

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-630

MEDICAL REVIEW

Medical Officer's Review

NDA	21-630 (Voriconazole Powder for Oral Suspension)
Submitted	14 March, 2003
Review completed	12 December, 2003
Action Date	19 December, 2003
Action Due Date	17 January, 2004
Drug name	Voriconazole
Generic name	Voriconazole
Trade name	VFEND®
Chemical name	(2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1H-1,2,4-triazol-1-yl)2-butanol
Sponsor	Pfizer Inc. 50 Pequot Avenue New London CT 06320
Pharmacologic Category	Antifungal agent
Proposed Form	Powder for Oral Suspension
Dosage Form(s)	40 mg/ml reconstituted suspension 50 and 200 mg tablets 200 mg /30 ml vial for intravenous infusion
Related NDA	21-266 (tablet) and 21-267 (for injection)
Related Reviews	Biopharmaceutics

This Medical Officer (MO) labeling review provides comments and recommendations to the Division Director related to NDA 21-630 VFEND® (voriconazole) for Oral Suspension. NDA 21-630 contains primarily Chemistry and Biopharmaceutics studies designed to investigate the comparability of voriconazole tablet form to the proposed oral suspension. There were no new efficacy or clinical safety issues identified in this review. The MO recommends **approval** of VFEND® (voriconazole) Oral Suspension. For details please review the Biopharmaceutics Review by Dr. Gerlie De Los Reyes.

Clinical Background

VFEND® (voriconazole) is a triazole antifungal agent. VFEND® (voriconazole) was approved by the FDA for marketing in the United States in May 24, 2002 under NDA 21-266 (oral tablets) & NDA 21-267 (intravenous injection) for therapy of patients (≥ 12 years), with aspergillosis (primary therapy or refractory/intolerant to other antifungal agents), *Fusarium* species, and *Scedosporium apiospermum* in patients intolerant or refractory to other antifungal treatment.

Due to the lack of an oral voriconazole suspension for pediatric or adult patients with fungal infections who are unable to swallow voriconazole tablets, the Applicant developed a new oral suspension formulation of voriconazole. In this submission, the Applicant is seeking approval for a new formulation of voriconazole (an oral suspension).

The Medical Officer acknowledges receipt of NDA 21-630 in electronic format. NDA 21-630 includes three pharmacokinetic studies designed to investigate the pharmacokinetic profile of the proposed oral suspension form to voriconazole tablet form, these three studies are briefly reviewed below:

Safety: A total of eighty eight healthy volunteer subjects (77 males, 11 females; age ranged from 18-43 years) were enrolled in three pharmacokinetic studies (tables below).

Seven subjects were discontinued from the studies (one subject experienced extrasystoles, one subject had an increased ALT, the other 5 subjects were discontinued unrelated to an adverse event (AE)). Visual AEs were common in the 3 studies (rates in the tables below).

MO Comment: *The rate of visual AEs after voriconazole administration is ~30% in the approved label, therefore the reported visual AEs rate in the 3 studies is comparable to what has been reported previously.*

MO Comment: *The MO reviewed the Clinical Report Forms in study A150-1019 for patients #0005, 0009, 0013, 0019, 0021, 0023, 0025; and from study 150-1028 patients #0007, 0018, 0034, 0042. The majority of these patients experienced a visual AE, which resolved after voriconazole was discontinued.*

Study-150-248 Open, Randomized, Two-Way Crossover, 7-day Washout POS Research Formulation vs. Tablet (Voriconazole) (14 healthy male adults)			
	POS research formulation		Tablet
Total AEs (N)	11	20 events	13 21 events
Abnormal vision (N, %)	8	(57%)	11 (79%)
Photophobia (N, %)	4	(29%)	6 (43%)
Headache (N, %)	2	(14%)	0
Serious AE	None		None
Laboratory	↑ pH urine 1 ↑ CPK/AST/ALT (exercise) 1		blood in urine 2

POS = voriconazole powder oral suspension
The only AE reported in >1 pt was abnormal vision & photophobia
Abnormal vision experienced by 14 pts. 5 pts experienced abnormal vision in both Rx periods

