CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21-266/S009
NDA 21-267/S009
NDA 21-630/S003

Trade Name: VFEND

Generic Name: voriconzole

Sponsor: Pfizer, Inc.

Approval Date: December 21, 2004

Indications: for candidemia in nonneutropenic patients and the following Candida infections: disseminated infections in skin and infections in abdomen, kidney, bladder wall, and wounds.

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NDA 21-267/S009
NDA 21-630/S003

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-266/S-009
NDA 21-267/S-009
NDA 21-630/S-003

C.P. Pharmaceuticals International C.V.
c/o Pfizer, Inc.
Attn: Maureen H. Garvey, Ph.D.
Senior Director, Worldwide Regulatory Strategy
235 East 42nd Street
New York, NY 10017

Dear Dr. Garvey:

Please refer to your new drug applications (NDA) dated March 15, 2004, received March 16, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product	NDA	Supplement Number
VFEND® (voriconazole) Tablets, 50 mg and 200 mg	21-266	S-009
VFEND® I.V. (voriconazole) for Injection, 10 mg/mL	21-267	S-009
VFEND® (voriconazole) for Oral Suspension, 45 mg/mL	21-630	S-003

We acknowledge receipt of your submissions dated:

March 15, 2004
April 9, 2004 (2)
April 26, 2004 (2)
May 14, 2004 (2)
May 18, 2004 (2)
July 22, 2004
July 23, 2004
August 13, 2004
September 29, 2004 (2)
September 30, 2004
December 14, 2004
December 17, 2004
December 20, 2004

These supplemental new drug applications provide for the use of VFEND® for candidemia in nonneutropenic patients and the following *Candida* infections: disseminated infections in skin and infections in abdomen, kidney, bladder wall, and wounds.

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert submitted December 20, 2004). Marketing the products with FPL that is not identical to the approved labeling text may render the products misbranded and unapproved new drugs.

The electronic labeling rule published December 11, 2003, (68 FR 69009) requires submission of labeling content in electronic format effective June 8, 2004. For additional information, consult the following guidance documents for industry regarding electronic submissions: *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999) and *Providing Regulatory Submissions in Electronic Format – Content of Labeling* (February 2004). The guidance documents specify that labeling be submitted in *pdf* format. To assist in our review, we request that labeling also be submitted in MS Word format. If formatted copies of all labeling pieces (i.e., package insert, patient package insert, container labels, and carton labels) are submitted electronically, labeling does not need to be submitted in paper.

For administrative purposes, designate these submissions "**FPL for approved supplements NDA 21-266/S-009, NDA 21-267/S-009, and NDA 21-630/S-003**." Approval of these submissions by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies for ages 0 to 16 years until December 31, 2010.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for the treatment of candidemia and invasive candidiasis infections in pediatric patients ages 0 to 16.

   Final Report Submission: December 31, 2010

Submit final study reports to these NDAs. For administrative purposes, all submissions related to this pediatric postmarketing study commitment must be clearly designated "**Required Pediatric Study Commitment**."

In addition, as required by 21 CFR 314.550, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock up form, not final print. Send one copy to this Division and two copies of both the promotional materials and the proposed package inserts directly to:

Division of Drug Marketing, Advertising
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville MD 20857

If you issue a letter communicating important information about these drug products (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Rebecca D. Saville, Pharm.D., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure

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

/s/

Renata Albrecht
12/21/04 05:14:25 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-266/S009
NDA 21-267/S009
NDA 21-630/S003

LABELING

69-5906-00-

VFEND^{È} I.V.

(voriconazole) for Injection

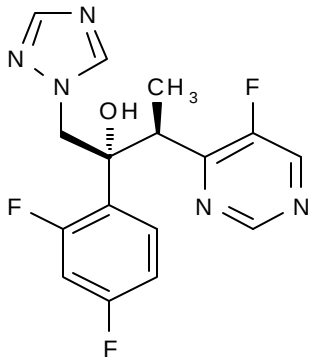
VFEND^{È} Tablets

(voriconazole)

VFEND^{È} (voriconazole) for Oral Suspension

DESCRIPTION

VFEND® (voriconazole), a triazole antifungal agent, is available as a lyophilized powder for solution for intravenous infusion, film-coated tablets for oral administration, and as a powder for oral suspension. The structural formula is:



Voriconazole is designated chemically as (2R, 3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol with an empirical formula of $C_{16}H_{14}F_3N_5O$ and a molecular weight of 349.3.

Voriconazole drug substance is a white to light-colored powder.

VFEND I.V. is a white lyophilized powder containing nominally 200 mg voriconazole and 3200 mg sulfobutyl ether beta-cyclodextrin sodium in a 30 mL Type I clear glass vial.

VFEND I.V. is intended for administration by intravenous infusion. It is a single dose, unpreserved product. Vials containing 200 mg lyophilized voriconazole are intended for reconstitution with Water for Injection to produce a solution containing 10 mg/mL VFEND and 160 mg/mL of sulfobutyl ether beta-cyclodextrin sodium. The resultant solution is further diluted prior to administration as an intravenous infusion (see DOSAGE AND ADMINISTRATION).

VFEND Tablets contain 50 mg or 200 mg of voriconazole. The inactive ingredients include lactose monohydrate, pregelatinized starch, croscarmellose sodium, povidone, magnesium stearate and a coating containing hypromellose, titanium dioxide, lactose monohydrate and triacetin.

VFEND for Oral Suspension is a white to off-white powder providing a white to off-white orange-flavored suspension when reconstituted. Bottles containing 45 g powder for oral suspension are intended for reconstitution with water to produce a suspension containing 40 mg/mL voriconazole. The inactive ingredients include colloidal silicon dioxide, titanium dioxide, xanthan gum, sodium citrate dihydrate, sodium benzoate, anhydrous citric acid, natural orange flavor, and sucrose.

CLINICAL PHARMACOLOGY

Pharmacokinetics

General Pharmacokinetic Characteristics
The pharmacokinetics of voriconazole have been characterized in healthy subjects, special populations and patients.

The pharmacokinetics of voriconazole are non-linear due to saturation of its metabolism. The interindividual variability of voriconazole pharmacokinetics is high. Greater than proportional increase in exposure is observed with increasing dose. It is estimated that, on average, increasing the oral dose in healthy subjects from 200 mg Q12h to 300 mg Q12h leads to a 2.5-fold increase in exposure (AUC_τ) while increasing the intravenous dose from 3 mg/kg Q12h to 4 mg/kg Q12h produces a 2.3-fold increase in exposure (Table 1).

Table 1
Population Pharmacokinetic Parameters of Voriconazole in Volunteers

	200 mg Oral Q12h	300 mg Oral Q12h	3 mg/kg IV Q12h	4 mg/kg IV Q12h
AUC_τ* (µg•h/mL) (CV%)	19.86 (94%)	50.32 (74%)	21.81 (100%)	50.40 (83%)

*Mean AUC_τ are predicted values from population pharmacokinetic analysis of data from 236 volunteers

During oral administration of 200 mg or 300 mg twice daily for 14 days in patients at risk of aspergillosis (mainly patients with malignant neoplasms of lymphatic or hematopoietic tissue), the observed pharmacokinetic characteristics were similar to those observed in healthy subjects (Table 2).

Table 2
Pharmacokinetic Parameters of Voriconazole in Patients at Risk for Aspergillosis

	200 mg Oral Q12h (n=9)	300 mg Oral Q12h (n=9)
AUC_τ* (µg•h/mL) (CV%)	20.31 (69%)	36.51 (45%)
C_{max}* (µg/mL) (CV%)	3.00 (51%)	4.66 (35%)

*Geometric mean values on Day 14 of multiple dosing in 2 cohorts of patients

Sparse plasma sampling for pharmacokinetics was conducted in the therapeutic studies in patients aged 12-18 years. In 11 adolescent patients who received a mean voriconazole maintenance dose of 4 mg/kg IV, the median of the calculated mean plasma concentrations was 1.60 µg/mL (inter-quartile range 0.28 to 2.73 µg/mL). In 17 adolescent patients for whom mean plasma concentrations were calculated following a mean oral maintenance dose of 200 mg Q12h, the median of the calculated mean plasma concentrations was 1.16 µg/mL (inter-quartile range 0.85 to 2.14 µg/mL).

When the recommended intravenous or oral loading dose regimens are administered to healthy subjects, peak plasma concentrations close to steady state are achieved within the first 24 hours of dosing. Without the loading dose, accumulation occurs during twice-daily multiple dosing with steady-state peak plasma voriconazole concentrations being achieved by day 6 in the majority of subjects (Table 3).

Table 3
Pharmacokinetic Parameters of Voriconazole from Loading Dose and Maintenance Dose Regimens (Individual Studies in Volunteers)

	400 mg Q12h on Day 1, 200 mg Q12h on Days 2 to 10 (n=17)		6 mg/kg IV** Q12h on Day 1, 3 mg/kg IV Q12h on Days 2 to 10 (n=9)	
	Day 1, 1st dose	Day 10	Day 1, 1st dose	Day 10
AUC_τ* (µg•h/mL) (CV%)	9.31 (38%)	11.13 (103%)	13.22 (22%)	13.25 (58%)
C_{max} (µg/mL) (CV%)	2.30 (19%)	2.08 (62%)	4.70 (22%)	3.06 (31%)

*AUC_τ values are calculated over dosing interval of 12 hours
Pharmacokinetic parameters for loading and maintenance doses summarized for same cohort of volunteers
**IV infusion over 60 minutes

Steady state trough plasma concentrations with voriconazole are achieved after approximately 5 days of oral or intravenous dosing without a loading dose regimen. However, when an intravenous loading dose regimen is used, steady state trough plasma concentrations are achieved within one day.

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 200 mg tablet and the 40 mg/mL oral suspension when administered as a 400 mg Q12h loading dose followed by a 200 mg Q12h maintenance dose.

Maximum plasma concentrations (C_{max}) are achieved 1-2 hours after dosing. When multiple doses of voriconazole are administered with high fat meals, the mean C_{max} and AUC_{τ} are reduced by 34% and 24%, respectively when administered as a tablet and by 58% and 37% respectively when administered as the oral suspension (see DOSAGE AND ADMINISTRATION).

In healthy subjects, the absorption of voriconazole is not affected by coadministration of oral ranitidine, cimetidine, or omeprazole, drugs that are known to increase gastric pH.

Distribution

The volume of distribution at steady state for voriconazole is estimated to be 4.6 L/kg, suggesting extensive distribution into tissues. Plasma protein binding is estimated to be 58% and was shown to be independent of plasma concentrations achieved following single and multiple oral doses of 200 mg or 300 mg (approximate range: 0.9-15 µg/mL). Varying degrees of hepatic and renal insufficiency do not affect the protein binding of voriconazole.

Metabolism

In vitro studies showed that voriconazole is metabolized by the human hepatic cytochrome P450 enzymes, CYP2C19, CYP2C9 and CYP3A4 (see CLINICAL PHARMACOLOGY - Drug Interactions).

In vivo studies indicated that CYP2C19 is significantly involved in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism. For example, 15-20% of Asian populations may be expected to be poor metabolizers. For Caucasians and Blacks, the prevalence of poor metabolizers is 3-5%. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolizers have, on average, 4-fold higher voriconazole exposure (AUC_{τ}) than their homozygous extensive metabolizer counterparts. Subjects who are heterozygous extensive metabolizers have, on average, 2-fold higher voriconazole exposure than their homozygous extensive metabolizer counterparts.

The major metabolite of voriconazole is the N-oxide, which accounts for 72% of the circulating radiolabelled metabolites in plasma. Since this metabolite has minimal antifungal activity, it does not contribute to the overall efficacy of voriconazole.

Excretion
Voriconazole is eliminated via hepatic metabolism with less than 2% of the dose excreted unchanged in the urine. After administration of a single radiolabelled dose of either oral or IV voriconazole, preceded by multiple oral or IV dosing, approximately 80% to 83% of the radioactivity is recovered in the urine. The majority (>94%) of the total radioactivity is excreted in the first 96 hours after both oral and intravenous dosing.

As a result of non-linear pharmacokinetics, the terminal half-life of voriconazole is dose dependent and therefore not useful in predicting the accumulation or elimination of voriconazole.

Pharmacokinetic-Pharmacodynamic Relationships

Clinical Efficacy and Safety

In ten clinical trials, the median values for the average and maximum voriconazole plasma concentrations in individual patients across these studies (N=1121) was 2.51 µg/mL (inter-quartile range 1.21 to 4.44 µg/mL) and 3.79 µg/mL (inter-quartile range 2.06 to 6.31 µg/mL), respectively. A pharmacokinetic-pharmacodynamic analysis of patient data from 6 of these 10 clinical trials (N=280) could not detect a positive association between mean, maximum or minimum plasma voriconazole concentration and efficacy. However, PK/PD analyses of the data from all 10 clinical trials identified positive associations between plasma voriconazole concentrations and rate of both liver function test abnormalities and visual disturbances (see ADVERSE REACTIONS).

Electrocardiogram

A placebo-controlled, randomized, crossover study to evaluate the effect on the QT interval of healthy male and female volunteers was conducted with three single oral doses of voriconazole and ketoconazole. Serial ECGs and plasma samples were obtained at specified intervals over a 24-hour post dose observation period. The placebo-adjusted mean maximum increases in QTc from baseline after 800, 1200 and 1600 mg of voriconazole and after ketoconazole 800 mg were all <10 msec. Females exhibited a greater increase in QTc than males, although all mean changes were <10 msec. Age was not found to affect the magnitude of increase in QTc. No subject in any group had an increase in QTc of =60 msec from baseline. No subject experienced an interval exceeding the potentially clinically relevant threshold of 500 msec. However, the QT effect of voriconazole combined with drugs known to prolong the QT interval is unknown. (See CONTRAINDICATIONS, PRECAUTIONS-Drug Interactions).

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 ($\geq$65 years). In a similar study, after dosing with the oral 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 oral suspension, respectively.

In the clinical program, no dosage adjustment was made on the basis of gender. The safety profile and plasma concentrations observed in male and female subjects were similar. Therefore, no dosage adjustment based on gender is necessary.

Geriatric

In an oral multiple dose study the mean C_{max} and AUC_{τ} in healthy elderly males (≥ 65 years) were 61% and 86% higher, respectively, than in young males (18-45 years). No significant differences in the mean C_{max} and AUC_{τ} were observed between healthy elderly females (≥ 65 years) and healthy young females (18-45 years).

In the clinical program, no dosage adjustment was made on the basis of age. An analysis of pharmacokinetic data obtained from 552 patients from 10 voriconazole clinical trials showed that the median voriconazole plasma concentrations in the elderly patients (>65 years) were approximately 80% to 90% higher than those in the younger patients (≤65 years) after either IV or oral administration. However, the safety profile of voriconazole in young and elderly subjects was similar and, therefore, no dosage adjustment is necessary for the elderly.

Pediatric

A population pharmacokinetic analysis was conducted on pooled data from 35 immunocompromised pediatric patients aged 2 to <12 years old who were included in two pharmacokinetic studies of intravenous voriconazole (single dose and multiple dose). Twenty-four of these patients received multiple intravenous maintenance doses of 3 mg/kg and 4 mg/kg. A comparison of the pediatric and adult population pharmacokinetic data revealed that the predicted average steady state plasma concentrations were similar at the maintenance dose of 4 mg/kg every 12 hours in children and 3 mg/kg every 12 hours in adults (medians of 1.19 μg/mL and 1.16 μg/mL in children and adults, respectively). (See PRECAUTIONS, Pediatric Use.)

Hepatic Insufficiency

After a single oral dose (200 mg) of voriconazole in 8 patients with mild (Child-Pugh Class A) and 4 patients with moderate (Child-Pugh Class B) hepatic insufficiency, the mean systemic exposure (AUC) was 3.2-fold higher than in age and weight matched controls with normal hepatic function. There was no difference in mean peak plasma concentrations (C_{max}) between the groups. When only the patients with mild (Child-Pugh Class A) hepatic insufficiency were compared to controls, there was still a 2.3-fold increase in the mean AUC in the group with hepatic insufficiency compared to controls.

In an oral multiple dose study, AUC_{τ} was similar in six subjects with moderate hepatic impairment (Child-Pugh Class B) given a lower maintenance dose of 100 mg twice daily compared to six subjects

with normal hepatic function given the standard 200 mg twice daily maintenance dose. The mean peak plasma concentrations (C_{max}) were 20% lower in the hepatically impaired group.

It is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B) receiving voriconazole. No pharmacokinetic data are available for patients with severe hepatic cirrhosis (Child-Pugh Class C) (see DOSAGE AND ADMINISTRATION).

Renal Insufficiency
In a single oral dose (200 mg) study in 24 subjects with normal renal function and mild to severe renal impairment, systemic exposure (AUC) and peak plasma concentration (C_{max}) of voriconazole were not significantly affected by renal impairment. Therefore, no adjustment is necessary for oral dosing in patients with mild to severe renal impairment.

In a multiple dose study of IV voriconazole (6 mg/kg IV loading dose x 2, then 3 mg/kg IV x 5.5 days) in 7 patients with moderate renal dysfunction (creatinine clearance 30-50 mL/min), the systemic exposure (AUC) and peak plasma concentrations (C_{max}) were not significantly different from those in 6 volunteers with normal renal function.

However, in patients with moderate renal dysfunction (creatinine clearance 30-50 mL/min), accumulation of the intravenous vehicle, SBECD, occurs. The mean systemic exposure (AUC) and peak plasma concentrations (C_{max}) of SBECD were increased by 4-fold and almost 50%, respectively, in the moderately impaired group compared to the normal control group.

Intravenous voriconazole should be avoided in patients with moderate or severe renal impairment (creatinine clearance <50 mL/min), unless an assessment of the benefit/risk to the patient justifies the use of intravenous voriconazole (see DOSAGE AND ADMINISTRATION - Dosage Adjustment).

A pharmacokinetic study in subjects with renal failure undergoing hemodialysis showed that voriconazole is dialyzed with clearance of 121 mL/min. The intravenous vehicle, SBECD, is hemodialyzed with clearance of 55 mL/min. A 4-hour hemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment.

Drug Interactions
Effects of Other Drugs on Voriconazole

Voriconazole is metabolized by the human hepatic cytochrome P450 enzymes CYP2C19, CYP2C9, and CYP3A4. Results of *in vitro* metabolism studies indicate that the affinity of voriconazole is highest for CYP2C19, followed by CYP2C9, and is appreciably lower for CYP3A4. Inhibitors or inducers of these three enzymes may increase or decrease voriconazole systemic exposure (plasma concentrations), respectively.

The systemic exposure to voriconazole is significantly reduced or is expected to be reduced by the concomitant administration of the following agents and their use is contraindicated:

***Rifampin* (potent CYP450 inducer):** Rifampin (600 mg once daily) decreased the steady state C_{max} and AUC_{τ} of voriconazole (200 mg Q12h x 7 days) by an average of 93% and 96%, respectively, in healthy subjects. Doubling the dose of voriconazole to 400 mg Q12h does not restore adequate exposure to voriconazole during coadministration with rifampin. **Coadministration of voriconazole and rifampin is contraindicated** (see CONTRAINDICATIONS, PRECAUTIONS - Drug Interactions).

***Ritonavir* (potent CYP450 inducer; CYP3A4 inhibitor and substrate):** Ritonavir (400 mg Q12h for 9 days) decreased the steady state C_{max} and AUC_{τ} of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 8 days) by an average of 66% and 82%, respectively, in healthy subjects. The effect of ritonavir (100 mg Q12h as used to inhibit CYP3A and increase concentrations of other antiretroviral drugs) on voriconazole concentrations has not been studied. Repeat oral administration of voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 8 days) did not have a significant effect on steady state C_{max} and AUC_{τ} of ritonavir following repeat dose administration (400 mg Q12h for 9 days) in healthy subjects. **Coadministration of voriconazole and ritonavir (400 mg Q12h) is contraindicated** (see CONTRAINDICATIONS, PRECAUTIONS - Drug Interactions).

***Carbamazepine and long acting barbiturates* (potent CYP450 inducers):** Although not studied *in vitro* or *in vivo*, carbamazepine and long acting barbiturates (e.g. phenobarbital, mephobarbital) are likely to significantly decrease plasma voriconazole concentrations. **Coadministration of voriconazole with carbamazepine or long acting barbiturates is contraindicated** (see CONTRAINDICATIONS, PRECAUTIONS - Drug Interactions).

Minor or no significant pharmacokinetic interactions that do not require dosage adjustment:

***Cimetidine* (non-specific CYP450 inhibitor and increases gastric pH):** Cimetidine (400 mg Q12h x 8 days) increased voriconazole steady state C_{max} and AUC_{τ} by an average of 18% (90% CI: 6%, 32%) and 23% (90% CI: 13%, 33%), respectively, following oral doses of 200 mg Q12h x 7 days to healthy subjects.

***Ranitidine* (increases gastric pH):** Ranitidine (150 mg Q12h) had no significant effect on voriconazole C_{max} and AUC_{τ} following oral doses of 200 mg Q12h x 7 days to healthy subjects.

***Macrolide antibiotics*:** Co-administration of **erythromycin** (CYP3A4 inhibitor;1g Q12h for 7 days) or **azithromycin** (500 mg qd for 3 days) with voriconazole 200 mg Q12h for 14 days had no significant effect on voriconazole steady state C_{max} and AUC_{τ} in healthy subjects. The effects of voriconazole on the pharmacokinetics of either erythromycin or azithromycin are not known.

Effects of Voriconazole on Other Drugs

In vitro studies with human hepatic microsomes show that voriconazole inhibits the metabolic activity of the cytochrome P450 enzymes CYP2C19, CYP2C9, and CYP3A4. In these studies, the inhibition potency of voriconazole for CYP3A4 metabolic activity was significantly less than that of two other azoles, ketoconazole and itraconazole. *In vitro* studies also show that the major metabolite of

voriconazole, voriconazole N-oxide, inhibits the metabolic activity of CYP2C9 and CYP3A4 to a greater extent than that of CYP2C19. Therefore, there is potential for voriconazole and its major metabolite to increase the systemic exposure (plasma concentrations) of other drugs metabolized by these CYP450 enzymes.

The systemic exposure of the following drugs is significantly increased or is expected to be significantly increased by coadministration of voriconazole and their use is contraindicated:

***Sirolimus* (CYP3A4 substrate):** Repeat dose administration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 8 days) increased the C_{max} and AUC of sirolimus (2 mg single dose) an average of 7-fold (90% CI: 5.7, 7.5) and 11-fold (90% CI: 9.9, 12.6), respectively, in healthy subjects. **Coadministration of voriconazole and sirolimus is contraindicated** (see CONTRAINDICATIONS, PRECAUTIONS - Drug Interactions).

***Terfenadine, astemizole, cisapride, pimozide and quinidine* (CYP3A4 substrates):** Although not studied *in vitro* or *in vivo*, concomitant administration of voriconazole with terfenadine, astemizole, cisapride, pimozide or quinidine may result in inhibition of the metabolism of these drugs. Increased plasma concentrations of these drugs can lead to QT prolongation and rare occurrences of *torsade de pointes*. **Coadministration of voriconazole and terfenadine, astemizole, cisapride, pimozide and quinidine is contraindicated** (see CONTRAINDICATIONS, PRECAUTIONS - Drug Interactions).

***Ergot alkaloids*:** Although not studied *in vitro* or *in vivo*, voriconazole may increase the plasma concentration of ergot alkaloids (ergotamine and dihydroergotamine) and lead to ergotism. **Coadministration of voriconazole with ergot alkaloids is contraindicated** (see CONTRAINDICATIONS, PRECAUTIONS - Drug Interactions).

Coadministration of voriconazole with the following agents results in increased exposure or is expected to result in increased exposure to these drugs. Therefore, careful monitoring and/or dosage adjustment of these drugs is needed:

***Cyclosporine* (CYP3A4 substrate):** In stable renal transplant recipients receiving chronic cyclosporine therapy, concomitant administration of oral voriconazole (200 mg Q12h for 8 days) increased cyclosporine C_{max} and AUC_{τ} an average of 1.1 times (90% CI: 0.9, 1.41) and 1.7 times (90% CI: 1.5, 2.0), respectively, as compared to when cyclosporine was administered without voriconazole. When initiating therapy with voriconazole in patients already receiving cyclosporine, it is recommended that the cyclosporine dose be reduced to one-half of the original dose and followed with frequent monitoring of the cyclosporine blood levels. Increased cyclosporine levels have been associated with nephrotoxicity. <u>When voriconazole is discontinued, cyclosporine levels should be frequently monitored and the dose increased as necessary</u> (see PRECAUTIONS - Drug Interactions).

***Tacrolimus* (CYP3A4 substrate):** Repeat oral dose administration of voriconazole (400 mg Q12h x 1 day then 200 mg Q12h x 6 days) increased tacrolimus (0.1 mg/kg single dose) C_{max} and AUC_{τ} in healthy subjects by an average of 2-fold (90% CI: 1.9, 2.5) and 3-fold (90% CI: 2.7, 3.8), respectively. When initiating therapy with voriconazole in patients already receiving tacrolimus, it is

recommended that the tacrolimus dose be reduced to one-third of the original dose and followed with frequent monitoring of the tacrolimus blood levels. Increased tacrolimus levels have been associated with nephrotoxicity. When voriconazole is discontinued, tacrolimus levels should be carefully monitored and the dose increased as necessary (see PRECAUTIONS - Drug Interactions).

***Warfarin* (CYP2C9 substrate):** Coadministration of voriconazole (300 mg Q12h x 12 days) with warfarin (30 mg single dose) significantly increased maximum prothrombin time by approximately 2-times that of placebo in healthy subjects. Close monitoring of prothrombin time or other suitable anti-coagulation tests is recommended if warfarin and voriconazole are coadministered and the warfarin dose adjusted accordingly (see PRECAUTIONS - Drug Interactions).

***Oral Coumarin Anticoagulants* (CYP2C9, CYP3A4 substrates):** Although not studied *in vitro* or *in vivo*, voriconazole may increase the plasma concentrations of coumarin anticoagulants and therefore may cause an increase in prothrombin time. If patients receiving coumarin preparations are treated simultaneously with voriconazole, the prothrombin time or other suitable anti-coagulation tests should be monitored at close intervals and the dosage of anticoagulants adjusted accordingly (see PRECAUTIONS - Drug Interactions).

