraconazole Capsule 2 x 100 mg - Reference - Mean ± STD | Itraconazole 200-mg film-coated tablet 1 x 200 mg - Test - Mean ± STD | Geometric Mean Ratio, % Test/Reference Ratio (90% CI) |
|---|---|---|---|---|
| **Itraconazole** | | | | |
| $T_{max}$ | (h) | 5.0 (2.0-8.0)[a] | 3.5 (2.0-8.0)[a] | -0.50 (-0.99--0.25)[b] |
| $C_{max}$ | (ng/mL) | 306±146 | 294±114 | 101.0 (91.3-111.7) |
| $AUC_t$ | (µg·h/mL) | 3.60±1.69 | 3.98±1.74 | 114.8 (103.9-126.9) |
| $AUC_\infty$ | (µg·h/mL) | 3.87±1.85 | 4.28±1.96 | 114.7 (103.7-126.8) |
| $t_{1/2term}$ | (h) | 26.0±8.8 | 28.4±9.5 | |
| **Hydroxy-itraconazole** | | | | |
| $T_{max}$ | (h) | 5.0 (2.0-8.0)[a] | 4.0 (2.0-12.0)[a] | -0.25 (-0.50-0.025)[b] |
| $C_{max}$ | (ng/mL) | 460±166 | 470±115 | 105.9 (98.2-114.2) |
| $AUC_t$ | (µg·h/mL) | 7.79±3.70 | 8.64±3.80 | 114.9 (103.3-127.8) |
| $AUC_\infty$ | (µg·h/mL) | 8.01±3.75 | 8.85±3.87 | 113.9 (102.6-126.5) |
| $t_{1/2term}$ | (h) | 9.0±2.3 | 9.3±2.4 | |

**Study BT0300-BEL-006 (fasting condition)**

| Parameter | | Itraconazole 200-mg film-coated tablet 1 x 200 mg - Fasted - Mean ± STD | Itraconazole 100-mg Capsule 2 x 100 mg - Fasted - Mean ± STD | Geometric Mean Ratio, % Tablet/Capsule Ratio (90% CI) |
|---|---|---|---|---|
| **Itraconazole** | | | | |
| $T_{max}$ | (h) | 3.0 (1.02-4.0)[a] | 3.0 (2.0-5.0)[a] | -0.50 (-1.00--0.00)[b] |
| $C_{max}$ | (ng/mL) | 162±107 | 135±68.2 | 105.3 (84.2-131.7) |
| $AUC_t$[c] | (µg·h/mL) | 2.12±1.38 | 1.73±0.95 | 114.0 (93.0-139.7) |
| $AUC_\infty$ | (µg·h/mL) | 2.27±1.44 | 1.87±0.99 | 114.7 (94.6-139.1) |
| $t_{1/2term}$ | (h) | 25.9±5.68 | 24.4±6.98 | |
| **Hydroxy-itraconazole** | | | | |
| $T_{max}$ | (h) | 3.25 (2.50-5.0)[a] | 3.5 (2.5-6.0)[a] | -0.50 (-0.99-0.00)[b] |
| $C_{max}$ | (ng/mL) | 264±109 | 232±70 | 106.7 (89.8-126.7) |
| $AUC_t$[c] | (µg·h/mL) | 4.42±2.79 | 3.57±1.95 | 116.3 (94.3-143.4) |
| $AUC_\infty$ | (µg·h/mL) | 4.58±2.80 | 3.73±2.00 | 116.3 (95.1-142.2) |
| $t_{1/2term}$ | (h) | 12.3±3.67 | 10.1±2.02 | |

**Table 8: Summary of the Equivalence Statistics of the Bioequivalence Studies (BT300-BEL-002, BT0300BEL005, and BT0300BEL006) Conducted in Various Food Conditions**

| Parameter | Itraconazole 200-mg film-coated tablet versus Itraconazole 100-mg capsules Point Estimate [90% Confidence Interval], %[a] | | |
|---|---|---|---|
| | Standard breakfast n = 52 | High-fat, high-calorie breakfast n = 56 | Fasting conditions n = 18 |
| **Itraconazole** | | | |
| $T_{max}$ | -0.50 [-0.99--0.25] | 0.50 [0.00-0.75] | -0.50 [-1.00-0.00] |
| $C_{max}$ | 101.0 [91.3-111.7] | 80.4 [70.1-92.4] | 105.3 [84.2-131.7] |
| $AUC_t$ | 114.8 [103.9-126.9] | 69.6 [60.4-80.2] | 114.0 [93.0-139.7] |
| $AUC_\infty$ | 114.7[103.7-126.8] | 70.4 [61.4-80.6] | 114.7 [94.6-139.1] |
| **Hydroxy-itraconazole** | | | |
| $T_{max}$ | -0.25 [-0.50-0.025] | 0.01 [-0.01-0.50] | -0.50 [-0.99-0.00] |
| $C_{max}$ | 105.9 [98.2-114.2] | 82.3 [73.5-92.0] | 106.7 [89.8-126.7] |
| $AUC_t$ | 114.9 [103.3-127.8] | 69.8 [60.3-80.8] | 116.3 [94.3-143.4] |
| $AUC_\infty$ | 113.9 [102.6-126.5] | 70.1 [60.9-80.8] | 116.3 [95.1-142.2] |

The results from all three studies collectively show that itraconazole 200-mg film-coated tablets and two 100-mg Sporanox capsules are not bioequivalent in any conditions, exceeding 80-125 % boundary for 90 % confidence interval. In addition, the effects of food on the PK of Hyphanox, compared to Sporanox, are not uniform and depend on the composition of the meal. Thus the total exposure of itraconazole was about 15% higher with the 200-mg film-coated tablet than with the 100-mg capsules, when dosing occurred in the fasted state as well as after a standard breakfast, while tablets had 30% lower bioavailability compared to capsules, when dosing occurred after a high-fat, high-calorie breakfast. To note, however, is that there were high inter-subject variabilities in the exposure in all studies with coefficient of variations (CV) for AUC in the range of 43-66 %. Another point that should be considered is that in a real world it is unlikely that patients will have a same fat content breakfast everyday for 12 weeks, affecting the plasma concentrations of itraconazole toward a consistent direction following administration of Hyphanox relative to Sporanox. Rather, it is anticipated that the mean plasma concentrations of Hyphanox will fluctuate around the mean plasma concentrations expected from Sporanox, depending on the composition of a daily meal.

Therefore it is this reviewer's opinion that the differences in the exposure between Hyphanox and Sporanox under studied meal conditions are clinically insignificant and will not have impacts on efficacy or safety.

The pivotal Phase 3 safety and efficacy trial was conducted following a standard breakfast. Based on the clinical summary, Hyphanox was non-inferior to Sporanox in both primary and secondary endpoints (treatment of toenail onychomycosis), consistent with what is expected from the exposure information. No PK parameters were examined, however, during the phase 3 trial and thus we could not determine exposure-safety and/or efficacy correlation.

Two PK studies were conducted to characterize the single and multiple dose PK profiles of Hyphanox tablets. Study BT0300-108-USA was multiple oral dose study in healthy subjects, administering one 200-mg tablet once daily for 2 weeks following a standard breakfast. Serial blood samples were collected on Days 1 and 14 and trough concentrations were measured at pre-dose on Days 2, 4, 7, 10, 12 and 13. Below is a summary table, listing PK parameters of itraconazole and hydroxy-itraconazole on days 1 and 14.

| | | | Analyte | |
|---|---|---|---|---|
| **Parameter** (units) | Statistic | Day | Itraconazole N=16 | OH-itraconazole N=16 |
| $C_{max}$ (ng/mL) | Mean (SD) | 1 | 116.8 (43.34) | 221.7 (69.21) |
| | | 14 | 658.1 (362.16) | 974.2 (479.92) |
| **$AUC_{0-24}$** (ng*h/mL) | Mean (SD) | 1 | 905.09 (384.239) | 2538.33 (1057.872) |
| | | 14 | 9046.81 (5320.516) | 19054.95 (10443.214) |
| $t_{max}$ (h) | Median (Range) | 1 | 4.00 (2.00-5.00) | 4.00 (2.00-5.00) |
| | | 14 | 4.00 (1.00-24.00) | 4.00 (3.00-24.00) |
| $t_{1/2}$ (h) | Mean (SD) | 14 | 36.84 (10.378) | 20.06 (6.998) |
| $C_{min}$ (ng/mL) | Mean (SD) | 14 | 262.1 (151.86) | 693.1 (431.38) |
| $C_{ss,avg}$ (ng/mL) | Mean (SD) | 14 | 377.0 (221.69) | 794.0 (435.13) |
| **Accumulation Ratio*** | Mean (SD) | 14 | 10.51 (5.510) | 8.20 (4.646) |
| **AUC ratio**** | Mean (SD) | 1 | 2.83 (0.513) | |
| | | 14 | 2.22 (0.420) | |

OH-itraconazole: Hydroxy-itraconazole

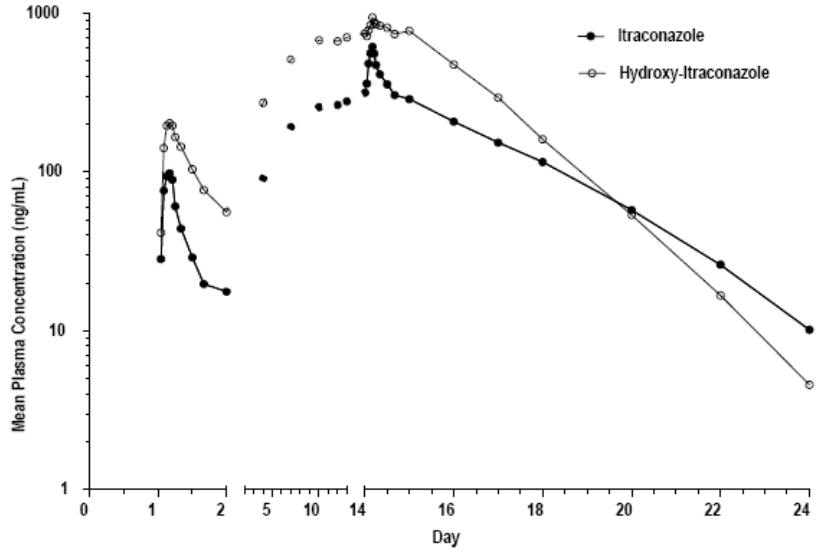
*Accumulation Ratio is defined as $AUC_{0-24}$ (Day 14) /$AUC_{0-24}$ (Day 1)

**AUC ratio is ratio of $AUC_{0-24}$ of hydroxy-itraconazole/itraconazole

Mean $C_{max}$ of itraconazole on Day 1 was 116.8 ng/mL and mean $C_{max}$ on Day 14 was 658.1 ng/mL, showing that Cmax of itraconazole increased by approximately 6 fold from Day 1 to Day 14. Similarly, mean $AUC_{0-24}$ of itraconazole on Day 1 was 905.09 ng*h/mL and mean $AUC_{0-24}$ of itraconazole on Day 14 was 9046.81 ng*h/mL. Therefore, the accumulation ratio of itraconazole at day 14 is 10.51. Time dependent accumulation of

itraconazole over the course of 14 day treatment was evident by the determination of trough concentrations of itraconazole on Days 2 through 14, consistent with the accumulation data obtained at Day 14. It can also be demonstrated that a steady state level of itraconazole was reached by day 10 following treatment with Hyphanox and PK parameters obtained at day 14 reflect the drug's disposition pattern at a steady state.

**Mean Plasma Itraconazole and Hydroxy-Itraconazole Concentrations versus Time (Day 1 through Day 24) (semi-log scale) – All Dosed Subjects**



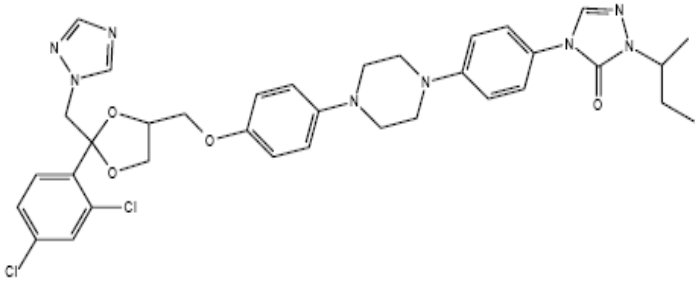

Study BT300-BEL-004 is single dose study, in which 400 mg (2 x 200 mg tablets) was administered once daily to healthy female subjects following high-fat, high-calorie breakfast. The dose and a population for this study were chosen based on an earlier program, pursuing the indication of vaginal candidiasis, which the sponsor states was discontinued later. As shown in the table below, the mean Cmax and AUC∞ were 307 ng/mL and 5.53 µg.h/mL, respectively. These results are greater than those expected from dose proportionality based on results from the study BT0300-108-USA. However study BT300-BEL-004 was conducted with a high-fat, high-calorie meal, so the PK parameters from these two studies cannot directly be compared.

| Parameter | Itraconazole | Hydroxy-itraconazole |
|---|---|---|
| $T_{max}$ (h) | 5.0 (2.0-6.0)[a] | 5.5 (2.0-12.0)[a] |
| $C_{max}$ (ng/mL) | 307±177 | 469±222 |
| $AUC_t$ (µg·h/mL) | 5.21±3.35 | 12.0±8.06 |
| $AUC_\infty$ (µg·h/mL) | 5.53±3.57 | 12.2±8.06 |
| $t_{1/2term}$ (h) | 29.0±7.50 | 11.3±2.99 |

## 2. QUESTION BASED REVIEW

### 2.1 General Attributes

Itraconazole is a broad spectrum oral antifungal agent, belonging to the class of the triazoles. Itraconazole is presently available as a 100-mg capsule and as a 10-mg/mL oral solution. In the United States, itraconazole (SporanoxTM, 100-mg capsule) is marketed to treat fungal infections blastomycosis, histoplasmosis, and aspergillosis in immunocompromised and non-immunocompromised patients. Itraconazole is also approved for treatment of nonimmunocompromised patients with onychomycosis of the toenail due to dermatophytes, with or without fingernail involvement, and for onychomycosis of the fingernail due to dermatophytes.



***What are the proposed mechanisms of action of itraconazole?***

Per Microbiology section in the label for Sporanox, itraconazole inhibits fungal cytochrome P450 in vitro, which is involved in the biosynthesis of ergosterol from lanosterol. Ergosterol is a vital cell membrane component in fungi and its inhibition by itraconazole results in inhibition of fungal growth.

***What are physico-chemical properties of the drug substance?***

The active pharmaceutical ingredient of Hyphanox is itraconazole, which is practically insoluble in water (less than 1 μg/mL in water and less than 5 μg/mL in diluted acidic solutions). The dissolution method was performed per the United States Pharmacopeia (USP) method using Apparatus 2. Itraconazole is classified as a Biopharmaceutics Classification System (BCS) Class II, which has high permeability and low solubility. The itraconazole tablets are white to slightly grey, oblong, biconvex and film-coated and are packaged in unit-dose foil blisters and placed in blister cards. The composition of itraconazole 200 mg film-coated tablets are listed below.

**Table 1: Qualitative and Quantitative Composition of Itraconazole Tablets**

| Ingredient | Unit Quantity (mg/tablet) | Function | Quality Standard |
|---|---|---|---|
| | (b) (4) | | |
| Itraconazole | 200 | Active ingredient | Ph. Eur. |
| Hypromellose (b) (4) | | | USP |
| (b) (4) | | | In-house |
| Lactose (b) (4) | | | NF |
| Microcrystalline cellulose | | | NF |
| Crospovidone | | | NF |
| Talc | | | USP |
| Hydrogenated vegetable oil (b) (4) | | | NF |
| Colloidal silicon dioxide | | | NF |
| Magnesium stearate | | | NF |
| (b) (4) | | | NF |
| | | | |
| | | | |
| Propylene glycol | | | NF |
| (b) (4) | | | USP |
| | | | In-house |
| Hypromellose (b) (4) | | | USP |
| Propylene glycol | | | NF |
| Titanium dioxide | | | USP |
| Talc | | | USP |
| **Total Film-Coated Tablet** | | | |

a. Not present in the final product

***What are approved and proposed indications and dosing regimen for Hyphanox?***

Itraconazole 200-mg film-coated tablets were developed initially by Janssen Pharmaceutica (Johnson & Johnson). Subsequently, Stiefel Laboratories, Inc. (Barrier Therapeutics) assumed ownership of the itraconazole film-coated tablet formulation. Stiefel is currently developing the itraconazole 200-mg film-coated tablet (HYPHANOX™) for the treatment of onychomycosis of the toenail (b) (4) The proposed dosing regimen is one itraconazole 200-mg film-coated tablet once daily (QD) for 12 consecutive weeks, which is the same as the approved dosing regimen for the itraconazole 100-mg capsule (200 mg [two 100-mg itraconazole capsules] once daily for 12 weeks) for the same indication.