Pivotal Study-150-1028 Open, Randomized, Three-Way, Crossover, 7-day Washout POS Commercial Formulation Batch 1 & 2 vs. Tablet (Voriconazole) 48 subjects randomized, 42 subjects completed all three dosing periods			
	POS Batch 1 43 subjects	POS Batch 2 44 subjects	Tablet 45 subjects
Total AEs	31 54 events	30 59 events	31 76 events
Abnormal vision (N, %)	5 (12%)	5 (11%)	12 (27%)
Photophobia (N, %)	8 (19%)	13 (30%)	15 (33%)
Headache			
Severe AE 4 subjects		Abnormal vision 1 Cheilitis & hemorrhage 1	photophobia 1 Abnormal dreams 1
Serious AE	None		None
Total visual abnormal	1/3 subjects	1/3 subjects	1/3 subjects
Discontinued subjects	[5 D/Cs: 2 unwilling to participate 1 left the country 2 (+) drug screen]		↑ ALT after 5 days, was normal at baseline (mild) 1 subject
Laboratory	↑ K 1 ↑ basophiles 1 ↑ eosinophiles 1	blood in urine 1 ↑ K 1 ↑ eosinophiles 1	blood in urine 2 ↑ K 2

D/C = discontinued study;
The only AE reported in >1 pt was abnormal vision & photophobia
Batch 1 & 2 differed only in particle size of the ingoing drug substance for manufacture
POS = voriconazole powder oral suspension

Study A150-1019 Open, Randomized, Three-Way, Crossover, 7-day Washout POS Multidose Commercial Formulation (Fed & Fasting) vs. Tablet			
	POS Fasted 25 subjects	POS Fed 26 subjects	Tablet (Fasted) 25 subjects
Total AEs (subjects, events)	23 86 events	22 73 events	21 70 events
Total AEs/subject	3.7	3.3	3.3
Abnormal vision (N, %)	11 (44%)	7 (27%)	9 (36%)
All visual AEs	11 subjects	8	12
Severe AEs (6 subjects)	Abnormal dream 1 Abnormal vision 1	headache 1 extrasystole (D/C) 1	headache 1 anxiety 1
Serious AE		24 ♀ with extrasystoles was D/C from study	
Labs	↓ MCV 1 ↓ K 1 blood in urine 5 ↓ protein/albumin/Ca 1	blood in urine 1 ↑ GGTP 1 ↓ K 1 ↓ MCV/GTTP 1	blood in urine 2 ↓ MCV/↑ GGTP 1

AEs higher in initial FASTING phase
POS = voriconazole powder oral suspension

There were no new efficacy or clinical safety issues for NDA 21-630. The reader is referred to the Biopharmaceutics Review by Dr. Gerlie De Los Reyes for details. In brief, Dr. Gerlie De Los Reyes reports:

"Two batches of the 'proposed commercial' POS formulation manufactured on a commercially representative scale, were shown to be bioequivalent to the commercial tablet in Study A1501028. Bioequivalence was also previously demonstrated between the 'research' POS and commercial tablet in Study 150-248. However, for the 'improved' or the 'initial multi-dose' POS formulation, the upper bound of the 90% CI for the C_{max} ratio versus the commercial tablet was outside of the acceptance criteria in Study A1501019. Bioequivalence was demonstrated amongst female subjects for both AUC_{fn} and C_{max} , and amongst male subjects for AUC_{fn} but not C_{max} . This 'improved' or initial multi-dose' POS formulation was used in the food effect study."

MO Comment: *Dr. De Los Reyes reported that the voriconazole (POS) submission was acceptable from a Clinical Pharmacology and Biopharmaceutics standpoint provided the Applicant implement labeling and Phase IV study recommendations as outlined in the labeling review of this Review and in the recommendations section.*

Severe AEs: As observed from the tables above, 6 patients were reported to have severe AEs in study A150-1019, and 4 patients from study 150-1028. These AEs are comparable to those observed in patients receiving voriconazole. Patient#2054_0019 from study 150-1019 developed palpitations (EKG: extrasystoles with periods of bigeminy), which resolved after voriconazole administration was discontinued. Heart rhythm disturbances such as extrasystole is described in the product label.

Dr. De Los Reyes, noted in her review that of the 11 women enrolled in Study-150-1019, 7 women were on oral contraceptives as concomitant medications. Oral contraceptives may decrease the hepatic metabolism of various drugs (tricyclic antidepressants, beta blockers, caffeine, corticosteroids, theophyllines) resulting in potential toxicity. In the Biopharmaceutics Review (study A150-1019), Dr. De Los Reyes reports:

"In vitro studies with human microsomes that were reviewed with the original voriconazole NDA showed that ethinyl estradiol had the potential to inhibit voriconazole metabolism ($IC_{50} = 19 \mu M$). Relative to the rest of the females listed in Table 6, Patient 21 (who was not taking OCs concurrently with voriconazole) had lower voriconazole AUC and C_{min} , following tablet and POS dosing. That the concurrent use of OCs by some of the female subjects of this study contributed to higher voriconazole exposures can not be ruled out at this time and may need to be further evaluated. " " Following both commercial tablet and the POS dosing, females had 1.5-fold higher mean voriconazole AUC, 2-fold higher C_{min} , and reported at least a 2-fold higher adverse event frequency, compared to males receiving the same dosage of the drug. These results show that there were intrinsic/extrinsic factors distinct to females enrolled in the study that increased their exposure to voriconazole and thus made them more susceptible to adverse effects associated with the drug. "