***Statins* (CYP3A4 substrates):** Although not studied clinically, voriconazole has been shown to inhibit lovastatin metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase the plasma concentrations of statins that are metabolized by CYP3A4. It is recommended that dose adjustment of the statin be considered during coadministration. Increased statin concentrations in plasma have been associated with rhabdomyolysis (see PRECAUTIONS - Drug Interactions).

***Benzodiazepines* (CYP3A4 substrates):** Although not studied clinically, voriconazole has been shown to inhibit midazolam metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase the plasma concentrations of benzodiazepines that are metabolized by CYP3A4 (e.g., midazolam, triazolam, and alprazolam) and lead to a prolonged sedative effect. It is recommended that dose adjustment of the benzodiazepine be considered during coadministration (see PRECAUTIONS - Drug Interactions).

***Calcium Channel Blockers* (CYP3A4 substrates):** Although not studied clinically, voriconazole has been shown to inhibit felodipine metabolism *in vitro* (human liver microsomes). Therefore, voriconazole may increase the plasma concentrations of calcium channel blockers that are metabolized by CYP3A4. Frequent monitoring for adverse events and toxicity related to calcium channel blockers is recommended during coadministration. Dose adjustment of the calcium channel blocker may be needed (see PRECAUTIONS - Drug Interactions).

***Sulfonylureas* (CYP2C9 substrates):** Although not studied *in vitro* or *in vivo*, voriconazole may increase plasma concentrations of sulfonylureas (e.g., tolbutamide, glipizide, and glyburide) and therefore cause hypoglycemia. Frequent monitoring of blood glucose and appropriate adjustment (i.e., reduction) of the sulfonylurea dosage is recommended during coadministration (see PRECAUTIONS - Drug Interactions).

***Vinca Alkaloids* (CYP3A4 substrates):** Although not studied *in vitro* or *in vivo*, voriconazole may increase the plasma concentrations of the vinca alkaloids (e.g., vincristine and vinblastine) and lead to neurotoxicity. Therefore, it is recommended that dose adjustment of the vinca alkaloid be considered.

No significant pharmacokinetic interactions were observed when voriconazole was coadministered with the following agents. Therefore, no dosage adjustment for these agents is recommended:

***Prednisolone* (CYP3A4 substrate):** Voriconazole (200 mg Q12h x 30 days) increased C_{max} and AUC of prednisolone (60 mg single dose) by an average of 11% and 34%, respectively, in healthy subjects.

***Digoxin* (P-glycoprotein mediated transport):** Voriconazole (200 mg Q12h x 12 days) had no significant effect on steady state C_{max} and AUC_{τ} of digoxin (0.25 mg once daily for 10 days) in healthy subjects.

***Mycophenolic acid* (UDP-glucuronyl transferase substrate):** Voriconazole (200 mg Q12h x 5 days) had no significant effect on the C_{max} and AUC_t of mycophenolic acid and its major metabolite, mycophenolic acid glucuronide after administration of a 1 g single oral dose of mycophenolate mofetil.

Two-Way Interactions
Concomitant use of the following agents with voriconazole is contraindicated:

***Efavirenz*, a non-nucleoside reverse transcriptase inhibitor (CYP450 inducer; CYP3A4 inhibitor and substrate):** Steady state efavirenz (400 mg PO QD) decreased the steady state C_{max} and AUC_{τ} of voriconazole (400 mg PO Q12h for 1 day, then 200 mg PO Q12h for 8 days) by an average of 61% and 77%, respectively, in healthy subjects. Voriconazole at steady state (400 mg PO Q12h for 1 day, then 200 mg Q12h for 8 days) increased the steady state C_{max} and AUC_{τ} of efavirenz (400 mg PO QD for 9 days) by an average of 38% and 44%, respectively, in healthy subjects. **Coadministration of voriconazole and efavirenz is contraindicated** (see CONTRAINDICATIONS, PRECAUTIONS – Drug Interactions).

***Rifabutin* (potent CYP450 inducer):** Rifabutin (300 mg once daily) decreased the C_{max} and AUC_{τ} of voriconazole at 200 mg twice daily by an average of 67% (90% CI: 58%, 73%) and 79% (90% CI: 71%, 84%), respectively, in healthy subjects. During coadministration with rifabutin (300 mg once daily), the steady state C_{max} and AUC_{τ} of voriconazole following an increased dose of 400 mg twice daily were on average approximately 2-times higher, compared with voriconazole alone at 200 mg twice daily. Coadministration of voriconazole at 400 mg twice daily with rifabutin 300 mg twice daily increased the C_{max} and AUC_{τ} of rifabutin by an average of 3-times (90% CI: 2.2, 4.0) and 4-times (90% CI: 3.5, 5.4), respectively, compared to rifabutin given alone. **Coadministration of voriconazole and rifabutin is contraindicated.**

Significant drug interactions that may require dosage adjustment, frequent monitoring of drug levels and/or frequent monitoring of drug-related adverse events/toxicity:

***Phenytoin* (CYP2C9 substrate and potent CYP450 inducer):** Repeat dose administration of phenytoin (300 mg once daily) decreased the steady state C_{max} and AUC_{τ} of orally administered voriconazole (200 mg Q12h x 14 days) by an average of 50% and 70%, respectively, in healthy subjects. Administration of a higher voriconazole dose (400 mg Q12h x 7 days) with phenytoin (300 mg once daily) resulted in comparable steady state voriconazole C_{max} and AUC_{τ} estimates as compared to when voriconazole was given at 200 mg Q12h without phenytoin.

Phenytoin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased from 4 mg/kg to 5 mg/kg intravenously every 12 hours or from 200 mg to 400 mg orally, every 12 hours (100 mg to 200 mg orally, every 12 hours in patients less than 40 kg) (see DOSAGE AND ADMINISTRATION).

Repeat dose administration of voriconazole (400 mg Q12h x 10 days) increased the steady state C_{max} and AUC_{τ} of phenytoin (300 mg once daily) by an average of 70% and 80%, respectively, in healthy subjects. The increase in phenytoin C_{max} and AUC when coadministered with voriconazole may be expected to be as high as 2-times the C_{max} and AUC estimates when phenytoin is given without voriconazole. Therefore, frequent monitoring of plasma phenytoin concentrations and phenytoin-related adverse effects is recommended when phenytoin is coadministered with voriconazole (see PRECAUTIONS - Drug Interactions).

***Omeprazole* (CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate)**: Coadministration of omeprazole (40 mg once daily x 10 days) with oral voriconazole (400 mg Q12h x 1 day, then 200 mg Q12h x 9 days) increased the steady state C_{max} and AUC_{τ} of voriconazole by an average of 15% (90% CI: 5%, 25%) and 40% (90% CI: 29%, 55%), respectively, in healthy subjects. No dosage adjustment of voriconazole is recommended.

Coadministration of voriconazole (400 mg Q12h x 1 day, then 200 mg x 6 days) with omeprazole (40 mg once daily x 7 days) to healthy subjects significantly increased the steady state C_{max} and AUC_{τ} of omeprazole an average of 2-times (90% CI: 1.8, 2.6) and 4-times (90% CI: 3.3, 4.4), respectively, as compared to when omeprazole is given without voriconazole. When initiating voriconazole in patients already receiving omeprazole doses of 40 mg or greater, it is recommended that the omeprazole dose be reduced by one-half (see PRECAUTIONS - Drug Interactions).

The metabolism of other proton pump inhibitors that are CYP2C19 substrates may also be inhibited by voriconazole and may result in increased plasma concentrations of these drugs.

No significant pharmacokinetic interaction was seen and no dosage adjustment of these drugs is recommended:

***Indinavir* (CYP3A4 inhibitor and substrate):** Repeat dose administration of indinavir (800 mg TID for 10 days) had no significant effect on voriconazole C_{max} and AUC following repeat dose administration (200 mg Q12h for 17 days) in healthy subjects.

Repeat dose administration of voriconazole (200 mg Q12h for 7 days) did not have a significant effect on steady state C_{max} and AUC_{τ} of indinavir following repeat dose administration (800 mg TID for 7 days) in healthy subjects.

Other Two-Way Interactions Expected to be Significant Based on *In Vitro* Findings:

***Other HIV Protease Inhibitors* (CYP3A4 substrates and inhibitors):** *In vitro* studies (human liver microsomes) suggest that voriconazole may inhibit the metabolism of HIV protease inhibitors (e.g. saquinavir, amprenavir and nelfinavir). *In vitro* studies (human liver microsomes) also show that the metabolism of voriconazole may be inhibited by HIV protease inhibitors (e.g., saquinavir and amprenavir). Patients should be frequently monitored for drug toxicity during the coadministration of voriconazole and HIV protease inhibitors (see PRECAUTIONS - Drug Interactions).

***Other Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)* (CYP3A4 substrates, inhibitors or CYP450 inducers)**: *In vitro* studies (human liver microsomes) show that the metabolism of voriconazole may be inhibited by an NNRTI (e.g., delavirdine). The findings of a clinical voriconazole-efavirenz drug interaction study in healthy volunteers suggest that the metabolism of voriconazole may be induced by an NNRTI. The *in vivo* study also showed that voriconazole may inhibit the metabolism of a NNRTI. Efavirenz and voricoanzole coadministration is contraindicated (see CLINICAL PHARMACOLOGY- Drug Interactions, CONTRAINDICATIONS, PRECAUTIONS-Drug Interactions). Patients should be frequently monitored for drug toxicity during the coadministration of voriconazole and other NNRTIs (e.g. nevirapine and delavirdine) (see PRECAUTIONS - Drug Interactions).

MICROBIOLOGY

Mechanism of Action

Voriconazole is a triazole antifungal agent. The primary mode of action of voriconazole is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell wall and may be responsible for the antifungal activity of voriconazole. Voriconazole has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.

Activity *In Vitro* and *In Vivo*

Voriconazole has demonstrated *in vitro* activity against *Aspergillus* species (*A. fumigatus, A. flavus, A. niger* and *A. terreus*), *Candida* species (*C. albicans, C. glabrata, C. krusei*, *C. parapsilosis* and *C. tropicalis*), *Scedosporium apiospermum* and *Fusarium* spp., including *Fusarium solani*.(see INDICATIONS AND USAGE, CLINICAL STUDIES).

In vitro susceptibility testing was performed according to the National Committee for Clinical Laboratory Standards (NCCLS) methods (M38-P for moulds and M27-A for yeasts). Voriconazole breakpoints have not been established for any fungi. The relationship between clinical outcome and *in vitro* susceptibility results remains to be elucidated.

Voriconazole was active in normal and/or immunocompromised guinea pigs with systemic and/or pulmonary infections due to *A. fumigatus* (including an isolate with reduced susceptibility to itraconazole) or *Candida* species *[C.albicans* (including an isolate with reduced susceptibility to fluconazole), *C. krusei and C. glabrata]* in which the endpoints were prolonged survival of infected animals and/or reduction of mycological burden from target organs. In one experiment, voriconazole exhibited activity against *Scedosporium apiospermum* infections in immune competent guinea pigs.

Drug Resistance

Voriconazole drug resistance development has not been adequately studied *in vitro* against *Candida, Aspergillus, Scedosporium* and *Fusarium* species. The frequency of drug resistance development for the various fungi for which this drug is indicated is not known.

Fungal isolates exhibiting reduced susceptibility to fluconazole or itraconazole may also show reduced susceptibility to voriconazole, suggesting cross-resistance can occur among these azoles. The relevance of cross-resistance and clinical outcome has not been fully characterized. Clinical cases where azole cross-resistance is demonstrated may require alternative antifungal therapy.

INDICATIONS AND USAGE

VFEND is indicated for use in the treatment of the following fungal infections:

Invasive aspergillosis. In clinical trials, the majority of isolates recovered were *Aspergillus fumigatus*. There was a small number of cases of culture-proven disease due to species of *Aspergillus* other than *A. fumigatus* (see CLINICAL STUDIES, MICROBIOLOGY).

Candidemia in nonneutropenic patients and the following *Candida* infections: disseminated infections in skin and infections in abdomen, kidney, bladder wall, and wounds. (see CLINICAL STUDIES, MICROBIOLOGY).

Esophageal candidiasis. (see CLINICAL STUDIES, MICROBIOLOGY).

Serious fungal infections caused by *Scedosporium apiospermum* (asexual form of *Pseudallescheria boydii*) and *Fusarium* spp. including *Fusarium solani,* in patients intolerant of, or refractory to, other therapy. (see CLINICAL STUDIES, MICROBIOLOGY).

Specimens for fungal culture and other relevant laboratory studies (including histopathology) should be obtained prior to therapy to isolate and identify causative organism(s). Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

CLINICAL STUDIES

Voriconazole, administered orally or parenterally, has been evaluated as primary or salvage therapy in 520 patients aged 12 years and older with infections caused by *Aspergillus* spp., *Fusarium* spp., and *Scedosporium* spp.

Invasive Aspergillosis

Voriconazole was studied in patients for primary therapy of invasive aspergillosis (randomized, controlled study 307/602), for primary and salvage therapy of aspergillosis (non-comparative study 304) and for treatment of patients with invasive aspergillosis who were refractory to, or intolerant of, other antifungal therapy (non-comparative study 309/604).

Study 307/602

The efficacy of voriconazole compared to amphotericin B in the primary treatment of acute invasive aspergillosis was demonstrated in 277 patients treated for 12 weeks in Study 307/602. The majority of study patients had underlying hematologic malignancies, including bone marrow transplantation. The study also included patients with solid organ transplantation, solid tumors, and AIDS. The patients were mainly treated for definite or probable invasive aspergillosis of the lungs. Other aspergillosis infections included disseminated disease, CNS infections and sinus infections. Diagnosis of definite or probable invasive aspergillosis was made according to criteria modified from those established by the National Institute of Allergy and Infectious Diseases Mycoses Study Group/European Organisation for Research and Treatment of Cancer (NIAID MSG/EORTC).

Voriconazole was administered intravenously with a loading dose of 6 mg/kg every 12 hours for the first 24 hours followed by a maintenance dose of 4 mg/kg every 12 hours for a minimum of seven days. Therapy could then be switched to the oral formulation at a dose of 200 mg Q12h. Median duration of IV voriconazole therapy was 10 days (range 2-90 days). After IV voriconazole therapy, the median duration of PO voriconazole therapy was 76 days (range 2-232 days).

Patients in the comparator group received conventional amphotericin B as a slow infusion at a daily dose of 1.0-1.5 mg/kg/day. Median duration of IV amphotericin therapy was 12 days (range 1-85 days). Treatment was then continued with other licensed antifungal therapy (OLAT), including itraconazole and lipid amphotericin B formulations. Although initial therapy with conventional amphotericin B was to be continued for at least two weeks, actual duration of therapy was at the discretion of the investigator. Patients who discontinued initial randomized therapy due to toxicity or lack of efficacy were eligible to continue in the study with OLAT treatment.

A satisfactory global response at 12 weeks (complete or partial resolution of all attributable symptoms, signs, radiographic/bronchoscopic abnormalities present at baseline) was seen in 53% of voriconazole treated patients compared to 32% of amphotericin B treated patients (Table 4). A benefit of voriconazole compared to amphotericin B on patient survival at Day 84 was seen with a 71% survival rate on voriconazole compared to 58% on amphotericin B (Table 4).

Table 4 also summarizes the response (success) based on mycological confirmation and species.

Table 4
Overall Efficacy and Success by Species in the Primary Treatment of Acute Invasive Aspergillosis
Study 307/602

	Voriconazole	**Ampho B** [c]	Stratified Difference (95% CI) [d]
	n/N (%)	n/N (%)	
Efficacy as Primary Therapy			
Satisfactory Global Response [a]	76/144 (53)	42/133 (32)	21.8% (10.5%, 33.0%) p<0.0001
Survival at Day 84 [b]	102/144 (71)	77/133 (58)	13.1% (2.1%, 24.2%)
Success by Species			
	Success n/N (%)		
Overall success	76/144 (53)	42/133 (32)	
Mycologically confirmed [e]	37/84 (44)	16/67 (24)	
Aspergillus spp.[f]			
A. fumigatus	28/63 (44)	12/47 (26)	
A. flavus	3/6	4/9	
A. terreus	2/3	0/3	
A. niger	1/4	0/9	
A. nidulans	1/1	0/0	

a Assessed by independent Data Review Committee (DRC)
b Proportion of subjects alive
c Amphotericin B followed by other licensed antifungal therapy
d Difference and corresponding 95% confidence interval are stratified by protocol
e Not all mycologically confirmed specimens were speciated
f Some patients had more than one species isolated at baseline

Study 304

The results of this comparative trial (Study 307/602) confirmed the results of an earlier trial in the primary and salvage treatment of patients with acute invasive aspergillosis (Study 304). In this earlier study, an overall success rate of 52% (26/50) was seen in patients treated with voriconazole for primary therapy. Success was seen in 17/29 (59%) with *Aspergillus fumigatus* infections and 3/6 (50%) patients with infections due to non-*fumigatus* species [*A. flavus* (1/1); *A. nidulans* (0/2); *A. niger* (2/2); *A. terreus* (0/1)]. Success in patients who received voriconazole as salvage therapy is presented in Table 5.

Study 309/604

Additional data regarding response rates in patients who were refractory to, or intolerant of, other antifungal agents are also provided in Table 5. Overall mycological eradication for culture-documented infections due to *fumigatus* and non-*fumigatus* species of *Aspergillus* was 36/82 (44%) and 12/30 (40%), respectively, in voriconazole treated patients. Patients had various underlying diseases and species other than *A. fumigatus* contributed to mixed infections in some cases.

For patients who were infected with a single pathogen and were refractory to, or intolerant of, other antifungal agents, the satisfactory response rates for voriconazole in studies 304 and 309/604 are presented in Table 5.

Table 5 Combined Response Data in Salvage Patients with Single Aspergillus Species (Studies 304 and 309/604)

	Success n/N
A. fumigatus	43/97 (44%)
A. flavus	5/12
A. nidulans	1/3
A. niger	4/5
A. terreus	3/8
A. versicolor	0/1

Nineteen patients had more than one species of *Aspergillus* isolated. Success was seen in 4/17 (24%) of these patients.

Candidemia in nonneutropenic patients and other deep tissue *Candida* infections

Voriconazole was compared to the regimen of amphotericin B followed by fluconazole in Study 608, an open label, comparative study in nonneutropenic patients with candidemia associated with clinical signs of infection. Patients were randomized in a 2:1 ratio to receive either voriconazole (n= 283) or the regimen of amphotericin B followed by fluconazole (n=139). Patients were treated with randomized study drug for a median of 15 days. Most of the candidemia in patients evaluated for efficacy was caused by *C. albicans* (46%), followed by *C. tropicalis* (19%), *C. parapsilosis* (17%), *C. glabrata* (15%), and *C. krusei* (1%).

An independent Data Review Committee (DRC), blinded to study treatment, reviewed the clinical and mycological data from this study, and generated one assessment of response for each patient. A successful response required all of the following: resolution or improvement in all clinical signs and symptoms of infection, blood cultures negative for *Candida*, infected deep tissue sites negative for *Candida* or resolution of all local signs of infection, and no systemic antifungal therapy other than study drug. The primary analysis, which counted DRC-assessed successes at the fixed time point (12 weeks

after End of therapy [EOT]), demonstrated that voriconazole was comparable to the regimen of amphotericin B followed by fluconazole (response rates of 41% and 41%, respectively) in the treatment of candidemia. Patients who did not have a 12-week assessment for any reason were considered a treatment failure.

The overall clinical and mycological success rates by *Candida* species in Study 150-608 are presented in Table 6.

Table 6: Overall Success Rates Sustained From EOT To The Fixed 12-Week Follow-Up Time Point By Baseline Pathogen[a,b]

Baseline Pathogen	**Clinical and Mycological Success (%)**	
	Voriconazole	**Amphotericin B --> Fluconazole**
C. albicans	46/107 (43%)	30/63 (48%)
C. tropicalis	17/53 (32%)	1/16 (6%)
C. parapsilosis	24/45 (53%)	10/19 (53%)
C. glabrata	12/36 (33%)	7/21 (33%)
C. krusei	1/4	0/1

[a]A few patients had more than one pathogen at baseline

[b]Patients who did not have a 12-week assessment for any reason were considered a treatment failure

In a secondary analysis, which counted DRC-assessed successes at any time point (EOT, or 2, 6, or 12 weeks after EOT), the response rates were 65% for voriconazole and 71% for the regimen of amphotericin B followed by fluconazole.

In Studies 608 and 309/604 (non-comparative study in patients with invasive fungal infections who were refractory to, or intolerant of, other antifungal agents), voriconazole was evaluated in 35 patients with deep tissue *Candida* infections. A favorable response was seen in 4 of 7 patients with intraabdominal infections, 5 of 6 patients with kidney and bladder wall infections, 3 of 3 patients with deep tissue abscess or wound infection, 1 of 2 patients with pneumonia/pleural space infections, 2 of 4 patients with skin lesions, 1 of 1 patients with mixed intraabdominal and pulmonary infection, 1 of 2 patients with suppurative phlebitis, 1 of 3 patients with hepatosplenic infection, 1 of 5 patients with osteomyelitis, 0 of 1 with liver infection, and 0 of 1 with cervical lymph node infection.

Esophageal Candidiasis

The efficacy of oral voriconazole 200 mg bid compared to oral fluconazole 200 mg od in the primary treatment of esophageal candidiasis was demonstrated in Study 150-305, a double-blind, double-dummy, study in immunocompromised patients with endoscopically-proven esophageal candidiasis. Patients were treated for a median of 15 days (range 1 to 49 days). Outcome was assessed by repeat endoscopy at end of treatment (EOT). A successful response was defined as a normal endoscopy at EOT or at least a 1 grade improvement over baseline endoscopic score. For patients in the Intent To

Treat (ITT) population with only a baseline endoscopy, a successful response was defined as symptomatic cure or improvement at EOT compared to baseline. Voriconazole and fluconazole (200 mg od) showed comparable efficacy rates against esophageal candidiasis, as presented in Table 7.

Table 7
Success Rates in Patients Treated for Esophageal Candidiasis

Population	Voriconazole	Fluconazole	Difference % (95% CI)[a]
PP[b]	113/115 (98.2%)	134/141 (95.0%)	3.2 (-1.1, 7.5)
ITT[c]	175/200 (87.5%)	171/191 (89.5%)	-2.0 (-8.3, 4.3)

[a] Confidence Interval for the difference (Voriconazole – Fluconazole) in success rates.
[b] PP (Per Protocol) patients had confirmation of *Candida* esophagitis by endoscopy, received at least 12 days of treatment, and had a repeat endoscopy at EOT (end of treatment).
[c] ITT (Intent to Treat) patients without endoscopy or clinical assessment at EOT were treated as failures.

Microbiologic success rates by *Candida* species are presented in Table 8.

Table 8
Clinical and mycological outcome by baseline pathogen in patients with esophageal candidiasis (Study 150-305).

Pathogen[a]	**Voriconazole**		**Fluconazole**	
	Favorable endoscopic response[b]	**Mycological eradication[b]**	**Favorable endoscopic response[b]**	**Mycological eradication[b]**
	Success/Total (%)	Eradication/Total (%)	Success/Total (%)	Eradication/Total (%)
C. albicans	134/140 (96%)	90/107 (84%)	147/156 (94%)	91/115 (79%)
C. glabrata	8/8 (100%)	4/7 (57%)	4/4 (100%)	1/4 (25%)
C. krusei	1/1	1/1	2/2 (100%)	0/0

[a] Some patients had more than one species isolated at baseline
[b] Patients with endoscopic and/or mycological assessment at end of therapy

Other Serious Fungal Pathogens

In pooled analyses of patients, voriconazole was shown to be effective against the following additional fungal pathogens:

Scedosporium apiospermum - Successful response to voriconazole therapy was seen in 15 of 24 patients (63%). Three of these patients relapsed within 4 weeks, including 1 patient with pulmonary, skin and eye infections, 1 patient with cerebral disease, and 1 patient with skin infection. Ten patients had evidence of cerebral disease and 6 of these had a successful outcome (1 relapse). In addition, a successful response was seen in one of three patients with mixed organism infections.

Fusarium spp. - Nine of 21 (43%) patients were successfully treated with voriconazole. Of these nine patients, three had eye infections, one had an eye and blood infection, one had a skin infection, one had

a blood infection alone, two had sinus infections, and one had disseminated infection (pulmonary, skin, hepatosplenic). Three of these patients (one with disseminated disease, one with an eye infection and one with a blood infection) had *Fusarium solani* and were complete successes. Two of these patients relapsed, one with a sinus infection and profound neutropenia and one post surgical patient with blood and eye infections.

CONTRAINDICATIONS

VFEND is contraindicated in patients with known hypersensitivity to voriconazole or its excipients. There is no information regarding cross-sensitivity between VFEND (voriconazole) and other azole antifungal agents. Caution should be used when prescribing VFEND to patients with hypersensitivity to other azoles.

Coadministration of the CYP3A4 substrates, terfenadine, astemizole, cisapride, pimozide or quinidine with VFEND are contraindicated since increased plasma concentrations of these drugs can lead to QT prolongation and rare occurrences of *torsade de pointes* (see CLINICAL PHARMACOLOGY - Drug Interactions, PRECAUTIONS - Drug Interactions).

Coadministration of VFEND with sirolimus is contraindicated because VFEND significantly increases sirolimus concentrations in healthy subjects (see CLINICAL PHARMACOLOGY - Drug Interactions, PRECAUTIONS - Drug Interactions).

Coadministration of VFEND with rifampin, carbamazepine and long-acting barbiturates is contraindicated since these drugs are likely to decrease plasma voriconazole concentrations significantly (see CLINICAL PHARMACOLOGY - Drug Interactions, PRECAUTIONS - Drug Interactions).

Coadministration of VFEND with ritonavir (400 mg Q12h) is contraindicated because ritonavir (400 mg Q12h) significantly decreases plasma voriconazole concentrations in healthy subjects. The effect of ritonavir (100 mg Q12h as used to inhibit CYP3A and increase concentrations of other antiretroviral drugs) on voriconazole concentrations has not been studied (see CLINICAL PHARMACOLOGY - Drug Interactions, PRECAUTIONS - Drug Interactions).

Coadministration of VFEND with efavirenz is contraindicated because efavirenz significantly decreases voriconazole plasma concentrations while VFEND also significantly increases efavirenz plasma concentrations (see CLINICAL PHARMACOLOGY - Drug Interactions, PRECAUTIONS - Drug Interactions).

