CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-464

21-466

MEDICAL REVIEW

Medical Officer's Labeling Review

NDA	21-464 (tablet) and 21-466(for injection)
Submitted:	17 November, 2000
Review completed:	01 November, 2003
Resubmission:	13 May, 2003
Action Date:	13 November, 2003
Drug name:	Voriconazole
Generic name:	Voriconazole
Trade name:	VFEND®
Chemical name:	(2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-l-(l H -1,2,4-triazol-l-yl)2-butanol
Sponsor:	Pfizer Inc. 50 Pequot Avenue New London CT 06320
Pharmacologic Category :	Antifungal agent
Proposed Indication:	Treatment of Esophageal Candidiasis
Dosage Form(s) and	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:	Microbiology Biopharmaceutics

This Medical Officer (MO) labeling review provides comments and recommendations to the Division Director related to the temporarily assigned NDA 21-464 & 21-466 VFEND® (voriconazole) tablets & for injection respectively. In this submission the Applicant provides a response to the deficiencies listed in the approvable letter dated December 17, 2001 for NDA 21-266 & NDA 21-267 VFEND® (voriconazole) tablets & for injection for the indication of **Esophageal Candidiasis (EC)**. There were no new clinical safety issues identified in this review. The MO recommends **approval** of VFEND® for the proposed indication of EC. In addition, this review includes the proposed label changes/additions with comments by the MO.

Regulatory 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 (first-line therapy), *Fusarium* species, and *Scedosporium apiospermum* in patients intolerant or refractory to other antifungal treatment.

The Applicant, Pfizer Inc, had requested at the time of submission of the NDA in November 17, 2000, the use of voriconazole for the indication of EC. However, the benefit/risk profile of voriconazole in the safety review done by the primary MO Dr. Rosemary Tiernen, did not support the approval for the indication of EC. The fundamental issue according to the MO's review was the *in vivo* studies in dogs, that demonstrated arrhythmia, PVC's, and prolonged QT interval when high doses of voriconazole were administered to the animals. Other concerns for the approval of voriconazole mentioned in the review for the indication included the potential for visual disturbances and drug-drug interactions.

Consequently, the Applicant attempted to investigate the effect of escalating doses of intravenous voriconazole on QTc interval in healthy subjects. On two occasions, the study could not be completed due to anaphylactoid reactions occurring in patients receiving the excipient sulfobutylether-cyclodextrin (SBECD) alone or SBECD and voriconazole. Due to their inability to complete these studies despite due diligence efforts on the Applicant's behalf to determine the cause of these reactions, the Applicant agreed to investigate the effect of an escalating oral regimen of voriconazole in healthy subjects adult subjects.

In December 17, 2001, the Agency's issued an approvable letter for the indication of esophageal candidiasis. In the letter, the Agency requested the following issues be addressed by the Applicant prior to approval of the application (Deficiencies in the Approvable letter for NDA 21-464 & NDA 21-466, dated Dec 17, 2001 are listed verbatim in Times New Roman Font):

1. During a recent inspection of the manufacturing facility for VFEND® (voriconazole for injection), our field investigator conveyed deficiencies to the facility's representative(s). The

methods to be used in, and the facility and controls proposed for, the manufacture, processing, packing, or holding of the drug product by

facility, do not comply with the current good manufacturing practice regulations in 21 CFR 210 and 211 (2001). Satisfactory resolution to these deficiencies is required before these applications may be approved.

2. Provide data allowing adequate labeling regarding the risk of QT prolongation. The final study report from your proposed study may satisfy this requirement.

In addition, it will be necessary for you to submit draft labeling.

We also remind you of the requirement under 21 CFR 54 to submit financial disclosure information for covered clinical studies. We note that information for studies 303 and 304 has not been submitted.

The Applicant responded to the Agency's Item 1 in the approvable letter on March 26, 2002 and NDAs 21-266 and 21-267 were approved on May 24, 2002; in addition, the Applicant provided in this submission the final study report for Study A1501041 (Item 2 in the approvable letter) "A multicenter, randomized, single-blind, single dose, placebo-controlled, 5-way crossover study to investigate the effect of 3 oral doses of voriconazole (800mg, 1200mg, and 1600mg) and active comparator (oral ketoconazole 800mg) on QTc interval in healthy subjects aged 18-65 years." This study was reviewed by the Biopharmaceutics Reviewer, Dr. Gerlie De Los Reyes, and the summary of the results are presented in brief in this review.