## 2.2 Clinical Pharmacology

***What are the bases of the proposed dose and a dosage form of Hyphanox?***

Itraconazole, an active ingredient in Hyphanox, is a broad spectrum oral antifungal, which is the same active ingredient contained in Sporanox. Sporanox is a 100 mg capsule that was approved for the treatment of toenail onychomycosis in the US in September 1992. The dosing regimen of Sporanox is once daily administration of two 100 mg capsules. The current submission is for a new formulation/dosage form of itraconazole, which allows patients to take one 200 mg tablet (Hyphanox) once daily, instead of two 100 mg capsules (Sporanox). A proposed rationale for this drug development, as indicated by the sponsor, is that it provides a simpler dosing regimen and thereby may enhance patient adherence and improve treatment outcomes. This postulated benefit, however, has not been clinically tested by the sponsor.

***What are the design features of the clinical pharmacology and clinical studies used to support the dosing or claims?***

Six clinical studies were conducted to support the proposed indication in this submission. These include 2 pharmacokinetic studies, 3 bioequivalence/bioavailability studies under fed or fast conditions, and 1 phase 3 study evaluating safety and efficacy. The design features of these studies are summarized in the table below and the key findings of these studies are presented in following sections under the relevant review questions.

| Protocol No. (Location) | Objective | Study Design | Subject Population (Plan/Actual) | # Sites | Study Drug Group(s) = # Subjects | Dosing Regimen/ Duration |
|---|---|---|---|---|---|---|
| BT300-BEL-002 (module 5, section 5.3.1.2) | To determine the bioequivalence of 1 itraconazole 200-mg tablet relative to 2 itraconazole 100-mg capsules taken in a single dose after a standard meal | Phase 1, open-label, randomized, 2-way crossover, single-center, oral dose study | Healthy subjects, 18 to 55 years of age (inclusive)<br><br>(56/56[a]) | 1 (Belgium) | itraconazole 200-mg tablet = 56<br><br>itraconazole 100-mg capsules = 56 | Single administration of 1 tablet or 2 capsules after a standard breakfast; 14-day washout period between study drugs; subjects followed for 4 days after each dosing |
| BT300-BEL-004 (module 5, section 5.3.3.1) | To assess the pharmacokinetics of itraconazole and hydroxy-itraconazole after a single dose of 2 itraconazole 200-mg tablets following a high-calorie, high-fat meal | Phase 1, open-label, single-center, single-arm, oral dose, descriptive study | Healthy female subjects, 18 to 65 years of age (inclusive)<br><br>(16/16) | 1 (Belgium) | itraconazole 200-mg tablets = 16 | Single administration of 2 tablets after a high-calorie, high-fat breakfast; subjects followed for 5 days after dosing |
| BT0300BEL005 (module 5, section 5.3.1.2) | To determine the bioequivalence of 1 itraconazole 200-mg tablet relative to 2 itraconazole 100-mg capsules taken in a single dose after a high-calorie, high-fat meal | Phase 1, open-label, randomized, 2-way crossover, single-center, oral dose study | Healthy subjects, 18 to 55 years of age (inclusive)<br><br>(56/56) | 1 (Belgium) | itraconazole 200-mg tablet = 56<br><br>itraconazole 100-mg capsules = 56 | Single administration of 1 tablet or 2 capsules after a high-calorie, high-fat breakfast; 14-day washout period between study drugs; subjects followed for 5 days after each dosing |

| | | | | | | |
|---|---|---|---|---|---|---|
| BT0300BEL006 (module 5, section 5.3.1.2) | To assess the effect of food on the bioavailability of itraconazole 200-mg tablets and to compare the bioavailability (fasting) of itraconazole 200-mg tablets and itraconazole 100-mg capsules | Phase 1, open-label, randomized, 3-way crossover, oral dose, single-center study | Healthy subjects, 18 to 55 years of age (inclusive)<br><br>(18/18) | 1 (Belgium) | itraconazole 200-mg tablet (fasting) = 18<br><br>itraconazole 200-mg tablet (fed) = 18<br><br>itraconazole 100-mg capsules (fasting) = 18 | Single administration of 1 tablet or 2 capsules under fasting conditions and of 1 tablet after a high-calorie, high-fat breakfast; 14-day washout period between study drugs; subjects followed for 5 days after each dosing |
| BT0300-108-USA (module 5, section 5.3.3.1) | To document the steady-state pharmacokinetics and safety of itraconazole 200-mg tablets when administered once daily for 14 days | Phase 1, open label, single-arm, oral dose, single-center study | Healthy subjects, 18 to 55 years of age (inclusive)<br><br>(16/16) | 1 (US) | itraconazole 200-mg tablet = 16 | Administration of 1 tablet, QD after a standard breakfast for 14 days; subjects followed for 14 days after dosing period |
| BT0300-302-INT (module 5, section 5.3.5.1) | To evaluate the safety and efficacy of itraconazole 200-mg tablets, itraconazole 100-mg capsules, and placebo tablets in the treatment of onychomycosis of the toenail | Phase 3, multi-center, 3-arm, randomized, evaluator-blind, active controlled, parallel group study | Subjects 16 to 75 years of age (inclusive) with onychomycosis<br><br>(1,288/1,381) | 47 (US)<br>6 (Canada)<br>4 (Latin America)<br>1 (South Africa) | itraconazole 200-mg tablet = 593 (582 evaluated for safety)<br><br>itraconazole 100-mg capsules) = 590 (581 evaluated for safety)<br><br>placebo tablet = 198 (191 evaluated for safety) | 1 tablet or 2 capsules taken once daily after breakfast for 12 weeks; subjects followed for 40 weeks after dosing period |

***What is the relative bioavailability of the proposed to-be-marketed formulation to the reference formulation?***

Comparative PK studies were conducted using the final (to-be-marketed) itraconazole 200-mg film-coated tablet formulation and the itraconazole 100-mg capsule. In Study BT0300-BEL-005, the drugs were administered after a high-fat, high-calorie breakfast, and in Study BT300-BEL-002, drugs were administered with a standard breakfast.

***Reviewer comments**: It should be noted that a "standard test meal" exemplified in the Agency's Food effect Bioavailability Guidance is a high-fat meal, consisting of 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 oz of hash brown potatoes and 8 oz of whole milk, which provide 800-1000 calories total, with 150, 250, and 500-600 calories (~20, ~30 and ~50 %) from protein, carbohydrate and fat, respectively. A standard breakfast that the sponsor referred to in this submission (such as used in Study BT300-BEL-002) consist of 4 slices of bread, one slice (1 ounce) of ham, one slice (1 ounce) of cheese, 15 g butter, 20 g jelly and one cup of decaffeinated coffee or tea (some milk or one cube of sugar was allowed if desired). It provides 500 calories total, with approximately 20, 30 and 50 % calories from protein, fat and carbohydrates,*

*respectively. Therefore it should be noted that a standard meal referred to in this review is the standard breakfast that the sponsor used as in the study BT300-BEL-002. In contrast, a high-fat, high calorie meal that the sponsor refers to in this submission is essentially equivalent to the standard test meal specified in the FDA guidance and is referred to as a high-fat, high calorie meal in this review.*

Study BT0300BEL-005 is a pivotal bioequivalence study that compared 1 itraconazole 200-mg film-coated tablet with 2 itraconzole100-mg capsules under fed (high-fat, high-calorie) conditions in 28 male and 28 female healthy subjects. The mean pharmacokinetic parameters of itraconazole and hydroxy-itraconazole and bioequivalence statistics are summarized below.

| Parameter | | Itraconazole Capsule 2 x 100 mg - Reference - Mean ± STD | Itraconazole 200-mg film-coated tablet 1 x 200 mg - Test - Mean ± STD | Geometric Mean Ratio, % Test/Reference Ratio (90% CI) |
|---|---|---|---|---|
| **Itraconazole** | | | | |
| $T_{max}$ | (h) | 4.0 (2.0-8.0)[a] | 5.0 (2.5-8.0)[a] | 0.50 (0.00-0.75)[b] |
| $C_{max}$ | (ng/mL) | 227±106 | 185±112 | 80.4 (70.1-92.4) |
| $AUC_t$[c] | (µg·h/mL) | 3.22±1.83 | 2.28±152 | 69.6 (60.4 -80.2) |
| $AUC_\infty$ | (µg·h/mL) | 3.38±1.96 | 2.41±1.62 | 70.4 (61.4-80.6) |
| $t_{1/2term}$ | (h) | 24.9±6.2 | 23.9±7.6 | |
| **Hydroxy-itraconazole** | | | | |
| $T_{max}$ | (h) | 5.0 (2.5-12.0)[a] | 5.0 (3.5-8.0)[a] | 0.01 (-0.01-0.50)[b] |
| $C_{max}$ | (ng/mL) | 354±130 | 288±108 | 82.3 (73.5-92.0) |
| $AUC_t$[c] | (µg·h/mL) | 7.02±4.08 | 4.85±2.96 | 69.8 (60.3-80.8) |
| $AUC_\infty$ | (µg·h/mL) | 7.25±4.16 | 5.04±2.99 | 70.1 (60.9-80.8) |
| $t_{1/2term}$ | (h) | 9.8 ±2.9 | 8.7±2.7 | |

*Note: while the sponsor reported both the parent drug and the major metabolite in this submission, the determination of bioequivalence is to be based only on the PK profiles of the parent drug.*

Following a high-fat, high-calorie breakfast, the Cmax of Hyphanox tablets was lower and occurred later compared to that of the 2 itraconazole capsules, resulting in the 90 % CI outside of 80-125% range. The AUC was also lower for Hyphanox tablet than for the 2 itraconazole 100-mg capsules. Hydroxy-itraconazole data were in line with the itraconazole data.

Study BT300-BEL-002 was an open-label, randomized, cross-over, pivotal bioequivalence study in 28 male and 28 female healthy subjects to assess the comparative bioavailability of the itraconazole 200-mg film-coated tablet and the 100-mg Sporanox capsule. Each formulation was given as a single dose of 200 mg, immediately after a standard breakfast. The mean pharmacokinetic parameters of itraconazole and hydroxy-itraconazole and bioequivalence statistics are summarized below.

| Parameter | | Itraconazole Capsule 2 x 100 mg - Reference - Mean ± STD | Itraconazole 200-mg film-coated tablet 1 x 200 mg - Test - Mean ± STD | Geometric Mean Ratio, % Test/Reference Ratio (90% CI) |
|---|---|---|---|---|
| **Itraconazole** | | | | |
| $T_{max}$ | (h) | 5.0 (2.0-8.0)[a] | 3.5 (2.0-8.0)[a] | -0.50 (-0.99--0.25)[b] |
| $C_{max}$ | (ng/mL) | 306±146 | 294±114 | 101.0 (91.3-111.7) |
| $AUC_t$ | (µg·h/mL) | 3.60±1.69 | 3.98±1.74 | 114.8 (103.9-126.9) |
| $AUC_\infty$ | (µg·h/mL) | 3.87±1.85 | 4.28±1.96 | 114.7 (103.7-126.8) |
| $t_{1/2term}$ | (h) | 26.0±8.8 | 28.4±9.5 | |
| **Hydroxy-itraconazole** | | | | |
| $T_{max}$ | (h) | 5.0 (2.0-8.0)[a] | 4.0 (2.0-12.0)[a] | -0.25 (-0.50-0.025)[b] |
| $C_{max}$ | (ng/mL) | 460±166 | 470±115 | 105.9 (98.2-114.2) |
| $AUC_t$ | (µg·h/mL) | 7.79±3.70 | 8.64±3.80 | 114.9 (103.3-127.8) |
| $AUC_\infty$ | (µg·h/mL) | 8.01±3.75 | 8.85±3.87 | 113.9 (102.6-126.5) |
| $t_{1/2term}$ | (h) | 9.0±2.3 | 9.3±2.4 | |

The Cmax of the itraconazole 200-mg film-coated tablet was comparable to that of the 2 itraconazole 100-mg capsules after a single dose. However, AUCt and AUC∞ were about 15% higher with the itraconazole 200-mg film-coated tablet, and the upper range of the 90% confidence interval (~127 %) exceeded the upper limit of 125%. Nonetheless, considering the variability in the AUCs for both formulations (CV ranging 44 – 48 %), the 15 % difference is not expected to have clinical significance. Although the number of the subjects in this study is not powered enough to detect any potential differences in AE profile between two drugs, the safety data showing no differences is consistent with the PK results ( 29 subjects (53%) experiencing 44 AE (46%) with tablets and 30 (57%) experiencing 43 AE (45%) with Sporanox).

Study BT300BEL006 was an open-label, randomized, single dose study to investigate the comparative bioavailability of the itraconazole 200-mg film-coated tablet and itraconazole 100-mg capsules in fasting conditions in 9 male and 9 female healthy subjects. The mean pharmacokinetic parameters of itraconazole and hydroxy-itraconazole and bioequivalence statistics are summarized below.

| Parameter | | Itraconazole 200-mg film-coated tablet 1 x 200 mg - Fasted - Mean ± STD | Itraconazole 100-mg Capsule 2 x 100 mg - Fasted - Mean ± STD | Geometric Mean Ratio, % Tablet/Capsule Ratio (90% CI) |
|---|---|---|---|---|
| **Itraconazole** | | | | |
| $T_{max}$ | (h) | 3.0 (1.02-4.0)[a] | 3.0 (2.0-5.0)[a] | -0.50 (-1.00--0.00)[b] |
| $C_{max}$ | (ng/mL) | 162±107 | 135±68.2 | 105.3 (84.2-131.7) |
| $AUC_t$[c] | (µg·h/mL) | 2.12±1.38 | 1.73±0.95 | 114.0 (93.0-139.7) |
| $AUC_\infty$ | (µg·h/mL) | 2.27±1.44 | 1.87±0.99 | 114.7 (94.6-139.1) |
| $t_{1/2term}$ | (h) | 25.9±5.68 | 24.4±6.98 | |
| **Hydroxy-itraconazole** | | | | |
| $T_{max}$ | (h) | 3.25 (2.50-5.0)[a] | 3.5 (2.5-6.0)[a] | -0.50 (-0.99-0.00)[b] |
| $C_{max}$ | (ng/mL) | 264±109 | 232±70 | 106.7 (89.8-126.7) |
| $AUC_t$[c] | (µg·h/mL) | 4.42±2.79 | 3.57±1.95 | 116.3 (94.3-143.4) |
| $AUC_\infty$ | (µg·h/mL) | 4.58±2.80 | 3.73±2.00 | 116.3 (95.1-142.2) |
| $t_{1/2term}$ | (h) | 12.3±3.67 | 10.1±2.02 | |

Under the fasted condition, AUC and Cmax of the itraconazole 200-mg film-coated tablet were about 15% and 5 % higher, respectively, than those for the 2 itraconazole 100-mg capsules, and exceeded 125 % boundary based on 90 % CI.

**Overall Conclusion from Three BE Studies:**
An itraconazole 200-mg film-coated tablet and two 100-mg Sporanox capsules are not bioequivalent based on the results from BT300-BEL-002, BT0300BEL005, and BT0300BEL006 studies. Total exposure of itraconazole was about 15% higher with the itraconazole 200-mg film-coated tablet than with the itraconazole 100-mg capsules, when dosing occurred in the fasted state and after a standard breakfast. When dosing occurred after a high-fat, high-calorie breakfast, however, the itraconazole 200-mg film-coated tablet had a 30% lower bioavailability. Below are a table, summarizing the mean and 90 % CI of Cmax, AUC and Tmax from all three studies, and this reviewer's conclusions.