Coadministration of VFEND with rifabutin is contraindicated since VFEND significantly increases rifabutin plasma concentrations and rifabutin also significantly decreases voriconazole plasma concentrations (see CLINICAL PHARMACOLOGY - Drug Interactions, PRECAUTIONS - Drug Interactions).

Coadministration of VFEND with ergot alkaloids (ergotamine and dihydroergotamine) is contraindicated because VFEND may increase the plasma concentration of ergot alkaloids, which may lead to ergotism.

WARNINGS

VISUAL DISTURBANCES: **The effect of VFEND on visual function is not known if treatment continues beyond 28 days.** If treatment continues beyond 28 days, visual function including visual acuity, visual field and color perception should be monitored **(see PRECAUTIONS ï Information for Patients and ADVERSE EVENTS ï Visual Disturbances).**

HEPATIC TOXICITY: In clinical trials, there have been uncommon cases of serious hepatic reactions during treatment with VFEND (including clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities). Instances of hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly hematological malignancy). Hepatic reactions, including hepatitis and jaundice, have occurred among patients with no other identifiable risk factors. Liver dysfunction has usually been reversible on discontinuation of therapy **(see PRECAUTIONS ï Laboratory Tests and ADVERSE EVENTS ï Clinical Laboratory Values).**

Monitoring of hepatic function: Liver function tests should be evaluated at the start of and during the course of VFEND therapy. Patients who develop abnormal liver function tests during VFEND therapy should be monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of VFEND must be considered if clinical signs and symptoms consistent with liver disease develop that may be attributable to VFEND (see PRECAUTIONS - Laboratory Tests, DOSAGE AND ADMINISTRATION - Dosage Adjustment, ADVERSE EVENTS - Clinical Laboratory Tests).

Pregnancy Category D: Voriconazole can cause fetal harm when administered to a pregnant woman.

Voriconazole was teratogenic in rats (cleft palates, hydronephrosis/hydroureter) from 10 mg/kg (0.3 times the recommended maintenance dose (RMD) on a mg/m^2 basis) and embryotoxic in rabbits at 100 mg/kg (6 times the RMD). Other effects in rats included reduced ossification of sacral and caudal vertebrae, skull, pubic and hyoid bone, super numerary ribs, anomalies of the sternebrae and dilatation of the ureter/renal pelvis. Plasma estradiol in pregnant rats was reduced at all dose levels. Voriconazole treatment in rats produced increased gestational length and dystocia, which were associated with increased perinatal pup mortality at the 10 mg/kg dose. The effects seen in rabbits were an increased embryomortality, reduced fetal weight and increased incidences of skeletal variations, cervical ribs and extra sternebral ossification sites.

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Galactose intolerance: VFEND tablets contain lactose and should not be given to patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

PRECAUTIONS

General

(See WARNINGS, DOSAGE AND ADMINISTRATION)

Arrhythmias and QT prolongation

Some azoles, including voriconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During clinical development and post-marketing surveillance, there have been rare cases of arrhythmias, (including ventricular arrhythmias such as torsade de pointes), cardiac arrests and sudden deaths in patients taking voriconazole. These cases usually involved seriously ill patients with multiple confounding risk factors, such as history of cardiotoxic chemotherapy, cardiomyopathy, hypokalemia and concomitant medications that may have been contributory.

Voriconazole should be administered with caution to patients with these potentially proarrhythmic conditions.

Rigorous attempts to correct potassium, magnesium and calcium should be made before starting voriconazole (see CLINICAL PHARMACOLOGY- Pharmacokinetic-pharmacodynamic Relationships - Electrocardiogram).

Infusion Related Reactions

During infusion of the intravenous formulation of voriconazole in healthy subjects, anaphylactoid-type reactions, including flushing, fever, sweating, tachycardia, chest tightness, dyspnea, faintness, nausea, pruritus and rash, have occurred uncommonly. Symptoms appeared immediately upon initiating the infusion. Consideration should be given to stopping the infusion should these reactions occur.

Information for Patients

Patients should be advised:

- that VFEND Tablets or Oral Suspension should be taken at least one hour before, or one hour following, a meal.
- **that they should not drive at night while taking VFEND. VFEND may cause changes to vision, including blurring and/or photophobia.**
- **that they should avoid potentially hazardous tasks, such as driving or operating machinery if they perceive any change in vision.**
- that strong, direct sunlight should be avoided during VFEND therapy.

- that VFEND for Oral Suspension contains sucrose and is not recommended for patients with rare hereditary problems of fructose intolerance, sucrase-isomaltase deficiency or glucose-galactose malabsorption.

Laboratory Tests

Electrolyte disturbances such as hypokalemia, hypomagnesemia and hypocalcemia should be corrected prior to initiation of VFEND therapy.

Patient management should include laboratory evaluation of renal (particularly serum creatinine) and hepatic function (particularly liver function tests and bilirubin).

Drug Interactions

Tables 9 and 10 provide a summary of significant drug interactions with voriconazole that either have been studied *in vivo* (clinically) or that may be expected to occur based on results of *in vitro* metabolism studies with human liver microsomes. For more details, see CLINICAL PHARMACOLOGY - Drug Interactions.

Table 9 Effect of Other Drugs on Voriconazole Pharmacokinetics

Drug/Drug Class (Mechanism of Interaction by the Drug)	**Voriconazole Plasma Exposure (C_{max} and AUC_t after 200 mg Q12h)**	**Recommendations for Voriconazole Dosage Adjustment/Comments**
Rifampin*, Efavirenz** and Rifabutin* (CYP450 Induction)	Significantly Reduced	**Contraindicated**
Ritonavir (400mg Q12h HIV Protease Inhibitor)** (CYP450 Induction)	Significantly Reduced	**Contraindicated** The effect of ritonavir (100 mg Q12h as used to inhibit CYP3A and increase concentrations of other antiretroviral drugs) on voriconazole concentrations has not been studied.
Carbamazepine (CYP450 Induction)	Not Studied *In Vivo* or *In Vitro*, but Likely to Result in Significant Reduction	**Contraindicated**
Long Acting Barbiturates (CYP450 Induction)	Not Studied *In Vivo* or *In Vitro*, but Likely to Result in Significant Reduction	**Contraindicated**
Phenytoin* (CYP450 Induction)	Significantly Reduced	Increase voriconazole maintenance dose from 4 mg/kg to 5 mg/kg IV every 12 hrs or from 200 mg to 400 mg orally every 12 hrs (100 mg to 200 mg orally every 12 hrs in patients weighing less than 40 kg)
Other HIV Protease Inhibitors (CYP3A4 Inhibition)	*In Vivo* Studies Showed No Significant Effects of Indinavir on Voriconazole Exposure *In Vitro* Studies Demonstrate Potential for Inhibition of Voriconazole Metabolism	No dosage adjustment in the voriconazole dosage needed when coadministered with indinavir Frequent monitoring for adverse events and toxicity related to voriconazole

	(Increased Plasma Exposure)	when coadministered with other HIV protease inhibitors
Other NNRTIs*** (CYP3A4 Inhibition or CYP450 Induction)	*In Vitro* Studies Demonstrate Potential for Inhibition of Voriconazole Metabolism by Delavirdine and Other NNRTIs (Increased Plasma Exposure) A Voriconazole-Efavirenz Drug Interaction Study Demonstrates the Potential for the Metabolism of Voriconazole to be Induced by Efavirenz and Other NNRTIs (Decreased Plasma Exposure)	Frequent monitoring for adverse events and toxicity related to voriconazole Careful assessment of voriconazole effectiveness

*Results based on *in vivo* clinical studies generally following repeat oral dosing with 200 mg Q12h voriconazole to healthy subjects
**Results based on *in vivo* clinical study following repeat oral dosing with 400 mg Q12h for 1 day, then 200 mg Q12h for 8 days voriconazole to healthy subjects
*** Non-Nucleoside Reverse Transcriptase Inhibitors

Table 10 Effect of Voriconazole on Pharmacokinetics of Other Drugs

Drug/Drug Class (Mechanism of Interaction by Voriconazole)	**Drug Plasma Exposure (C_{max} and AUC_{t})**	**Recommendations for Drug Dosage Adjustment/Comments**
Sirolimus* (CYP3A4 Inhibition)	Significantly Increased	**Contraindicated**
Rifabutin* and Efavirenz** (CYP3A4 Inhibition)	Significantly Increased	**Contraindicated**
Ritonavir (400 mg Q12h HIV Protease Inhibitor)**(CYP3A4 Inhibition)	No significant effect of voriconazole on ritonavir C_{max} or AUC_{τ}	**Contraindicated** because of significant reduction of voriconazole C_{max} and AUC_{τ}
Terfenadine, Astemizole, Cisapride, Pimozide, Quinidine (CYP3A4 Inhibition)	Not Studied *In Vivo* or *In Vitro*, but Drug Plasma Exposure Likely to be Increased	**Contraindicated** because of potential for QT prolongation and rare occurrence of *torsade de pointes*
Ergot Alkaloids (CYP450 Inhibition)	Not Studied *In Vivo* or *In Vitro*, but Drug Plasma Exposure Likely to be Increased	**Contraindicated**
Cyclosporine* (CYP3A4 Inhibition)	AUC_{τ} Significantly Increased; No Significant Effect on C_{max}	When initiating therapy with VFEND in patients already receiving cyclosporine, reduce the cyclosporine dose to one-half of the starting dose and follow with frequent monitoring of cyclosporine blood levels. Increased cyclosporine levels have been associated with nephrotoxicity. When VFEND is discontinued, cyclosporine concentrations must be frequently monitored and the dose increased as necessary.
Tacrolimus* (CYP3A4 Inhibition)	Significantly Increased	When initiating therapy with VFEND in patients already receiving tacrolimus,

Drug/Drug Class (Mechanism of Interaction by Voriconazole)	Drug Plasma Exposure (C_{max} and AUC_t)	Recommendations for Drug Dosage Adjustment/Comments
		reduce the tacrolimus dose to one-third of the starting dose and follow with frequent monitoring of tacrolimus blood levels. Increased tacrolimus levels have been associated with nephrotoxicity. When VFEND is discontinued, tacrolimus concentrations must be frequently monitored and the dose increased as necessary.
Phenytoin* (CYP2C9 Inhibition)	Significantly Increased	Frequent monitoring of phenytoin plasma concentrations and frequent monitoring of adverse effects related to phenytoin.
Warfarin* (CYP2C9 Inhibition)	Prothrombin Time Significantly Increased	Monitor PT or other suitable anti-coagulation tests. Adjustment of warfarin dosage may be needed.
Omeprazole* (CYP2C19/3A4 Inhibition)	Significantly Increased	When initiating therapy with VFEND in patients already receiving omeprazole doses of 40 mg or greater, reduce the omeprazole dose by one-half. The metabolism of other proton pump inhibitors that are CYP2C19 substrates may also be inhibited by voriconazole and may result in increased plasma concentrations of other proton pump inhibitors.
Other HIV Protease Inhibitors (CYP3A4 Inhibition)	*In Vivo* Studies showed No Significant Effects on Indinavir Exposure *In Vitro* Studies Demonstrate Potential for Voriconazole to Inhibit Metabolism (Increased Plasma Exposure)	No dosage adjustment for indinavir when coadministered with VFEND Frequent monitoring for adverse events and toxicity related to other HIV protease inhibitors
Other NNRTIs*** (CYP3A4 Inhibition)	A Voriconazole-Efavirenz Drug Interaction Study Demonstrates the Potential for Voriconazole to Inhibit Metabolism of Other NNRTIs (Increased Plasma Exposure)	Frequent monitoring for adverse events and toxicity related to NNRTI
Benzodiazepines (CYP3A4 Inhibition)	*In Vitro* Studies Demonstrate Potential for Voriconazole to Inhibit Metabolism (Increased Plasma Exposure)	Frequent monitoring for adverse events and toxicity (i.e., prolonged sedation) related to benzodiazepines metabolized by CYP3A4 (e.g., midazolam, triazolam, alprazolam). Adjustment of benzodiazepine dosage may be needed.
HMG-CoA Reductase Inhibitors (Statins) (CYP3A4 Inhibition)	*In Vitro* Studies Demonstrate Potential for Voriconazole to Inhibit Metabolism (Increased Plasma Exposure)	Frequent monitoring for adverse events and toxicity related to statins. Increased statin concentrations in plasma have been associated with rhabdomyolysis. Adjustment of the statin dosage may be needed.

Drug/Drug Class (Mechanism of Interaction by Voriconazole)	Drug Plasma Exposure (C_{max} and AUC_t)	Recommendations for Drug Dosage Adjustment/Comments
Dihydropyridine Calcium Channel Blockers (CYP3A4 Inhibition)	*In Vitro* Studies Demonstrate Potential for Voriconazole to Inhibit Metabolism (Increased Plasma Exposure)	Frequent monitoring for adverse events and toxicity related to calcium channel blockers. Adjustment of calcium channel blocker dosage may be needed.
Sulfonylurea Oral Hypoglycemics (CYP2C9 Inhibition)	Not Studied *In Vivo* or *In Vitro*, but Drug Plasma Exposure Likely to be Increased	Frequent monitoring of blood glucose and for signs and symptoms of hypoglycemia. Adjustment of oral hypoglycemic drug dosage may be needed.
Vinca Alkaloids (CYP3A4 Inhibition)	Not Studied *In Vivo* or *In Vitro*, but Drug Plasma Exposure Likely to be Increased	Frequent monitoring for adverse events and toxicity (i.e., neurotoxicity) related to vinca alkaloids. Adjustment of vinca alkaloid dosage may be needed.

*Results based on *in vivo* clinical studies generally following repeat oral dosing with 200 mg BID voriconazole to healthy subjects
**Results based on *in vivo* clinical study following repeat oral dosing with 400 mg Q12h for 1 day, then 200 mg Q12h for 8 days voriconazole to healthy subjects
*** Non-Nucleoside Reverse Transcriptase Inhibitors

Patients with Hepatic Insufficiency

It is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B) receiving VFEND (see CLINICAL PHARMACOLOGY - Hepatic Insufficiency, DOSAGE and ADMINISTRATION - Hepatic Insufficiency).

VFEND has not been studied in patients with severe cirrhosis (Child-Pugh Class C). VFEND has been associated with elevations in liver function tests and clinical signs of liver damage, such as jaundice, and should only be used in patients with severe hepatic insufficiency if the benefit outweighs the potential risk. Patients with hepatic insufficiency must be carefully monitored for drug toxicity.

Patients with Renal Insufficiency

In patients with moderate to severe renal dysfunction (creatinine clearance <50 mL/min), accumulation of the intravenous vehicle, SBECD, occurs. Oral voriconazole should be administered to these patients, unless an assessment of the benefit/risk to the patient justifies the use of intravenous voriconazole. Serum creatinine levels should be closely monitored in these patients, and if increases occur, consideration should be given to changing to oral voriconazole therapy (see CLINICAL PHARMACOLOGY - Renal Insufficiency, DOSAGE AND ADMINISTRATION - Renal Insufficiency).

Renal Adverse Events

Acute renal failure has been observed in severely ill patients undergoing treatment with VFEND. Patients being treated with voriconazole are likely to be treated concomitantly with nephrotoxic medications and have concurrent conditions that may result in decreased renal function.

Monitoring of Renal Function
Patients should be monitored for the development of abnormal renal function. This should include laboratory evaluation, particularly serum creatinine.

Dermatological Reactions
Patients have rarely developed serious cutaneous reactions, such as Stevens-Johnson syndrome, during treatment with VFEND. If patients develop a rash, they should be monitored closely and consideration given to discontinuation of VFEND. VFEND has been infrequently associated with photosensitivity skin reaction, especially during long-term therapy. It is recommended that patients avoid strong, direct sunlight during VFEND therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Two-year carcinogenicity studies were conducted in rats and mice. Rats were given oral doses of 6, 18 or 50 mg/kg voriconazole, or 0.2, 0.6, or 1.6 times the recommended maintenance dose (RMD) on a mg/m^2 basis. Hepatocellular adenomas were detected in females at 50 mg/kg and hepatocellular carcinomas were found in males at 6 and 50 mg/kg. Mice were given oral doses of 10, 30 or 100 mg/kg voriconazole, or 0.1, 0.4, or 1.4 times the RMD on a mg/m^2 basis. In mice, hepatocellular adenomas were detected in males and females and hepatocellular carcinomas were detected in males at 1.4 times the RMD of voriconazole.

Voriconazole demonstrated clastogenic activity (mostly chromosome breaks) in human lymphocyte cultures *in vitro*. Voriconazole was not genotoxic in the Ames assay, CHO assay, the mouse micronucleus assay or the DNA repair test (Unscheduled DNA Synthesis assay).

Voriconazole produced a reduction in the pregnancy rates of rats dosed at 50 mg/kg, or 1.6 times the RMD. This was statistically significant only in the preliminary study and not in a larger fertility study.

Teratogenic Effects
Pregnancy category D. See WARNINGS

Women of Childbearing Potential
Women of childbearing potential should use effective contraception during treatment.

Nursing Mothers
The excretion of voriconazole in breast milk has not been investigated. VFEND should not be used by nursing mothers unless the benefit clearly outweighs the risk.

Pediatric Use
Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

A total of 22 patients aged 12-18 years with invasive aspergillosis were included in the therapeutic studies. Twelve out of 22 (55%) patients had successful response after treatment with a maintenance dose of voriconazole 4 mg/kg Q12h.

Sparse plasma sampling for pharmacokinetics in adolescents was conducted in the therapeutic studies (see CLINICAL PHARMACOLOGY - Pharmacokinetics, General Pharmacokinetic Characteristics).

Geriatric Use

In multiple dose therapeutic trials of voriconazole, 9.2% of patients were ≥ 65 years of age and 1.8% of patients were ≥ 75 years of age. In a study in healthy volunteers, the systemic exposure (AUC) and peak plasma concentrations (C_{max}) were increased in elderly males compared to young males. Pharmacokinetic data obtained from 552 patients from 10 voriconazole therapeutic trials showed that voriconazole plasma concentrations in the elderly patients were approximately 80% to 90% higher than those in younger patients after either IV or oral administration. However, the overall safety profile of the elderly patients was similar to that of the young so no dosage adjustment is recommended (see CLINICAL PHARMACOLOGY - Pharmacokinetics in Special Populations).

ADVERSE REACTIONS

Overview

The most frequently reported adverse events (all causalities) in the therapeutic trials were visual disturbances, fever, rash, vomiting, nausea, diarrhea, headache, sepsis, peripheral edema, abdominal pain, and respiratory disorder. The treatment-related adverse events which most often led to discontinuation of voriconazole therapy were elevated liver function tests, rash, and visual disturbances (see hepatic toxicity under WARNINGS and discussion of Clinical Laboratory Values and dermatological and visual adverse events below).

Discussion of Adverse Reactions

The data described in Table 11 reflect exposure to voriconazole in 1655 patients in the therapeutic studies. This represents a heterogeneous population, including immunocompromised patients, e.g., patients with hematological malignancy or HIV and nonneutropenic patients. This subgroup does not include healthy volunteers and patients treated in the compassionate use and non-therapeutic studies. This patient population was 62% male, had a mean age of 46 years (range 11-90, including 51 patients aged 12-18 years), and was 78% white and 10% black. In the initial regulatory filing, 561 patients had a duration of voriconazole therapy of greater than 12 weeks, with 136 patients receiving voriconazole for over six months. Table 11 includes all adverse events which were reported at an incidence of ≥2% during voriconazole therapy in the all therapeutic studies population, studies 307/602 and 608 combined, or study 305, as well as events of concern which occurred at an incidence of <2%.

In study 307/602, 381 patients (196 on voriconazole, 185 on amphotericin B) were treated to compare voriconazole to amphotericin B followed by other licensed antifungal therapy in the primary treatment of patients with acute invasive aspergillosis. In study 608, 403 patients with candidemia were treated to

compare voriconazole (272 patients) to the regimen of amphotericin B followed by fluconazole (131 patients). Study 305 evaluated the effects of oral voriconazole (200 patients) and oral fluconazole (191 patients) in the treatment of esophageal candidiasis. Laboratory test abnormalities for these studies are discussed under Clinical Laboratory Values below.

Table 11
Treatment Emergent Adverse Events

Rate [3] 2% on Voriconazole or Adverse Events of Concern in All Therapeutic Studies population, Studies 307/602-608 combined, or Study 305. Possibly Related to Therapy or Causality UnknownÀ

	All Therapeutic Studies	Studies 307/602 and 608 (IV/ oral therapy)			Study 305 (oral therapy)	
	Voriconazole N = 1655	Voriconazole N = 468	Ampho B* N=185	Ampho B? Fluconazole N= 131	Voriconazole N = 200	Fluconazole N =191
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Special Senses**						
Abnormal vision	310 (18.7)	63 (13.5)	1 (0.5)	0	31 (15.5)	8 (4.2)
Photophobia	37 (2.2)	8 (1.7)	0	0	5 (2.5)	2 (1.0)
Chromatopsia	20 (1.2)	2 (0.4)	0	0	2 (1.0)	0
Body as a Whole						
Fever	94 (5.7)	8 (1.7)	22 (11.9)	5 (3.8)	0	0
Chills	61 (3.7)	1 (0.2)	36 (19.5)	8 (6.1)	1 (0.5)	0
Headache	49 (3.0)	9 (1.9)	7 (3.8)	1 (0.8)	0	1 (0.5)
Cardiovascular System						
Tachycardia	39 (2.4)	6 (1.3)	3 (1.6)	0	0	0
Digestive System						
Nausea	89 (5.4)	18 (3.8)	25 (13.5)	2 (1.5)	2 (1.0)	3 (1.6)
Vomiting	72 (4.4)	15 (3.2)	17 (9.2)	1 (0.8)	2 (1.0)	1 (0.5)
Liver function tests abnormal	45 (2.7)	15 (3.2)	4 (2.2)	1 (0.8)	6 (3.0)	2 (1.0)
Cholestatic jaundice	17 (1.0)	8 (1.7)	0	1 (0.8)	3 (1.5)	0
Metabolic and Nutritional Systems						

	All Therapeutic Studies	Studies 307/602 and 608 (IV/ oral therapy)			Study 305 (oral therapy)	
	Voriconazole N = 1655	Voriconazole N = 468	Ampho B* N=185	Ampho B? Fluconazole N= 131	Voriconazole N = 200	Fluconazole N =191
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Alkaline phosphatase increased	59 (3.6)	19 (4.1)	3 (1.6)	3 (2.3)	10 (5.0)	3 (1.6)
Hepatic enzymes increased	30 (1.8)	11 (2.4)	3 (1.6)	1 (0.8)	3 (1.5)	0
SGOT increased	31 (1.9)	9 (1.9)	0	1 (0.8)	8 (4.0)	2 (1.0)
SGPT increased	29 (1.8)	9 (1.9)	1 (0.5)	2 (1.5)	6 (3.0)	2 (1.0)
Hypokalemia	26 (1.6)	3 (0.6)	35 (18.9)	16 (12.2)	0	0
Bilirubinemia	15 (0.9)	5 (1.1)	3 (1.6)	2 (1.5)	1 (0.5)	0
Creatinine increased	4 (0.2)	0	54 (29.2)	10 (7.6)	1 (0.5)	0
Nervous System						
Hallucinations	39 (2.4)	13 (2.8)	1 (0.5)	0	0	0
Skin and Appendages						
Rash	88 (5.3)	20 (4.3)	5 (2.7)	1 (0.8)	3 (1.5)	1 (0.5)
Urogenital						
Kidney function abnormal	10 (0.6)	6 (1.3)	30 (16.2)	9 (6.9)	1 (0.5)	1 (0.5)
Acute kidney failure	7 (0.4)	2 (0.4)	48 (25.9)	7 (5.3)	0	0

ÀStudy 307/602: invasive aspergillosis; Study 608: candidemia; Study 305: esophageal candidiasis
*Amphotericin B followed by other licensed antifungal therapy
** See WARNINGS – Visual Disturbances, PRECAUTIONS – Information For Patients

VISUAL DISTURBANCES: Voriconazole treatment-related visual disturbances are common. In clinical trials, approximately 30% of patients experienced altered/enhanced visual perception, blurred vision, color vision change and/or photophobia. The visual disturbances were generally mild and rarely resulted in discontinuation. Visual disturbances may be associated with higher plasma concentrations and/or doses.

The mechanism of action of the visual disturbance is unknown, although the site of action is most likely to be within the retina. In a study in healthy volunteers investigating the effect of 28-day treatment with voriconazole on retinal function, voriconazole caused a decrease in the electroretinogram (ERG) waveform amplitude, a decrease in the visual field, and an alteration in color perception. The ERG

measures electrical currents in the retina. The effects were noted early in administration of voriconazole and continued through the course of study drug dosing. Fourteen days after end of dosing, ERG, visual fields and color perception returned to normal (see WARNINGS, PRECAUTIONS – Information For Patients).

Dermatological Reactions: Dermatological reactions were common in the patients treated with voriconazole. The mechanism underlying these dermatologic adverse events remains unknown. In clinical trials, rashes considered related to therapy were reported by 7% (110/1655) of voriconazole-treated patients. The majority of rashes were of mild to moderate severity. Cases of photosensitivity reactions appear to be more likely to occur with long-term treatment. Patients have rarely developed serious cutaneous reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme during treatment with VFEND. If patients develop a rash, they should be monitored closely and consideration given to discontinuation of VFEND. It is recommended that patients avoid strong, direct sunlight during VFEND therapy.

Less Common Adverse Events

The following adverse events occurred in <2% of all voriconazole-treated patients in all therapeutic studies (N=1655). This listing includes events where a causal relationship to voriconazole cannot be ruled out or those which may help the physician in managing the risks to the patients. The list does not include events included in Table 11 above and does not include every event reported in the voriconazole clinical program.