MO Comment: *Because of the increased exposure to voriconazole in women compared to men (study A1501019), the Biopharmaceutics Reviewer recommends the following phase IV study: "A two-way drug interaction study between voriconazole and oral contraceptives containing ethinyl estradiol in younger women (18-45 years).*

Label Review: (Unmarked text is Applicant submission, Agency recommendations are highlighted in yellow marker, and deletions use strikethrough black line). [Text in Times New Roman was copied verbatim from the proposed label.]

Clinical Pharmacology Section

Absorption

The pharmacokinetic properties of voriconazole are similar following administration by the intravenous and oral routes. Based on a population pharmacokinetic analysis of pooled data in healthy subjects (N=207), the oral bioavailability of voriconazole is estimated to be 96% (CV 13%). Bioequivalence was established between the 200mg tablet and the 40mg/ml oral suspension when administered as a 400mg BID loading dose followed by a 200mg — BID maintenance dose.

MO Comment: *The purpose of the addition is to reflect the dosage used in the actual studies to determine absorption after administering voriconazole.*

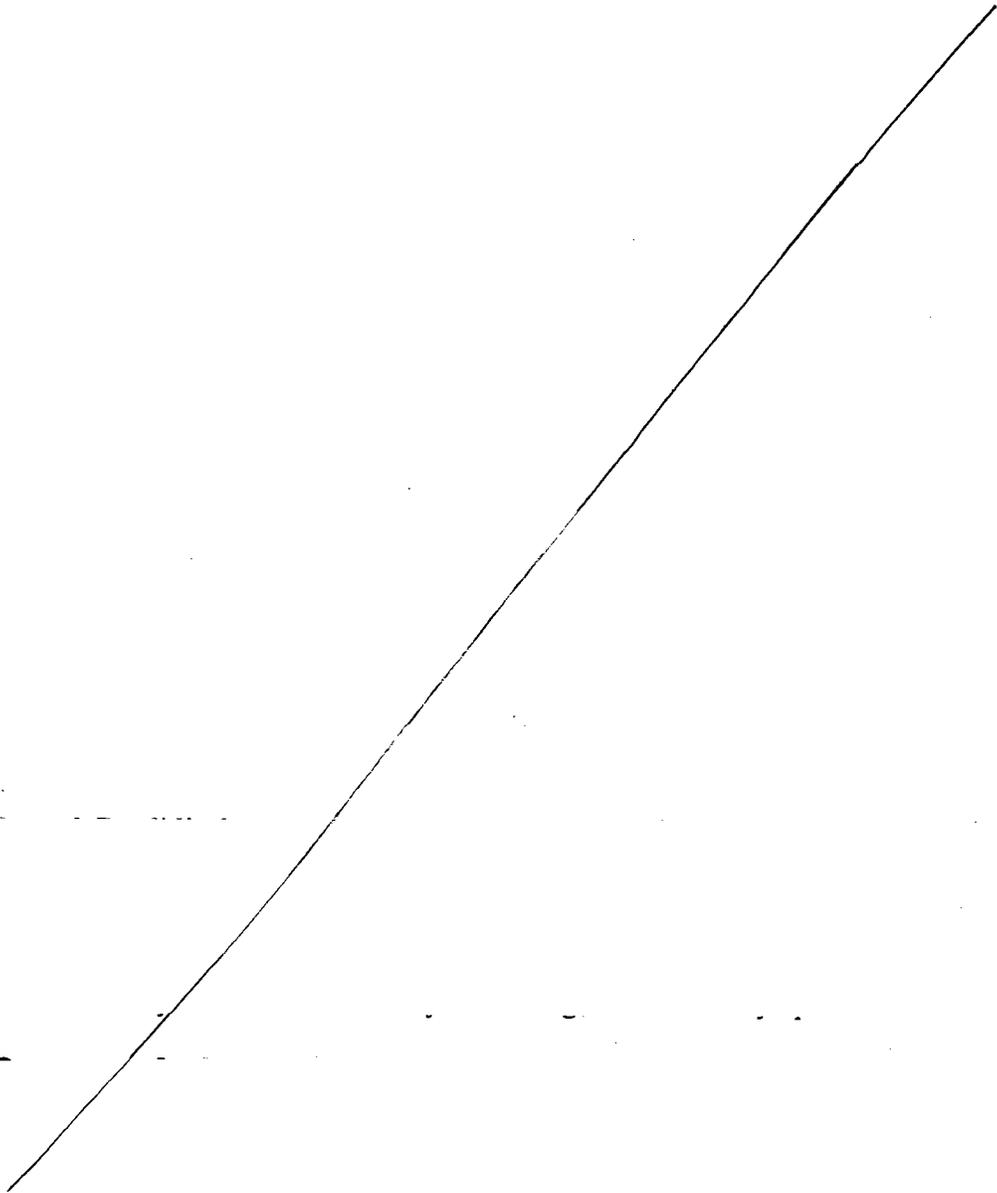
Pharmacokinetics in Special Populations

Gender

In a multiple oral dose study, the mean C_{max} and AUC_{τ} for healthy young females were 83% and 113% higher, respectively, than in healthy young males (18-45 years), after tablet dosing. In the same study, no significant differences in the mean C_{max} and AUC_{τ} were observed between healthy elderly males and healthy elderly females (≥ 65 years). In a similar study, after dosing with the suspension, the mean AUC for healthy young females was 45% higher than in healthy young males whereas the mean C_{max} was comparable between genders. The steady state trough voriconazole concentrations (C_{min}) seen in females were 100% and 91% higher than in males receiving the tablet and the suspension, respectively.

MO Comment: *The purpose of the changes made by the Agency in this section were to describe the expected pharmacokinetic differences between the tablet and the oral suspension when administered to men and women.*





Clinical Section: There were no new clinical label comments in this submission.

Recommendations:

- 1 The MO recommends approval of the new voriconazole oral suspension formulation (reviewed by Dr. Gerlie De Los Reyes, the Biopharmaceutical

Reviewer). This new formulation benefits patients who are unable to swallow the tablet form of voriconazole, and therefore provides a marked improvement in the product.