**Table 8: Summary of the Equivalence Statistics of the Bioequivalence Studies (BT300-BEL-002, BT0300BEL005, and BT0300BEL006) Conducted in Various Food Conditions**

| Parameter | Itraconazole 200-mg film-coated tablet versus Itraconazole 100-mg capsules Point Estimate [90% Confidence Interval], %[a] | | |
|---|---|---|---|
| | Standard breakfast n = 52 | High-fat, high-calorie breakfast n = 56 | Fasting conditions n = 18 |
| **Itraconazole** | | | |
| $T_{max}$ | -0.50 [-0.99--0.25] | 0.50 [0.00-0.75] | -0.50 [-1.00-0.00] |
| $C_{max}$ | 101.0 [91.3-111.7] | 80.4 [70.1-92.4] | 105.3 [84.2-131.7] |
| $AUC_t$ | 114.8 [103.9-126.9] | 69.6 [60.4-80.2] | 114.0 [93.0-139.7] |
| $AUC_\infty$ | 114.7[103.7-126.8] | 70.4 [61.4-80.6] | 114.7 [94.6-139.1] |
| **Hydroxy-itraconazole** | | | |
| $T_{max}$ | -0.25 [-0.50-0.025] | 0.01 [-0.01-0.50] | -0.50 [-0.99-0.00] |
| $C_{max}$ | 105.9 [98.2-114.2] | 82.3 [73.5-92.0] | 106.7 [89.8-126.7] |
| $AUC_t$ | 114.9 [103.3-127.8] | 69.8 [60.3-80.8] | 116.3 [94.3-143.4] |
| $AUC_\infty$ | 113.9 [102.6-126.5] | 70.1 [60.9-80.8] | 116.3 [95.1-142.2] |

- The effects of food on the comparative BA of Hyphanox vs. Sporanox are not uni-directional and depend on the composition of the meal.
- Under a high-fat high-calorie meal condition, the exposure of Hyphanox was 30 % lower than that for Sporanox. As such, safety related to the systemic exposure to itraconazole is not of a particular issue under this condition, while it may raise a question regarding its potential impact on the efficacy. To note, however, is that there is high inter-subject variability in the exposure with coefficient of variations (CV) for AUC in the range of 56-66 %, which may be accounted by the itraconazole's intrinsic property of low solubility. Furthermore, in reality it is unlikely that patients will have high-fat high-calorie breakfast everyday for 12 weeks, leading to a consistent reduction in the systemic concentrations of itraconazole. Rather, it is anticipated that the mean plasma concentrations of Hyphanox will be fluctuate around the mean plasma concentrations expected from Sporanox, depending on the composition of a daily meal. Therefore it is the reviewer's opinion that the differences in the exposure between Hyphanox and Sporanox under this specific high-fat high-calorie meal condition will not have significant clinical impact.

- Under a standard meal condition, Cmax of Hyphanox was equivalent to that of Sporanox, while the exposure was ~15 % higher than Sporanox. However, the CVs of AUC for Hyphanox and Sporanox observed in this study are large, ranging 44 – 48 %, and the 15 % difference is unlikely to have clinical significance.

- The Phase 3 study for safety and efficacy evaluation of itraconazole tablets or capsules were conducted following administration of drugs after a full meal. Based on the clinical summary, Hyphanox was non-inferior to Sporanox in both primary and secondary endpoints (treatment of toenail onychomycosis). No PK parameters were examined, however, during the phase 3 trial and thus we could not determine exposure-safety/efficacy correlation.

- Under a fasting condition, the exposure of Hyphanox was higher (15 %) than Sporanox. To note is Hyphanox is to be taken with a full meal as per the proposed labeling. Additionally, AUC following Hyphanox administration under fasting status was still lower than those observed for both Sporanox and Hyphanox under fed conditions, and therefore no safety issues are expected.

- **Overall Conclusions**: While the exposure of Hyphanox did not meet the bioequivalent criteria compared to Sporanox, the slight differences described above are unlikely to have clinical significance due to inherent high inter-subject variability.

***What is the effect of food on the bioavailability of Hyphanox?***

Study BT300BEL006 investigated the bioavailability of Hyphanox under fasting condition when compared to that after a high-fat, high-calorie breakfast. The mean pharmacokinetic parameters and bioequivalence statistics are summarized below.

| Parameter | | Itraconazole 200-mg film-coated tablet 1 x 200 mg - Fed - Mean ± STD | Itraconazole 200-mg film-coated tablet 1 x 200 mg - Fasted - Mean ± STD | Geometric Mean Ratio, % Fasted /Fed Ratio (90% CI) |
|---|---|---|---|---|
| **Itraconazole** | | | | |
| $T_{max}$ | (h) | 5.0 (2.5-12.0)[a] | 3.0 (1.0-4.0)[a] | -1.47 (-2.00--0.76)[b] |
| $C_{max}$ | (ng/mL) | 213±117 | 162±107 | 68.5 (54.7-85.6) |
| $AUC_t$[c] | (µg·h/mL) | 3.16±1.86 | 2.12±1.38 | 65.3 (53.3-80.0) |
| $AUC_\infty$ | (µg·h/mL) | 3.34±1.98 | 2.27±1.44 | 67.6 (55.8-82.0) |
| $t_{1/2term}$ | (h) | 25.1±8.44 | 25.9±5.68 | |
| **Hydroxy-itraconazole** | | | | |
| $T_{max}$ | (h) | 5.0 (3.0-12.0)[a] | 3.3 (2.5-5.0)[a] | -1.40 (-3.25--1.00)[b] |
| $C_{max}$ | (ng/mL) | 332±118 | 264±109 | 77.9 (65.6-92.5) |
| $AUC_t$[c] | (µg·h/mL) | 6.89±3.93 | 4.42±2.79 | 62.3 (50.5-76.9) |
| $AUC_\infty$ | (µg·h/mL) | 7.05±3.94 | 4.58±2.80 | 63.4 (51.9-77.6) |
| $t_{1/2term}$ | (h) | 10.6±2.70 | 12.3±3.67 | |

The bioavailability of Hyphanox was ~30 % higher under fed vs. fasted conditions and accordingly, the proposed labeling suggests Hyphanox to be taken with a full meal.

***What are the single and multiple dose PK parameters?***

The sponsor conducted 2 pharmacokinetic studies to characterize itraconazole and its active metabolite, hydroxy-itraconazole, after administration of itraconazole 200-mg film-coated tablets.

A tabular listing of PK studies is shown below.

| Reference | Design | Treatments | No. of Subjects | Age, yrs mean (range) | Weight, kg mean (range) |
|---|---|---|---|---|---|
| BT300-BEL-004 | Open | Two itraconazole 200-mg film-coated tablets dosed after a high-fat, high-calorie breakfast. | 16F | 35.8 (19-58) | 63.6 (46-81) |
| BT0300-108-USA | Open | One itraconazole 200-mg film-coated tablet after a standard breakfast, QD for 14 days | 8M/8F | 36.3 (23-53) | 69.6 (49.9-93.4) |

Study BT0300-108-USA was open-label, single-arm, single-center multiple oral dose study in healthy subjects to assess the pharmacokinetics of itraconazole and hydroxy-itraconazole at steady state after administration of 200-mg itraconazole tablets once daily for 2 weeks, followed by a 10-day follow-up period. Daily doses of 200 mg itraconazole were administered within 5 minutes of completing a standard breakfast (approximately 500 calories, 30% of which were derived from fat and 20% and 50% from protein and carbohydrates, respectively). Blood samples were collected on Days 1 and 14 at time 0 (pre-dose), 1, 2, 3, 4, 5, 6, 8, 12, 16 and 24 hours post-dose; predose on Days 2 (same as Day 1, 24 h post-dose sample), 4, 7, 10, 12 and 13; and at times 48, 72, 96, 144, 192 and 240 hour post-last dose (day 14). The mean pharmacokinetic parameters of itraconazole and hydroxy-itraconazole are summarized below.

| Parameter (units) | Statistic | Day | Analyte: Itraconazole N=16 | Analyte: OH-itraconazole N=16 |
|---|---|---|---|---|
| $C_{max}$ (ng/mL) | Mean (SD) | 1 | 116.8 (43.34) | 221.7 (69.21) |
| | | 14 | 658.1 (362.16) | 974.2 (479.92) |
| $AUC_{0-24}$ (ng*h/mL) | Mean (SD) | 1 | 905.09 (384.239) | 2538.33 (1057.872) |
| | | 14 | 9046.81 (5320.516) | 19054.95 (10443.214) |
| $t_{max}$ (h) | Median (Range) | 1 | 4.00 (2.00-5.00) | 4.00 (2.00-5.00) |
| | | 14 | 4.00 (1.00-24.00) | 4.00 (3.00-24.00) |
| $t_{1/2}$ (h) | Mean (SD) | 14 | 36.84 (10.378) | 20.06 (6.998) |
| $C_{min}$ (ng/mL) | Mean (SD) | 14 | 262.1 (151.86) | 693.1 (431.38) |
| $C_{ss,avg}$ (ng/mL) | Mean (SD) | 14 | 377.0 (221.69) | 794.0 (435.13) |
| **Accumulation Ratio*** | Mean (SD) | 14 | 10.51 (5.510) | 8.20 (4.646) |
| **AUC ratio**** | Mean (SD) | 1 | 2.83 (0.513) | |
| | | 14 | 2.22 (0.420) | |

OH-itraconazole: Hydroxy-itraconazole

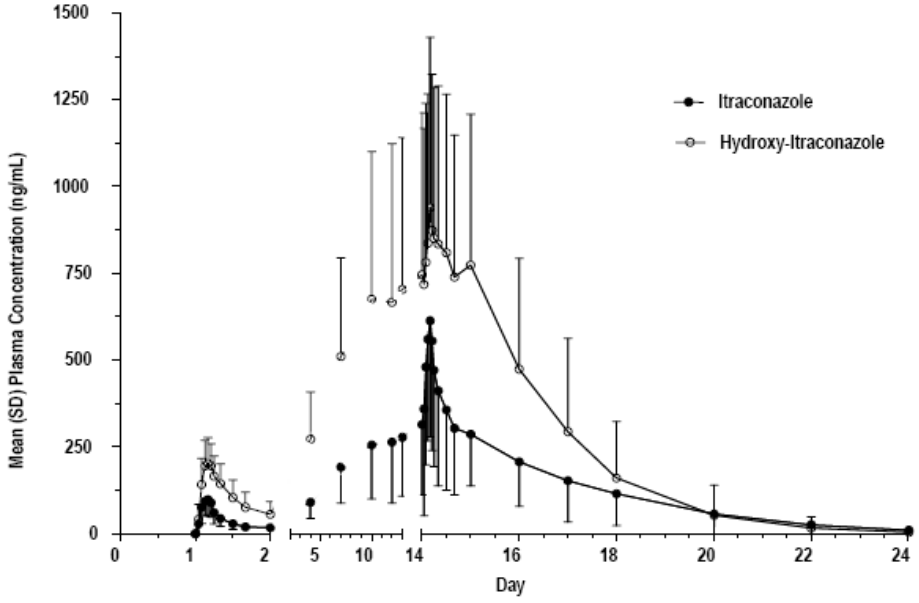
*Accumulation Ratio is defined as $AUC_{0-24}$ (Day 14) /$AUC_{0-24}$ (Day 1)

**AUC ratio is ratio of $AUC_{0-24}$ of hydroxy-itraconazole/itraconazole

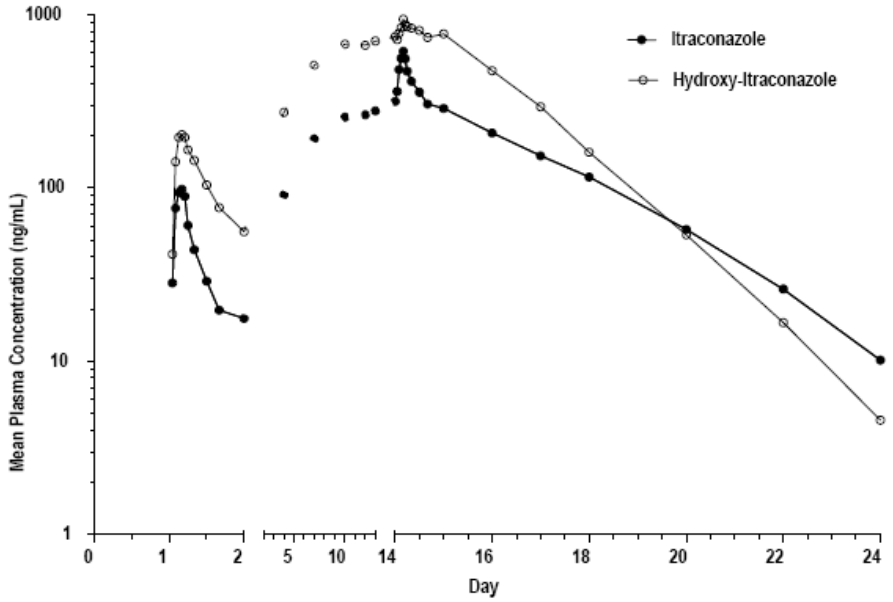
Mean $C_{max}$ (SD) of itraconazole and hydroxy-itraconazole on Day 1 was 116.8 (43.34) and 221.7 (69.21) ng/mL, respectively, and mean $C_{max}$ (SD) of itraconazole and hydroxyitraconazole on Day 14 was 658.1 (362.16) and 974.2 (479.92) ng/mL, respectively. These results show that Cmax of itraconazole and hydroxy-itraconazole increased from Day 1 to Day 14 by approximately 6- and 4-fold, respectively.

Mean $AUC_{0-24}$ (SD) of itraconazole and hydroxy-itraconazole on Day 1 was 905.09 (384.239) and 2538.33 (1057.872) ng*h/mL, respectively, and mean $AUC_{0-24}$ (SD) of itraconazole and hydroxyitraconazole on Day 14 was 9046.81 (5320.516) and 19054.95 (10443.214) ng*h/mL, respectively. Therefore, the accumulation ratios of itraconazole and hydroxy-itraconazole at day 14 are 10.51 (5.510) and 8.20 (4.646), respectively. Measurements of trough concentrations of itraconazole and hydroxy-itraconazole on Days 2 to 14 provide the concentration-time profile across the study duration, as shown below.

**Mean (SD) Plasma Itraconazole and Hydroxy-Itraconazole Concentrations versus Time: Day 1 through Day 24 (linear scale) – All Dosed Subjects**




**Mean Plasma Itraconazole and Hydroxy-Itraconazole Concentrations versus Time (Day 1 through Day 24) (semi-log scale) – All Dosed Subjects**




Similar to the results from the other studies, inter-subject variability was relatively high, with coefficient of variation (CV) ranging from 31 to 55% for $C_{max}$ and 42 to 59% for $AUC_{0-24}$. Nonetheless, it can be shown from the mean plasma profile that a steady state level of itraconazole was reached by day 10 and that PK parameters obtained at day 14 reflect the drug's disposition pattern at the steady state.

Study BT300-BEL-004 is an open-label, single oral dose study, in which 400 mg (2 x 200 mg tablets) was administered once daily to healthy female subjects. The sponsor states that the dose and a population for this study were chosen based on the initial potential indication of the drug for the treatment of vaginal candidiasis. This development program was later discontinued. The mean pharmacokinetic parameters of itraconazole and hydroxy-itraconazole are summarized below.

| Parameter | Itraconazole | Hydroxy-itraconazole |
|---|---|---|
| $T_{max}$ (h) | 5.0 (2.0-6.0)[a] | 5.5 (2.0-12.0)[a] |
| $C_{max}$ (ng/mL) | 307±177 | 469±222 |
| $AUC_t$ (μg·h/mL) | 5.21±3.35 | 12.0±8.06 |
| $AUC_\infty$ (μg·h/mL) | 5.53±3.57 | 12.2±8.06 |
| $t_{1/2term}$ (h) | 29.0±7.50 | 11.3±2.99 |

After single oral administration of two itraconazole 200-mg film-coated tablets following high-fat, high-calorie breakfast, Cmax and AUC∞ averaged 307 ng/mL and 5.53 μg·h/mL, respectively. While these numbers are higher than the estimates from the above mentioned study (BT0300-108-USA) from a dose proportionality perspective, it should be noted that this study was conducted with high-fat, high-calorie breakfast. Under this meal condition, the PK profiles from this study were comparable to those in other studies.

No information is provided in this submission on the metabolism of itraconazole following administration of 200-mg film-coated tablets. However, it is found in the Clinical Pharmacology section of the Sporanox label that itraconazole is metabolized predominantly by CYP3A4, resulting in the formation of several metabolites including hydroxy-itraconazole, the major and bioactive metabolite. Fecal excretion of the parent drug was 3-18% of the dose and renal excretion of the parent drug is less than 0.03% of the dose. About 40% of the dose is excreted as inactive metabolites in the urine. No single excreted metabolite represents more than 5% of a dose.

## 2.3 Intrinsic factors

***What intrinsic factors (gender, age, ethnicity, or disease) affect exposure or response?***

No formal studies were conducted to evaluate the effects of intrinsic factors on the exposure to itraconazole with the proposed formulation. As mentioned above, there was no PK sampling during the phase 3 trial and there were significant differences in the number of subjects belonging to any particular demographic group (75% male, 25% female; 82% Non-Hispanic, 17% Hispanic; 86% Caucasian, 14% other races), making AE analysis based on sub-groups not meaningful. However, it is not expected that the systemic exposure to Hyphanox is to be affected by gender, disease or ethnicity, and consistently, there are no such information/signals found in the Sporanox package insert in this regard.