Body as a Whole: abdominal pain, abdomen enlarged, allergic reaction, anaphylactoid reaction (see PRECAUTIONS), ascites, asthenia, back pain, chest pain, cellulitis, edema, face edema, flank pain, flu syndrome, graft versus host reaction, granuloma, infection, bacterial infection, fungal infection, injection site pain, injection site infection/inflammation, mucous membrane disorder, multi-organ failure, pain, pelvic pain, peritonitis, sepsis, substernal chest pain

Cardiovascular: atrial arrhythmia, atrial fibrillation, AV block complete, bigeminy, bradycardia, bundle branch block, cardiomegaly, cardiomyopathy, cerebral hemorrhage, cerebral ischemia, cerebrovascular accident, congestive heart failure, deep thrombophlebitis, endocarditis, extrasystoles, heart arrest, hypertension, hypotension, myocardial infarction, nodal arrhythmia, palpitation, phlebitis, postural hypotension, pulmonary embolus, QT interval prolonged, supraventricular extrasystoles, supraventricular tachycardia, syncope, thrombophlebitis, vasodilatation, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia (including *torsade de pointes)*

Digestive: anorexia, cheilitis, cholecystitis, cholelithiasis, constipation, diarrhea, duodenal ulcer perforation, duodenitis, dyspepsia, dysphagia, dry mouth, esophageal ulcer, esophagitis, flatulence, gastroenteritis, gastrointestinal hemorrhage, GGT/LDH elevated, gingivitis, glossitis, gum hemorrhage, gum hyperplasia, hematemesis, hepatic coma, hepatic failure, hepatitis, intestinal perforation, intestinal ulcer, jaundice, enlarged liver, melena, mouth ulceration, pancreatitis, parotid gland enlargement,

periodontitis, proctitis, pseudomembranous colitis, rectal disorder, rectal hemorrhage, stomach ulcer, stomatitis, tongue edema

Endocrine: adrenal cortex insufficiency, diabetes insipidus, hyperthyroidism, hypothyroidism

Hemic and Lymphatic: agranulocytosis, anemia (macrocytic, megaloblastic, microcytic, normocytic), aplastic anemia, hemolytic anemia, bleeding time increased, cyanosis, DIC, ecchymosis, eosinophilia, hypervolemia, leukopenia, lymphadenopathy, lymphangitis, marrow depression, pancytopenia, petechia, purpura, enlarged spleen, thrombocytopenia, thrombotic thrombocytopenic purpura

Metabolic and Nutritional: albuminuria, BUN increased, creatine phosphokinase increased, edema, glucose tolerance decreased, hypercalcemia, hypercholesteremia, hyperglycemia, hyperkalemia, hypermagnesemia, hypernatremia, hyperuricemia, hypocalcemia, hypoglycemia, hypomagnesemia, hyponatremia, hypophosphatemia, peripheral edema, uremia

Musculoskeletal: arthralgia, arthritis, bone necrosis, bone pain, leg cramps, myalgia, myasthenia, myopathy, osteomalacia, osteoporosis

Nervous System: abnormal dreams, acute brain syndrome, agitation, akathisia, amnesia, anxiety, ataxia, brain edema, coma, confusion, convulsion, delirium, dementia, depersonalization, depression, diplopia, dizziness, encephalitis, encephalopathy, euphoria, Extrapyramidal Syndrome, grand mal convulsion, Guillain-Barré syndrome, hypertonia, hypesthesia, insomnia, intracranial hypertension, libido decreased, neuralgia, neuropathy, nystagmus, oculogyric crisis, paresthesia, psychosis, somnolence, suicidal ideation, tremor, vertigo

Respiratory System: cough increased, dyspnea, epistaxis, hemoptysis, hypoxia, lung edema, pharyngitis, pleural effusion, pneumonia, respiratory disorder, respiratory distress syndrome, respiratory tract infection, rhinitis, sinusitis, voice alteration

Skin and Appendages: alopecia, angioedema, contact dermatitis, discoid lupus erythematosis, eczema, erythema multiforme, exfoliative dermatitis, fixed drug eruption, furunculosis, herpes simplex, maculopapular rash, melanosis, photosensitivity skin reaction, pruritus, psoriasis, skin discoloration, skin disorder, skin dry, Stevens-Johnson syndrome, sweating, toxic epidermal necrolysis, urticaria

Special Senses: abnormality of accommodation, blepharitis, color blindness, conjunctivitis, corneal opacity, deafness, ear pain, eye pain, eye hemorrhage, dry eyes, hypoacusis, keratitis, keratoconjunctivitis, mydriasis, night blindness, optic atrophy, optic neuritis, otitis externa, papilledema, retinal hemorrhage, retinitis, scleritis, taste loss, taste perversion, tinnitus, uveitis, visual field defect

Urogenital: anuria, blighted ovum, creatinine clearance decreased, dysmenorrhea, dysuria, epididymitis, glycosuria, hemorrhagic cystitis, hematuria, hydronephrosis, impotence, kidney pain,

kidney tubular necrosis, metrorrhagia, nephritis, nephrosis, oliguria, scrotal edema, urinary incontinence, urinary retention, urinary tract infection, uterine hemorrhage, vaginal hemorrhage

Clinical Laboratory Values

The overall incidence of clinically significant transaminase abnormalities in all therapeutic studies was 12.4% (206/1655) of patients treated with voriconazole. Increased incidence of liver function test abnormalities may be associated with higher plasma concentrations and/or doses. The majority of abnormal liver function tests either resolved during treatment without dose adjustment or following dose adjustment, including discontinuation of therapy.

Voriconazole has been infrequently associated with cases of serious hepatic toxicity including cases of jaundice and rare cases of hepatitis and hepatic failure leading to death. Most of these patients had other serious underlying conditions.

Liver function tests should be evaluated at the start of and during the course of VFEND therapy. Patients who develop abnormal liver function tests during VFEND therapy should be monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of VFEND must be considered if clinical signs and symptoms consistent with liver disease develop that may be attributable to VFEND (see WARNINGS and PRECAUTIONS - Laboratory Tests).

Acute renal failure has been observed in severely ill patients undergoing treatment with VFEND. Patients being treated with voriconazole are likely to be treated concomitantly with nephrotoxic medications and have concurrent conditions that may result in decreased renal function. It is recommended that patients are monitored for the development of abnormal renal function. This should include laboratory evaluation, particularly serum creatinine.

Tables 12, 13 and 14 show the number of patients with hypokalemia and clinically significant changes in renal and liver function tests in three randomized, comparative multicenter studies. In study 305, patients with esophageal candidiasis were randomized to either oral voriconazole or oral fluconazole. In study 307/602, patients with definite or probable invasive aspergillosis were randomized to either voriconazole or amphotericin B therapy. In study 608, patients with candidemia were randomized to either voriconazole or the regimen of amphotericin B followed by fluconazole.

Table 12
PROTOCOL 305
Clinically Significant Laboratory Test Abnormalities

	Criteria*	VORICONAZOLE	FLUCONAZOLE
		n/N (%)	n /N (%)
T. Bilirubin	>1.5x ULN	8/185 (4.3)	7/186 (3.8)
AST	>3.0x ULN	38/187 (20.3)	15/186 (8.1)
ALT	>3.0x ULN	20/187 (10.7)	12/186 (6.5)
Alk phos	>3.0x ULN	19/187 (10.2)	14/186 (7.5)

* Without regard to baseline value
n number of patients with a clinically significant abnormality while on study therapy
N total number of patients with at least one observation of the given lab test while on study therapy
ULN upper limit of normal

Table 13
PROTOCOL 307/602
Clinically Significant Laboratory Test Abnormalities

	Criteria*	VORICONAZOLE	AMPHOTERICIN B**
		n/N (%)	n/N (%)
T. Bilirubin	>1.5x ULN	35/180 (19.4)	46/173 (26.6)
AST	>3.0x ULN	21/180 (11.7)	18/174 (10.3)
ALT	>3.0x ULN	34/180 (18.9)	40/173 (23.1)
Alk phos	>3.0x ULN	29/181 (16.0)	38/173 (22.0)
Creatinine	>1.3x ULN	39/182 (21.4)	102/177 (57.6)
Potassium	<0.9x LLN	30/181 (16.6)	70/178 (39.3)

* Without regard to baseline value
** Amphotericin B followed by other licensed antifungal therapy
n number of patients with a clinically significant abnormality while on study therapy
N total number of patients with at least one observation of the given lab test while on study therapy
ULN upper limit of normal
LLN lower limit of normal

Table 14
PROTOCOL 608
Clinically Significant Laboratory Test Abnormalities

	Criteria*	VORICONAZOLE	AMPHOTERICIN B followed by FLUCONAZOLE
		n/N (%)	n/N (%)
T. Bilirubin	>1.5x ULN	50/261 (19.2)	31/115 (27.0)
AST	>3.0x ULN	40/261 (15.3)	16/116 (13.8)

ALT	>3.0x ULN	22/261 (8.4)	15/116 (12.9)
Alk phos	>3.0x ULN	59/261 (22.6)	26/115 (22.6)
Creatinine	>1.3x ULN	39/260 (15.0)	32/118 (27.1)
Potassium	<0.9x LLN	43/258 (16.7)	35/118 (29.7)

* Without regard to baseline value
n number of patients with a clinically significant abnormality while on study therapy
N total number of patients with at least one observation of the given lab test while on study therapy
ULN upper limit of normal
LLN lower limit of normal

OVERDOSE

In clinical trials, there were three cases of accidental overdose. All occurred in pediatric patients who received up to five times the recommended intravenous dose of voriconazole. A single adverse event of photophobia of 10 minutes duration was reported.

There is no known antidote to voriconazole.

Voriconazole is hemodialyzed with clearance of 121 mL/min. The intravenous vehicle, SBECD, is hemodialyzed with clearance of 55 mL/min. In an overdose, hemodialysis may assist in the removal of voriconazole and SBECD from the body.

The minimum lethal oral dose in mice and rats was 300 mg/kg (equivalent to 4 and 7 times the recommended maintenance dose (RMD), based on body surface area). At this dose, clinical signs observed in both mice and rats included salivation, mydriasis, titubation (loss of balance while moving), depressed behavior, prostration, partially closed eyes, and dyspnea. Other signs in mice were convulsions, corneal opacification and swollen abdomen.

DOSAGE AND ADMINISTRATION

Administration

VFEND Tablets or Oral Suspension should be taken at least one hour before, or one hour following, a meal.

VFEND I.V. for Injection requires reconstitution to 10 mg/mL and subsequent dilution to 5 mg/mL or less prior to administration as an infusion, at a maximum rate of 3 mg/kg per hour over 1-2 hours (see Intravenous Administration).

NOT FOR IV BOLUS INJECTION

Electrolyte disturbances such as hypokalemia, hypomagnesemia and hypocalcemia should be corrected prior to initiation of VFEND therapy (see PRECAUTIONS).

Use In Adults

Invasive aspergillosis and serious fungal infections due to *Fusarium* spp. and *Scedosporium apiospermum*:

For the treatment of adults with invasive aspergillosis and infections due to *Fusarium* spp. and *Scedosporium apiospermum*, therapy must be initiated with the specified loading dose regimen of intravenous VFEND to achieve plasma concentrations on Day 1 that are close to steady state. On the basis of high oral bioavailability, switching between intravenous and oral administration is appropriate when clinically indicated (see CLINICAL PHARMACOLOGY). Once the patient can tolerate medication given by mouth, the oral tablet form or oral suspension form of VFEND may be utilized. See Table 15)

Candidemia in nonneutropenic patients and other deep tissue *Candida* infections:
See Table 15. Patients should be treated for at least 14 days following resolution of symptoms or following last positive culture, whichever is longer.

Esophageal Candidiasis:
See Table 15. Patients should be treated for a minimum of 14 days and for at least 7 days following resolution of symptoms.

Table 15

Recommended Dosing Regimen

Infection	Loading dose	Maintenance Dose	
	IV	IV	Oral[a]
Invasive Aspergillosis	6 mg/kg q12h for the first 24 hours	4 mg/kg q12h	200 mg q12h
Candidemia in nonneutropenic patients and other deep tissue *Candida* infections	6 mg/kg q12h for the first 24 hours	3-4 mg/kg q12h[b]	200 mg q12h
Esophageal Candidiasis	[c]	[c]	200 mg q12h
Scedosporiosis and Fusariosis	6 mg/kg q12h for the first 24 hours	4 mg/kg q12h	200 mg q12h

[a]Patients who weigh 40 kg or more should receive an oral maintenance dose of 200 mg VFEND every 12 hours. Adult patients who weigh less than 40 kg should receive an oral maintenance dose of 100 mg every 12 hours.

[b] In clinical trials patients with candidemia received 3 mg/kg q12h as primary therapy while patients with other deep tissue *Candida* infections received 4 mg/kg as salvage therapy. Appropriate dose should be based on the severity and nature of the infection.
[c] Not evaluated in patients with esophageal candidiasis.

Dosage Adjustment
If patient response is inadequate, the oral maintenance dose may be increased from 200 mg every 12 hours to 300 mg every 12 hours. For adult patients weighing less than 40 kg, the oral maintenance dose may be increased from 100 mg every 12 hours to 150 mg every 12 hours. If patients are unable to tolerate 300 mg orally every 12 hours, reduce the oral maintenance dose by 50 mg steps to a minimum of 200 mg every 12 hours (or to 100 mg every 12 hours for adult patients weighing less than 40 kg).

If patients are unable to tolerate 4 mg/kg IV, reduce the intravenous maintenance dose to 3 mg/kg every 12 hours.

Phenytoin may be coadministered with VFEND if the intravenous maintenance dose of VFEND is increased to 5 mg/kg every 12 hours, or the oral maintenance dose is increased from 200 mg to 400 mg every 12 hours (100 mg to 200 mg every 12 hours in adult patients weighing less than 40 kg) (see CLINICAL PHARMACOLOGY, PRECAUTIONS - Drug Interactions).

Duration of therapy should be based on the severity of the patient's underlying disease, recovery from immunosuppression, and clinical response.

Use in Geriatric Patients
No dose adjustment is necessary for geriatric patients.

Use in Patients with Hepatic Insufficiency
In the clinical program, patients were included who had baseline liver function tests (ALT, AST) up to 5 times the upper limit of normal. No dose adjustment is necessary in patients with this degree of abnormal liver function, but continued monitoring of liver function tests for further elevations is recommended (see WARNINGS).

It is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B).

VFEND has not been studied in patients with severe hepatic cirrhosis (Child-Pugh Class C) or in patients with chronic hepatitis B or chronic hepatitis C disease. VFEND has been associated with elevations in liver function tests and clinical signs of liver damage, such as jaundice, and should only be used in patients with severe hepatic insufficiency if the benefit outweighs the potential risk. Patients with hepatic insufficiency must be carefully monitored for drug toxicity.

Use in Patients with Renal Insufficiency

The pharmacokinetics of orally administered VFEND are not significantly affected by renal insufficiency. Therefore, no adjustment is necessary for oral dosing in patients with mild to severe renal impairment (see CLINICAL PHARMACOLOGY - Special Populations).

In patients with moderate or severe renal insufficiency (creatinine clearance <50 mL/min), accumulation of the intravenous vehicle, SBECD, occurs. Oral voriconazole should be administered to these patients, unless an assessment of the benefit/risk to the patient justifies the use of intravenous voriconazole. Serum creatinine levels should be closely monitored in these patients, and, if increases occur, consideration should be given to changing to oral voriconazole therapy (see DOSAGE and ADMINISTRATION).

Voriconazole is hemodialyzed with clearance of 121 mL/min. The intravenous vehicle, SBECD, is hemodialyzed with clearance of 55 mL/min. A 4-hour hemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment.

Intravenous Administration
VFEND I.V. For Injection:

Reconstitution
The powder is reconstituted with 19 mL of Water For Injection to obtain an extractable volume of 20 mL of clear concentrate containing 10 mg/mL of voriconazole. It is recommended that a standard 20 mL (non-automated) syringe be used to ensure that the exact amount (19.0 mL) of water for injection is dispensed. Discard the vial if a vacuum does not pull the diluent into the vial. Shake the vial until all the powder is dissolved.

Dilution
VFEND must be infused over 1-2 hours, at a concentration of 5 mg/mL or less. Therefore, the required volume of the 10 mg/mL VFEND concentrate should be further diluted as follows (appropriate diluents listed below):

1. Calculate the volume of 10 mg/mL VFEND concentrate required based on the patient's weight (see Table 16).

2. In order to allow the required volume of VFEND concentrate to be added, withdraw and discard at least an equal volume of diluent from the infusion bag or bottle to be used. The volume of diluent remaining in the bag or bottle should be such that when the 10 mg/mL VFEND concentrate is added, the final concentration is not less than 0.5 mg/mL nor greater than 5 mg/mL.

3. Using a suitable size syringe and aseptic technique, withdraw the required volume of VFEND concentrate from the appropriate number of vials and add to the infusion bag or bottle. DISCARD PARTIALLY USED VIALS.

The final VFEND solution must be infused over 1-2 hours at a maximum rate of 3 mg/kg per hour.

Table 16 Required Volumes of 10 mg/mL VFEND Concentrate

Body Weight (kg)	Volume of VFEND Concentrate (10 mg/mL) required for:		
	3 mg/kg dose (number of vials)	4 mg/kg dose (number of vials)	6 mg/kg dose (number of vials)
30	9.0 mL (1)	12 mL (1)	18 mL (1)
35	10.5 mL (1)	14 mL (1)	21 mL (2)
40	12.0 mL (1)	16 mL (1)	24 mL (2)
45	13.5 mL (1)	18 mL (1)	27 mL (2)
50	15.0 mL (1)	20 mL (1)	30 mL (2)
55	16.5 mL (1)	22 mL (2)	33 mL (2)
60	18.0 mL (1)	24 mL (2)	36 mL (2)
65	19.5 mL (1)	26 mL (2)	39 mL (2)
70	21.0 mL (2)	28 mL (2)	42 mL (3)
75	22.5 mL (2)	30 mL (2)	45 mL (3)
80	24.0 mL (2)	32 mL (2)	48 mL (3)
85	25.5 mL (2)	34 mL (2)	51 mL (3)
90	27.0 mL (2)	36 mL (2)	54 mL (3)
95	28.5 mL (2)	38 mL (2)	57 mL (3)
100	30.0 mL (2)	40 mL (2)	60 mL (3)

VFEND I.V. for Injection is a single dose unpreserved sterile lyophile. Therefore, from a microbiological point of view, once reconstituted, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2° to 8°C (36° to 46°F). This medicinal product is for single use only and any unused solution should be discarded. Only clear solutions without particles should be used.

The reconstituted solution can be diluted with:

9 mg/mL (0.9%) Sodium Chloride USP
Lactated Ringers USP
5% Dextrose and Lactated Ringers USP
5% Dextrose and 0.45% Sodium Chloride, USP
5% Dextrose USP
5% Dextrose and 20 mEq Potassium Chloride, USP
0.45% Sodium Chloride USP
5% Dextrose and 0.9% Sodium Chloride, USP

The compatibility of VFEND I.V. with diluents other than those described above is unknown (see Incompatibilities below).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Incompatibilities:

VFEND I.V. must not be infused into the same line or cannula concomitantly with other drug infusions, including parenteral nutrition, e.g., Aminofusin 10% Plus. Aminofusin 10% Plus is physically incompatible, with an increase in subvisible particulate matter after 24 hours storage at 4ºC.

Infusions of blood products must not occur simultaneously with VFEND I.V.

Infusions of total parenteral nutrition can occur simultaneously with VFEND I.V.

VFEND I.V. must not be diluted with 4.2% Sodium Bicarbonate Infusion. The mildly alkaline nature of this diluent caused slight degradation of VFEND after 24 hours storage at room temperature. Although refrigerated storage is recommended following reconstitution, use of this diluent is not recommended as a precautionary measure. Compatibility with other concentrations is unknown.

VFEND for Oral Suspension

Reconstitution
Tap the bottle to release the powder. Add 46 mL of water to the bottle. Shake the closed bottle vigorously for about 1 minute. Remove child-resistant cap and push bottle adaptor into the neck of the bottle. Replace the cap. Write the date of expiration of the reconstituted suspension on the bottle label (the shelf-life of the reconstituted suspension is 14 days at controlled room temperature 15-30°C (59-86°F)).

Instructions for use
Shake the closed bottle of reconstituted suspension for approximately 10 seconds before each use. The reconstituted oral suspension should only be administered using the oral dispenser supplied with each pack.

Incompatibilities
VFEND for Oral Suspension and the 40 mg/mL reconstituted oral suspension should not be mixed with any other medication or additional flavoring agent. It is not intended that the suspension be further diluted with water or other vehicles.

HOW SUPPLIED

Powder for Solution for Injection
VFEND I.V. for Injection is supplied in a single use vial as a sterile lyophilized powder equivalent to 200 mg VFEND and 3200 mg sulfobutyl ether beta-cyclodextrin sodium (SBECD).

Individually packaged vials of 200 mg VFEND I.V.
(NDC 0049-3190-28)

Tablets

VFEND 50 mg tablets - white, film-coated, round, debossed with “Pfizer” on one side and “VOR50” on the reverse.

Bottles of 30 (NDC 0049-3170-30)

VFEND 200 mg tablets – white, film-coated, capsule shaped, debossed with “Pfizer” on one side and “VOR200” on the reverse.

Bottles of 30 (NDC 0049-3180-30)

Powder for Oral Suspension

VFEND for Oral Suspension is supplied in 100 mL high density polyethylene (HDPE) bottles. Each bottle contains 45 g of powder for oral suspension. Following reconstitution, the volume of the suspension is 75 mL, providing a usable volume of 70 mL (40 mg voriconazole/mL). A 5 mL oral dispenser and a press-in bottle adaptor are also provided.

(NDC 0049-3160-44)

STORAGE

VFEND I.V. for injection unreconstituted-vials should be stored at 15° - 30°C (59° - 86°F) [see USP Controlled Room Temperature]. VFEND is a single dose unpreserved sterile lyophile. From a microbiological point of view, following reconstitution of the lyophile with Water for Injection, the reconstituted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2° to 8°C (36° to 46°F). Chemical and physical in-use stability has been demonstrated for 24 hours at 2° to 8°C (36° to 46°F). This medicinal product is for single use only and any unused solution should be discarded. Only clear solutions without particles should be used (see DOSAGE AND ADMINISTRATION - Intravenous Administration).

VFEND Tablets should be stored at 15° - 30°C (59° - 86°F) [see USP Controlled Room Temperature].

VFEND Powder for Oral Suspension should be stored at 2 - 8°C (36- 46° F) (in a refrigerator) before reconstitution. The shelf-life of the powder for oral suspension is 18 months.
The reconstituted suspension should be stored at 15 - 30°C (59 - 86°F) [see USP Controlled Room Temperature]. Do not refrigerate or freeze. Keep the container tightly closed. The shelf-life of the reconstituted suspension is 14 days. Any remaining suspension should be discarded 14 days after reconstitution.

REFERENCES

1. National Committee for Clinical Laboratory Standards. Reference method for broth dilution antifungal susceptibility testing of conidium-forming filamentous fungi. Approved Standard M38-P. National Committee for Clinical Laboratory Standards, Villanova, Pa.

2. National Committee for Clinical Laboratory Standards. Reference method for broth dilution antifungal susceptibility testing of yeasts. Approved Standard M27-A. National Committee for Clinical Laboratory Standards, Villanova, Pa.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-266/S009
NDA 21-267/S009
NDA 21-630/S003

OFFICE DIRECTOR MEMO

Division Director Review of Voriconazole for candidemia (b) (4)

NDAs/Serial Number:	21-266 SE1-009 21-267 SE1-009 21-630 SE1-003
Drug Name:	VFEND™ (voriconazole) tablets , intravenous solution and powder for oral suspension
Indication(s):	Candidemia (b) (4)
Applicant:	Pfizer, Inc.
Date(s):	Stamp date: March 15, 2004 PDUFA date: January 15, 2005 Review date: December 20, 2004
Review Priority:	Standard

Recommended Regulatory Action:

I concur with the review team's recommendation that these supplemental efficacy applications be approved.

Labeling:

The company has requested the following wording for the indications section:

(b) (4)

After extensive internal discussion, review of other product labeling, including the labeling for the most recently approved product for this indication, caspofungin, as well as the recommendations at the 1995 advisory committee meeting on ABLC, the decision is that voriconazole has provided adequate data on patients with candidemia (b) (4) as part of the labeling (see detailed discussion below). Therefore, the wording for the indication in the labeling should be

(b) (4)

In addition, results of the studies that serve as the basis of approval are summarized in the CLINICAL STUDIES section (see 12/21/2004 submission of labeling).

(b) (4)

Post Marketing Commitments:

None identified for this application.

REVIEW:

The clinical, microbiology and statistical staff reviewed this application and some of their findings regarding efficacy are briefly summarized below.

NOTE: This review does not further address safety because this is covered in the clinical and ODS reviews. The labeling proposed by the applicant is acceptable and the applicant has agreed to revised the PRECAUTIONS section by including an update on arrhythmias and QT prolongation in the PRECAUTIONS section that was included in the present labeling based on post-marketing information and recommendations from the Office of Drug Safety.

Study Design:
The main study was 150-608, an open comparative study of voriconazole 6 mg/kg q 12 hours x 24 hours iv loading dose, followed by 3 mg/kg q 12 hours iv or (200 mg po q 12 hours) maintenance dose, compared to amphotericin B deoxycholate followed by oral fluconazole. A total of 422 patients were randomized (2:1). In this trial, the majority of patients had candidemia and a minority had other sites of infection, as seen in the table below.

Site of Infection: see table

SITE OF INFECTION				
Site of Infection (Definite/Probable)	VORICONAZOLE = 248		Amphotericin/fluoconazole = 122	
Candidemia/Invasive Candidiasis				
Eye *	28	(11.3%)	13	(10.7%)
Intra-abdominal	3	(1.2%)	3	(2.5%)
Joints	0		1	(0.8%)
Liver	1	(0.4%)	0	
Other (vascular thrombus)	5	(2.0%)	0	
Pulmonary	1	(0.4%)	1	(0.8%)
Renal	6	(2.4%)	5	(4.1%)
Candidemia	210	(84.7%)	100	(82.0%)

(b) (4)

(b) (4)

Patients enrolled in Study:
Risk factors for Candida infection include colonization by Candida species, use of intravascular devices, prior exposure to antibiotic use, neutropenia, surgical procedures, parenteral nutrition, renal failure, use of steroids, use of H_2 blockers, a high severity of illness score, or longer ICU stay [1]. Abdominal surgery is also predisposing factor for candidemia. Patients in Study-150-608 were relatively at high risk for fungal infection based on their inherent risk factors, such as ICU hospitalization, exposure to antimicrobials, surgery, mechanical ventilation, and prolonged intravascular access. Approximately, 99% of patients from either treatment groups were treated with antibiotics and half the patients were surgical patients (ratio of abdominal to non-abdominal surgery 3:1).