Clinical Background

In the first decade of the HIV epidemic, oropharyngeal (OPC) & esophageal candidiasis were common in patients with AIDS. With the advent of improved medications for HIV and the associated opportunistic infections, the rates of OPC and EC have shown a considerable decline [1, 2]. This decrease in incidence of EC is related to immune reconstitution in these patients and to improved therapies for fungal infections, especially with the introduction of azoles [3]. In general, the current agents approved for treating EC (Table-1), in addition to the availability of amphotericin B compounds, provided adequate therapies for treating EC. therefore, when the Applicant requested an EC indication for voriconazole, the division requested proof of efficacy and safety for voriconazole in light of the extensive list of drug-drug interactions and potential for prolongation of the QTc interval when it is administered to patients with EC.

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[1] Kaplan JE, Hanson D, Dworkin M, et al. Epidemiology of HIV associated OIs in the US in the era of HAART. CID 2000;30:S5-S14.

[2] Chiou C, Groll A, Mavrogriorgos N, et al. EC in HIV infected pediatric patients after the introduction of HAART. Pediatr Infect Dis J. 2002;21:388-392.

[3] Jones J, Hanson D, Dworkin M, et al. Trends in AIDS related OI's among men who have sex with men and among injecting drug users, 1991-1996. JID 1998;178:114-20.

Table-1 Approved systemic antifungal agents in the US for EC Source: Physicians Desk Reference			
Diflucan	fluconazole	200 mg po first day followed by 100 mg qd	≥3 weeks
Sporonox	Itraconazole	100 mg po qd	≥3 weeks
Cancidas	Caspofungin	50 mg iv qd	≥9 days

Summary of Clinical Studies supporting the EC indication for voriconazole:

The Applicant performed one pivotal clinical study 150-305 to support the EC indication. This pivotal study was a randomized, double-blind, double dummy, comparative multicenter trial of voriconazole versus fluconazole in the treatment of EC in immune compromised patients. Dr. Rosemary Tiernen the Clinical Reviewer recommended an approvable status be granted for the EC indication pending fulfillment of the remaining deficiencies as outlined in the approvable letter dated December 17, 2001. The second study A1501041, is a multicenter, randomized, single-blind, single-dose, placebo-controlled, five-way crossover study to evaluate the effect of an escalating oral dose of voriconazole on the QTc interval in healthy adults. This study was completed in response to the approvable letter.

Study A1501041: "A multicenter, randomized, single-blind, single dose, placebo-controlled, five-way crossover study to investigate the effect of three oral doses of voriconazole (800mg, 1200mg, and 1600mg) and active comparator (oral ketoconazole 800mg) on QTc interval in healthy subjects aged 18 to 65 years."

Please refer to the review done by the Biopharmaceutics Reviewer, Dr. Gerlie De Los Reyes for the detailed review. In summary, Protocol A1501041 was a five-arm study, three arms incorporated escalating doses of voriconazole (800mg, 1200mg, and 1600mg), a fourth arm used an active comparator (ketoconazole 800mg), and the fifth arm was placebo. The objective of the study was to investigate the effect of voriconazole on QTc interval in healthy subjects. The Applicant reported a total of 384 adult healthy male and female subjects; each one of the five groups in the study had a comparable number of healthy adult subjects. At each one of the five crossover periods, study subjects were administered one dose of either voriconazole, ketoconazole, or placebo; the minimum washout period between each dosing was 7 days.

In the analysis of results, the Applicant used Fridericia's correction factor for presenting QTc data. For all three doses of voriconazole (800mg, 1200mg, and 1600mg), the mean increase in QTc interval compared to placebo was <10msec. No subjects in the study had an increase of ≥60msec from baseline.

MO Comment: *The results of this study, provide a reasonable and satisfactory estimate for the magnitude of risk on the effect voriconazole may have on prolonging QTc interval in patients who use voriconazole for EC. In the Biopharmaceutics review, a <10msec increase in QTc interval correlates with a no dose effect and therefore is not considered to be clinically significant. The reviewing MO concurs with the findings from the Biopharmaceutics review.*

Study 150-305: "A randomized, double-blind, double dummy, comparative multicenter trial of voriconazole and fluconazole in the treatment of esophageal candidiasis in immune compromised patients."