***Pediatrics***

Sponsor has requested a full waiver for the pediatric use (children less than 16 years of age). The rationale is that onychomycosis is more prevalent in the elderly (60%) and is rare in children, estimated at 2%. The clinical trial submitted in this application includes patients with 16 – 75 years of age. Based on the rationale and the design of the efficacy trial conducted, the reviewer agrees that the sponsor's request for a pediatric waiver is reasonable.

***Renal or hepatic impairments***

No studies have been conducted in patients with renal or hepatic impairments. However, the Sporanox package inset contains the following information. While these data are from different dosage forms and formulations than Hyphanox, these intrinsic factors should have similar impacts on the disposition of itraconazole, independent of the formulation, and the information below should be included in the Hyphanox package insert.

> Renal Insufficiency
> A pharmacokinetic study using a single 200-mg dose of itraconazole (four 50-mg capsules) was conducted in three groups of patients with renal impairment (uremia: n=7; hemodialysis: n=7; and continuous ambulatory peritoneal dialysis: n=5). In uremic subjects with a mean creatinine clearance of 13 mL/min. × 1.73 m2, the bioavailability was slightly reduced compared with normal population parameters. This study did not demonstrate any significant effect of hemodialysis or continuous ambulatory peritoneal dialysis on the pharmacokinetics of itraconazole (Tmax, Cmax, and AUC0-8). Plasma concentration-versus-time profiles showed wide intersubject variation in all three groups.
>
> Hepatic Insufficiency
> A pharmacokinetic study using a single 100-mg dose of itraconazole (one 100-mg capsule) was conducted in 6 healthy and 12 cirrhotic subjects. No statistically significant differences in AUC were seen between these two groups. A statistically significant reduction in mean Cmax (47%) and a twofold increase in the elimination half-life (37 ± 17 hours) of itraconazole were noted in cirrhotic subjects compared with healthy subjects. Patients with impaired hepatic function should be carefully monitored when taking itraconazole. The prolonged elimination half-life of itraconazole observed in cirrhotic patients should be considered when deciding to initiate therapy with other medications metabolized by CYP3A4. (See BOX WARNING, CONTRAINDICATIONS, PRECAUTIONS: Drug Interactions )
>
> Decreased Cardiac Contractility
> When itraconazole was administered intravenously to anesthetized dogs, a dose-related negative inotropic effect was documented. In a healthy volunteer study of SPORANOX® Injection (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® Capsules, SPORANOX® should be discontinued. (See CONTRAINDICATIONS, WARNINGS, PRECAUTIONS: Drug Interactions and ADVERSE REACTIONS: Post-marketing Experience for more information.)

## 2.4 Extrinsic factors

***What are extrinsic factors that affect exposure or response?***

Other than the food effects that were described in the above sections, no additional studies were conducted for Hyphanox to evaluate the effects of extrinsic factors on the exposure. In general, the extrinsic factors that are known to affect pharmacokinetic properties of Sporanox should also be applicable to Hyphanox.

***Drug interactions***

No formal drug-drug interaction trials were conducted with the proposed dosage form in this submission. However, numerous drug interactions are known for itraconazole and clinical pharmacology studies were previously conducted and reviewed under NDA 20-083 to support the approval of itraconazole 100-mg capsules. Because both the itraconazole 100-mg capsules and 200-mg tablets contain the same active ingredient, the sponsor referred to NDA 20-083 for the complete clinical pharmacology information of Hyphanox. The following is found in the Sporanox package inset, and similar information should also be included in the Hyphanox package insert. See Section 3 Labeling Recommendations for details.

- 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®.
- SPORANOX® should not be administered for the treatment of onychomycosis to pregnant patients or to women contemplating pregnancy.
- SPORANOX® is contraindicated for patients who have shown hypersensitivity to itraconazole or its excipients. There is no information regarding cross-hypersensitivity between itraconazole and other azole antifungal agents. Caution should be used when prescribing SPORANOX® to patients with hypersensitivity to other azoles.

## 2.5 Analytical section

***Were the active moieties identified and measured in the plasma in the clinical pharmacology study?***

Yes. The concentrations of itraconazole and its primary metabolite, hydroxy-itraconazole, were determined in human plasma in the above mentioned studies using two assay methods. Method 1 employed a liquid-liquid extraction followed by HPLC with ultraviolet (UV) detection and used in the following studies: BT0300-BEL-001 (also listed as SGS Biopharma report B103506), BT300-BEL-002, BT0300BEL005, BT0300BEL006 and BT300-BEL-004. Method 2 used a protein precipitation followed by HPLC with tandem mass spectrometry (MS/MS) detection, which was used for Study BT0300-108-USA. A review of cross-validation of these two methods is presented in the following section.

***Was the validation of the analytical method used to determine drug concentrations in this NDA acceptable?***

Yes. Method BTM-1053-RO is an HPLC method for the determination of itraconazole and hydroxyl-itraconazole in human plasma using R051012 as the internal standard (IS). Method BTM-1054-RO is an LC/MS/MS method for the determination of itraconazole and hydroxyl-itraconazole in human plasma using itraconazole-ds and hydroxy itraconazole-ds as the internal standards (IS).

As for the HPLC-UV method, itraconazole and hydroxy-itraconazole were extracted from plasma samples by increasing the pH to basic conditions and extracting the resulting samples with a heptane/isoamyl alcohol mixture and analyzed by reverse phase HPLC with UV detection. The lower limits of quantification (LLOQ) were 2 ng/mL for the 2 compounds. Standard curves were linear in the evaluated concentration ranges (2.0-5000 ng/mL) and the overall precision ranged from 2.6 % to 8.6 % (12.7-1979 ng/mL) for itraconazole and 3.4 - 10.1 % (12.5-1961 ng/mL) for hydroxyl-itraconazole.

For LC-MS/MS method, a cross-validation was performed to HPLC/UV method. The lower limits of quantification (LLOQ) were 1 ng/mL plasma for the 2 compounds. Standard curves were linear in the evaluated concentration ranges (1-500 ng/mL) and the overall precision ranged from 6.9% to 9.1% (3-380 ng/mL) for itraconazole and from 8.9 to 10.4 % (3-380 ng/mL) for hydroxyl itraconazole.

The accuracy (% nominal) of the QC sample concentrations for itraconazole and hydroxyl-itraconazole are shown in Table 3 and 4 for BTM-1053-RO and BTM-1054-RO, respectively. All QC samples met pre-set acceptance criteria.

**Table 3. Accuracy of Itraconazole and Hydroxy Itraconazole QC Samples for Method BTM-1053-R0**

| Accuracy | QC Sample No. | Itraconazole Concentration, ng/mL | | | Hydroxy Itraconazole Concentration, ng/mL | | |
|---|---|---|---|---|---|---|---|
| | | 6 | 400 | 3800 | 6 | 400 | 3800 |
| %Nominal | 1 | 100.8 | 89.5 | 93.6 | 95.7 | 98.3 | 99.9 |
| | 2 | 98.5 | 88.9 | 93.2 | 108.5 | 96.8 | 99.1 |
| Acceptance Criteria | | (b) (4) | | | (b) (4) | | |

**Table 4. Accuracy of Itraconazole and Hydroxy Itraconazole QC Samples for Method BTM-1054-R0**

| Accuracy | QC Sample No. | Itraconazole Concentration, ng/mL | | | Hydroxy Itraconazole Concentration, ng/mL | | |
|---|---|---|---|---|---|---|---|
| | | 3 | 40 | 380 | 3 | 40 | 380 |
| %Nominal | 1 | 88.8 | 93.8 | 92.4 | 87.0 | 94.3 | 93.9 |
| | 2 | 90.4 | 94.3 | 95.2 | 93.4 | 90.9 | 91.4 |
| Acceptance Criteria | | (b) (4) | | | (b) (4) | | |

The accuracy of the back-calculated concentrations of the calibration standards for itraconazole and hydroxyl-itraconazole is shown in the tables below. Tables 5 and 6 are for method BTM-1053-RO, and Tables 7 and 8 are for method BTM-1054-RO. The calibration standard data met the acceptance criteria.

**Table 5. Accuracy of Itraconazole Calibration Standards for Method BTM-1053-R0**

| Accuracy | Itracoanzole Concentration, ng/mL | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 2 | 4 | 50 | 100 | 500 | 2000 | 4000 | 5000 |
| %Nominal | 104.8 | 98.4 | 97.3 | 98.1 | 98.6 | 98.1 | 102.4 | 102.6 |
| Acceptance Criteria | (b) (4) | | | | (b) (4) | | | |

**Table 6. Accuracy of Hydroxy Itraconazole Calibration Standards for Method BTM-1053-R0**

| Accuracy | Hydroxy Itraconazole Concentration, ng/mL | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 2 | 4 | 50 | 100 | 500 | 2000 | 4000 | 5000 |
| %Nominal | 103.1 | 93.9 | 102.5 | 102.1 | 102.0 | 97.1 | 101.3 | 98.4 |
| Acceptance Criteria | (b) (4) | | | | (b) (4) | | | |

**Table 7. Accuracy of Itraconazole Calibration Standards for Method BTM-1054-R0**

| Accuracy | Itraconazole Concentration, ng/mL | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 10 | 20 | 50 | 200 | 400 | 500 |
| %Nominal | 99.5 | 98.8 | 110.5 | 100.0 | 102.1 | 98.7 | 94.9 | 95.5 |
| Acceptance Criteria | (b) (4) | | | | (b) (4) | | | |

**Table 8. Accuracy of Hydroxy Itraconazole Calibration Standards for Method BTM-1054-R0**

| Accuracy | Hydroxy Itraconazole Concentration, ng/mL | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 10 | 20 | 50 | 200 | 400 | 500 |
| %Nominal | 101.2 | 95.7 | 110.5 | 98.7 | 101.7 | 98.9 | 96.3 | 97.1 |
| Acceptance Criteria | (b) (4) | | | | (b) (4) | | | |

The calibration curves in both assays showed the coefficient of determination (r2) greater than 0.99.

In order to cross-validate the two methods, QC samples were prepared at the concentrations of 6/6 ng/mL, 40/40 ng/mL, and 380/380 ng/mL for itraconazole/hydroxy-itraconazole. Six replicates were made at each concentration. The results were then compared using the % Difference calculation below.

$$\%Difference = \frac{C_{LC/MS/MS} - C_{LC/UV}}{Mean\ of\ C_{LC/MS/MS}\ and\ C_{LC/UV}} \times 100$$

The table below shows less than 5% differences in the mean values at each concentration between methods BTM-I 053RO and BTM-1054-RO.

**Table 11. Cross-Validation Results**

| Concentration, ng/mL | Sample No. | Itraconazole | | % Difference | Hydroxy Itraconazole | | % Difference |
|---|---|---|---|---|---|---|---|
| | | LC/UV BTM-1053-R0 | LC/MS/MS BTM-1054-R0 | | LC/UV BTM-1053-R0 | LC/MS/MS BTM-1054-R0 | |
| 6 | 1 | 5.384 | 5.882 | 2.5 | 5.207 | 5.680 | -0.3 |
| | 2 | 5.347 | 5.577 | | 5.157 | 5.443 | |
| | 3 | 5.263 | 5.565 | | 5.177 | 5.746 | |
| | 4 | 5.483 | 5.394 | | 6.793 | 5.605 | |
| | 5 | 5.414 | 5.304 | | 5.164 | 5.668 | |
| | 6 | 5.272 | 5.265 | | 6.210 | 5.473 | |
| | Mean | 5.361 | 5.498 | | 5.618 | 5.603 | |
| | %Nom | 89.3 | 91.6 | | 93.6 | 93.4 | |
| | %CV | 1.6 | 4.2 | | 12.6 | 2.2 | |
| 40 | 1 | 35.946 | 37.307 | 4.1 | 42.138 | 39.086 | -4.0 |
| | 2 | 35.758 | 36.141 | | 40.077 | 38.150 | |
| | 3 | 35.421 | 37.290 | | 37.003 | 38.392 | |
| | 4 | 35.444 | 36.484 | | 40.102 | 37.792 | |
| | 5 | 35.728 | 38.151 | | 42.253 | 39.256 | |
| | 6 | 35.559 | 37.374 | | 39.341 | 38.709 | |
| | Mean | 35.643 | 37.125 | | 40.152 | 38.564 | |
| | %Nom | 89.1 | 92.8 | | 100.4 | 96.4 | |
| | %CV | 0.6 | 1.9 | | 4.8 | 1.5 | |
| 380 | 1 | 337.024 | 353.509 | 3.6 | 369.194 | 360.937 | -1.8 |
| | 2 | 338.786 | 347.901 | | 370.475 | 361.751 | |
| | 3 | 337.999 | 346.232 | | 370.913 | 349.670 | |
| | 4 | 340.671 | 362.458 | | 375.411 | 358.863 | |
| | 5 | 346.262 | 347.951 | | 370.497 | 349.944 | |
| | 6 | 334.175 | 352.405 | | 314.060 | 349.900 | |
| | Mean | 339.153 | 351.743 | | 361.758 | 355.178 | |
| | %Nom | 89.3 | 92.6 | | 95.2 | 93.5 | |
| | %CV | 1.2 | 1.7 | | 6.5 | 1.7 | |

## 3. DETAILED LABELING RECOMMENDATIONS

Sections related to Clinical Pharmacology only are listed below. Note that the revision of section 7. Drug Interaction has not been finalized and will be completed upon sponsor's provision of updated information.

~~Strikethrough text~~ means deletion of the sponsor's proposed text. Underscored blue text means recommended addition.

(b) (4)

[redacted]



18 pages of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)


## 4.2 OCP filing form

# Office of Clinical Pharmacology

## *New Drug Application Filing and Review Form*

***General Information About the Submission***

| | Information | | Information |
|---|---|---|---|
| **NDA/BLA Number** | **22-484** | **Brand Name** | **Hyphanox** |
| **OCP Division (I, II, III, IV, V)** | **III** | **Generic Name** | **Itraconazole** |
| **Medical Division** | **Derm** | **Drug Class** | **Triazol anti-fungal** |
| **OCP Reviewer** | **Julia Cho** | **Indication(s)** | **Onychomycosis** |
| **OCP Team Leader** | **Dennis Bashaw** | **Dosage Form** | **Film-coated tablet** |
| **Pharmacometrics Reviewer** | | **Dosing Regimen** | **Once daily** |
| **Date of Submission** | **03/31/09** | **Route of Administration** | **Oral** |
| **Estimated Due Date of OCP Review** | **11/30/09** | **Sponsor** | **Stiefel Laboratories** |
| **Medical Division Due Date** | **11/30/09** | **Priority Classification** | **Standard** |
| **PDUFA Due Date** | **01/31/10** | | |

### *Clin. Pharm. and Biopharm. Information*

| | **"X" if included at filing** | **Number of studies submitted** | **Number of studies reviewed** | **Critical Comments If any** |
|---|---|---|---|---|
| **STUDY TYPE** | | | | |

| | | | | |
|---|---|---|---|---|
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | **X** | | | |
| **Tabular Listing of All Human Studies** | **X** | | | |
| **HPK Summary** | **X** | | | |
| **Labeling** | **X** | | | |
| **Reference Bioanalytical and Analytical Methods** | | | | |
| **I. Clinical Pharmacology** | | | | |
| **Mass balance:** | | | | |
| **Isozyme characterization:** | | | | |
| **Blood/plasma ratio:** | | | | |
| **Plasma protein binding:** | | | | |
| **Pharmacokinetics (e.g., Phase I) -** | | | | |
| **Healthy Volunteers-** | | | | |
| single dose: | **X** | **1** | **1** | |
| multiple dose: | **X** | **1** | **1** | |
| **Patients-** | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |
| **Subpopulation studies -** | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | | | | |
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| **PD -** | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| **PK/PD -** | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| **Population Analyses -** | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability** | | | | |
| **Relative bioavailability -** | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | **X** | **1** | **1** | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | **X** | **2** | **2** | |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies** | | | | |
| **Bio-waiver request based on BCS** | | | | |
| **BCS class** | | | | |
| **Dissolution study to evaluate alcohol induced dose-dumping** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | | | | |
| **Total Number of Studies** | | **5** | **5** | |
| | | | | |

On **initial** review of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | N/A | Comment |
|---|---|---|---|---|---|
| **Criteria for Refusal to File (RTF)** | | | | | |
| 1 | Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials? | x | | | |
| 2 | Has the applicant provided metabolism and drug-drug interaction information? | | **x** | | Refer to Sporanox label |
| 3 | Has the sponsor submitted bioavailability data satisfying the CFR requirements? | **x** | | | |
| 4 | Did the sponsor submit data to allow the evaluation of the validity of the analytical assay? | | x | | Cross-validation study report between HLPC-UV and HPLC MS/MS not provided |
| 5 | Has a rationale for dose selection been submitted? | | **x** | | |
| 6 | Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin? | **x** | | | |
| 7 | Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin? | **x** | | | |
| 8 | Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work? | **x** | | | |
| **Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)** | | | | | |
| | **Data** | | | | |
| 9 | Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)? | **x** | | | |
| 10 | If applicable, are the pharmacogenomic data sets submitted in the appropriate format? | | | N/A | |
| | **Studies and Analyses** | | | | |
| 11 | Is the appropriate pharmacokinetic information submitted? | **x** | | | |
| 12 | Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)? | | **x** | | |
| 13 | Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance? | | **x** | | |
| 14 | Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics? | | **x** | | |
| 15 | Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is | | | x | |

| | | | | | |
|---|---|---|---|---|---|
| | indeed effective? | | | | |
| 16 | Did the applicant submit all the pediatric exclusivity data, as described in the WR? | | X | | A waiver from pediatric study in children below the age of 12 is being requested |
| 17 | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label? | X | | | |
| | **General** | | | | |
| 18 | Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? | X | | | |
| 19 | Was the translation (of study reports or other study information) from another language needed and provided in this submission? | | X | | |

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? __ __yes____**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- A study report documenting cross-validation of two analytical methods (HLPC-UV and HPLC MS/MS) was not provided. The referenced document, BTM-1054-R0, is regarding a method development for HPLC/MS/MS. Please submit the cross-validation analytical study report.