Efficacy Outcome:
The rates of outcome are presented in the table below. Success in the study was defined as patients who reached an endpoint of cure plus improvement. As can be seen, the success rates are approximately 40% for each arm, and the 95% confidence interval for the MITT and per protocol populations are -10.6, +10.6 and -11.1, +11.6, respectively, both of which are within the prespecified -15% delta.

> Cured (all criteria must be satisfied): All clinical signs and symptoms of fungal infection resolved, blood cultures for *Candida* were negative at two weeks post EOT, infected deep tissue sites remain negative for *Candida* or clinical signs and symptoms resolved, no other systemic antifungal agent was administered, ocular examination was negative for *Candida* endophthalmitis. This outcome was again documented at 12 weeks.
>
> Improved (all criteria must be satisfied): signs & symptoms of fungal infection showed improvement; blood cultures for *Candida* became negative, infected deep tissue sites with *Candida* became negative or signs of local infection have resolved, and no other systemic antifungal agent was administered for the episode of candidemia.

Study-150-608: Summary of DRC assessment of response to antifungal therapy at EOT+12-week (MITT & PP populations)
Source: 608.pdf Table 5.2.1 & 5.2.2 page:266-267

	Voriconazole		A→F		95% CI
	N	(%)	N	(%)	
MITT population					
Number of Subjects	248		122		
Outcome					
Cured	101	(40.7)	49	(40.2)	0.04%
Improved	0		1	(0.8)	{-10.6-10.6%}
Failed	147	(59.3)	72	(59.0)	
PP population					
Number of Subjects	214		105		
Outcome					
Cured	85	(39.7)	41	(39.0)	0.26%

1 Eggimann P, Garbino J, Pittet D. Epidemiology of *Candida* species infections in critically ill non-immunosuppressed patients. Lancet Infect Dis 2003;3:685-702.

Improved	0		1	(1.0)	{-11.1-11.6%}
Failed	129	(60.3)	63	(60.0)	

Note: All subjects not categorized by the DRC as cured or improved at 12 week follow-up are counted as failures.

In addition, a look at mortality in this trial shows a comparable rate with numerically a slightly greater percentage of patients alive on the voriconazole arm.

Study-150-608 Summary of DRC assessment of cause of death MITT population
Source: Section 13 Table 2.1.2

	Voriconazole		A→F	
	N	(%)	N	(%)
Number of Subjects	248		122	
Patient was alive at last follow-up	160	(64.5)	72	(59.0)
Died, candidemia probably contributory	27	(10.9)	14	(11.5)
Died, candidemia not contributory	1	(0.4)	1	(0.8)
Died, candidemia probably not contributory	60	(24.2)	35	(28.7)

Microbiological outcome for the study as a whole is presented below: *C albicans, C. parapsilosis, C. glabrata* and *C. tropicalis* were isolated most frequently. The efficacy of voriconazole is similar to the control, although patients with *C. tropicalis* did better on voriconazole.

Study-150-608 Summary of DRC assessment of response to antifungal therapy at EOT+12-week follow up by pathogen - MITT population
Source: 608.pdf Table 5.9.1 p:287,288, 289

		Voriconazole		A→F	
Pathogen	Outcome	N	(%)	N	(%)
Number of Subjects		248		122	
Candida albicans	Total	107		63	
	Cured	46	(43.0)	29	(46.0)
	Improved	0		1	(1.6)
	Failed	61	(57.0)	33	(52.4)
Non-albicans	Total	150		61	
	Cured	58	(38.7)	20	(32.8)
	Failed	92	(61.3)	41	(67.2)
Candida glabrata	Total	36		21	
	Cured	12	(33.3)	7	(33.3)
	Failed	24	(66.7)	14	(66.7)
Candida guilliermondii	Total	3		0	
	Cured	2	(66.7)	0	
	Failed	1	(33.3)	0	
Candida inconspicua	Total	2		0	
	Cured	0		0	
	Failed	2	(100.0)	0	
Candida kefyr	Total	2		0	
	Cured	1	(50.0)	0	
	Failed	1	(50.0)	0	
Candida krusei	Total	4		1	
	Cured	1	(25.0)	0	
	Failed	3	(75.0)	1	(100.0)
Candida lipolytica	Total	0		2	
	Cured	0		2	(100.0)
	Failed	0		0	

Study-150-608 Summary of DRC assessment of response to antifungal therapy at EOT+12-week follow up by pathogen - MITT population
Source: 608.pdf Table 5.9.1 p:287,288, 289

Candida lusitaniae	Total	2		1	
	Cured	1	(50.0)	0	
	Failed	1	(50.0)	1	(100.0)
Candida parapsilosis	Total	45		19	
	Cured	24	(53.3)	10	(52.6)
	Failed	21	(46.7)	9	(47.4)
Candida pelliculosa	Total	1		0	
	Cured	0		0	
	Failed	1	(100.0)	0	
Candida species	Total	5		2	
	Cured	1	(20.0)	0	
	Failed	4	(80.0)	2	(100.0)
Candida tropicalis	Total	53		16	
Candida tropicalis	Cured	17	(32.1)	1	(6.3)
	Failed	36	(67.9)	15	(93.8)
Subjects may have more than one pathogen					

An interesting evaluation challenge was presented by the study design in 150-608. In this trial, patients on the voriconazole arm were given IV voriconazole followed by PO voriconazole. Therefore, patients switched to another systemic antifungal due to toxicity were classified as failure. In the control arm, however, the IV agent was amphotericin while the oral control was fluconazole, and patients who discontinued amphotericin treatment and continued on fluconazole were not considered as failures. This helped explain the apparent difference in efficacy seen between the treatment arms at the end of therapy. In contrast, efficacy failure based on clinical and microbiology criteria was similar (see table below).

Study-150-608 Summary DRC assessment for failure at EOT (MITT population)
Pdf.608 Table 5.4.1 & 5.11.1 p:270, 297

	Voriconazole N=248	A→F N=122
DRC successful response (*cured* or *improved*)	162 (65.3%)	87 (71.3%)
DRC non-successful responses – All	86 (34.7%)	35 (28.7%)
Failure at EOT	**65 (26.2%)**	**26 (21.3%)**
Reasons for Failure[a]		
Blood cultures did not become negative (F0)	28 (11.3%)	12 (9.8%)
Study drug stopped for toxicity (F1)	22 (8.9%)	5 (4.1%)
Additional antifungal required (F2)	42 (16.9%)	12 (9.8%)
Failed: 'Other' reasons (F3)	19 (7.7%)	10 (8.2%)
Other non-successful outcomes	**21 (8.5%)**	**9 (7.4%)**
Indeterminate (A4)	3	2
Withdrawn (A5)	7	4
Relapse	11 (4.4%)	3 (2.5%)

Source: Tables 5.4.1 and 5.11.1; [a]a subject may have had more than one reasons for failure.
Other reasons (F3): example- progressive sepsis, no clinical improvement, slow clearance of blood cultures, persistent fever, renal failure, poor catheter management

Therefore, both the clinical and mycological efficacy supports the approval of these applications.

Specific Sites of Infection, other than bloodstream candidemia

As seen above, the majority of patients in this study had candidemia and there was a minimum number of patients with deep tissue infections. Therefore, an evaluation was done of deep tissue infection in Study 150-608, and also included in the evaluation were 26 patients from the non-comparative Study 309/604 in patients refractory and intolerant to other antifungal therapy.

The applicant presented a total of 14 patients from the MITT population in Study-150-608 had a "definite" site of deep tissue Candida infection. In addition, another 26 subjects with microbiologically confirmed deep tissue infection were identified from study 309/604. The success rate for deep tissue Candida infections from Study-150-608 was 5/9 (40.7%) patients in the voriconazole treatment group and 3/5 (40.2%) in the A→F treatment group. And success rate in Study 309/604 was 14/26 patients (53.8%).

Summary of Sites of Deep Tissue *Candida* Infection & Response to treatment
Source: clinical. PDF, modified Tables 11.2, 11.3 and 11.4, page:40/900

	Study-150-608 MITT (Category: Definite) Success/total		Study 309/604 (Mycologically confirmed)
Site of Infection	Voriconazole (n=9)	A→F (n=5)	Voriconazole (n=26)
Bone/Joints	0	0/1	1/5
Cervical lymph node	0	0	0/1
Hepatosplenic	0	0	1/3
Intra-abdominal	½	1/2	3/5
Intra-abdominal/pulmonary	1	0	0
Liver	0/1	0	0
Pulmonary	0	0	½
Renal	2/3	2/2	3/3
Skin lesion	0	0	2/4
Vascular thrombus	½	0	0
Wound abscess	0	0	3/3
Success/Total	5/9 (40.7%)	3/5 (40.2%)	14/26 (53.8%)

The microbiological outcome is presented below; there are too few individual isolates to draw valid conclusions regarding efficacy.

Summary of Response by Species at Deep Tissue sites
Source: clinical. PDF, modified Table 11.2 11.3, 11.4, page:51/900

Species	Primary Candidemia MITT (n=370)		Salvage Invasive Candidiasis (n=47)
	Voriconazole (n=9)	A→F (n=5)	Voriconazole* (n=26)
Total Pathogens	N=12	N=5	N=28
C albicans	5/7	2/3	4/7
C glabrata	2/2	1/1	3/7
C krusei	0/1	-	1/1
C parapsilosis	-	-	1/1
C tropicalis	½	0/1	2/3
C species	-	-	3/9

* One subject with *C species* had no outcome and was counted as a failure

(b) (4) In the table above, the overall response rates for definite deep tissue Candida infection in Study-150-608 appear similar in the

two treatment groups. Study 309/604 primarily enrolled a refractory/intolerant to standard antifungal therapy population of patients, which may be considered in support of patients from Study-150-608, but because of differences in study design and patient selection, should not be pooled.

A more detailed summary of the 9 patients from 150-608 is provided below

Liver: A patient with liver candidiasis failed voriconazole therapy
Kidney & Bladder: Nephrolithiasis was the underlying risk factor for infection in all 3 cases in Study-150-608. C. albicans & C. glabrata were isolated from one of the success cases, and C. glabrata was isolated from the second successful case. C. albicans was isolated from the third case that was a failure; incidentally, this failed therapy case was in a diabetic. Of the 3 Applicant designated successes from the salvage studies, one case was from a patient with C. krusi invasive bladder infection, the second case was in a patient with C. tropicalis; however, the third case should be indeterminate, due to lack of clarity in the CRF about further antifungal treatment, presence of fever, elevated white cell blood count, and abnormal imaging studies for the kidney.
Thrombus: Two patients had fungal thrombophlebitis, one was successfully treated.
Intraabdominal: There were 2/3 patients with intra-abdominal infection treated, primarily patients with post-surgical abscesses.

The following patients were studied in 150-309/604:

(b) (4)

Relevant Regulatory guidance and precedents taken into consideration:

(b) (4)

1 Page Immediately Following Withheld - b(4)

(b) (4)

(b) (4)

SUMMARY:

(b) (4) the applicant has provided adequate evidence that voriconazole is safe and effective in non-neutorpenic patients with candidiasis, (b) (4) Additional limited data is provided from the noncomparative compassionate use study in refractory/intolerant patients. (b) (4)

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/s/

Rebecca Saville
12/21/04 04:54:47 PM
CSO

Renata Albrecht
12/21/04 05:13:44 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-266/S009
NDA 21-267/S009
NDA 21-630/S003

CROSS DISCIPLINE TEAM LEADER REVIEW

MEDICAL OFFICER TEAM LEADER'S REVIEW

Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center fro Drug Evaluation and Research
US Food and Drug Administration
Marc Cavaillé-Coll, M.D., Ph.D.

NDAs/Serial Number:	21-266 SE1-009
	21-267 SE1-009
	21-630 SE1-003
Drug Name:	VFEND™ (voriconazole) tablets , intravenous solution and powder for oral suspension
Indication(s):	Candidemia (b) (4)
Applicant:	Pfizer, Inc.
Date(s):	Stamp date: March 15, 2004
	PDUFA date: January 15, 2005
	Review date: December 21, 2004
Review Priority:	Standard

I. Introduction:

Voriconazole is a triazole antifungal with activity against a wide range of yeasts and filamentous fungi, including *Candida, Aspergillus, Fusarium,* and *Scedosporium.* It has previously been approved for the treatment of invasive aspergillosis, the treatment of esophageal candidiasis, and the treatment of serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* spp, in patients intolerant of, or refractory to other therapy.

The indication being sought by the applicant in these supplemental NDAs is the treatment of candidemia (b) (4) including infections of the abdomen, kidney and bladder (b) (4) wounds, (b) (4) and disseminated skin infection. The proposed therapeutic dose and regimen voriconazole for candidemia is (b) (4) /kg I.V. or 200 mg oral tablet q12 following a loading dose of 6 mg/kg I.V. q12 for the first 24 hours. (b) (4) .

(b) (4)

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(b) (4)

The primary clinical review of these supplements was assigned to and conducted by Medical Officer, Dr. Sary Beidas. Dr. Beidas is (b) (6) before he could finalize his written review. This Medical Officer Team Leader's Review will present the essential findings and conclusions that were discussed with Dr. Beidas, as well as input from meetings and discussions with other members of the review team, and provide an overview of the important issues. Tables and citations have been abstracted from Dr. Beidas' drafts, and reflect much of the comprehensive review conducted by Dr. Beidas and the rest of the review team.

II. Summary of Clinical Findings

II.A. Brief Overview of the Clinical Program

The submission is supported by one adequate well-controlled, randomized, open-label, global study of the efficacy and safety of voriconazole versus conventional amphotericin B followed by fluconazole in the treatment of candidemia in non-neuropenic patients (Study-150-608) also referred to as the Global Candidemia Study. This study was designed in collaboration with the (b) (4) Efficacy conclusions from Study-150-608 support the use of voriconazole for the treatment of candidemia (b) (4) the non-neutropenic host.

Supportive efficacy data was also provided from Study 150-309/604, an open-label, non-comparative multicenter study of the efficacy and safety of voriconazole in the primary or secondary treatment of invasive fungal infections. The evaluation of treatment outcome in mycologically confirmed cases of Candida infection from Study 150-309/604 was used to support the efficacy of voriconazole in the treatment of Candida infection in specific sites or tissues.

II.B Efficacy

Study-150-608 was an open-label, randomized, comparative study designed to compare the efficacy of voriconazole [6 mg/kg q 12 hours x 24 hours, iv loading dose, followed by 3 mg/kg q 12 hours iv or (200 mg po q 12 hours) maintenance dose] to amphotericin B 0.7 mg/kg iv daily followed by fluconazole 400 mg po qd. The approved active study controls were acceptable comparators to voriconazole.

The enrollment period for the study was Sep 1988 through May 2003. Clinical sites recruited patients from 31 countries spanning the continents: Africa, Asia, Australia, Europe, North & South America. A total of 422 patients were randomized in a 2:1 ratio [283 voriconazole & 139 amphotericin B to fluconazole (A→F)].

Male and female subjects >12 years of age with a positive blood culture for Candida were eligible for enrollment in the study. The MITT (efficacy) population (defined as all patients with a positive blood culture for Candida in the 96 hours prior to study entry who received at least one dose of study medication) included 248 patients treated with voriconazole and 122 patients treated with A→F. A comparable proportion of patients in both treatment groups received prior antifungal therapy (<2 days) and in the majority of cases the antifungal agent was fluconazole (31% voriconazole group vs. 36% A→F group). Baseline demographic characteristics of the MITT population were comparable across treatment groups:

Demographic and Baseline Characteristics (MITT)

	Treatment Group	
	voriconazole	**ampho B → fluconazole**
# Patients	248	122
Gender		
Male	145 (58.5)	71 (58.2)
Female	103 (41.5)	51 (41.8)
Age mean (SD)	53.6 (18.1)	53.3 (19.4)
Min, max	13, 90	13, 87
Race		
White	151 (60.9)	61 (50.0)
Black	36 (14.5)	20 (16.4)
Asian	50 (20.2)	33 (27.1)
Other	11 (4.4)	8 (6.6)
Predisposing factor		
Abdominal surgery	95 (38.3)	46 (37.7)
Non-abdominal surgery	32 (12.9)	15 (12.3)
Non-surgical	121 (48.8)	61 (50.0)
Site of Infection		
Candidemia only	210 (84.7)	100 (82.0)
(b) (4)	(b) (4)	(b) (4)
Candidiasis		
Mechanical Ventilation		
Yes	89 (35.9)	47 (38.5)
No	159 (64.1)	75 (61.5)
ICU Hospitalization		
Yes	119 (48.0)	61 (50.0)
No	129 (52.0)	61 (50.0)

The primary objective of the study was to show that voriconazole was non-inferior to amphotericin B → fluconazole in the treatment of nonneutropenic subjects with candidemia.

For the primary analysis, the assessment of treatment outcome was performed by a Data Review Committee (DRC) blinded to study drug assignment. The following criteria were used to characterize the outcome.

- Improved (all criteria had to be satisfied)
  1. Clinical signs and symptoms of fungal infection present at baseline during the episode of candidemia had improved but persistent systemic candidiasis could not be completely excluded.
  2. Blood cultures had become negative for *Candida*.
  3. Infected deep tissue sites had become negative for *Candida* or all clinical signs of local infection had resolved.
  4. No systemic antifungal agent, other than study drug, was administered for the candidemia episode.
- Cured (at 2, 6 or 12 weeks after EOT only; all criteria had to be satisfied)
  1. All clinical signs and symptoms of fungal infection present during the candidemia episode had resolved.
  2. Blood cultures remained negative for *Candida*.
  3. Infected deep tissue sites remained negative for *Candida* or all clinical signs of local infection had resolved.
  4. No systemic antifungal agent, other than study drug, was administered for the candidemia episode.
  5. Ocular examination did not show lesions of *Candida* endophthalmitis.
- Failed
  1. Unresponsive or progressive fungal infection while receiving treatment, or
  2. the subject required additional antifungal therapy for the candidemia episode after study drug discontinuation.
- Relapsed [at 2, 6, and 12 weeks after end of therapy only (EOT)]

Subjects who were considered cured or improved at a previous evaluation but had subsequently developed positive blood cultures for *Candida*, developed a deep-seated *Candida* infection, or required additional treatment with a systemic antifungal for the candidemia episode.

- Indeterminate (at EOT only)

Subjects who cannot be classified as improving or failing.

The primary efficacy endpoint was the DRC success rate 12 weeks after EOT. Subjects the DRC defined as cured or improved 12 weeks after EOT were classified as a success. Any subject not scored as cured or improved 12 weeks after EOT was considered a failure.

The primary efficacy analysis was based on the MITT population. This population included all patients who received at least 1 dose of therapy, had a positive blood culture

of a *Candida spp.* from a sample taken in the 96 hours prior to study entry, and had not previously participated in the study.

A similar proportion of patients across the treatment groups were treatment successes [voriconazole 40.7% (101/248) compared to A→F 40.7% (50/122)]. The difference in the point estimates of the primary efficacy endpoint, success, (voriconazole minus A→F) at 12-weeks after EOT was 0.04% with a 95% confidence interval of ,-10.55 to +10.63%, which was within the pre-specified lower bound of the 95% confidence interval used to define non-inferiority, -15.0 . The primary efficacy results were supported by the Medical Officer's exploratory review of a random sample of cases.

Note that for the primary endpoint, any subject not scored as a success at 12 weeks after EOT was considered a failure. Thus, in addition to actual DRC-assessed failures, subjects who did not have a 12 week after EOT assessment including those who died after being considered successfully treated at EOT or were lost to follow-up were also considered failures in the above analysis. Therefore, two additional analyses were performed to determine to robustness of the primary analysis. One was response at EOT which is most consistent with the time point used to assess the efficacy of the last antifungal approved for candidemia. The other was the DRC response at the latest available timepoint, a secondary endpoint stated by the applicant. This endpoint can be interpreted as an EOT analysis which counts anyone who relapses after EOT as a failure. These results are summarized in the table below (Table 3 from the FDA Statistical Review and Evaluation).

Sensitvity Analysis MITT Population

	voriconazole (n=248)	**ampho B → fluc** (n=122)	**Difference (95% CI)***
EOT	173 (69.8)	90 (73.8)	-3.9 (-14.2, 6.4)
Last available timepoint	162 (65.3)	87 (71.3)	-5.9 (-16.5, 4.7)

*Difference (vori- ampho B →fluc) and confidence interval are stratified by region.

Study-150-309/604 was an open-label, non-comparative, multicenter, phase III study of voriconazole for the treatment of invasive fungal infections in patients refractory or intolerant to approved antifungal therapies. The dosing regimen for voriconazole was similar to the dose used in Study-150-608 (exception: during the iv maintenance phase, 4 mg/kg q 12 was used instead of 3 mg/kg). The efficacy population included 130 patients from study-309 and 150 patients from study-604. The subset of patients from both studies with candidemia was 21 patients; an additional 11 patients had disseminated candidiasis and 17 patients were listed under the category "other than candidemia." The clinical review focused on the latter (11+17) cases (b) (4)

Site of infection: In study 150-608 the majority of the subjects had candidemia alone (87.4% in the voriconazole group and 82.0% in the amphotericin B to fluconazole group). Due to the small number of cases of definite deep tissue infection in Study-150-608 and

in Study 309/604, the analysis presented here is a consolidated analysis rather than a comparative analysis.

The Applicant identified 14 patients from the MITT population in Study-150-608 with a "definite" site of deep tissue Candida infection. In addition, another 26 subjects with microbiologically confirmed deep tissue infection were identified from Study-150-309/604.

The success rate for deep tissue Candida infections from Study-150-608 was 5/9 (40.7%) patients in the voriconazole treatment group and 3/5 (40.2%) in the A→F treatment group. The success rate in Study-150-309/604 was 14/26 patients (53.8%).

Summary of Sites of Deep Tissue *Candida* Infection & Response to treatment
Source: clinical. PDF, modified Tables 11.2, 11.3 and 11.4, page:40/900

	Study-150-608 MITT (Category: Definite) Success/total		Study 309/604 (Mycologically confirmed)
Site of Infection	Voriconazole (n=9)	A→F (n=5)	Voriconazole (n=26)
Bone/Joints	0	0/1	1/5
Cervical lymph node	0	0	0/1
Hepatosplenic	0	0	1/3
Intra-abdominal	1/2	½	3/5
Intra-abdominal/pulmonary	1	0	0
Liver	0/1	0	0
Pulmonary	0	0	½
Renal	2/3	2/2	3/3
Skin lesion	0	0	2/4
Vascular thrombus	1/2	0	0
Wound abscess	0	0	3/3
Success/Total	5/9 (40.7%)	3/5 (40.2%)	14/26 (53.8%)

The individual cases were reviewed by the Medical Officer. Additional information was provided by the applicant on two cases that needed clarification. This information was reviewed by the Medical Officer Team Leader. In the end, we are in general agreement with the Applicant's data as presented in the table above. Although the amount of cases evaluated is small, there is sufficient information to support the indications of treatment of the following *Candida* infections: disseminated infections of the skin, and infections of the abdomen, in kidney, bladder wall and wounds.

(b) (4)

(b) (4)

Clinical Microbiology: In Study-150-608, non-albicans *Candida* were isolated with the same or higher frequency from both treatment groups, see table below.

Study-150-608 Baseline Candida species isolated at Baseline (MITT population)
Source: 608.pdf p:50

No of Subjects	Voriconazole (N=248)	Amphotericin B → fluconazole (N=122)
Candida albicans	107 (43%)	63 (52%)
Non-*albicans Candida*	150 (60%)	61 (50%)
C. glabrata	36	21
C. guilliermondii	3	0
C. inconspicua	2	0
C. kefyr	2	0
C. krusei	4	1
C. lipolytica	0	2
C. lusitaniae	2	1
C. parapsilosis	45	19
C. pelliculosa	1	0
C. species	5	2
C. tropicalis	53	16

Source: Tables 5.9.1 and 5.9.2; Subjects could have more than one baseline pathogen

The overall clinical and mycological success rates by *Candida* species in Study 150-608 are presented in the table below:

Overall Success Rates Sustained From EOT To The Fixed 12-Week Follow-Up Time Point By Baseline Pathogen [a,b]

Baseline Pathogen	Clinical and Mycological Success (%)	
	Voriconazole	Amphotericin B --> Fluconazole
C. albicans	46/107 (43%)	30/63 (48%)
C. tropicalis	17/53 (32%)	1/16 (6%)
C. parapsilosis	24/45 (53%)	10/19 (53%)
C. glabrata	12/36 (33%)	7/21 (33%)
C. krusei	1/4	0/1

[a]Some patients had more than one pathogen at baseline.
[b]Patients who did not have a 12-week assessment for any reason were considered a treatment failure.

Voricinazole showed efficacy against *C. albicans, C. tropicalis* and *C. parapsilosis*. (b) (4)
For more information, please see the Microbiological Review by Dr. Survana.

Efficacy Conclusions: There is sufficient information to support the efficacy of voriconazole in the treatment of Candidemia in non-neutropenic patients and the following *Candida* infections: disseminated infections of the skin, and infections of the abdomen, in kidney, bladder wall and wounds. (b) (4)

(b) (4)

II.C Safety

The Applicant submitted safety data from 3 studies (Table below). Safety population in was defined as all subjects who receive at least one dose of study treatment. This safety review focuses primarily on safety findings from Study-150-608, because the other studies were reviewed in the original NDA. In addition, the supportive studies were not limited to the proposed indication of candidemia, but included a variety of infections with different fungal microorganisms. Information from the supportive studies was reviewed primarily for efficacy.

Studies included in this submission
Source: M2 clinical. PDF Table 1, p:146/900.

Study/ number	Design	Number of subjects treated	Study population
150-608	Open, MC, randomized, comparative,	Voriconazole = 272 A→F = 131	Non-neutropenic subjects with candidemia. Safety population in Study-150-608 was defined as all subjects who receive at least one dose of study treatment.
150-309/604 (Salvage Invasive Fungal Infection)	Open, non-comparative, MC	Voriconazole = 372	Subjects with a diagnosis at baseline of a systemic or invasive fungal infection for which there was no licensed therapy or systemic or invasive fungal infections(including *Aspergillus* and *Candida* infections) with evidence of failure and/or intolerance/toxicity to currently approved treatments.
150-603 (Empirical Therapy)	Open, MC, randomized, comparative,	Voriconazole = 421 L-AMB = 428	Immunocompromised subjects with persistent fever and neutropenia

MC = multicenter, A = conventional amphotericin B, L-AMB = liposomal amphotericin B

In the report of Study 150-608 the sponsor tabulated treatment emergent adverse events (AE) occurring during the study period or within 7 days of end of treatment by body system, severity, and relationship to study drug.