For a detailed review of study 150-305, the reader is referred to Dr. Rosemary Tiernen's Clinical Review. In brief, study 150-305 was the pivotal study that demonstrated non-inferiority of voriconazole to fluconazole for the treatment of EC. In that study, voriconazole 200 mg po bid was compared to fluconazole 400 mg po on day one followed by 200 mg po qd. Table-2 provides a summary of study 150-305. Demographically, this study was conducted in a mostly white (68%), male group (75%), the mean age for patients in the study was 36 years. The majority of patients in the study were diagnosed with HIV (88%). Antiviral medications were administered in the study to 94/200 (47%) patients in the voriconazole group, and 95/191 (50%) in the fluconazole group. Highly active antiretroviral therapy (HAART) was not provided to most patients since this study was completed just as the principle of HAART was evolving.

Table-2 Overview for Study 150-305: Randomized, double-blind, comparative multicenter study of voriconazole versus fluconazole for EC in immune compromised (88% HIV) patients. (Study centers: Europe, Africa, Asia)

	Voriconazole 200 mg po bid	Fluconazole 200 mg po qd	Difference % (95% CI)
Success ITT population at EOT	175/200 87.5%	171/191 89.5%	-2.0 (-8.3, 4.3)
Success PP population at EOT	113/115 98.2%	134/141 95%	3.2 (-1.1, 7.5)
Completed study	131/200	136/191	
D/C study	69/200	55/191	

The PP population was the primary population analyzed for efficacy

Intent to treat (ITT), End of Therapy (EOT), Per Protocol (PP)

Duration of therapy 15-43 days

Success was defined as cured or improved

90% of isolates were *Candida albicans*

Patients evaluable for the Per Protocol (PP) population had to satisfy the following criteria:

- confirmation of *Candida* esophagitis by endoscopy, including presence of hyphae on biopsy or brushing and a positive culture
- received at least 12 days of treatment
- an EOT evaluation including a repeat endoscopy
- evidence of adequate compliance
- visits at each assessment time within the ± five day window not received a forbidden study medication

MO Comment: *HAART has modified HIV disease course and made EC less common than before, and since there are other medications available to treat EC without the potential concomitant drug-drug interactions, the MO does not expect the market use of voriconazole to markedly expand to treat EC.*

The median duration of therapy for patients in this study was 14 days. A comparable number of patients in both groups (~83%) received therapy for 8-28 days. In the voriconazole group, 95/200 (48%) of patients received medication for 15-60 days, and in the fluconazole group, 116/191 (61%) of patients received medication for 15-60 days. No patients in the study received medication beyond 60 days.

MO Comment: *Most patients who were excluded from both groups of the study were due to absence of a second endoscopy (endoscopy at the beginning and end of therapy was required for inclusion). Of those patients excluded in the voriconazole arm 85 patients. Of these 35/85 (40%)had one endoscopy. Of these 35 patients, 7 patients were due to lack of efficacy or a drug-related adverse event, 4 patients died, and 7 patients had non-related adverse events. In the fluconazole group, there were 50 exclusions. Fifteen of the fifty (30%) had one endoscopy only, and of these, 2 patients were excluded due to lack of efficacy, 2 patients died, and 1 patient had a non-related adverse event.*

MO Comment: *Caspofungin is an approved antifungal agent for the indication EC. The clinical trials used to approve caspofungin for the indication also used fluconazole as the active comparator. However, there are major differences between the caspofungin and the voriconazole clinical trials for the EC indication such that a comparison between both has the potential to lead to erroneous conclusions. For example, the caspofungin clinical studies used endoscopic and clinical criteria for assessment of success, whereas voriconazole used endoscopy criteria. Furthermore, endoscopy improvement in the caspofungin studies required 2 grades of improvement, versus 1 grade of improvement for voriconazole. Perhaps the biggest difference is the mode of administration, caspofungin is available in intravenous form only, whereas the oral voriconazole formulation was used for EC. The active control was fluconazole 100 mg qd in the caspofungin study versus 200 mg in the voriconazole study. Efficacy in the caspofungin study was evaluated using the ITT and the PP populations, whereas in the voriconazole study the primary population was the PP.*