Seongeun Julia Cho

Reviewing Clinical Pharmacologist Date

E. Dennis Bashaw

Team Leader/Supervisor Date

## 4.3 Individual Study Review

**Study BT300-BEL-002**

**Study title**
A two period open-label randomized crossover pivotal bioequivalence trial to assess the bioequivalence of a new 200 mg itraconazole tablet formulation as compared with the marketed 100 mg itraconazole capsule Sporanox given as a single dose of 200 mg in 56 healthy subjects

**Investigator**
Dr. W. Haazen (principal investigator) (b) (4)

**Study Center**
SGS Biopharma Research Unit Stuivenberg
Lange Beeldekensstraat 267, B-2060 Antwerpen (Belgium)

**Phase of development**: Phase 1

**Objective**
Primary objective – To test after a single oral dose in fed conditions the bioequivalence of a new melt extrusion tablet formulation of 200 mg itraconazole with a reference, the marketed 100 mg itraconazole capsule Sporanox.

Secondary objective – To obtain bioavailability of the new melt extrusion tablet formulation of 200 mg itraconazole of Barrier Therapeutics to allow comparison with a melt-extrusion tablet formulation of 200 mg itraconazole that Janssesn Pharmaceutica had developed and used in clinical trials in (b) (4). Sporanox capsules served as a reference.

Third objective – To obtain information on the safety and tolerability of the new melt-extrusion formulation

**Methodology**
Open, randomized, 2-way cross-over, single oral dose study, with a 14-day wash-out period in 56 healthy subjects (28 males and 28 females) after a standardized breakfast

**Main criteria for inclusion**
Healthy male and female subjects aged 18-55 years inclusive

**Results**
Itraconazole:
The peak concentration was similar after the two treatments with a 90 % CI for the table/capsule ratio (91 – 112 %), which is within the bioequivalence limits. However, the peak concentration occurred significantly earlier (3.5 vs. 5 hour) after administration of the tablet than after the capsule, with a 90 % CI for the medians difference (-0.99 to -0.25

h) entirely shifted below 0. AUCt and AUC∞ were significantly increased with the new tablet and the upper limit of the 90 % CI (104 – 127 %) exceeded the 125 % bioequivalence limit. The apparent terminal half-life was longer with the new tablet (p=0.023).

Hydroxy-itraconazole:
The differences between the two study treatments were generally similar to that observed for itraconazole.
The peak concentration was similar after the two treatments and occurred slightly earlier after administration of the tablet than after the capsules but without statistical significance. AUCt and AUC∞ were significantly increased with the new tablet. The 90% CIs exceeded the predefined upper bioequivalence limit of 125%. The apparent terminal half-life was similar after both treatments.

| Itraconazole | | Sporanox® 2 x 100-mg capsules * | Melt-extrusion 200-mg tablet * | p | Melt-extrusion 200-mg tablet vs. Sporanox® 2 x 100-mg capsules | |
|---|---|---|---|---|---|---|
| | | | | | PE | 90% CI |
| $C_{max}$ | ng/mL | 272 (54.8) | 274 (39.4) | 0.87 | 101.02 | [91.33;111.74] |
| $t_{max}$ | h | 5.00 (2.00 - 8.00) | 3.51 (2.00 - 8.00) | 0.002 | -0.50 | [-0.99;-0.25] |
| $AUC_t$ | h·µg/mL | 3.19 (56.4) | 3.65 (43.2) | 0.025 | 114.81 | [103.91;126.86] |
| $AUC_\infty$ | h·µg/mL | 3.42 (56.3) | 3.92 (43.7) | 0.026 | 114.67 | [103.74;126.76] |
| $t_{½z}$ | h | 24.7 (32.5) | 27.0 (33.6) | 0.023 | 109.00 | [102.48;115.92] |
| **Hydroxy-itraconazole** | | **Sporanox® 2 x 100-mg capsules *** | **Melt-extrusion 200-mg tablet *** | **p** | **Melt-extrusion 200-mg tablet vs. Sporanox® 2 x 100-mg capsules** | |
| | | | | | **PE** | **90% CI** |
| $C_{max}$ | ng/mL | 430 (39.0) | 455 (26.7) | 0.21 | 105.90 | [98.19;114.21] |
| $t_{max}$ | h | 5.00 (2.00 - 8.00) | 4.00 (2.00 - 12.00) | 0.31 | -0.25 | [-0.50;0.025] |
| $AUC_t$ | h·µg/mL | 6.88 (56.6) | 7.89 (45.6) | 0.033 | 114.89 | [103.32;127.76] |
| $AUC_\infty$ | h·µg/mL | 7.11 (55.4) | 8.08 (45.4) | 0.043 | 113.88 | [102.55;126.46] |
| $t_{½z}$ | h | 8.76 (24.2) | 9.02 (23.3) | 0.31 | 102.77 | [98.30;107.43] |

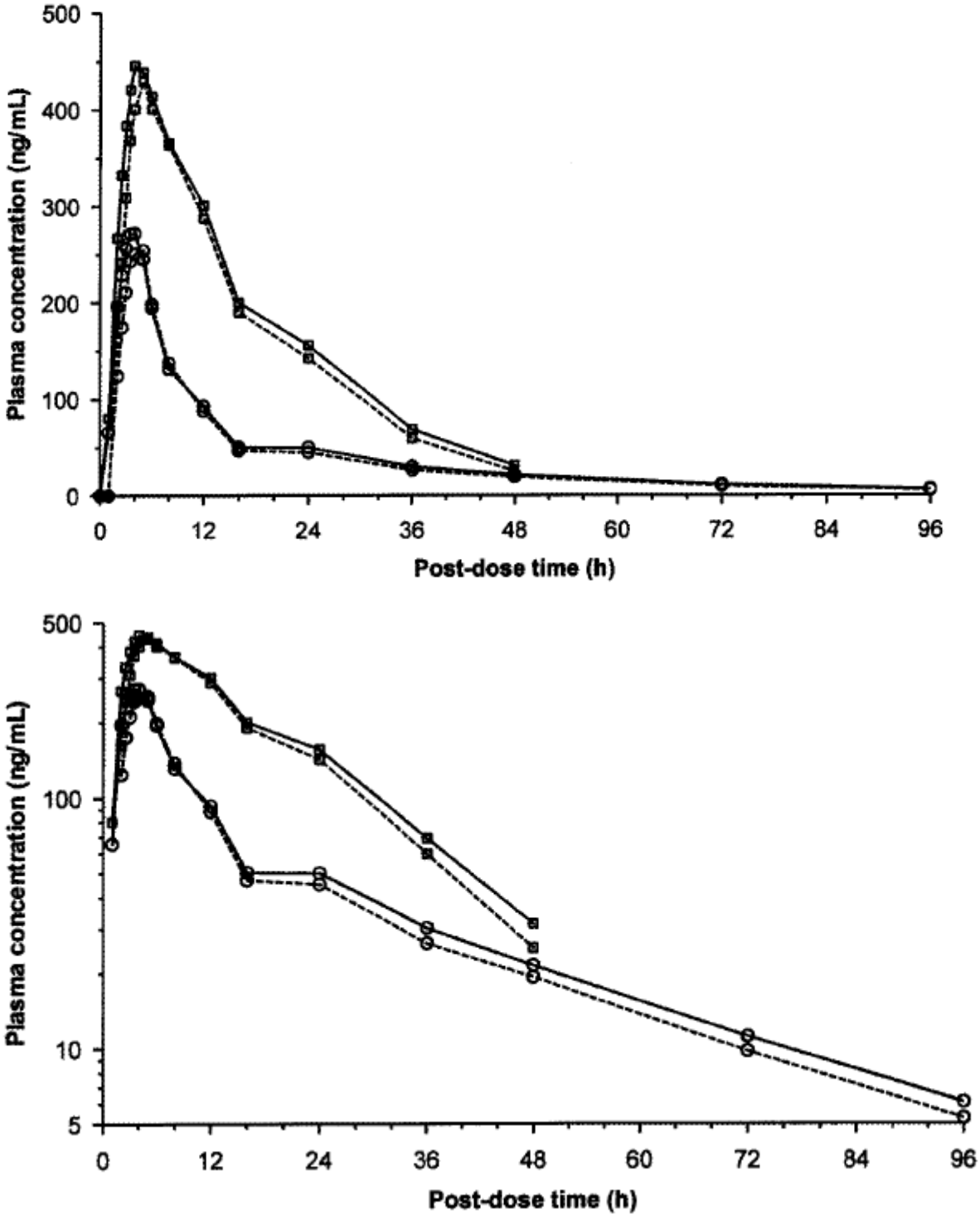



Figure 14.2.1: Average itraconazole and hydroxy-itraconazole plasma concentration versus time

Circles: itraconazole, squares: hydroxy-itraconazole
Solid line: 200-mg melt-extrusion tablet, dashed line: 2 x 100-mg Sporanox® capsules
Values are arithmetic means. Top: linear scale, bottom: semi-log scale

**Conclusion**
The new 200 mg tablet is bioequivalent to two Sporanox 100 mg capsules in terms of peak exposure to itraconzaole and hydroxyl-itraconazole. However, since the tablet has higher AUC, it is concluded not to be bioequivqlent to two 100 mg Sporanox capsules.

**Study BT300-BEL-005**

**Study title**
Pivotal bioequivalence study of itraconazole in a 200 mg film-coated tablet (Hyphanox) and in 100 mg capsules (SporanoX) under fed (high-fat, high calorie) conditions.

**Investigators**
Dr. E. Vets (principal investigator) (b) (4)

**Study Center**
SGS Biopharma Research Unit Stuivenberg
Lange Beeldekensstraat 267, B-2060 Antwerpen (Belgium)

**Phase of development**: Phase 1

**Objectives**:
Primary objective – to test the bioequivalence of a new film-coated tablet formulation of 200 mg itraconazole (F1) with a reference, the marketed 100 mg itraconazole capsule Sporanox®, when a single oral 200 mg dose of each formulation was administered after a high-fat, high-calorie meal.

Secondary objective – to document the safety and tolerability of the new tablet formulation.

**Methodology**:
Open, randomized, two-way cross-over, single oral dose study. There was a wash-out period of at least two weeks in between drug intakes.

**Number of subjects:**
56 healthy subjects (28 male and 28 female)

**Diagnosis and main criteria for inclusion:**
Healthy male and female subjects, aged 18-55 years inclusive.

**Test product, dose and mode of administration, batch number/expo date:**
Treatment A (reference treatment)

- 100 mg itraconazole capsule (Sporanox®), Janssen Pharmaceutica Products. A single oral dose of two 100 mg itraconazole capsules (total 200 mg) was taken with 240 mL of water, 30 minutes after the start of a high-fat, highcalorie breakfast.

Treatment B (test treatment)

- 200 mg itraconazole film-coated tablet (F1), Barrier Therapeutics. A single oral dose of one 200 mg itraconazole tablet was taken with 240 mL of water, 30 minutes after the start of a high-fat, high-calorie breakfast.

**Results**

After single oral administration of a 200 mg tablet of itraconazole under fed conditions, the peak plasma concentration was lower and occurred later (Tmax 5 hour) and the extent of absorption was lower (AUC∞ 2.41 ug.h/mL) when compared to administration of two capsules of 100 mg of itraconazole under fed conditions (Tmax 4 hour and AUC∞ 3.38 ug.h/mL).

When administered after a high fat, high calorie meal, the 200 mg tablet of itraconazole is not bioequivalent to the two 100 mg capsules of itraconazole.

| | Capsules fed (reference)* | Tablet fed (test)* | p | Tablet (fed) vs. Capsules (fed) | |
|---|---|---|---|---|---|
| | | | | PE | 90% CI |
| **Itraconazole** | | | | | |
| **$C_{max}$ (ng/mL)** | 227 ± 106 | 185 ± 112 | 0.0109 | 80.44 | [70.06 ;92.36] |
| **$t_{max}$ (h)** | 4.00 (2.00-8.00) | 5.00 (2.50-8.00) | 0.0326 | 0.50 | [0.00 ;0.75] |
| **$AUC_{last}$ (µg.h/mL)** | 3.22 ± 1.83 | 2.28 ± 1.52 | <0.0001 | 69.56 | [60.35 ;80.16] |
| **$AUC_{\infty}$ (µg.h/mL)** | 3.38 ± 1.96 | 2.41 ± 1.62 | <0.0001 | 70.37 | [61.42;80.62] |
| **$t_{1/2term}$ (h)** | 24.9 ± 6.16 | 23.9 ± 7.60 | 0.137 | -0.957 | [-2.017;0.103] |
| **Hydroxy-Itraconazole** | | | | | |
| **$C_{max}$ (ng/mL)** | 354 ± 130 | 288 ± 108 | 0.0052 | 82.26 | [73.53;92.02] |
| **$t_{max}$ (h)** | 5.00 (2.53-12.02) | 5.00 (3.50-8.00) | 0.428 | 0.01 | [-0.01;0.50] |
| **$AUC_{last}$ (µg.h/mL)** | 7.02 ± 4.08 | 4.85 ± 2.96 | 0.0001 | 69.80 | [60.29;80.81] |
| **$AUC_{\infty}$ (µg.h/mL)** | 7.25 ± 4.16 | 5.04 ± 2.99 | < 0.0001 | 70.13 | [60.91;80.75] |
| **$t_{1/2term}$ (h)** | 9.77 ± 2.90 | 8.70 ± 2.71 | < 0.0001 | -1.07 | [-1.44;-0.707] |