- 2 Phase IV commitments: The Applicant should conduct a two-way drug interaction study between voriconazole and oral contraceptives containing ethinyl estradiol in younger women (18-45 years). This is especially important given the non-linear pharmacokinetics of voriconazole and the observed *in vitro* liver microsomal interaction between voriconazole and ethinyl estradiol. The Applicant agreed to the commitment at the teleconference on December 16, 2003. Pfizer plans to submit the protocol in March 15, 2004; plans to start the study in April 15, 2004, and to submit the final study report in March 15, 2005.

The significance of this phase IV commitment becomes evident when one considers that the issue of potential voriconazole/oral contraceptive interactions was not as relevant when voriconazole was approved for treatment of invasive aspergillosis, an infection occurring primarily in the severely immunocompromised host. Whereas today, the broadening indications for voriconazole (for example esophageal candidiasis), is expected to result in a much larger population of women of childbearing potential who may use oral contraceptives that may lead to an increased exposure to voriconazole in women on contraceptives, thereby increasing their susceptibility to adverse events.

- 3 Label changes as noted in the review above included Clinical Pharmacology, Incompatibilities, and Dosage & Administration sections. Also, the Applicant agreed to merge the label changes for this NDA with the label changes for NDA 21-466 (Voriconazole for Esophageal Candidiasis) at the teleconference on December 12, 2003. On December 17, 2003 the Applicant agreed to changes requested by the Agency in the Dosage & Administration section of the label. The Applicant submitted these labeling changes on December 19, 2003 [Final USPI for VFEND for Oral Suspension 19Dec03]. The final label includes the Esophageal Candidiasis dosing information.

The MO approves the Final USPI label for VFEND for Oral Suspension received on December 19, 2003. This Final USPI contains minor capitalization errors; the Applicant was informed about these errors and asked to correct them.

Sary O. Beidas, MD
Reviewing Medical Officer / HFD-590

Concurrences Only: _____

Renata Albrecht, MD HFD-590 / Division Director
Marc Cavillé-Coll, MD, PhD HFD-590 / Team Leader

HFD-590/Divisional File, NDA 21-464, & NDA 21-466
HFD-590/MedTL/Cavaillé-Coll
HFD-590/Micro/Kalavati
HFD-590/Micro/Bala
HFD-590/Chem/Holbert
HFD-590/MO/Beidas
HFD-590/Biopharm/Colanglo
HFD-590/Biopharm/DeLosReyes
HFD-590/Stat/Dixon
HFD-590/Pharm/McMaster
HFD-590/TML/Molinaro
HFD-590/PM/Saville

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

/s/

Sary Beidas
12/19/03 02:34:53 PM
MEDICAL OFFICER

Marc Cavaille Coll
12/19/03 02:37:53 PM
MEDICAL OFFICER

Renata Albrecht
12/19/03 04:25:33 PM
MEDICAL OFFICER