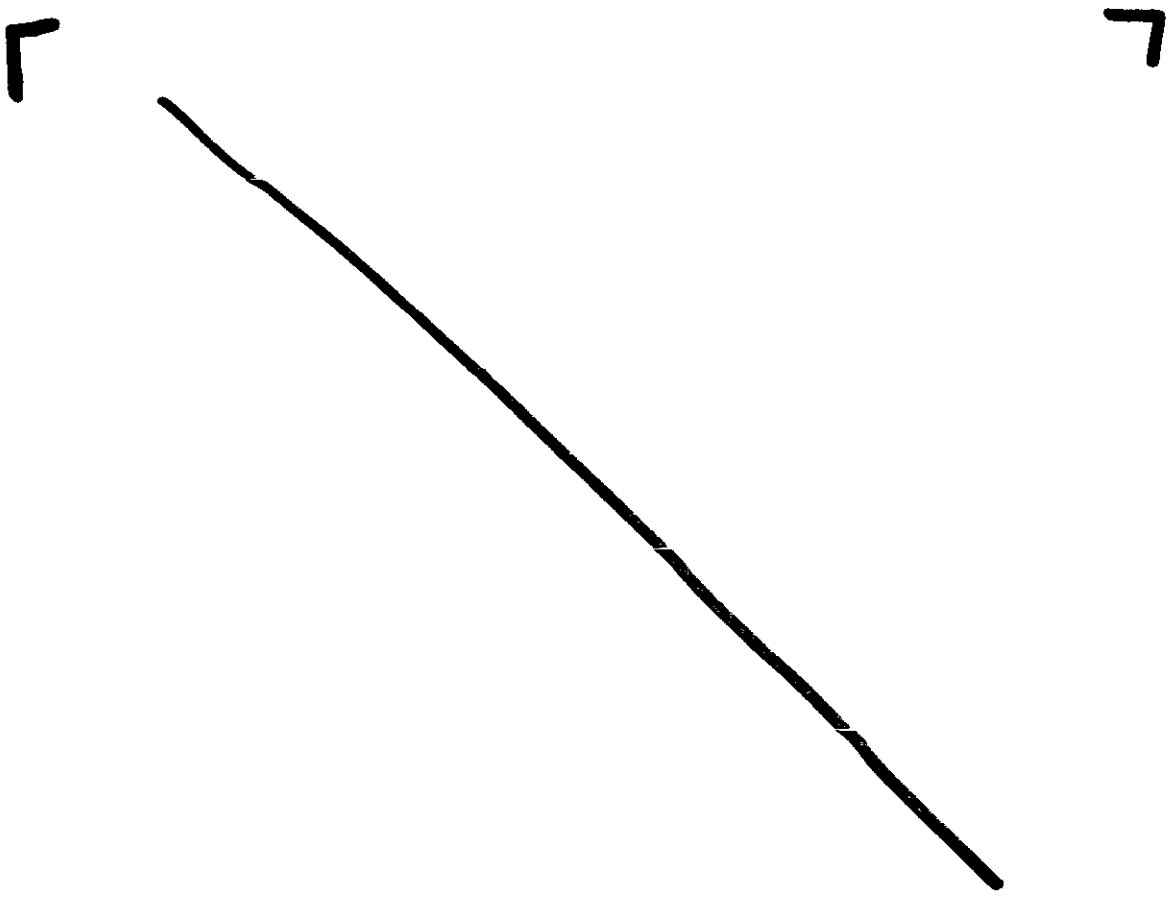
Biopharmaceutics Review: Refer to Dr. De Los Reyes, Biopharmaceutics Reviewer for a detailed discussion on findings. In brief, Study A1501041 (described in the Clinical Studies Section), provides reasonable evidence that the use of voriconazole (single oral dose) up to 1600 mg results in a clinically insignificant increase in QTc interval of <10 msec.

Microbiology Review: Refer to Dr. Kalavati Suvarna, the Microbiology Reviewer for a detailed discussion on findings. In her Review, Dr. Suvarna noted that the majority of clinical isolates collected at baseline from patients with EC were *Candida albicans*, and therefore that should be reflected in the label. The number of non-albicans species was too small to allow interpretation of efficacy.