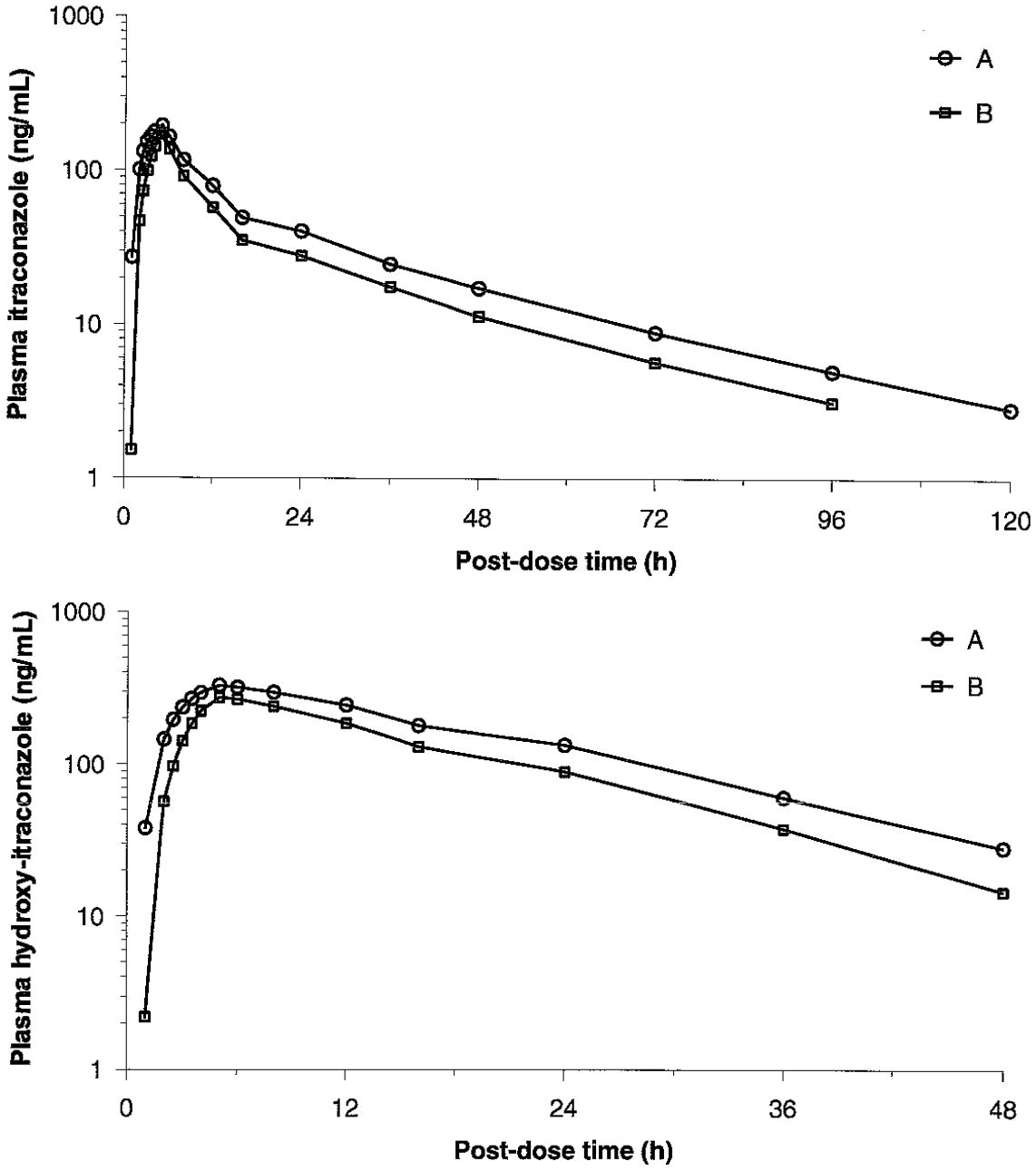



Figure 14.3.1 Average itraconazole and hydroxy-itraconazole plasma concentration versus time (continued)

**Conclusion:**

When administered after a high fat, high calorie meal, the 200 mg tablet of itraconazole is not bioequivalent to the two 100 mg capsules of itraconazole.

Safety: A single oral administration of a 200 mg tablet and two 100 mg capsules of itraconazole were well tolerated. Most frequent reported AEs were headache, injection site reaction and fatigue. Most AEs were mild in intensity and no severe or serious AEs were reported.

**Study BT300-BEL-006**

**Study title**
Food effect on the bioavailability of itraconazole in a 200-mg film-coated tablet (Hyphanox™) and comparative bioavailability of the tablet and the 100-mg itraconazole capsule (Sporanox®) under fasting conditions.

**Investigators**
Dr. W. Haazen (principal investigator) (b) (4)

**Study Center**
SGS Biopharma Research Unit Stuivenberg
Lange Beeldekensstraat 267, B-2060 Antwerpen (Belgium)

**Phase of development**: Phase 1

**Objectives**:
Primary objective – to assess the effect of food on the bioavailability of itraconazole from a new 200 mg film-coated tablet (formulation F1)

Secondary objective – to document the comparative bioavailability of this tablet with the 100 mg marketed capsule (Sporanox®) under fasting conditions.

**Methodology:**
Open, randomized, three-way cross-over, single oral dose study. Drug intakes were separated by two-week wash-out periods.

**Number of subjects:**
18 Healthy subjects (9 male, 9 female). Drop outs were not replaced.

**Diagnosis and main criteria for inclusion:**
Healthy male and female subjects aged 18 to 55 years inclusive.

**Test product, dose and mode of administration:**
- Treatment A: 200 mg itraconazole film-coated tablet (F1), Barrier Therapeutics
A single oral dose of one 200 mg itraconazole tablet with 240 mL of water, after at least 10 hours of fasting (batch no. 05A04, expo date: 01/2007).
- Treatment B: 200 mg itraconazole film-coated tablet (F1), Barrier Therapeutics
A single oral dose of one 200 mg itraconazole tablet with 240 mL of water, 30 minutes after the start of a high-fat, high-calorie breakfast (two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces (120 g) of hash brown potatoes and eight ounces (240 mL) of whole milk (batch no. 05A04, expo date: 01/2007).

**Reference product, dose and mode of administration:**

- Treatment C: 100 mg itraconazole capsule (SporanoX®), Janssen Pharmaceutica Products, LP. A single oral dose of two 100 mg itraconazole capsules with 240 mL of water, after at least 10 hours of fasting (batch 4LG487-X, expo date: 03/2006).

**Bioanalysis:**
Plasma concentrations of itraconazole and hydroxy-itraconazole were determined by a validated HPLC method with UV detection. LLOQ was 2 ng/mL for itraconazole and 5 ng/mL for hydroxy-itraconazole.

**Results**

The bioavailability of itraconazole from the tablet formulation is on average about 30% lower in the fasted state than in fed conditions (the fasted/fed ratio is 67.62%).

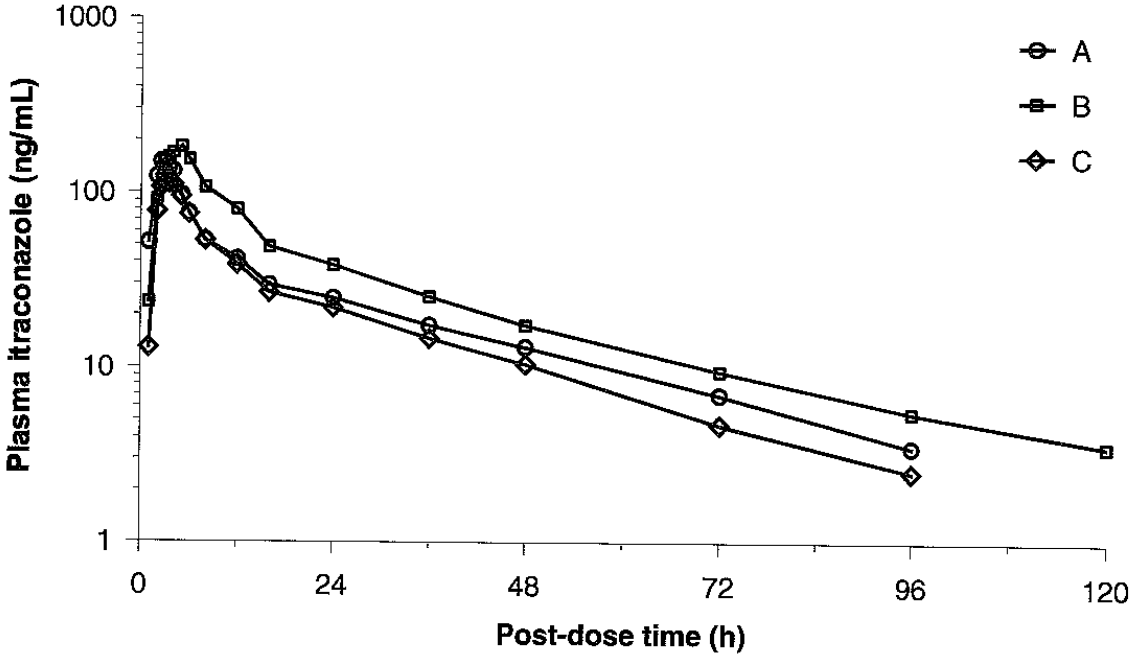
When administered in the fasting state, the 200 mg film-coated tablet (F1) is not bioequivalent to two 100 mg Sporanox capsules. In the fasted state, the bioavailability of itraconazole from the 200 mg film-coated tablet (F1) is on average about 15% higher than from the two 100 mg Sporanox capsules (the test/reference ratio is 114.74%). The hydroxy-itraconazole data are in line with the results of itraconazole.

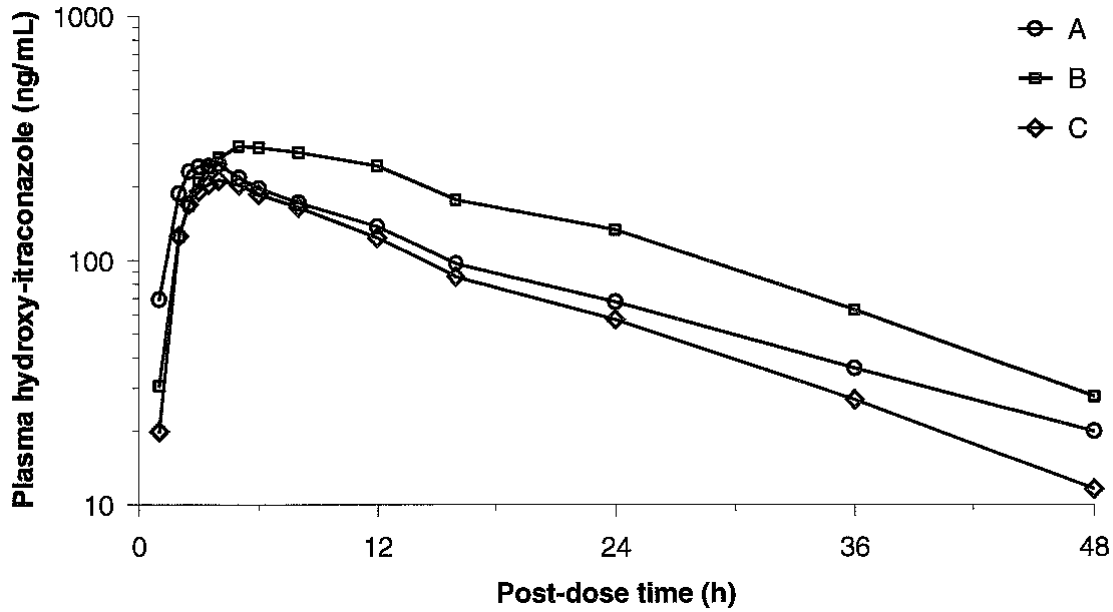
| PK Parameters | Treatment A (Tablet fasted) | | Treatment B (Tablet fed) | | Treatment C (Capsules fasted) | |
|---|---|---|---|---|---|---|
| | Itraconazole | Hydroxy-itraconazole | Itraconazole | Hydroxy-itraconazole | Itraconazole | Hydroxy-itraconazole |
| $C_{max}$ (ng/mL) | 162 ± 107 | 264 ± 109 | 213 ± 117 | 332 ± 118 | 135 ± 68.2 | 232 ± 70.0 |
| $t_{max}$ (h) | 3.00 (1.02;4.00) | 3.25 (2.50;5.00) | 5.00 (2.50;12.02) | 5.00 (3.00;12.02) | 3.00 (2.00;5.00) | 3.50 (2.50;6.00) |
| $AUC_{last}$ (µg.h/mL) | 2.12 ± 1.38 | 4.42 ± 2.79 | 3.16 ± 1.86 | 6.89 ± 3.93 | 1.73 ± 0.947 | 3.57 ± 1.95 |
| $AUC_{\infty}$ (µg.h/mL) | 2.27 ± 1.44 | 4.58 ± 2.80 | 3.34 ± 1.98 | 7.05 ± 3.94 | 1.87 ± 0.987 | 3.73 ± 2.00 |
| $t½_{term}$ (h) | 25.9 ± 5.68 | 12.3 ± 3.67 | 25.1 ± 8.44 | 10.6 ± 2.70 | 24.4 ± 6.98 | 10.1 ± 2.02 |

Values are arithmetic means ± SD; except $t_{max}$: median (range)

| Itraconazole | A (Tablet fasted) vs B (Tablet fed) | | | A (Tablet fasted) vs C (Capsules fasted) | | |
|---|---|---|---|---|---|---|
| | PE | 90% CI | | PE | 90% CI | |
| $C_{max}$ (%) | 68.45 | 54.72 | 85.63 | 105.27 | 84.15 | 131.68 |
| $t_{max}$ (h) | -1.47 | -2.00 | -0.76 | -0.50 | -1.00 | 0.00 |
| $AUC_{last}$ (%) | 65.26 | 53.26 | 79.96 | 114.00 | 93.04 | 139.67 |
| $AUC_{\infty}$ (%) | 67.62 | 55.78 | 81.98 | 114.74 | 94.64 | 139.10 |
| **Hydroxy-itraconazole** | **A (Tablet fasted) vs B (Tablet fed)** | | | **A (Tablet fasted) vs C (Capsules fasted)** | | |
| | PE | 90% CI | | PE | 90% CI | |
| $C_{max}$ (%) | 77.88 | 65.55 | 92.53 | 106.66 | 89.77 | 126.71 |
| $t_{max}$ (h) | -1.40 | -3.25 | -1.00 | -0.50 | -0.99 | 0.00 |
| $AUC_{last}$ (%) | 62.31 | 50.51 | 76.87 | 116.27 | 94.25 | 143.44 |
| $AUC_{\infty}$ (%) | 63.44 | 51.87 | 77.59 | 116.29 | 95.08 | 142.22 |

PE and 90% CI: Point estimate and 90% CI of the least-squares geometric means ratio (ANOVA), except $t_{max}$: median of differences and non parametric 90% CI (according to the method of Moses)




**A** - one single oral dose of one 200 mg itraconazole film-coated tablet (F1, Barrier Therapeutics) in fasting conditions.
**B** - one single oral dose of one 200 mg itraconazole film-coated tablet (F1, Barrier Therapeutics) after a high-fat, high-calorie breakfast.
**C** - one single oral dose of two 100 mg itraconazole capsules (Sporanox®, Janssen Pharmaceutica Products, LP) in fasting conditions.

**Conclusion:**

- The bioavailability of itraconazole from the tablet formulation is about 30% lower in the fasted state than in fed conditions (the fasted/fed ratio is 67.62%).
- Under the fasting state, the 200 mg film-coated tablet (F1) is not bioequivalent to two100 mg Sporanox capsules. The bioavailability of itraconazole from the 200 mg film-coated tablet is about 15% higher than from the two 100 mg Sporanox capsules.

**Study BT300-BEL-004**

**Study title**

A study to assess the pharmacokinetics of itraconazole and hydroxy-itraconazole in healthy women after single administration of 400 mg itraconazole in a new 200-mg tablet formulation (Hyphanox™) in fed conditions.

**Investigators**

Dr. W. Haazen (principal investigator) (b) (4)

**Study Center**

SGS Biopharma Research Unit Stuivenberg
Lange Beeldekensstraat 267, B-2060 Antwerpen (Belgium)

**Phase of development**: Phase 1

**Objectives**:

To assess the pharmacokinetics of itraconazole and hydroxy-itraconazole in healthy women after single administration of 400 mg itraconazole as two itraconazole 200-mg tablets following a high-fat, high calorie breakfast.

**Methodology:**

Open, single oral-dose study

**Number of subjects:**

16 healthy female subjects

**Diagnosis and main criteria for inclusion:**

Healthy female subjects aged 18 to 65 years inclusive.

**Test product, dose and mode of administration:**

200 mg itraconazole tablet (F1), Barrier Therapeutics, Batch: 04C09, expiry date: 09 March, 2006
Single oral dose of two 200-mg itraconazole tablets with 240 mL of room temperature non-carbonated water after a high-calorie, high-fat breakfast.

**Duration of treatment:**

One single dose in one study period of 37 hours (-13h until 24h post dose) of Clinical Centre residency with returns to the Clinical Centre for the 36h, 48h, 72h, 96 and 120 hour blood samples post dose.

**Criteria for evaluation:**
Concentration-time profiles of itraconazole and hydroxy-itraconazole in plasma (determined by a validated HPLC-UV method: LLOQ was 2 ng/mL for itraconazole and 5 ng/mL for hydroxyitraconazole) and derived pharmacoklnetic parameters. Assessment of general tolerability of the treatment.

**Statistical methods:**
Individual estimates of pharmacokinetic parameters reported and summarized as sample size, mean value, geometric mean, median value, standard deviation, coefficients of variation, minimum and maximum.