Note that subjects switched to fluconazole from amphotericin B because of intolerance or adverse event were not counted as treatment discontinuations, whereas subjects switched from voriconazole to another antifungal regimen were considered as treatment discontinuations. Thus, one should interpret with caution rates of discontinuation from study due to AEs across study groups.

Serious AEs were defined as events that resulted in death, life threatening, required hospitalization or prolongation of existing hospitalization, resulted in persistent disability

or congenital anomaly/birth defect. Laboratory data for patients were evaluated for clinically significant abnormalities from baseline to the last treatment visit. Median values for laboratory changes were calculated and presented in tables. The sponsor also provided other safety measures including vital signs, ECG analysis, and visual function tests.

Baseline demographic characteristics (safety population): In Study-150-608 the baseline demographic characteristics (for age, race, weight, and height) were comparable across the treatment groups (Table below). Underlying medical conditions were comparable across the treatment groups with the exception of a slightly higher rate of thrombocytopenia in the A→F group 16/131 (12%) compared to the voriconazole group 17/272 (6%). The rate of ischemic heart disease [voriconazole group 34/272 (12.5%) compared to A→F group 11/131 (8.4%)] and similarly cardiac dysrhythmias were numerically higher in the voriconazole group[voriconazole 37/272 13.6%) compared to A→F 13/131 (9.9%)]. Other baseline demographic characteristics such as APACHE II score, site of infection, risk factors for candidemia were comparable across the treatment groups.

Study-150-608 Baseline demographic characteristics (Safety population)
Source: 608.pdf Table 2.1.1 page 93

		VORICONAZOLE			A→F		
		TOTAL	FEMALE	MALE	TOTAL	FEMALE	MALE
NUMBER OF SUBJECTS		272	114	158	131	56	75
Age (years)	< 18	5	0	5	6	4	2
	18 - 44	75	34	41	35	17	18
	45 - 64	103	40	63	44	16	28
	>= 65	89	40	49	46	19	27
Range	From:	13	18.0	13.0	13.0	14.0	13.0
	To:	90	90.0	89.0	87.0	85.0	87.0
Mean Age		53.8	55.6	52.4	53.2	51.4	54.5
Race:	White	165	68	97	63	30	33
	Black	42	17	25	23	9	14
	Asian	51	22	29	37	15	22
	Other	14	7	7	8	2	6
Weight Range (kg)	From:	30	30.0	35.0	25.0	31.6	25.0
	To:	129.5	125.0	129.5	130.0	130.0	120.4
Mean Weight		69.1	64.3	72.6	63.7	59.2	67.1
Height Range (cm)	From:	140	140.0	147.0	139.7	139.7	140.0
	To:	190	175.3	190.0	183.0	180.0	183.0
Mean Height		168.3	160.8	173.3	166.0	159.3	171.1

Exposure to study drug: Voriconazole was administered as a loading dose 6 mg/kg iv every 12 hours for 24 hours followed by maintenance doses of 3 mg/kg iv every 12

hours. The oral dose of voriconazole was 200 mg twice daily, but this could be reduced to 100 mg bid for subjects weighing less than 40 kg. It could be escalated to 300 mg bid or to 150 mg for subjects weighing less than 40 kg. Amphotericin B was administered as 0.7 mg/kg/day. Fluconazole was administered as 400 mg, iv or oral, daily.

Overall, the median duration of therapy with voriconazole was 15 days. All patients in the voriconazole group received iv voriconazole and 114/272 (42%) also received oral voriconazole. Median duration of treatment for iv administered voriconazole was 9 days and for oral voriconazole 11 days. A majority of patients in the voriconazole group 57% (157/272) received study drug for >14 days.

Deaths: By Day-98 after randomization the death rates were, 98/272 (36%) & 55/131 (42%) of patients in the voriconazole and amphotericin B to fluconazole groups respectively. Common reasons for death included sepsis or septic shock, multiorgan failure, cardiac or respiratory arrest, and respiratory failure. The death rates were comparable for the two treatment groups.

Other Serious Adverse Events: The proportion of patients in the safety population who experienced a serious AE was 64% (175/272) and 81% (106/131) in the voriconazole and A→F groups respectively. Common serious AEs included, sepsis, respiratory failure, cardiac arrest, hypotension and cardio-respiratory arrest in descending order of frequency. The rates of these events were comparable across treatment groups.

Study-150-608 All causality serious AEs by (Safety population)
Source: Modified 608.pdf Table 6.4.1 p:350-359

No of Subjects	Voriconazole	A→F
Treated	272	131
With ≥1 adverse event	175 (64%)	106 (81%)
Cardiac arrest	21 (8%)	12 (9%)
Cardio-respiratory arrest	14 (5%)	8 (6%)
Multi-organ failure	9 (3%)	11 (8%)
Sepsis (not otherwise specified)	32 (12%)	20 (15%)
Septic shock	13 (5%)	6 (5%)
Acute renal failure	11 (4%)	7 (5%)
Respiratory failure	26 (10%)	16 (12%)
Hypotension (not otherwise specified)	16 (6%)	11 (8%)

Treatment related serious adverse events were also analyzed. There were 17 patients (6.3%) with treatment related serious AEs (causality assigned by investigator) in the voriconazole group compared to 11 patients (8.4%) in the amphotericin B→fluconazole group. Patients in the amphotericin B→fluconazole group were switched to fluconazole when a serious AE occurred. As expected, serious AEs in the amphotericin B→fluconazole group were related to renal, cardiovascular, respiratory systems.

Discontinuation from study: A similar proportion of patients in both treatment groups were discontinued from the study [voriconazole 150/272 (55%) vs. amphotericin B to

fluconazole 72/131 (55%)]. Common causes for discontinuation were death, adverse events, laboratory abnormality, protocol violation. Less common reasons (≤4%) included: withdrawn consent, lost to follow/up, insufficient clinical response, other, and did not meet entrance criteria. A comparable proportion of patients in the study discontinued due to an adverse event related to study drug [voriconazole 17 (6.3%) patients and 6 (4.6%) patients in the amphotericin B to fluconazole]. Frequent causes of study discontinuation due to adverse event included cardiovascular 13 (4.8%), urogenital 12 (4.4%), and digestive 10 (3.7%) events in the voriconazole group compared to a frequency of 2 (1.5%0, 2(1.5%), and 2 (1.5%) in the respective body systems for amphotericin B to fluconazole groups.

Study-150-608 Discontinuations from study (Safety population N=403)
Source: 608.pdf Table 4.1 p:231

	Voriconazole		Amphotericin B →fluconazole	
NUMBER(%) OF SUBJECTS	272		131	
SUBJECT DIED	56	(20.6)	35	(26.7)
RELATED TO STUDY DRUG	33	(12.1)	11	(8.4)
Insufficient clinical response	8	(2.9)	3	(2.3)
Adverse Event	17	(6.3)	6	(4.6)
Laboratory abnormality	8	(2.9)	2	(1.5)
NOT RELATED TO STUDY DRUG	61	(22.4)	26	(19.8)
Adverse Event	23	(8.5)	3	(2.3)
Laboratory abnormality	5	(1.8)	3	(2.3)
Protocol Violation	7	(2.6)	6	(4.6)
Lost to follow-up	7	(2.6)	3	(2.3)
Does not meet entrance criteria	1	(0.4)	2	(1.5)
Withdrawn consent	11	(4.0)	5	(3.8)
Other	7	(2.6)	4	(3.1)
TOTAL	150	(55.1)	72	(55.0)

A greater proportion of subjects in the voriconazole treated group who discontinued study drug because of an adverse event judged by the investigator not related to study drug compared to the amphotericin B →fluconazole group. This difference should be interpreted with caution, because patients in the latter group could switch from amphotericin B to fluconazole, without being considered a discontinuation from study drug. Indeed, a higher number of subjects (13) received < 80% of the expected dose of amphotericin B than failed to receive at least 80% of the expected dose of voriconazole (3). Thus, it is plausible that a certain amount of amphotericin B toxicity may have limited the use of recommended doses.

The type of adverse events associated with discontinuation from the study are summarized in the table below. There were no specific trends or patterns identified in the study. The rates for AEs associated with dropouts were similar in both treatment groups.

Study-150-608 AEs associated with study dropouts (Safety population) Source: 608.pdf Table 6.1.3		
No of Subjects	Voriconazole (N=272)	Amphotericin B → fluconazole (N=131)
Sepsis	57 (21.0%)	33 (25%)
↑ AST	14 (5.1%)	4 (3%)
↑ ALT	9 (3.3%)	6 (5%)
↑ Alkaline phosphatase	28 (10.3%)	10 (8%)
Acute kidney failure	20 (7.4%)	14 (11%)
Heart arrest	20 (7.4%)	10 (8%)
Rash	16 (5.9%)	7 (5%)

The gross rates of treatment emergent adverse events of all causalities are described in the table below. Although there was a greater proportion of discontinuations due to adverse events in the voriconazole group compared to the control group, there was a greater proportion of subjects with dose reductions or temporary dosing discontinuation in the amphotericin B/fluconazole group.

Study-150-608 Treatment emergent adverse events (all causalities) Source: 608.pdf Table 6.1.1 p:303				
	Voriconazole		Amphotericin b → fluconazole	
NUMBER OF:		(%)		(%)
Subjects Treated	272		131	
Subjects-Days of Drug Exposure	4182		2062	
Subjects with Adverse Events	266	(97.8)	130	(99.2)
Adverse Events	1565		880	
Subjects with Serious Adverse Events	125	(46.0)	74	(56.5)
Subjects with Severe Adverse Events	137	(50.4)	74	(56.5)
Subjects discontinued due to Adverse Events	53	(19.5)	13	(9.9)
Subjects with dose reduced or temporary discontinuation due to Adverse Events	11	(4.0)	18	(13.7)

Common treatment emergent adverse events are presented by body system in the table below. The most common AEs reported within the body groups were sepsis, hypotension, fever, hypokalemia, and respiratory disorder respectively. In general the rates for adverse events were comparable across treatment groups. Although voriconazole is known to commonly cause visual abnormalities, few were reported in this study. Other than fundoscopic examination, a formal specialized exam was not a part of the study.

Study-150-608 Treatment Emergent AEs by body system and selected AEs reported for >5% of patients.

Source: Modified608.pdf Table 6.1.1, 6.1.2 & 6.1.3 p:303-318

No of Subjects	Voriconazole	A→F
Treated	272	131
With ≥1 adverse event	266 (97.8%)	130 (99.2%)
Body as a whole	182 (66.9%)	97 (74%)
Abdominal pain	12 (4.4%)	9 (6.9%)
Chills	8 (2.9%)	10 (7.6%)
Fever	41 (15.1%)	24 (18.3%)
Headache	14 (5.1%)	5 (3.8%)
Multi-organ failure	9 (3.3%)	8 (6.1%)
Sepsis	57 (21.0%)	33 (25.2%)
Cardiovascular	127 (46.7%)	67 (51.1%)
Heart arrest	20 (7.4%)	10 (7.6%)
Hypotension	33 (12.1%)	27 (20.6%)
Phlebitis	10 (3.7%)	12 (9.2%)
Digestive	121 (44.5%)	62 (47.3%)
Vomiting	24 (8.8%)	17 (13.0%)
Haemic and lymphatic	74(27.2%)	30 (22.9%)
Anemia	32 (11.8%)	16 (12.2%)
Thrombocythemia	14 (5.1%)	1 (0.8%)
Metabolic and nutritional	127 (46.7%)	73 (55.7%)
↑Alkaline phosphatase	28 (10.3%)	10 (7.6%)
↑Creatinine	2 (0.7%)	14 (10.7%)
Dehydration	6 (2.2%)	7 (5.3%)
Hypokalemia	33 (12.1%)	29 (22.1%)
↑AST	14 (5.1%)	4 (3.1%)
Nervous	81 (29.8%)	35 (26.7%)
Special senses	46 (16.9%)	13 (9.9%)
Respiratory	121 (44.5%)	71 (54.2%)
Hypoxia	13 (4.8%)	12 (9.2%)
Pneumonia	22 (8.1%)	6 (4.6%)
Respiratory disorder	31 (11.4%)	19 (14.5%)
Respiratory distress syndrome	14 (5.1%)	7 (5.3%)
Skin and appendages	68 (25%)	28 (21.4%)
Rash	16 (5.9%)	7 (5.3%)
Urogenital	80 (29.4%)	56 (42.7)
Acute kidney failure	20 (7.4%)	14 (10.7%)
Abnormal kidney function	11 (4.0%)	11 (8.4%)
Urinary tract infection	30 (11.0%)	14 (10.7%)
Musculoskeletal	15 (5.5%)	7 (5.3%)
Endocrine	*3 (1.1%)*	*1 (0.8%)*

Table includes one count/subject/body system

Selected AEs: by MO due to potential differences in rates

Cardiac Monitoring and Safety: Cardiac monitoring in patients receiving intravenous infusion of study drug was brought into study 608 as part of Amendment 5 to the protocol, in order to manage the potential risk for ventricular arrhythmia, after a single patient had experienced a fatal episode of ventricular fibrillation (b) (6) 150-603-90021485. Patient was in Study 150-603 not Study 150-608.) The requirement for cardiac monitoring applied to subjects randomized to both treatment groups. Cardiac monitoring was mandatory for all subjects judged to be at risk of cardiac arrhythmia, and requested for all subjects undergoing continuous telemetry as part of their routine care. The assessment of risk of arrhythmia was made by the investigator or cardiologist, and recorded within a specific cardiac history module of the CRF. ECGs were to be recorded just before infusion, at the end of infusion and 2 hours after infusion. ECGs were not required or requested in patients receiving oral therapy. The results of ECG monitoring were summarized in Section 11 Item 11 of the Study Report in the Application.

In a submission dated September 30, 2004, the Applicant provided additional information on the extent of cardiac monitoring undertaken during the study as summarized in the table below:

Safety population – all subjects	Voriconazole 272	Amphotericin B Fluconazole 131
Pre-amendment 5	47	25
Post Amendment 5: Safety population available for cardiac assessment	225	106
At risk of cardiac arrhythmia (ECGs mandatory)	35 (16%)	14 (13%)
ECGs done	32 (91%)	11 (79%)
Not at risk of cardiac arrhythmia	190 (84%)	92 (87%)
In ICU (ECGs requested)	82 (43%)	40 (43%)
ECGs done	52 (52/82= 63%)	17 (17/40 = 42%)
Not in ICU (ECGs not expected)	108 (57%)	52 (57%)
ECGS s done	27 (27/108 = 25%)	6 (6/52 = 12%)
Total subjects with ECGs	111 (111/225=49%)	34 (34/106= 32%)

There was reasonably good compliance with mandatory cardiac monitoring across treatment groups.

The proportion of subjects considered at risk or cardiac arrhythmia was similar in both groups: 16% in the voriconazole group versus 13% in the amphotericin B to fluconazole group. However a higher proportion of voriconazole-treated subjects, 91% had ECGs performed compared to 79% in the amphotericin B to fluconazole group.

A similar proportion of subjects assessed not at risk of cardiac arrhythmia, 43%, in both groups were in an ICU at baseline. Among these a greater proportion of subjects in the voriconazole group had ECGs performed, 63%, compared to the amphotericin B to fluconazole group's 42%. Among those assessed not at risk of cardiac arrhythmia who were also not in an ICU at baseline, a greater proportion of voriconazole-treated subjects had ECGs performed (25%) compared to the amphotericin B to fluconazole group (12%).

Overall, a greater proportion of subjects treated with voriconazole had ECGs performed compared to amphotericin B to fluconazole group.

Further clarification of the ECG monitoring data was sought from the Applicant in a telecon with Pfizer on 12-09-2004. The total of 111 Voriconazole subjects and 34 amphotericin B/fluconazole subjects in the table above reflects the total number of subjects who had at least one ECG performed at any time of the study under Amendment 5, that was sent for analysis to a central specialized lab. Not all strips were interpretable. The numbers in the summary tables on cardiac monitoring in Section 11 Item 11, are smaller because not all subjects had an interpretable day 1 pretreatment ECG, and/or did not have ECGs on every treatment day.

We agreed that the cardiac monitoring under Amendment 5 was conducted to manage a potential risk of fatal cardiac arrhythmia in high risk subjects, and not intended to be a formal comparative investigation of the effect of treatment drug on QTc. We agreed that there was reasonably good compliance with the cardiac monitoring in the high risk subjects. The management plan was successful in that there were no clinically significant differences across treatment arms with respect to serious cardiac events such as cardiac arrest, or ventricular arrhythmia. The table below summarizes the cardiovascular adverse events observed in the safety population.

Study-150-608 Incidence & severity of Rx emergent cardiovascular AEs – All causality (Safety population)
Source: M2, clinical. PDF, Modified Table 6.3.1.1, p:741/900

	Voriconazole				A→F			
COSTART Preferred Term	n=272 n(%)	Mild	Mod	Severe	n=131 n(%)	Mild	Mod	Severe
CARDIOVASCULAR	127(46.7)	33	52	42	67(51.1)	10	28	29
Bradycardia	12 (4.4)	3	5	4	8 (6.1)	0	3	5
Sinus bradycardia	2 (0.7)	0	1	1	0	0	0	0
Tachycardia	17 (6.3)	6	8	3	5 (3.8)	2	3	0
Worsening heart failure	1 (0.4)	0	0	1	1 (0.8)	0	0	1
Heart failure	1 (0.4)	0	1	0	1 (0.8)	0	0	1
Left heart failure	1 (0.4)	0	0	1	0	0	0	0
Congestive heart failure	1 (0.4)	0	0	1	0	0	0	0
Myocardial infarct	1 (0.4)	1	0	0	4 (3.1)	1	0	3
Cardiomegaly	2 (0.7)	1	1	0	2 (1.5)	2	0	0
Cardiovascular disorder	6 (2.2)	4	2	0	2 (1.5)	1	1	0
Qt interval prolonged	1 (0.4)	0	1	0	0	0	0	0
Arrhythmia	0	0	0	0	2 (1.5)	2	0	0
Atrial arrhythmia	5 (1.8)	3	2	0	1 (0.8)	0	1	0
Atrial fibrillation	10 (3.7)	3	6	1	4 (3.1)	0	3	1
Supraventricular	1 (0.4)	1	0	0	1 (0.8)	0	1	0

Study-150-608 Incidence & severity of Rx emergent cardiovascular AEs – All causality (Safety population)
Source: M2, clinical. PDF, Modified Table 6.3.1.1, p:741/900

	Voriconazole				A→F			
COSTART Preferred Term	n=272 n(%)	Mild	Mod	Severe	n=131 n(%)	Mild	Mod	Severe
extrasystoles								
Supraventricular tachycardia	6 (2.2)	1	2	3	1 (0.8)	0	1	0
Ventricular arrhythmia	3 (1.1)	1	1	1	5 (3.8)	1	3	1
Ventricular fibrillation	2 (0.7)	0	0	2	1 (0.8)	0	0	1
Ventricular tachycardia	7 (2.6)	1	2	4	3 (2.3)	1	1	1
Nodal arrhythmia	1 (0.4)	0	0	1	0	0	0	0
Av block	1 (0.4)	0	1	0	0	0	0	0
Av block first degree	1 (0.4)	1	0	0	2 (1.5)	1	1	0
Bigeminy	1 (0.4)	0	1	0	0	0	0	0
Extrasystoles	5 (1.8)	4	1	0	0	0	0	0
Heart arrest	20 (7.4)	0	0	20	10 (7.6)	0	0	10

Table includes only one count per subject per body system. * Any missing severities have been summarized as severe. Mod = Moderate
This table was modified by the MO to include only cardiovascular AEs potentially related to arrhythmias.

Section 11, Item 11 of the application lists the ECG results. The QTcB, QTcF, heart rate and RR interval were summarized by day and time. The number and % of male subjects with QTcB and QTcF values of <430 msec, 430 to 449 msec and > 449 msec and female subjects with QTcB and QTcF values of <450 msec, 450 msec to 469 msec and > 469 msec were summarized. Table 10.2.1, Classification of QTcB – Absolute values sorts the number of subjects with maximum QTc within these ranges, and by gender. The maximum absolute value could come from any ECG performed after day one pretreatment baseline.

Examination of Table 10.4.1 in Section 11 Item 11, Classification of QTcB by Day – Absolute Values, reveals that a total of 682 ECGs were performed in voriconazole treated subjects (385 in males and 297 in females) over a period of up to 37 days compared to 140 in amphotericin B to fluconazole group (95 in males and 45 in females). Despite the disparate increased proportion of ECG observations in the voriconazole treated subjects, the distribution of maximum absolute values of QTcB were similar across treatment groups. In particular there were no significant differences in proportion of subjects with maximum QTcB > 449 msec in males (voriconazole 41/54 =76%, amphotericin B to fluconazole 13/19=68%) or > 469 msec in females (voriconazole 22/34=65%, amphotericin B to fluconazole 5/6=83%).

The number of subjects with maximum QTcB and QTcF increases from day one pre-treatment baseline of < 0 msec, 0 to 29 msec, 30 to 59 msec and > 60 msec were also summarized. Note that such maximum increase could be between day one pretreatment baseline and any subsequent ECGs on any treatment day when an ECG was performed during or after infusion.

Examination of Table 10.5.1 in Section 11 Item 11, Classification of QTcB by Day – Change from Base line which sorts the number of subjects with maximum increase

inform baseline in QTc by treatment group and day (Day 1 through 37), reveals that the number of QTc observations per day decreases over time. Overall, a disproportionate larger number of observations were made in the voriconazole treated subjects, compared to the amphotericin B to fluconazole group (429 versus 66).

Table 10.3.1 summarizes the maximum changes in QTc from baseline by treatment arm. The number of subjects (50 in the voriconazole arm and 13 in the amphotericin B to fluconazole arm) represent a non-random selected subset, which had an interpretable baseline ECGs (with measurable QTc) on Day -1 prior to treatment and another ECG after infusion of drug on any treatment day. Out of 50 subjects from the voriconazole treatment group, 11 had at one observation a change in QTc from baseline greater than 60 msec. Out of the 13 subjects from the amphotericin B to fluconazole group, none had at any time a QTc change from baseline greater than 60 msec.

Note that one can not make valid statistical comparisons across treatment groups because of the non-random nature of this selected subset, and the added fact that there were disproportionately more observations in the voriconazole arm compared to the amphotericin B to fluconazole arm. Cross treatment comparisons would be potentially misleading. We are simply left with the observation of what changes in QTc length were recorded in a subset of patients on various selected treatment days. Note that the current labeling for VFEND® already contains wording in the PRECAUTIONS section regarding QTc prolongation: "Some azoles, including voriconazole, have been associated with prolongation of the QT interval on the electrocardiogram."

During the review of this submission a consultative post marketing safety review was requested from the Office of Drug Safety with the specific intent to review cases of QT prolongation and arrhythmias that have been reported to FDA in association with voriconazole administration (See ODS Review Dated October 1, 2004).

The review identified 36 unduplicated, nonexcluded cases of arrhythmia, cardiac arrest, sudden death, and/or QT interval prolongation associated with voriconazole. More than half (20/36) were foreign. Ventricular arrhythmias (14 cases) were the most frequently reported type of arrhythmia; 2 additional patients were reported to have experienced QT prolongation with no mention of arrhythmia.

Although most of the reports were confounded or poorly documented, voriconazole could not be ruled out as the cause in any of the cases. Therefore it was recommended that the PRECAUTIONS sections of the VFEND labeling, which currently addresses only QT prolongation and torsade de pointes, be amended as follows:

PRECAUTIONS

Arrhythmias and QT prolongation

Some azoles, including voriconazole, have been associated with prolongation of the QT interval on the electrocardiogram,. During clinical development and post-

marketing surveillance, there have been rare cases of arrhythmias, (including ventricular arrhythmias such as torsade de pointes), cardiac arrests, and sudden deaths, in patients taking voriconazole. These cases usually involved seriously ill patients with multiple confounding risk factors, such as history of cardiotoxic chemotherapy,, cardiomyopathy, hypokalemia and concomitant medications that may have been contributory.

This wording was accepted by the applicant during a telephone conference on December 15, 2004 and will be incorporated in the VFEND labeling.

Safety Conclusions and Recommendations: No new serious safety concerns associated with the administration of voriconazole in this application. The safety of voriconazole was comparable to that of the control. The updated information on post-marketing cardiac safety is adequately described in the revised section of the VFEND labeling (See above).

III. Dosing Regimen and Administration
Drug

The Recommended therapeutic dose and regimen voriconazole for candidemia is (b) (4) /kg I.V. or 200 mg oral tablet q12 following a loading dose of 6 mg/kg I.V. q12 for the first 24 hours (b) (4)

IV. Conclusions and Recommendations

I concur with the conclusions of the review team that there is sufficient information to support the efficacy of voriconazole in the treatment of Candidemia in non-neutropenic patients and the following *Candida* infections: disseminated infections of the skin, and infections of the abdomen, in kidney, bladder wall and wounds. (b) (4)

The safety profile of voriconazole is adequately described in the proposed labeling, dated December 20, 2004, and the potential risks are outweighed by the potential benefits.

VFEND® (voriconazole) should be approved for the treatment of Candidemia in non-neutropenic patients and the following *Candida* infections: disseminated infections of the skin, and infections of the abdomen, in kidney, bladder wall and wounds.

V. Recommendations for Post Marketing Activity

There are no new recommendations for post-marketing activity, except for the one described under the following pediatric section.

VI. Pediatric Issues

Study 150(b) (4) enrolled only subjects 12 years old or older. There is insufficient information in this application to know how to use voriconazole in children with candidemia or *Candida* infection.

We are deferring submission of pediatric studies for ages 0 to 16 years until December 31, 2007.

The deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required post-marketing study commitments. The status of these post-marketing studies shall be reported annually according to 21 CFR 314.81. This commitment is listed below.

1. Deferred pediatric study under PREA for the treatment of candidemia in non-neutropenic patients and the following *Candida* infections in pediatric patients ages 0 to 16.