Labeling Review:

VFEND® is approved for use in the United States. The Applicant's proposed labeling additions/changes for the EC indication:

1 Pharmacokinetic-pharmacodynamic Relationships



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✓ § 552(b)(5) Draft Labeling

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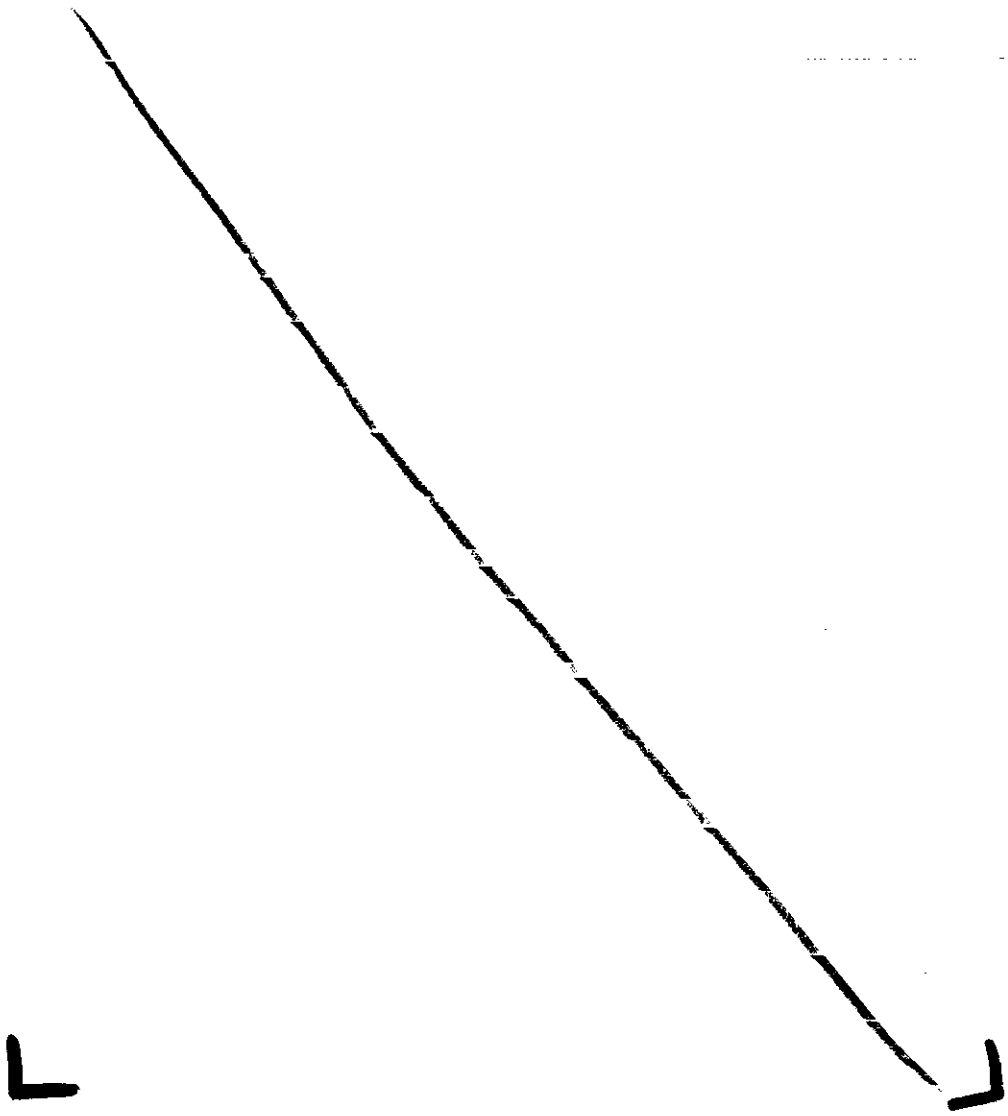

Recommendations:

The Agency held an Internal meeting to evaluate the proposed labeling changes for the EC indication on October 2, 2003. The recommendations of the MO are:

1 Approve NDA 21-464 & NDA 21-466 for the indication of EC. The basis for approval is fulfillment of the deficiencies listed in the original NDA 21-266 and NDA 21-267 in the approvable letter dated December 17, 2001.

2 Amendment of labeling changes as reviewed to include treatment of EC caused by C. albicans. The Applicant did not have sufficient numbers of non-albicans species. The Agency communicated by fax the desired labeling changes as reviewed above with the Applicant. Further label negotiations requested by the Applicant to discuss the Agency's changes to the proposed label are scheduled on October 27, 2003.

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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/Cavaillè-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
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