**Results**

| PK parameters | | Itraconazole | Hydroxy-itraconazole |
|---|---|---|---|
| $C_{max}$ | ng/mL | 307 ± 177 | 469 ± 222 |
| $t_{max}$ | h | 4.19 ± 1.23 | 5.76 ± 2.41 |
| $AUC_t$ | µg.h/mL | 5.21 ± 3.35 | 12.0 ± 8.06 |
| $AUC_\infty$ | µg.h/mL | 5.53 ± 3.57 | 12.2 ± 8.06 |
| $t_{½term}$ | h | 29.0 ± 7.50 | 11.3 ± 2.99 |

**Conclusion:**
After single oral administration of two melt-extrusion 200-mg itraconazole tablets to 16 healthy women in fed condition, Cmax and AUC∞ of itraconazole were 307 ng/mL and 5.53 ug.h/mL, respectively. The mean terminal half-life was 29 h. Hydroxy-itraconazole peak plasma concentration averaged 469 ng/mL and AUC∞ averaged 12.2 µg·h/mL while the mean t1/2term was 11 hours. The single administration of 400 mg itraconazole by intake of two 200 mg tablets of new melt extrusion formulation (Hyphanox™) in fed condition was well tolerated, without serious or severe adverse events.

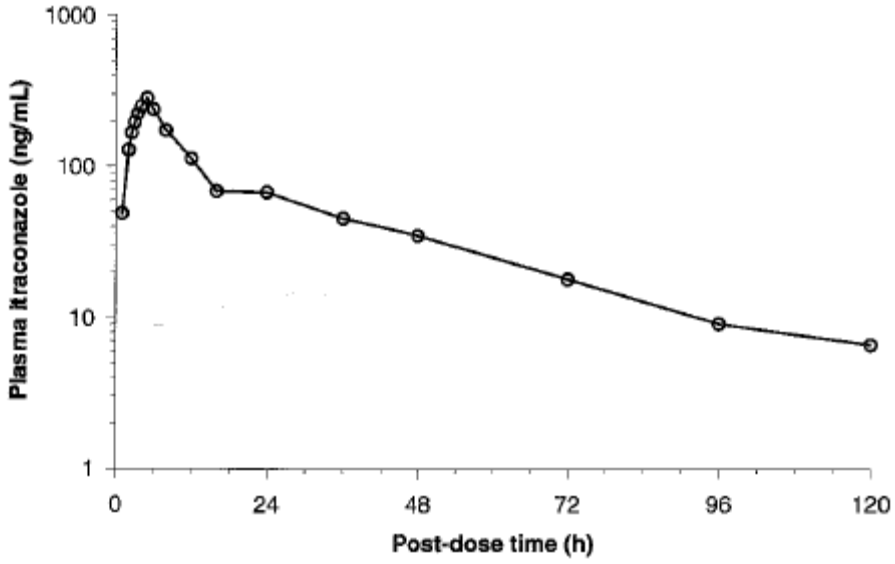



Figure 14.2.1: Mean plasma itraconazole concentration versus time curves

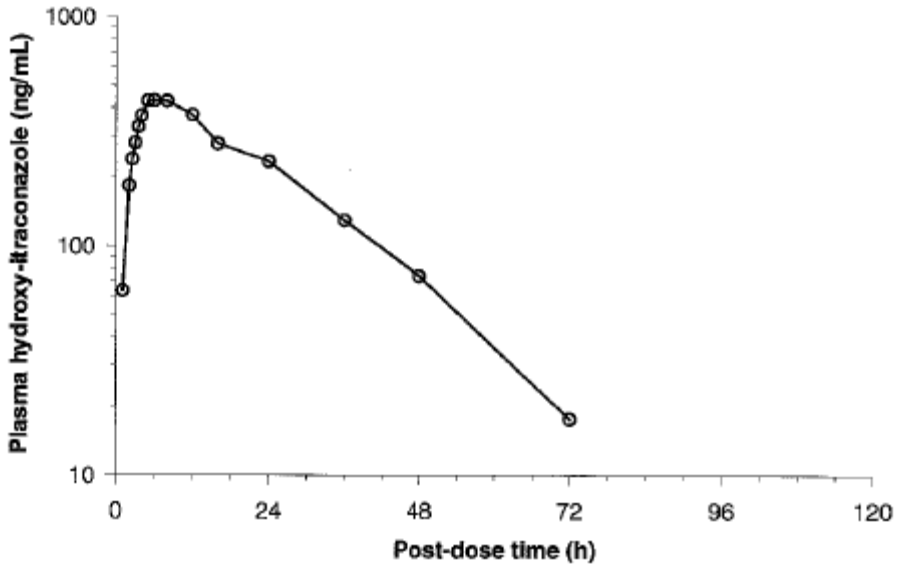



Figure 14.2.3: Mean plasma hydroxy-itraconazole concentration versus time curves

**Study BT0300-108-USA**

**Study title**

Assessment of the Steady State Pharmacokinetics of Itraconazole and Hydroxy-Itraconazole in Healthy Subjects after Administration of a New Itraconazole 200 mg Film Coated Tablet Once Daily for Fourteen Days in Fed Condition

**Principal investigator**
Benno G. Roesch, MD, Advanced Biomedical Research, Inc. (ABR)

**Study Center**
Advanced Biomedical Research, Inc., Clinical Research Center, 241 Main Street, Hackensack, New Jersey 07601, USA

**Phase of development**: Phase 1

**Objectives**:
To document the steady state pharmacokinetics and safety of a new itraconazole 200 mg film coated tablet

**Methodology:**
Open-label, one-arm, single-center multiple oral dose study. There were 2 phases to the study: a 21-day screening period followed by a 24-day study period. Up to 16 healthy eligible subjects (8 male and 8 female) were to receive single daily doses of study drug for 14 consecutive days, followed by a 10-day follow-up period for collection of blood samples for pharmacokinetic (PK) analysis. All breakfasts were to be served at approximately 0730 h and all doses were to be administered at approximately 0800 h. Breakfasts consisted of approximately 500 calories total, with approximately 30%, 20% and 50% calories from fat, protein and carbohydrates, respectively. Blood samples for measurement of plasma itraconazole and hydroxy-itraconazole concentrations were collected on Days 1 and 14 at time 0 (pre-dose) and at 1, 2, 3, 4, 5, 6, 8, 12, 16 and 24 hours post-dose; predose on Days 2 (same as Day 1, 24 h post-dose sample), 4, 7, 10, 12 and 13; and on Days 16, 17, 18, 20, 22 and 24 for the 48, 72, 96, 144, 192 and 240 hour post-dose blood samples, respectively. All females had a
serum or urine pregnancy test at screening, Day -1, Day 15 and Day 24. Adverse event (AE) and concomitant medication information was collected by questioning subjects and spontaneous reporting by the subjects throughout the study.

**Number of subjects:**
16 healthy (8 male and 8 female) subjects

**Major criteria for Inclusion**
Healthy adult males or females between the ages 18 and 55 years, inclusive with a body mass index (BMI) of 18.0 to 28.0 kg/m2, inclusive. Females had to be non-pregnant, non-lactating and willing to practice adequate contraception if of child-bearing potential.

**Duration of Treatment**
This study included a screening visit within 21 days prior to study drug administration, a 14-day treatment period and a 10-day follow-up period for collection of PK samples. The study duration was 45 days.

**Criteria for Evaluation**

The pharmacokinetic profiles of itraconazole and hydroxy-itraconazole were evaluated by the individual plasma concentrations and pharmacokinetic parameters following a single oral dose and following 14 consecutive oral doses of study drug. Safety evaluations included assessment of AEs, physical examination findings, vital signs, clinical laboratory test results and resting 12-lead ECG evaluations.

**Results**

Sixteen healthy subjects (8 male, 8 female) received study drug and 16 (100%) subjects completed the study as planned.

Demographics: Subjects were representative of a healthy adult male and female population, ranging from 23 - 53 years of age. Mean (SD) age was 36.3 (9.62) years and mean (SD) BMI was 24.0 (2.44) kg/m2. The overall racial distribution in descending order was 12 (75%) Caucasian, 2 (12.5%) Black and 2 (12.5%) Asian.

Pharmacokinetic Results: Summary statistics of pharmacokinetics parameters for all dosed subjects are displayed below:

| | | | Analyte | |
|---|---|---|---|---|
| **Parameter** (units) | Statistic | Day | Itraconazole N=16 | OH-itraconazole N=16 |
| $C_{max}$ (ng/mL) | Mean (SD) | 1 | 116.8 (43.34) | 221.7 (69.21) |
| | | 14 | 658.1 (362.16) | 974.2 (479.92) |
| $AUC_{0-24}$ (ng*h/mL) | Mean (SD) | 1 | 905.09 (384.239) | 2538.33 (1057.872) |
| | | 14 | 9046.81 (5320.516) | 19054.95 (10443.214) |
| $t_{max}$ (h) | Median (Range) | 1 | 4.00 (2.00-5.00) | 4.00 (2.00-5.00) |
| | | 14 | 4.00 (1.00-24.00) | 4.00 (3.00-24.00) |
| $t_{1/2}$ (h) | Mean (SD) | 14 | 36.84 (10.378) | 20.06 (6.998) |
| $C_{min}$ (ng/mL) | Mean (SD) | 14 | 262.1 (151.86) | 693.1 (431.38) |
| $C_{ss,avg}$ (ng/mL) | Mean (SD) | 14 | 377.0 (221.69) | 794.0 (435.13) |
| **Accumulation Ratio*** | Mean (SD) | 14 | 10.51 (5.510) | 8.20 (4.646) |
| **AUC ratio**** | Mean (SD) | 1 | 2.83 (0.513) | |
| | | 14 | 2.22 (0.420) | |

OH-itraconazole: hydroxy-itraconazole
*Accumulation Ratio is defined as $AUC_{0-24}$ (Day 14) /$AUC_{0-24}$ (Day 1)
**AUC ratio is ratio of $AUC_{0-24}$ of hydroxy-itraconazole/itraconazole

Mean (SD) $C_{max}$ of itraconazole and hydroxy-itraconazole on Day 1 was 116.8 (43.34) and 221.7 (69.21) ng/mL, respectively, and mean (SD) $C_{max}$ of itraconazole and hydroxyitraconazole on Day 14 was 658.1 (362.16) and 974.2 (479.92) ng/mL, respectively. Mean maximum plasma levels of itraconazole and hydroxy-itraconazole increased from Day 1 to Day 14 by approximately 6- and 4-fold, respectively.

Mean (SD) $AUC_{0-24}$ of itraconazole and hydroxy-itraconazole on Day 1 was 905.09 (384.239) and 2538.33 (1057.872) ng*h/mL, respectively, and mean (SD) $AUC_{0-24}$ of itraconazole and hydroxyitraconazole on Day 14 was 9046.81 (5320.516) and 19054.95 (10443.214) ng*h/mL, respectively. The mean (SD) accumulation ratio ($AUC_{0-24}$ Day 14/$AUC_{0-24}$ Day 1) of itraconazole and hydroxy-itraconazole was 10.51 (5.510) and 8.20 (4.646), respectively.

Overall, intersubject variability was relatively high. Coefficient of variation (CV) for both analytes ranged from 31 to 55% for $C_{max}$ and 42 to 59% for $AUC_{0-24}$.

Visual inspection of the data revealed that plasma concentration versus time profiles for two subjects were different from other subjects in this study, and Day 14 plasma levels of itraconazole and hydroxyitraconazole, and associated PK parameters were comparatively low for these two subjects. These data were consistent with an interpretation that little-to-no study drug was absorbed during the Day 7 or Day 10 to Day 14 period. Summary pharmacokinetic data that excluded data from these two subjects (PK population) was therefore generated. Mean Cmax, AUC0-24 and CSS(avg) were higher (approximately 12%) at steady-state (Day 14) in the PK population compared to all dosed subjects. No apparent changes were noted in tmax or t½ in the PK population versus all dosed subjects. Intersubject variability in the PK population was somewhat reduced compared to all dosed subjects, but was still relatively high. CV for both analytes ranged from 33 to 41% for Cmax and from 41 to 46% for AUC0-24.

Figure 14.2.5
Mean (SD) plasma itraconazole and hydroxy-itraconazole concentrations versus time:
Day 1 through Day 24 (linear scale)
All dosed subjects

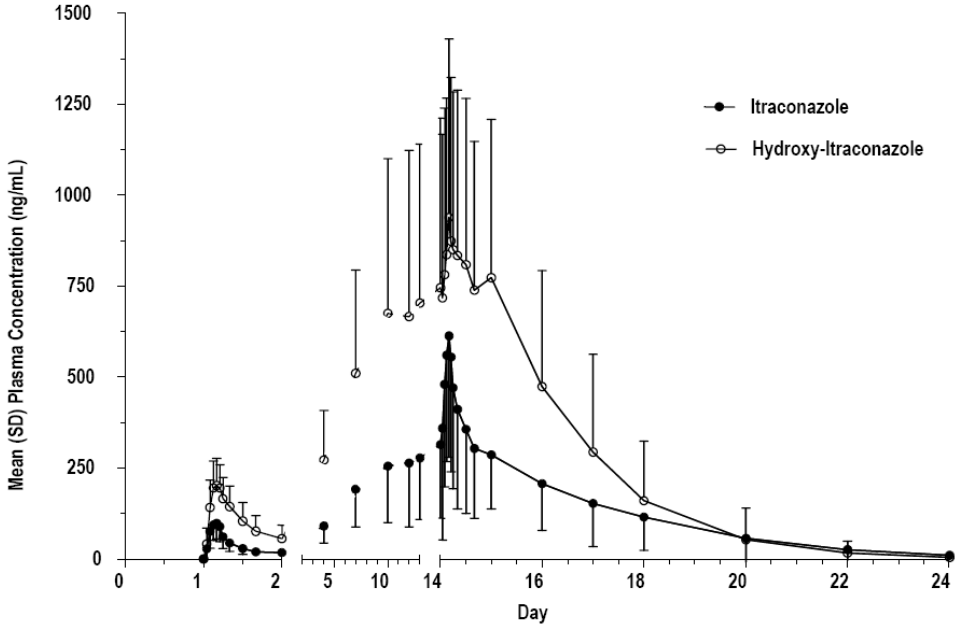
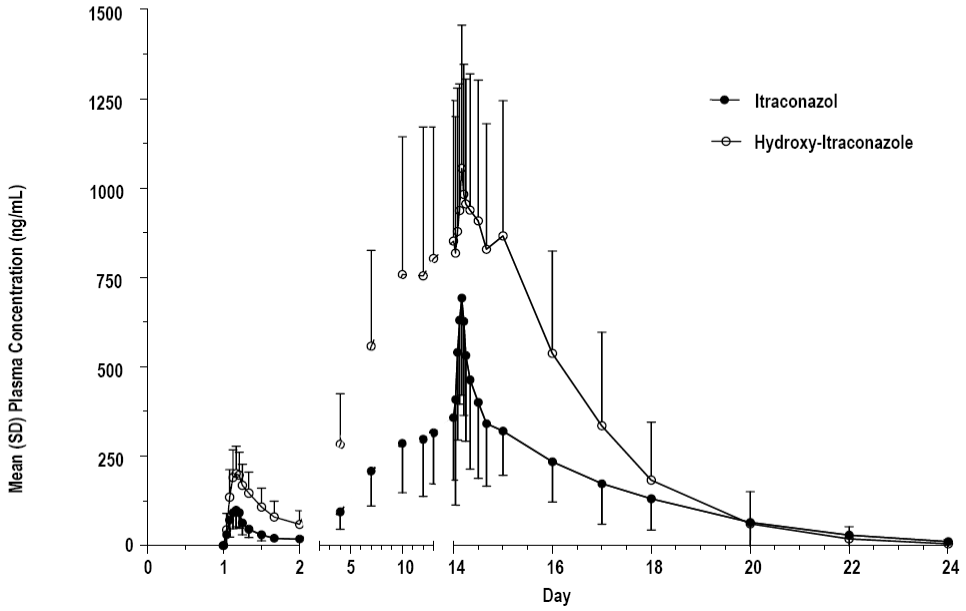


Figure 14.2.5a
Mean (SD) plasma itraconazole and hydroxy-itraconazole concentrations versus time:
Day 1 through Day 24 (linear scale)
PK population




Safety Results: Fourteen consecutive oral doses of a new itraconazole 200 mg film coated tablet administered under fed condition were safe and well-tolerated. Five (31.3%) subjects reported at least one treatment-emergent adverse event. All AEs were considered mild in severity, and either possibly related or unrelated to study drug. All AEs resolved without intervention. No subjects discontinued study drug due to an AE and no severe or serious AEs were reported. Following dosing, there were no clinically meaningful or significant trends or changes in clinical laboratory parameters, vital signs or ECG evaluation results.