_____/s/_____
Marc Cavaillé-Coll, M.D., Ph.D.
Medical Officer Team Leader
FDA/CDER/OND/ODE4/DSPIDP

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

/s/

Marc Cavaille Coll
12/21/04 04:51:32 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-266/S009
NDA 21-267/S009
NDA 21-630/S003

CHEMISTRY REVIEW(S)

SUPPLEMENTAL NDA CHEMIST'S REVIEW	1. ORGANIZATION: HFD-590	2. NDA NUMBER: 21-266, 21-267, 21-630

3. NAME AND ADDRESS OF APPLICANT: *(City and State)*	4. SUBMISSION TYPE:	
C.P. Pharmaceuticals International C.V. c/o Pfizer Inc. 235 East 42nd Street New York, NY 10017	Prior Approval	
	5. SUPPLEMENT(S):	
	NUMBER(S):	DATE(S):
	21-266/SE1-009 21-267/SE1-009 21-630/SE1-003	15-MAR-2004

6. NAME OF DRUG:	7. NONPROPRIETARY NAME:
VFEND	voriconazole

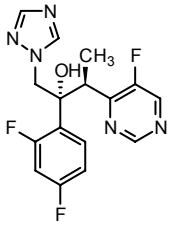
8. SUPPLEMENT PROVIDES FOR: A new indication for VFEND® (voriconazole) as treatment for (b) (4) candidiasis.	9. AMENDMENTS/REPORTS:

10. PHARMACOLOGICAL CATEGORY:	11. HOW DISPENSED:	12. RELATED IND/NDA/DMF(S):
Antifungal	[X] Rx [ ]OTC	

13. DOSAGE FORM(S):	14. POTENCY(IES):
Tablets (NDA 21-266) Injection (NDA 211-267) Powder for Oral Suspension (NDA 21630)	50, 200 mg 200 mg/vial 40 mg/mL when reconstituted

15. CHEMICAL NAME AND STRUCTURE:

(2*R*, 3*S*)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol



16. MEMORANDA:

17. COMMENTS: This supplement was submitted to provide evidence to support the use of voriconazole in the treatment of patients for (b) (4) candidiasis. There are no CMC changes. The sponsor has claimed categorical exclusion from environmental assessment under the provisions of 21 CFR 25.31(b) since approval of this application will result in increased use of the product but the estimated concentration of the drug substance at the point of entry into the aquatic environment will be below 1 ppb. C.P. Pharmaceuticals International also states that there are no extraordinary circumstances to the best of their knowledge.

18. CONCLUSIONS AND RECOMMENDATIONS: The sponsor's claim of categorical exclusion is acceptable. APPROVAL of this supplement is recommended.

19. REVIEWER:	SIGNATURE:	DATE COMPLETED:
Gene W. Holbert, Ph.D.	*{See appended electronic signature page}*	16-NOV-2004
20. CONCURRENCE: Mark R. Seggel, Ph.D.	*{See appended electronic signature page}*	

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

/s/

Gene Holbert
11/22/04 02:42:09 PM
CHEMIST

Mark Seggel
11/22/04 05:15:28 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-266/S009
NDA 21-267/S009
NDA 21-630/S003

PHARMACOLOGY REVIEW(S)

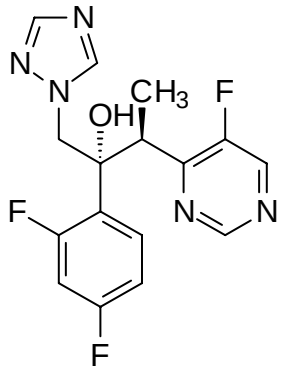
PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA numbers: 21266, 21267, 21-630
Review number: 1
Sequence number: 000
Date submitted: March 15, 2004
Information to sponsor: No
Sponsor : Pfizer Inc. Eastern Point Road. Groton, Connecticut 06340
Manufacturer for drug substance: Pfizer Inc. 630 Flushing Ave. Brooklyn, New York 11206.

Reviewer name: Owen McMaster, PhD.
Division: Division of Special Pathogen and Immunologic Drug Products HFD-590
Review completion date: November 31, 2004

Drug Trade name: VFEND
Generic name : Voriconazole
Code name: UK-109,496
Chemical name: (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyimidinyl)-1-(1*H* –1,2,4-triazol-1-yl)-2-butanol
CAS registry number: 137234-62-9
Molecular formula: $C_{16}H_{14}F_3N_5O$
Molecular weight: 349.3

Structure:



Relevant INDs/NDAs/DMFs: IND 50-410, NDA 21267, DMF(b) (4)

Drug class: Triazole antifungal
Indication: (b) (4) candidemia

Table 1. Clinical formulation of voriconazole tablet

(b) (4)

Table 2. Clinical formulation of voriconazole for injection

(b) (4)

Route of administration: Oral and Intravenous

Proposed use: Treatment of (b) (4) candidemia

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Executive Summary

Recommendations

A. Recommendation on Approvability.

There is no information in this submission that would preclude the approval of VFEND for (b) (4) candidemia.

B. Recommendation for Nonclinical Studies

No additional studies are being recommended at this time.

C. Recommendations on Labeling

No preclinical labeling changes are being recommended at this time.

Summary of Nonclinical Findings

The following information was obtained from the review of the initial NDA for voriconazole. The new preclinical toxicology study submitted with this NDA is discussed under "Toxicology Studies Review".

In preclinical toxicology testing, voriconazole produced adverse effects in the eyes, liver, heart and kidneys and was shown to produce tumors in experimental animals. Toxicology studies were conducted with oral and intravenous voriconazole. Studies were up to 24 months duration for the oral formulation and up to six months duration for the intravenous formulation. Safety pharmacology studies included examination of the effects of voriconazole on cardiac function.

Visual effects

In clinical trials, the most common adverse effects reported were transient visual disturbances. Approximately 30 % of the treated patients experienced altered/enhanced visual perception, blurred vision, color vision change or photophobia. Other visual disturbances, such as corneal opacity, were less common. Visual disturbances were also detected in preclinical studies.

In dogs, voriconazole administration produced dose-related effects in the electroretinogram (study CG/1/99). These findings were detected at voriconazole plasma levels similar to those measured in human studies. Specifically, dogs showed reductions in the amplitude and specific time of the a-wave and reduction in the amplitude of the b-wave.

In the 24-month rat carcinogenicity study, histopathological examination of the eyes of rats treated with voriconazole showed a small reduction in the thickness of the outer nuclear layer

of the retina in high dose females. Although slight, these changes suggest that chronic administration of voriconazole could result in permanent changes to the eye.

In an acute study of oral voriconazole in mice (Study # 90157), where mice were treated at doses up to 500 mg/kg (approximately equal to six times the recommended human dose based on body surface area comparisons) mice showed corneal opacification, as they did in clinical trials.

Cardiac Effects

In a number of animal studies, high doses of voriconazole were shown to produce arrhythmia, including premature contractions and prolonged QT intervals.

In study DI/102/91, 3 dogs were treated intravenously with five escalating doses of voriconazole at doses intended to achieve plasma concentrations of 4, 10, 20, 30 and 60 µg/ml. Three vehicle-treated animals served as controls. Actual concentrations were 10, 23, 52, 73 and 220 µg/ml (higher than predicted). Cardiovascular parameters were recorded.

Voriconazole produced an arrhythmia at the fourth dose in one of the three voriconazole treated dogs, at a plasma level around 42 µg/ml. The arrhythmia was diagnosed as a nodal premature contraction. Atrial and ventricular depolarizations occurred simultaneously. The P-wave fell within the QRS complex and the summation complex (QRS +P) was wider than the normal QRS complex. There was a coupling between the normal R-wave and the abnormal beat. Where the abnormal beat occurred, there was no cardiac pump action and the effective heart rate was effectively halved. Blood pressure was essentially maintained by an increase in inotrophy (as indicated by a 30% drop in QA interval). This effect continued for the remainder of the experiment.

QT interval was increased by up to 9% over control values, in the animals which did not show an arrhythmia. The QT interval was increased by 6% before the third dog experienced an arrhythmia. In a second study, CG/1/91, voriconazole at 30 mg/kg produced blood levels of 8 µg/ml and increased QT intervals. In a third study, QT intervals were increased by up to 33 %. In one repeat-dose study, premature contractions were observed at 24 mg/kg without evidence of QT prolongation. Studies performed at lower doses have failed to consistently produce QT prolongation.

(b) (4)

Liver effects

Voriconazole administration in animals was associated with a number of hepatic changes including increased liver weights, centrilobular hypertrophy, vacuolation, granulomas, eosinophilic foci, hepatocellular cystic change, pigmentation, basophilic foci, clear cell foci, increased transaminase activity, enlarged, pale or marbled liver, hepatocellular fatty change, single cell necrosis and subcapsular necrosis.

24-month oral administration of voriconazole resulted in an increase in the incidence of hepatocellular adenoma and hepatocellular carcinoma in rats and mice. These neoplastic changes were observed at doses similar to those used in the clinic.

Kidney Effects

The vehicle used with voriconazole, sulfobutly ether cyclodextrin (SBECD), is associated with toxic effects in the kidney. Specifically, SBECD caused cytoplasmic vacuolation in the epithelium of the renal tubules, renal pelvis and urinary bladder. These effects were seen in both drug and vehicle treated animals

Carcinogenesis and Mutagenesis

Two-year carcinogenicity studies were conducted in rats and mice. Rats were given oral doses of 6, 18 or 50 mg/kg voriconazole, or 0.2, 0.6, or 1.6 times the recommended maintenance dose (RMD) on a mg/m^2 basis. Hepatocellular adenomas were detected in females at 50 mg/kg and hepatocellular carcinomas were found in males at 6 and 50 mg/kg. Mice were given oral doses of 10, 30 or 100 mg/kg voriconazole, or 0.1, 0.4, or 1.4 times the RMD on a mg/m^2 basis. In mice, hepatocellular adenomas were detected in males and females and hepatocellular carcinomas were detected in males at 1.4 times the RMD of voriconazole.

Voriconazole demonstrated clastogenic activity (mostly chromosome breaks) in human lymphocyte cultures *in vitro* . Voriconazole was not genotoxic in the Ames assay, CHO assay, the mouse micronucleus assay or the DNA repair test (Unscheduled DNA Synthesis assay).

Toxicology Study Review

1. Study title: *In Vivo/In Vitro* Unscheduled DNA Synthesis Study Oral Route**.**
Key study findings: Did not demonstrate the potential to damage DNA.
Study no: 01-844-02
Conducting laboratory: Drug Evaluation Department. Pfizer Global Research and Development. Pfizer Inc. Groton, Connecticut 06340. USA
Date of study initiation: April 4, 2001
GLP compliance: Yes
QA report: Yes
Drug lot # 03680225
Purity: 99.95 %.
Formulation/vehicle: (b) (4)

The purpose of this experiment was to determine if voriconazole showed the potential to induce unscheduled DNA synthesis. Hepatocytes were isolated from the livers of rats treated *in vivo* with voriconazole and cultured with methyl-(^{3}H) thymidine. Incorporation of tritiated thymidine into DNA during the culture period is used as a measure of repair of DNA damage caused by treatment with voriconazole.

Groups of eight male rats each [CDF (F-344)/Crl Br strain], were treated with vehicle (negative control), 75 or 150 mg/kg voriconazole, or 20 mg/kg dimethylnitrosamine (positive control). An additional group of twelve rats were treated with 150 mg/kg voriconazole for determining pharmacokinetic parameters. Animals were observed throughout the treatment period for clinical signs and mortality. Two hours after dosing, half the animals were sacrificed and, blood and/or livers were harvested. Hepatocytes were isolated, cultured and processed for autoradiography. The second half of the animals were sacrificed for plasma and hepatocytes 16 hours after dosing. Three cultures were prepared per animal (liver) and at least 50 non S-phase nuclei were scored for each culture.

No animals died during the study. The predominant clinical signs were salivation, hunched posture, ataxia, piloerection and loose stools.

Voriconazole-treated animals did not show an increase in nuclear grains over background. In fact the change in net nuclear grain count was negative and comparable to the change seen in animals treated with vehicle. On the other hand, hepatocytes from animals treated with the positive control agent dimethylnitrosamine, showed large increases in nuclear grain count over background at both time points. Thus, in this experimental model, which is shown to be sensitive to agents which induce DNA damage (and subsequent incorporation of methyl-(^{3}H) thymidine during unscheduled DNA synthesis), voriconazole does not demonstrate the potential to induce DNA damage.

Table 3. Unscheduled DNA Synthesis Assay (Two hour Time point).

Treatment group	Nuclear Count	Background count	Net nuclear grain count
Vehicle control	1.3	1.6	-0.4
Voriconazole 75 mg/kg	1.6	2.0	-0.4
Voriconazole 150 mg/kg	2.1	2.7	-0.7
Positive control	24.8	3.6	21.3

Table 4. Unscheduled DNA Synthesis Assay (16 hour Time point).

Treatment group	Nuclear Count (NC)	Background count (BC)	Net nuclear grain count
Vehicle control	1.8	3.2	-1.4
Voriconazole 75 mg/kg	1.7	2.2	-0.5
Voriconazole 150 mg/kg	2.0	2.1	-0.1
Positive control	15.2	2.2	13.1

Nuclear count (NC) is defined as the number of (radioactive) grains located over the nuclear area. Background count (BC) is the number of grains located over an extracellular area of nuclear size adjacent to the nucleus being scored. The net nuclear grain count is the NC minus BC.

Table 5. Mean voriconazole levels in rats treated with 150 mg/kg voriconazole.

	Plasma (µg/ml)	Liver (µg/g)
2 hours postdose	72	220
16 hours postdose	62	269

In clinical studies, patients achieve blood levels up to about 5 µg/ml. In this study, plasma levels up to 14 times the typical clinical Cmax, did not show the potential to induce unscheduled DNA synthesis.

Conclusion: Voriconazole did not demonstrate the potential to induce DNA damage as evaluated by its ability to induce unscheduled DNA synthesis.

Overall Summary and Conclusions

Toxicology studies were conducted with oral and intravenous voriconazole. Studies were up to 24 months duration for the oral formulation and up to six months duration for the intravenous formulation. In preclinical toxicology testing, voriconazole adversely effected the eyes, liver, heart, kidney and the unborn fetus. Voriconazole also produced hepatocellular adenomas and carcinomas in experimental animals. These changes are reflected in the label and there are no findings that would preclude the approval of this drug. The study submitted to these NDAs will not result in any changes to the label.

Owen G. McMaster, Ph.D.
Pharmacology/Toxicology Reviewer, DSPIDP

Concurrences:
HFD-590/DeputyDivDir/GittermanS
HFD-590/ActingPharm/ToxTL/OsterbergB
cc:
HFD-590 Original IND50410
HFD-590 Original (b) (4)
HFD-590/Biopharm/delosReyesG
HFD-590/BiopharmTL/Colangelo
HFD-590/PM/SavilleR
HFD-590 Division File
HFD-590/MicroTL/BalaS
HFD-590/MO/BeidasS
HFD-590/MOTL/CavailleCollM
HFD-590/Pharm/McMasterO
HFD-590/PharmTL/OsterbergB
HFD-590/Stat/DixonC
HFD-590/StatTL/HigginsKar
HFD-340

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-266/S009
NDA 21-267/S009
NDA 21-630/S003

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDAs/Serial Number:	21-266 SE1-009
	21-267 SE1-009
	21-630 SE1-003
Drug Name:	VFEND™ (voriconazole) oral, IV, and POS
Indication(s):	Candidemia (b) (4)
Applicant:	Pfizer, Inc.
Date(s):	Stamp date: March 15, 2004
	PDUFA date: January 15, 2005
	Review date: December 3, 2004
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III (HFD-725)
Statistical Reviewer:	Cheryl Dixon, Ph.D.
Concurring Reviewer:	Karen Higgins, Sc.D., Team Leader
Medical Division:	Division of Special Pathogen and Immunologic Drug Products (HFD-590)
Clinical Team:	Sary Beidas, M.D., Medical Officer
	Marc Cavaillé Coll, M.D., Ph. D., Team Leader
Project Manager:	Rebecca Saville

Keywords: clinical studies, NDA review, one study application, anti-fungal, Candidiasis, Candidemia

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The efficacy of voriconazole for the treatment of candidemia in non-neutropenic patients was supported by one controlled study. This study demonstrated that the overall efficacy (as assessed by the DRC success rate at 12 weeks after EOT) of voriconazole is non-inferior to amphotericin B followed by fluconazole assuming a non-inferiority margin of 15%. A small subgroup of patients in this study had candidiasis at other sites in addition to their candidemia. There was a favorable outcome in these patients. It is left to the clinical reviewer to determine any labeling claims regarding additional infections due to *Candida* that may be made based on this data.

1.2 Brief Overview of Clinical Studies

One pivotal study, Protocol 608, has been submitted to provide support for the use of voriconazole in the treatment of candidemia in non-neutropenic patients. Protocol 608 was a Phase 3, randomized, open label comparative study to evaluate the safety and efficacy of voriconazole versus conventional amphotericin B followed by (→) fluconazole in the treatment of candidemia in non-neutropenic patients. The study was conducted at sites in the United States, Canada, India, South America, Europe, North Africa, Southern Africa, the Middle East, and South East Asia. Subjects were randomized to receive either voriconazole or the treatment regimen of amphotericin B → fluconazole in a 2:1 ratio. Voriconazole was administered as a loading dose of 6 mg/kg iv every 12 hours for 24 hours followed by maintenance dose of 3 mg/kg iv every 12 hours. The oral dose of voriconazole was 200 mg twice daily. Amphotericin B was administered as 0.7 mg/kg/day. Fluconazole was administered as 400 mg, iv or oral, daily. Therapy was to continue for at least 14 days after candidemia resolution. The primary efficacy endpoint was the Data Review Committee (DRC) assessed response at 12 weeks after end of treatment (EOT).

1.3 Statistical Issues and Findings

A total of 422 patients were randomized to receive treatment in Protocol 608. The modified intent to treat (MITT) population included 370 patients (248 in the voriconazole group and 122 in the amphotericin B → fluconazole group). The rates of DRC success at 12 weeks after EOT in the MITT population were 40.7% for voriconazole and 41.0% for amphotericin B → fluconazole. A 95% stratified confidence interval about the difference between the success rates (voriconazole - amphotericin B → fluconazole) stratified by region was calculated to demonstrate the non-inferiority of voriconazole to amphotericin B → fluconazole. The lower bound of this confidence interval was greater than the non-inferiority margin of -15%. The results at EOT and the investigator's assessed response at the various timepoints support the claim of non-inferiority of voriconazole compared to amphotericin B → fluconazole.

2. INTRODUCTION

2.1 Overview

This is a supplemental NDA submission for voriconazole. Voriconazole is a triazole antifungal with activity against a wide range of yeasts and filamentous fungi, including *Candida*, *Aspergillus*, *Fusarium*, and *Scedosporium*. It has previously been approved for the treatment of invasive aspergillosis, the treatment of esophageal candidiasis, and the treatment of serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* spp, in patients intolerant of, or refractory to other therapy. The indication being sought by the applicant in this supplemental NDA is the treatment of candidemia (b) (4) including infections of the abdomen, kidney and bladder wall, (b) (4) wounds, (b) (4) and disseminated skin infection. The proposed therapeutic dose and regimen voriconazole for candidemia is (b) (4) mg/kg I.V. or 200 mg oral tablet q12 following a loading dose of 6 mg/kg I.V. q12 for the first 24 hours.

(b) (4)

2.2 Data Sources

The data analyzed in this review comes from the pivotal, Phase 3 study submitted as primary support. The Protocol 608 study report and datasets provided in the electronic submission were reviewed. These can be found in the electronic submission located at: \\Cdsesub1\n21266\S_009\2004-03-15.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design

Study 608 was a Phase 3 randomized, open label, non-inferiority study of voriconazole versus amphotericin B → fluconazole in the treatment of candidemia in non-neutropenic patients. The study was conducted at 103 centers in the United States and internationally. Most sites enrolled 5 or fewer subjects. Subjects were randomized to receive either

voriconazole or amphotericin B → fluconazole. Subjects received iv treatment for 3 to 7 days before switching to oral therapy. Therapy was to continue for at least 14 days after candidemia resolution and the maximum duration was up to 8 weeks. Voriconazole was administered as a loading dose 6 mg/kg iv every 12 hours for 24 hours followed by maintenance doses of 3 mg/kg iv every 12 hours. The oral dose of voriconazole was 200 mg twice daily, but this could be reduced to 100 mg bid for subjects weighing less than 40 kg. It could be escalated to 300 mg bid or to 150 mg for subjects weighing less than 40 kg. Amphotericin B was administered as 0.7 mg/kg/day. Fluconazole was administered as 400 mg, iv or oral, daily.

Patients 12 years or older who had at least one positive blood culture for *Candida* within 96 hours and signs of *Candida* infection within 24 hours of randomization were enrolled in the study. Signs of *Candida* infection included at least one of the following: temperature > 100° F on two occasions at least 4 hours apart or one determination >101.5° F, systolic blood pressure < 90 or a > 30mm Hg decrease in systolic blood pressure from the subject's normal baseline, or signs of inflammation (swelling, heat, erythema, purulent drainage) from a site infected with *Candida* (e.g., joint, eye, skin, bone, esophagus). Subjects were randomized to voriconazole or amphotericin B → fluconazole in a 2:1 ratio and stratified according to region. The sponsor intended to group centers into regions which shared similar medical practices and standards. Two regions were identified, one comprising centers in the United States and Canada and the other comprising centers in Europe. However, during the study, the sponsor added centers from countries outside these regions in order to increase the overall subject recruitment rate. Each new country was added to one of the existing groups based on administrative center. At the end of the study, Region 1 was compromised of centers from the United States, Canada, India, and South America. Region 2 was compromised of centers from Europe, North Africa, Southern Africa, the Middle East, and South East Asia. These groupings did not necessarily represent two groups that shared similar medical practice but since randomization was stratified by region, this factor will be included in the analyses.

Blood samples were taken at baseline, on Days 1, 2, 3, 4, and 7, thereafter twice weekly during antifungal therapy and at two weeks after end of therapy (EOT). If clinically indicated, blood samples were also taken at 6 and 12 weeks after EOT. Where other sites of *Candida* infection were suspected, investigators could sample sites for further *Candida* microscopy, culture and histopathology or perform clinical indicated radiographic, or other imaging techniques to help establish the extent of invasive *Candida* infection. Subjects were assessed for safety, including visual safety testing throughout the study and those at risk of cardiac arrhythmia or who had telemetric monitoring as part of routine care had continuous cardiac monitoring during drug infusion.

Investigators assessed clinical response at EOT and at 2, 6, and 12 weeks after EOT. Response could be assessed by the investigator as the following:

- Improved (all criteria had to be satisfied)
    1. Clinical signs and symptoms of fungal infection present at baseline during the episode of candidemia had improved but persistent systemic candidiasis could not be completely excluded.
    2. Blood cultures had become negative for *Candida*.

3. Infected deep tissue sites had become negative for *Candida* or all clinical signs of local infection had resolved.
4. No systemic antifungal agent, other than study drug, was administered for the candidemia episode.

- Cured (at 2, 6 or 12 weeks after EOT only; all criteria had to be satisfied)
  1. All clinical signs and symptoms of fungal infection present during the candidemia episode had resolved.
  2. Blood cultures remained negative for *Candida*.
  3. Infected deep tissue sites remained negative for *Candida* or all clinical signs of local infection had resolved.
  4. No systemic antifungal agent, other than study drug, was administered for the candidemia episode.
  5. Ocular examination did not show lesions of *Candida* endophthalmitis.
- Failed
  1. Unresponsive or progressive fungal infection while receiving treatment, or
  2. the subject required additional antifungal therapy for the candidemia episode after study drug discontinuation.
- Relapsed (at 2, 6, and 12 weeks after EOT only)
  Subjects who were considered cured or improved at a previous evaluation but had subsequently developed positive blood cultures for *Candida*, developed a deep-seated *Candida* infection, or required additional treatment with a systemic antifungal for the candidemia episode.
- Indeterminate (at EOT only)
  Subjects who cannot be classified as improving or failing.

A Data Review Committee (DRC) was established to provide a standardized blinded efficacy assessment of a subject's response to antifungal therapy. This was done with the hopes to minimize the potential for investigator bias that may occur in an open label study. The DRC was comprised of originally six (then five) fungal infectious disease experts. They reviewed individual subject data eligibility and efficacy outcomes. The DRC assigned a single outcome response per subject at the latest timepoint, unlike the investigator response which was given at each of the protocol timepoints. The DRC assessment was used for the primary efficacy analysis.

The primary objective of the study was to show that voriconazole was non-inferior to amphotericin B → fluconazole in the treatment of non-neutropenic subjects with candidemia. Voriconazole was considered non-inferior to amphotericin B → fluconazole if the lower limit of the approximate two-sided 95% confidence interval for the difference between the success rates (voriconazole - amphotericin B → fluconazole) was at least -15%, the non-inferiority margin agreed to during protocol development. Assuming a success rate of 65% for both treatment groups, a sample size of 318 patients was needed to demonstrate non-inferiority with 80% power. This sample size was increased by 12.5% to produce the number of subjects required for the 2:1 ratio. Therefore, 240 voriconazole and 120 amphotericin B → fluconazole subjects were to be enrolled.

The primary efficacy analysis was based on the MITT population. This population included all patients who received at least 1 dose of therapy, had a positive blood culture of a *Candida spp.* from a sample taken in the 96 hours prior to study entry, and had not previously participated in the study. A per protocol (PP) population was also defined to provide supportive data to confirm the results of the MITT analysis. The PP population consisted of patients who met the criteria for inclusion in the MITT population; had signs and symptoms of candidemia within 48 hours prior to study entry; received study drug as primary treatment; had not received a concomitant systemic antifungal from Day 2; did not take rifampicin, rifampin, rifamycin, carbamazepine, and barbiturates within 14 days prior to or during the study; were not neutropenic or otherwise immunocompromised by AIDS, aplastic anemia, or chronic granulomatous disease; were not on hemodialysis at baseline when receiving iv study drug; and survived > 24 hours after study start. The safety population consisted of all patients who received at least one dose of study treatment.