**Conclusions**

Fourteen consecutive oral doses of a new itraconazole 200 mg film coated tablet administered under fed condition were safe and well-tolerated. For all dosed subjects, mean maximum plasma levels of itraconazole and hydroxy-itraconazole increased from Day 1 to Day 14 by approximately 6- and 4-fold, respectively. Mean (SD) accumulation ratio (AUC0-24 Day 14 /AUC0-24 Day 1) of itraconazole and hydroxy-itraconazole was 10.51 (5.510) and 8.20 (4.646), respectively. At steady-state (Day 14), mean (SD) Cmax of itraconazole and hydroxy-itraconazole was 658.1 (362.16) and 974.2 (479.92) ng/mL, respectively, and mean (SD) AUC0-24 of itraconazole and hydroxy-itraconazole was 9046.81 (5320.516) and 19054.95 (10443.214) ng*h/mL, respectively. Median time to Cmax (tmax) for itraconazole and hydroxy-itraconazole was 4 hours. Mean (SD) plasma half-life (t½) of itraconazole and hydroxy-itraconazole on Day 14 was 36.84 (10.378) and 20.06 (6.998) hours, respectively. Overall, intersubject variability was relatively high. Coefficient of variation (CV) for both analytes ranged from 31 to 55% for Cmax and from 42 to 59% for AUC0-24.

**Study BT0300-BEL-001**

**Title of Study**
A four period open-label randomized cross-over pilot trial to assess the bioequivalence of three batches of a 200-mg itraconazole tablet formulation (001, 002 and 003) as compared with the 100-mg itraconazole capsule SporanoxTM given at a single dose of 200 mg in 13 healthy subjects. Itraconazole was administered immediately after a standard breakfast.

**Development Phase**: Phase I

**Principal Investigator**: Dr. S. Ramael, SGS Biopharma S.A. Research Unit, Stuivenberg Lange Beeldekensstraat 267 B-2060 Antwerpen, Belgium

**Methodology**
Open, randomised, 4-way cross-over, single oral-dose study, with 7-day wash-out periods in 12 healthy subjects after a standardised breakfast.

**Number of subjects**
13 randomized, 13 included (6 males, 7 females), 11 completed (6 males, 5 females), 13 analyzed.

**Main criteria for inclusion**
Healthy male and female subjects, aged 18-55 years inclusive.

**Duration of treatment**
Four study periods of 36 hours clinical residency with returns to the clinical centre for the 36h, 48h, 72h and 96h blood samples, separated by 7-day wash-out periods, single dose administration on each period.

Treatment A: single oral dose of 2 itraconazole 100-mg capsules
Treatment B: single oral dose of 1 itraconazole 200-mg film-coated tablet (batch no. 001)
Treatment C: single oral dose of 1 itraconazole 200-mg film-coated tablet (batch no. 002)
Treatment D: single oral dose of 1 itraconazole 200-mg film-coated tablet (batch no. 003)

| Sequence | **Period 1** Day 1 | **Period 2** Day 8 | **Period 3** Day 15 | **Period 4** Day 22 |
|---|---|---|---|---|
| 1 | Treatment A | Treatment D | Treatment B | Treatment C |
| 2 | Treatment D | Treatment C | Treatment A | Treatment B |
| 3 | Treatment C | Treatment B | Treatment D | Treatment A |
| 4 | Treatment B | Treatment A | Treatment C | Treatment D |

Pharmacokinetic parameters including Tmax, Cmax, AUCt, AUC∞, t1/2 were estimated using non-compartmental methods and the results are presented as the mean ± SD below.

**Results**

Cmax and AUC of all 3 batches of the itraconazole 200-mg tablet were lower than for the itraconazole capsule. Based on the 90% confidence intervals, none of the 3 batches were within the 80-125% bioequivalence limits compared to two 100-mg capsules of itraconazole. Only batch 002 resulted in the test/reference mean ratios above 80% for both Cmax and AUC. Therefore, batch 002 was selected for further optimization of the production process. Tablets produced by this optimized process are intended for further clinical development.

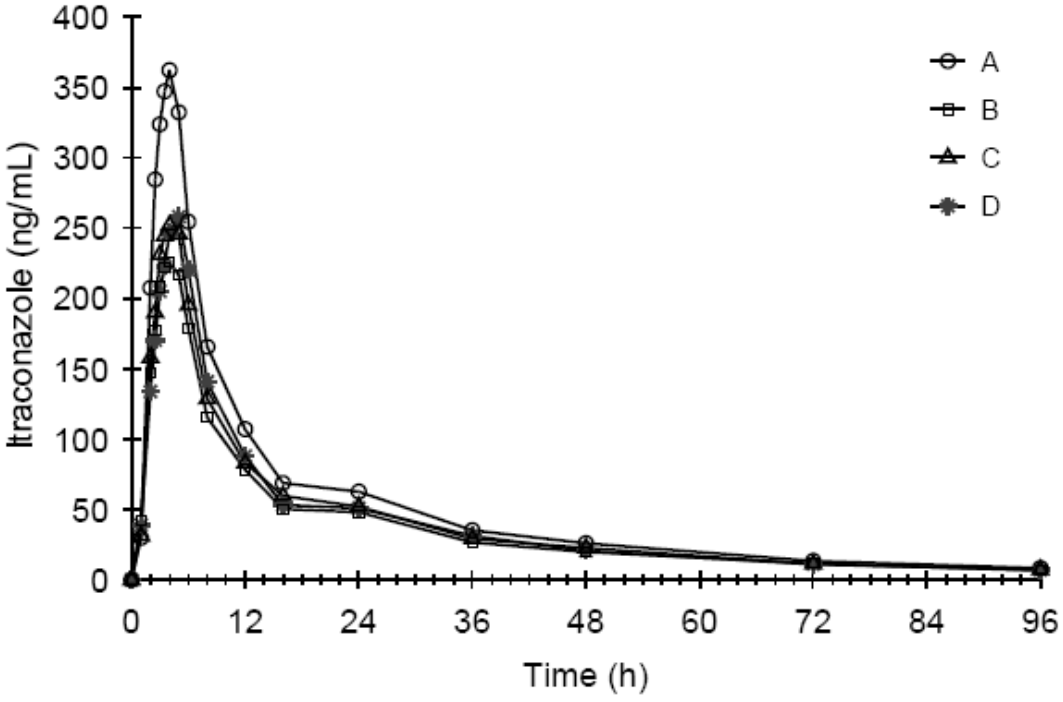


**Table 3: Pharmacokinetic Parameters of Itraconazole and Hydroxy-itraconazole and Summary of the Equivalence Analysis after Single Oral Doses of 200 mg Itraconazole Administered Following a Controlled (Standard) Breakfast to Healthy Subjects**

| Parameter | | Itraconazole 200-mg film-coated tablet Batch 001 1 x 200 mg Mean ± STD (n = 11) | Itraconazole 200-mg film-coated tablet Batch 002 1 x 200 mg Mean ± STD (n = 11) | Itraconazole 200-mg film-coated tablet Batch 003 1 x 200 mg Mean ± STD (n = 13) | Itraconazole 100-mg capsule 2 x 100 mg Mean ± STD (n = 13) |
|---|---|---|---|---|---|
| **Itraconazole** | | | | | |
| $T_{max}$ | (h) | 4.0 (3.5-6.0)[a] | 4.0 (2.5-5.0)[a] | 5.0 (3.0-5.0)[a] | 3.5 (2.0-5.0)[a] |
| $C_{max}$ | (ng/mL) | 252±123 | 297±81 | 291±159 | 416±196 |
| $AUC_t$ | (µg·h/mL) | 3.58±1.99 | 3.92±1.70 | 3.90±2.26 | 4.92±2.22 |
| $AUC_\infty$ | (µg·h/mL) | 3.99±2.52 | 4.26±2.06 | 4.41±3.26 | 5.34±2.66 |
| $t_{1/2term}$ | (h) | 29.7±14.2 | 28.2±9.0 | 28.9±15.6 | 26.7±10.9 |
| **Hydroxy-itraconazole** | | | | | |
| $T_{max}$ | (h) | 5.0 (4.0-6.0)[a] | 5.0 (3.0-6.0)[a] | 5.0 (3.5-5.0)[a] | 5.0 (3.0-6.0)[a] |
| $C_{max}$ | (ng/mL) | 400±107 | 444±76 | 485±220 | 614±280 |
| $AUC_t$ | (µg·h/mL) | 8.15±4.44 | 8.85±4.32 | 9.15±5.04 | 11.7±5.9 |
| $AUC_\infty$ | (µg·h/mL) | 8.44±4.62 | 9.05±4.42 | 9.40±5.15 | 12.0±6.0 |
| $t_{1/2term}$ | (h) | 10.5±4.4 | 10.3±4.1 | 10.3±3.0 | 10.4±3.3 |

| | Geometric Mean Ratio (%) and Associated 90% Confidence Interval | | |
|---|---|---|---|
| | Batch 001/Capsules | Batch 002/Capsules | Batch 003/Capsules |
| **Itraconazole** | | | |
| $T_{max}$ | 0.25 (-0.75-1.25)[b] | 0.13 (-0.25-0.75)[b] | 0.75 (0.01-1.50)[b] |
| $C_{max}$ | 66.0 (52.2-83.4) | 82.4 (65.2-104.1) | 69.4 (55.7-86.4) |
| $AUC_t$ | 73.5 (58.7-92.0) | 84.3 (67.3-105.6) | 76.9 (62.3-95.0) |
| $AUC_\infty$ | 73.8 (58.7-92.8) | 83.3 (66.3-104.7) | 77.6 (62.6-96.2) |
| **Hydroxy-itraconazole** | | | |
| $T_{max}$ | 0.00 (-1.00-0.50)[b] | -0.34 (-0.75-0.00)[b] | -0.49 (-0.50-0.01)[b] |
| $C_{max}$ | 76.3 (63.0-92.3) | 86.4 (71.4-104.6) | 81.7 (68.3-97.7) |
| $AUC_t$ | 72.1 (57.2-90.9) | 80.7 (64.1-101.8) | 78.3 (63.0-97.3) |
| $AUC_\infty$ | 72.4 (57.5-91.1) | 80.4 (63.8-101.2) | 78.5 (63.2-97.4) |

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22484 | ORIG-1 | STIEFEL LABORATORIES INC | HYPHANOX 200MG FILM-COATED TABLETS |

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

SEONGEUN CHO
11/10/2009

EDWARD D BASHAW
11/13/2009

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

# Office of Clinical Pharmacology

## *New Drug Application Filing and Review Form*

***General Information About the Submission***

| | Information | | Information |
|---|---|---|---|
| **NDA/BLA Number** | **22-484** | **Brand Name** | **Hyphanox** |
| **OCP Division (I, II, III, IV, V)** | **III** | **Generic Name** | **Itraconazole** |
| **Medical Division** | **Derm** | **Drug Class** | **Triazol anti-fungal** |
| **OCP Reviewer** | **Julia Cho** | **Indication(s)** | **Onychomycosis** |
| **OCP Team Leader** | **Dennis Bashaw** | **Dosage Form** | **Film-coated tablet** |
| **Pharmacometrics Reviewer** | | **Dosing Regimen** | **Once daily** |
| **Date of Submission** | **03/31/09** | **Route of Administration** | **Oral** |
| **Estimated Due Date of OCP Review** | **11/30/09** | **Sponsor** | **Stiefel Laboratories** |
| **Medical Division Due Date** | **11/30/09** | **Priority Classification** | **Standard** |
| **PDUFA Due Date** | **01/31/10** | | |

### *Clin. Pharm. and Biopharm. Information*

| | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any |
|---|---|---|---|---|
| **STUDY TYPE** | | | | |
| **Table of Contents present and sufficient to locate reports, tables, data, etc.** | **X** | | | |
| **Tabular Listing of All Human Studies** | **X** | | | |
| **HPK Summary** | **X** | | | |
| **Labeling** | **X** | | | |
| **Reference Bioanalytical and Analytical Methods** | | | | |
| **I. Clinical Pharmacology** | | | | |
| **Mass balance:** | | | | |
| **Isozyme characterization:** | | | | |
| **Blood/plasma ratio:** | | | | |
| **Plasma protein binding:** | | | | |
| **Pharmacokinetics (e.g., Phase I) -** | | | | |
| **Healthy Volunteers-** | | | | |
| single dose: | **X** | **1** | **1** | |
| multiple dose: | **X** | **1** | **1** | |
| **Patients-** | | | | |
| single dose: | | | | |
| multiple dose: | | | | |
| **Dose proportionality -** | | | | |
| fasting / non-fasting single dose: | | | | |
| fasting / non-fasting multiple dose: | | | | |
| **Drug-drug interaction studies -** | | | | |
| In-vivo effects on primary drug: | | | | |
| In-vivo effects of primary drug: | | | | |
| In-vitro: | | | | |
| **Subpopulation studies -** | | | | |
| ethnicity: | | | | |
| gender: | | | | |
| pediatrics: | | | | |
| geriatrics: | | | | |

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

| | | | | |
|---|---|---|---|---|
| renal impairment: | | | | |
| hepatic impairment: | | | | |
| **PD -** | | | | |
| Phase 2: | | | | |
| Phase 3: | | | | |
| **PK/PD -** | | | | |
| Phase 1 and/or 2, proof of concept: | | | | |
| Phase 3 clinical trial: | | | | |
| **Population Analyses -** | | | | |
| Data rich: | | | | |
| Data sparse: | | | | |
| **II. Biopharmaceutics** | | | | |
| **Absolute bioavailability** | | | | |
| **Relative bioavailability -** | | | | |
| solution as reference: | | | | |
| alternate formulation as reference: | **X** | **1** | **1** | |
| **Bioequivalence studies -** | | | | |
| traditional design; single / multi dose: | **X** | **2** | **2** | |
| replicate design; single / multi dose: | | | | |
| **Food-drug interaction studies** | | | | |
| **Bio-waiver request based on BCS** | | | | |
| **BCS class** | | | | |
| **Dissolution study to evaluate alcohol induced dose-dumping** | | | | |
| **III. Other CPB Studies** | | | | |
| **Genotype/phenotype studies** | | | | |
| **Chronopharmacokinetics** | | | | |
| **Pediatric development plan** | | | | |
| **Literature References** | | | | |
| **Total Number of Studies** | | **5** | **5** | |
| | | | | |

On **initial** review of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | N/A | Comment |
|---|---|---|---|---|---|
| **Criteria for Refusal to File (RTF)** | | | | | |
| 1 | Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials? | x | | | |
| 2 | Has the applicant provided metabolism and drug-drug interaction information? | | **X** | | Refer to Sporanox label |
| 3 | Has the sponsor submitted bioavailability data satisfying the CFR requirements? | **X** | | | |
| 4 | Did the sponsor submit data to allow the evaluation of the validity of the analytical assay? | | x | | Cross-validation study report between HLPC-UV and HPLC MS/MS not provided |
| 5 | Has a rationale for dose selection been submitted? | | **X** | | |
| 6 | Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin? | **X** | | | |
| 7 | Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin? | **X** | | | |
| 8 | Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work? | **X** | | | |

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

| | | | | | |
|---|---|---|---|---|---|
| **Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)** | | | | | |
| | **Data** | | | | |
| 9 | Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)? | x | | | |
| 10 | If applicable, are the pharmacogenomic data sets submitted in the appropriate format? | | | N/A | |
| | **Studies and Analyses** | | | | |
| 11 | Is the appropriate pharmacokinetic information submitted? | x | | | |
| 12 | Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)? | | x | | |
| 13 | Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance? | | x | | |
| 14 | Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics? | | x | | |
| 15 | Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective? | | | x | |
| 16 | Did the applicant submit all the pediatric exclusivity data, as described in the WR? | | x | | A waiver from pediatric study in children below the age of 12 is being requested |
| 17 | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label? | x | | | |
| | **General** | | | | |
| 18 | Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? | x | | | |
| 19 | Was the translation (of study reports or other study information) from another language needed and provided in this submission? | | x | | |

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? __ __yes____**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- A study report documenting cross-validation of two analytical methods (HLPC-UV and HPLC MS/MS) was not provided. The referenced document, BTM-1054-R0, is regarding a method development for HPLC/MS/MS. Please submit the cross-validation analytical study report.

Seongeun Julia Cho

Reviewing Clinical Pharmacologist Date

E. Dennis Bashaw

Team Leader/Supervisor Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/
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Seongeun Cho
6/4/2009 11:08:51 AM
BIOPHARMACEUTICS

Dennis Bashaw
6/4/2009 05:52:38 PM
BIOPHARMACEUTICS