The primary efficacy endpoint was the DRC success rate 12 weeks after EOT. Subjects the DRC defined as cured or improved 12 weeks after EOT were classified as a success. Any subject not scored as cured or improved 12 weeks after EOT was considered a failure. A two-sided 95% confidence interval was used to estimate the difference in success rates between the treatment groups. The confidence interval was calculated using a Mantel-Haenszel stratified approach adjusting for region. Secondary endpoints included the DRC assessment at the latest timepoint available, time to death, and the investigator assessment at EOT, 2, 6 and 12 weeks after EOT.

There was a protocol specified administrative data analysis when approximately 10% of the subjects had completed the study. The purpose of this analysis was to provide available data for the first regulatory submission. No formal analyses were carried out and efficacy endpoints were only summarized. No penalty was applied to the final 5% significance level. A formal interim analysis was planned when 50% of the subjects completed the study. Since recruitment had not met the requirements in the time available, this analysis was considered unnecessary to perform. The Data Safety Monitoring Board (DSMB) did review 50% of the safety data but no sponsor personnel directly involved with the conduct of the trial had access to the DSMB interim analysis results. Since there was no intention to stop the trial early for efficacy based on this look at the safety data and careful control over the results were made to maintain the integrity of the trial, no penalty was applied to the final 5% significance level.

3.1.2 Patient Demographics

A total of 422 patients were randomized into the study, 283 patients were randomized to receive voriconazole and 139 to receive amphotericin B → fluconazole. The MITT population included 370 patients (248 in the voriconazole group and 122 in the amphotericin B → fluconazole group). The most common reason for exclusion from the MITT population was the absence of a positive blood culture within 96 hours of starting the study (21 in the voriconazole group and 9 in the amphotericin B → fluconazole group). Of the remaining subjects excluded from the MITT population, 11 voriconazole subjects and 8 amphotericin B → fluconazole subjects did not receive at least one dose of study drug. The PP population consisted of 214 voriconazole patients and 105 amphotericin B → fluconazole patients. The

most common reasons for exclusion from the PP population were exclusion from MITT population, followed by no signs and symptoms of candidemia and receiving rifampicin, rifamycin, carbamazepine, or barbiturates in the 14 days before randomization and up to EOT.

Table 1 summarizes the demographic and baseline characteristics of the MITT population. There were no significant differences across treatment groups. More than half of the patients were male and were white. The mean age of the patients was 53 years with a range of 13 to 90 years. The most common predisposing factor to candidemia was non-surgical followed by abdominal surgery and non-abdominal surgery. Between 15 and 18% of the patients had another site of definite or probable infection in addition to candidemia. A little more than one-third of the patients were mechanically ventilated at baseline and approximately half of patients were hospitalized in an ICU at baseline.

Table 1
Demographic and Baseline Characteristics (MITT)

	Treatment Group	
	voriconazole	**ampho B → fluc**
# Patients	248	122
Gender		
Male	145 (58.5)	71 (58.2)
Female	103 (41.5)	51 (41.8)
Age mean (SD)	53.6 (18.1)	53.3 (19.4)
Min, max	13, 90	13, 87
Race		
White	151 (60.9)	61 (50.0)
Black	36 (14.5)	20 (16.4)
Asian	50 (20.2)	33 (27.1)
Other	11 (4.4)	8 (6.6)
Predisposing factor		
Abdominal surgery	95 (38.3)	46 (37.7)
Non-abdominal surgery	32 (12.9)	15 (12.3)
Non-surgical	121 (48.8)	61 (50.0)
Site of Infection		
Candidemia only	210 (84.7)	100 (82.0)
(b) (4)	(b) (4)	(b) (4)
Mechanical Ventilation		
Yes	89 (35.9)	47 (38.5)
No	159 (64.1)	75 (61.5)
ICU Hospitalization		
Yes	119 (48.0)	61 (50.0)
No	129 (52.0)	61 (50.0)

3.1.3 Efficacy Results

Table 2 summarizes the results of the primary endpoint, DRC assessment of response 12 weeks after EOT, for the MITT and PP populations. For the MITT population, the success

rate was 40.7% for voriconazole and 41.0% for amphotericin B → fluconazole. The lower limit of the 95% stratified confidence interval about the difference in response rates is greater than the non-inferiority margin of –15%. The PP results support the claim of non-inferiority of voriconazole compared to amphotericin B → fluconazole.

Table 2
DRC Response 12 Weeks after EOT

	voriconazole	**ampho B → fluc**	**Difference and 95% CI***
MITT	101/248 (40.7)	50/122 (41.0)	-0.1 (-11.4, 11.1)
PP	85/214 (39.7)	42/105 (40.0)	0.0 (-12.1, 12.1)

*A difference (vori- ampho B →fluc) and 95% confidence interval stratified by region is reported.

Reviewer's Comment**:** *The stratified differences and 95% confidence intervals reported in this review are slightly different than those reported in the Applicant's study report due to differences in the method of calculation. The conclusions drawn, however, are the same.*

As can be seen from the above table, the response rate of 65% assumed for the sample size calculation was not achieved. This may in part be due to timing of the primary assessment not occurring until 12 weeks after EOT. For primary endpoint, any subject not scored as a success at 12 weeks after EOT was considered a failure. Thus, in addition to actual DRC-assessed failures, subjects who did not have a 12 week after EOT assessment including those who died after being considered successfully treated at EOT or were lost to follow-up were also considered failures in the above analysis. Therefore, two additional analyses were performed to determine to robustness of the primary analysis. One was response at EOT which is most consistent with the time point used to assess the efficacy of the last antifungal approved for candidemia. The other was the DRC response at the latest available timepoint, a secondary endpoint stated by the applicant. This endpoint can be interpreted as an EOT analysis which counts anyone who relapses after EOT as a failure. These results are summarized in Table 3.

Table 3
Sensitivity Analyses
MITT Population

	voriconazole (n=248)	**ampho B → fluc** (n=122)	**Difference (95% CI)***
EOT	173 (69.8)	90 (73.8)	-3.9 (-14.2, 6.4)
Last available timepoint	162 (65.3)	87 (71.3)	-5.9 (-16.5, 4.7)

*Difference (vori- ampho B →fluc) and confidence interval are stratified by region.

The above analyses indicate a slightly lower response rate for voriconazole compared to amphotericin B → fluconazole than was seen with the primary analysis at Week 12 after EOT. Though not prespecified, the secondary endpoint using the DRC's last available timepoint would not achieve non-inferiority with a margin of -15%. To determine the cause for this lower response rate, the reasons for non-success were investigated. The DRC could assess subjects as failures at EOT if blood cultures did not become negative, study drug was stopped for toxicity, additional antifungal therapy was required, and/or for other reasons. If a

subject withdrew or was indeterminate at EOT, they were considered a non-successful response. Relapses after EOT were also non-successful outcomes. Table 4 summarizes the reasons for non-successful outcome as assessed by the DRC.

Table 4
Reason for DRC Non-successful Outcome
MITT Population

	voriconazole (n=248)	**ampho B → fluc** (n=122)
Failure at EOT*	65 (26.2)	26 (21.3)
Blood cultures did not become negative	28 (11.3)	12 (9.8)
Study drug stopped due to toxicity	22 (8.9)	5 (4.1)
Additional antifungal required	42 (16.9)	12 (9.8)
Other	19 (7.7)	10 (8.2)
Withdrawn/indeterminate at EOT	10 (4.0)	6 (4.9)
Relapsed (after EOT)	11 (4.4)	3 (2.5)

*Subject may have had more than 1 reason for failure at EOT.

The number of subjects who failed at EOT due to blood cultures not becoming negative or who failed for other reasons were similar between the two treatment groups. There were a disproportionately greater number of subjects in the voriconazole group compared to the amphotericin B → fluconazole group who failed because the study drug was stopped for toxicity or because of the need of additional antifungal therapy. The increased rate of discontinuations due to toxicity in the voriconazole group compared to the amphotericin B → fluconazole group may be in part due to study design. Subjects who switched treatment from amphotericin B to fluconazole because of toxicity were not counted as treatment failures since they were able to complete their assigned treatment regimen. Whereas, a voriconazole subject who had to complete their antifungal treatment course with an alternate antifungal were considered failures.

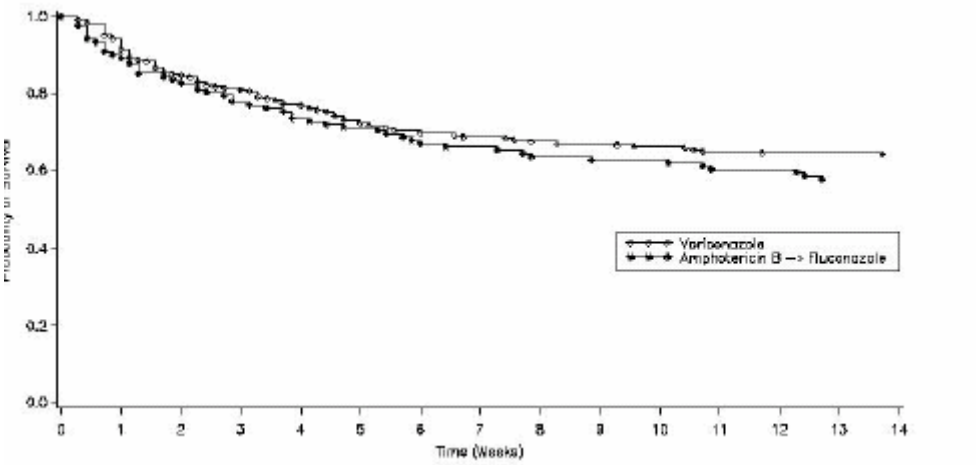
Table 5 summarizes the success rates as assessed by the investigator for the MITT population. The investigator assessment of response was similar for both treatment groups at all four timepoints. The DRC and investigator assessments agreed on the majority of assessments. There were some discrepancies between the assessments, most of which involved a downgrading of the investigator assessment by the DRC.

Table 5
Investigator Success
MITT Population

	voriconazole (n=248)	**ampho B → fluc** (n=122)
EOT	178 (71.7)	88 (72.1)
2 weeks after EOT	125 (50.4)	62 (50.8)
6 weeks after EOT	104 (41.9)	55 (45.1)
12 weeks after EOT	104 (41.9)	51 (41.8)

In the MITT population, 88 (35.5%) voriconazole subjects and 51 (41.8%) amphotericin B → fluconazole had died by Day 98 (Week 14). The difference in survival rates was not statistically significant [hazard ratio 0.822, 95% CI (0.582, 1.161)]. Figure 1 shows the Kaplan Meier plot of the time to death for the MITT population.

Figure 1
Time to Death (MITT Population)



3.2 Evaluation of Safety

A total of 266 patients (97.8%) in the voriconazole group and 130 patients (99.2%) in the amphotericin B → fluconazole group had at least one clinical adverse event. Serious adverse events were reported in 175 (64.3%) voriconazole patients and 106 (80.9%) amphotericin B → fluconazole patients. There were 128 deaths during the study or within 30 days after EOT, 82 patients (30.1%) from the voriconazole group and 46 patients (35.1%) from the amphotericin B → fluconazole group. (Note: These numbers are different than those presented in Figure 1. The number of deaths presented in Section 3.1.3 is for the MITT population by Day 98. The number of deaths presented here are for the Safety population during the study or with in 30 days after EOT.)

For a detailed review of the safety data, please see the medical officer's review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The following table summarizes the number of patients who had a favorable overall response for gender, race, and age. There are no significant treatment by subgroup interactions. Male

voriconazole subjects and female amphotericin B → fluconazole subjects have higher success rates than their gender counterparts within the treatment groups. Further investigation did not provide any meaningful reason for these differences. Similar success rates were achieved in both treatment groups when compared within the ≤ 65 and > 65 subgroups. Younger subjects had slightly higher response rates than the older subjects. There were no noteworthy differences with regard to race.

Table 6
Subgroup Analyses DRC Success at Week 12 after EOT
MITT Population

	Treatment Group	
	voriconazole	**ampho B → fluc**
Gender		
Male	67/145 (46.2)	28/71 (39.4)
Female	34/103 (33.0)	22/51 (43.1)
Age		
≤ 65	78/174 (44.8)	36/82 (43.9)
> 65	23/74 (31.1)	14/40 (35.0)
Race		
White	59/151 (39.1)	26/61 (42.6)
Others	42/97 (43.3)	24/61 (39.3)

4.2 Other Special/Subgroup Populations

The study was primarily performed on a population of subjects with candidemia. There were a small proportion of subjects who in addition to their candidemia had another site of infection. The DRC success rates at Week 12 after EOT were comparable between treatment groups for the subgroup of patients with candidemia only (87/210 [41.4%] voriconazole vs. 39/100 [39.0%] amphotericin B → fluconazole). (b) (4)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The evidence provided in this single study of the treatment of candidemia in non-neutropenic patients supports the claim that voriconazole is non-inferior amphotericin B → fluconazole. This conclusion is fairly robust to the timing of the endpoint with respect to the length of follow-up after EOT. Additional evidence that voriconazole is effective against *Candida* comes from the previously approved indication of esophageal candidiasis.

5.2 Conclusions and Recommendations

In a single Phase 3 study of voriconazole versus amphotericin B followed by fluconazole in the treatment of candidemia in non-neutropenic patients, voriconazole was shown to be non-inferior to amphotericin B followed by fluconazole. (b) (4)

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/s/

Cheryl Dixon
12/3/04 04:09:39 PM
BIOMETRICS

Karen Higgins
12/3/04 04:17:38 PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-266/S009
NDA 21-267/S009
NDA 21-630/S003

MICROBIOLOGY REVIEW(S)

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

NDA #: 21-630, 21-266, and 21-267	**REVIEWER**	**:** Kalavati Suvarna
	CORRESPONDENCE DATE	**:** 03-15-04, 04-26-04, 09-29-04
	CDER RECEIPT DATE	**:** 03-16-04, 04-30-04, 09-30-04
	REVIEW ASSIGN DATE	**:** 03-16-04, 05-08-04, 10-05-04
	REVIEW COMPLETE DATE	**:** 10-22-04

SPONSOR: C. P. Pharmaceuticals International C.V.
c/o Pfizer Inc.
235 East 42nd Street,
New York, NY 10017.

SUBMISSION REVIEWED: SE1-009 (original, BZ, C)

DRUG CATEGORY: Anti-fungal

INDICATION: Treatment of candidemia (b) (4)

DOSAGE FORM: Oral suspension, Oral tablets and Intravenous injection

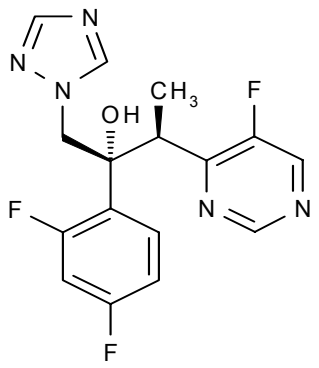
PRODUCT NAMES:

a. **PROPRIETARY:** Vfend®

b. **NONPROPRIETARY:** Voriconazole, UK-109,496

c. **CHEMICAL:** (2R, 3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1*H* -1,2,4-triazol-1-yl)-2-butanol

STRUCTURAL FORMULA:



Molecular weight: 349.3
Empirical formula: $C_{16}H_{14}F_3N_5O$

SUPPORTING DOCUMENTS: NDA 21-266, 21-267, and 21-630; IND (b) (4) 50410, and 66410.

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1. EXECUTIVE SUMMARY:

The sponsor is seeking approval of voriconazole for the treatment of candidemia (b) (4) including infections of the abdomen, kidney and bladder wall; (b) (4) wounds; (b) (4) and disseminated skin infections. Voriconazole is approved for the treatment of invasive aspergillosis, esophageal candidiasis, and serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* species in patients intolerant to other therapy.

No new preclinical information was included in this submission. Data reviewed previously suggests that voriconazole was active *in vitro* against *Candida albicans, Candida glabrata,* and *Candida krusei*. Additionally, voriconazole was effective in reducing the fungal burden in the tissues of normal and/or immunocompromised guinea pigs infected with *C. albicans*, *C. glabrata,* and *C. krusei*.

The pivotal study 150-608, and supporting studies 150-309, 150-609, (b) (4), suggest that voriconazole is active against *C. albicans, C. glabrata*, *C. krusei*, *C. parapsilosis,* and *C. tropicalis*. The activity of voriconazole against *C. glabrata* appears to be lower than other *Candida* species. However, similar observation was made in patients with esophageal candidiasis due to *C. glabrata*. Overall, 11 patients treated with voriconazole relapsed. The most common pathogen in patients that relapsed was *C. albicans*. The other species responsible for relapse were *C. tropicalis*, *C. parapsilosis*, and *C. krusei*. There was no evidence of decrease in the *in vitro* susceptibility of isolates from these patients to voriconazole.

Voriconazole breakpoints could not be established as the MIC values against the clinical isolates did not correlate with clinical outcome. A positive correlation was observed between the *in vitro* activity of voriconazole and those of fluconazole and itraconazole, suggesting cross-resistance. The clinical significance of the *in vitro* observation is unclear.

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2. INTRODUCTION AND BACKGROUND:

The subject of this NDA supplement is Vfend® (voriconazole), an approved drug for the treatment of esophageal candidiasis, invasive aspergillosis, and serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* species (in patients intolerant or refractory to other therapy). In this re-submission, the sponsor is seeking approval for the treatment of candidemia (b) (4) including infections of the abdomen, kidney and bladder wall; (b) (4) wounds; (b) (4) and disseminated skin infections. The proposed dosage is a loading dose of 6 mg/kg intravenous (IV) voriconazole (b) (4) every 12 hours for the first 24 hours followed by a maintenance dose of 3 to 4 mg/kg IV voriconazole or 200 mg oral voriconazole every 12 hours for at least 14 days following resolution of symptoms. (b) (4) The proposed oral dose of voriconazole is based on pharmacokinetic data.

3. PRECLINICAL MICROBIOLOGY:

3.1. Mechanism of Action:

No new information was included in this submission. Voriconazole belongs to the azole class of antifungal agents and inhibit the enzyme, cytochrome P-450 dependent 14 α-lanosterol demethylase, essential for the synthesis of the fungal cell wall component, ergosterol (for details see microbiology review dated 11-02-01, NDA# 21-266/21-267, N-000).

3.2. Activity *in vitro* against *Candida* species:

No new information was included in this submission. The studies reviewed earlier (for details see microbiology review dated 11-02-01, NDA# 21-266/21-267, N-000) show variability in the *in vitro* activity of voriconazole against the different *Candida* species.

3.3. Activity *in vivo* against *Candida* species:

No new information was included in this submission. The studies reviewed earlier (for details see microbiology review dated 11-02-01, NDA# 21-266/21-267, N-000) demonstrated that oral voriconazole was effective in reducing the fungal burden in the tissues of normal and/or immunocompromised guinea pigs infected with *C. albicans*, *C. glabrata,* and *C. krusei*.

4. CLINICAL MICROBIOLOGY:

There were (b) (4) clinical studies included to support the safety and efficacy of voriconazole for the treatment of (b) (4) candidiasis. The pivotal study (#150-608), compared the safety and efficacy of voriconazole with a regimen of amphotericin B followed by fluconazole (ampB → FLZ) for the treatment of (b) (4) candidiasis in nonneutropenic patients. Supporting data was provided from a subset of (b) (4) candidiasis cases treated with voriconazole in (b) (4) the salvage therapy study 150-309/604 (b) (4)

4.1. Study 150-608:

This was a randomized, open label, comparative, multi-center study conducted to compare the safety and efficacy of voriconazole to ampB → FLZ in the treatment of (b) (4) candidiasis including candidemia in non-neutropenic patients. Patients who had at least one positive blood culture for a *Candida* species within 96 hours of randomization were eligible to participate in the study. The study entry criteria excluded immunocompromised patients, and those who had previously failed antifungal therapy. The patients were administered a loading dose of 6 mg/kg intravenous (IV) voriconazole or 400 mg oral voriconazole every 12 hours for the first 24 hours followed by maintenance dose of 3 to 4 mg/kg IV voriconazole or 200 mg oral voriconazole (100 mg for patients weighing <40 kg) every 12 hours for at least 14 days following resolution of symptoms. At the discretion of the investigator, the dose could be escalated up to 300 mg BID (150 mg for subjects weighing <40 kg). Patients in the comparator arm received 0.7 mg/kg IV amp B daily for ≥ 3 days followed by 400 mg IV or oral FLZ daily. Patients could switch to oral therapy after 3 days of IV therapy. The maximum duration of treatment was eight weeks. The clinical response was assessed at end of therapy (EOT), and at 2, 6, and 12 weeks after EOT. Blood samples (5 ml) were obtained for fungal culture on days 1, 2, 3, 4, and 7, and then twice weekly during therapy and at 2 weeks after EOT. If clinically indicated, samples were obtained at 6 and 12 weeks after EOT. Sabouraud's dextrose agar containing chloramphenicol was used for fungal culture. The (b) (4) (b) (4) performed species identification and susceptibility testing on fungal isolates sent from participating centers. The identifications made by the (b) (4) were used for data analysis, except in cases where cultures sent to the (b) (4) failed to grow or no cultures were sent. In such cases, the identification made by the local laboratory was used for data analysis. Please note that about 80% of isolates obtained from patients enrolled in study 150-608 were sent to the (b) (4) for speciation and *in vitro* susceptibility testing. In general, there was good agreement between the identification of fungal isolates made by the central versus local laboratories. However, differences in identification were noted in 24 out of the 370 patients evaluated. The sponsor has stated that differences in identifications may be due to mixed cultures not detected by the local laboratory, unusual pathogens not commonly tested for by local laboratories or species where the taxonomy remains controversial.

In cases where sites of infection other than blood were suspected, samples from the sites were examined by microscopy, culture, and histopathology. Imaging techniques were used to diagnose dissemination of *Candida* infection.

A Data Review Committee (DRC) assessed each patient on the basis of eradication of *Candida* species from the bloodstream, resolution of signs and symptoms of candidemia, absence of signs of dissemination of infection, as well as the requirement for other systemic antifungal treatment. Based on an assessment of these parameters, the DRC assigned the overall outcome as follows: '*Cured'* or '*Improved'* or '*Failed'* or '*Relapsed'*. Relapse was defined as the re-occurrence of clinical signs of infection and/or isolation of *Candida* species during the 12 week follow up period. Thus, the mycological outcome was not evaluated separately from the clinical outcome but incorporated into the overall outcome. The primary efficacy endpoint was success rate at 12 weeks after EOT (defined as number of patients that were cured plus improved based on the DRC's assessment of response to antifungal therapy) in the two treatment arms. The secondary endpoint was the overall (clinical and mycological) response at the last available time point (which could be at EOT, 2, 6 or 12 weeks after EOT).

The modified intent to treat (MITT) efficacy population consisted of patients who had *Candida* species cultured from blood drawn within the 96 hours preceding the start of the study and had at least one dose of study drug. There were 370 patients (voriconazole arm = 248; ampB → FLZ arm = 122) in the MITT population.

The most common *Candida* isolate at baseline was C*andida albicans* followed by *C. tropicalis*, *C. parapsilosis,* and *C. glabrata* (Table 1). Other species isolated at low frequencies were *C. guilliermondii, C. inconspicua, C. kefyr, C. krusei, C. lipolytica, C. lusitaniae,* and *C. pelliculosa*. The distribution of species across the study arms was similar, except for *C. tropicalis,* which was isolated more frequently in the voriconazole group. There were 12 patients in the voriconazole arm and 3 patients in the ampB → FLZ arm with mixed fungal infections. The success rates at 12 weeks after EOT were similar in the two treatment groups (Table 2). For *C. albicans*, the rate of favorable response was 43% (46/107) in the voriconazole arm and 48% (30/63) in the ampB → FLZ arm. The response rates were similar in the two groups for *C. glabrata* [voriconazole, 12/36 (33%); ampB → FLZ, 7/21 (33%)], and *C. parapsilosis* [voriconazole, 24/45 (53%) and ampB → FLZ, 10/19 (53%)], but higher in the voriconazole arm (32%, 17/53) than the ampB → FLZ arm (6%, 1/16) for *C. tropicalis*. The response rates for *C. krusei* infections were 1/5 (20%) in the voriconazole arm and 0/1 (0%) in the ampB → FLZ arm.

Table 1: Baseline pathogens and overall (clinical + mycological) outcome of patients at **12 weeks after EOT** in study 150-608.

Pathogen*	**Voriconazole (n = 248)**	**Amphotericin B -->Fluconazole (n = 122)**
	Success (%)	**Success (%)**
C. albicans	43/98 (44%)	30/61(49%)
C. albicans + C. glabrata	1/3 (33%)	0/1
C. albicans + C. lusitaniae	1/1	0
C. albicans + C. parapsilosis	0/3 (0%)	0/1
C. albicans + C. tropicalis	1/2 (50%)	0
C. glabrata	11/33 (33%)	7/19 (37%)
C. glabrata + C. krusei	0	0/1
C. guillermondii	2/2 (100%)	0
C. guillermondii + C. parapsilosis	0/1	0
C. inconspicua	0/1	0
C. inconspicua + C. tropicalis	0/1	0
C. kefyr	1/2 (50%)	0
C. krusei	1/3 (33%)	0
C. lipolytica	0	2/2 (100%)
C. lusitaniae	0/1	0/1
C. parapsilosis	24/41 (59%)	10/18 (56%)
C. pelliculosa	0/1	0
Candida species	0/4 (0%)	0/2 (0%)
C. tropicalis	15/49 (31%)	1/16 (6%)
C. tropicalis + Candida species	1/0	0

EOT = End of therapy
*The identifications made by the (b) (4) were used for data analysis, except in cases where cultures sent to the (b) (4) failed to grow or no cultures were sent. In such cases, the identification made by the local laboratory was used for data analysis.

Table 2: Baseline pathogens (irrespective of mixed infections) in patients with a successful clinical and mycological outcome at **12 weeks after EOT** in study 150-608.

Baseline Pathogen*	**Clinical and mycological success (%)**	
	Voriconazole	**Amphotericin B --> Fluconazole**
C. albicans	46/107 (43%)	30/63 (48%)
C. tropicalis	17/53 (32%)	1/16 (6%)
C. parapsilosis	24/45 (53%)	10/19 (53%)
C. glabrata	12/36 (33%)	7/21 (33%)
C. guilliermondii	2/3 (67%)	0/0
C. inconspicua	0/2 (0%)	0/0
C. kefyr	1/2 (50%)	0/0
C. krusei	1/4 (25%)	0/1
C. lipolytica	0/0	2/2 (100%)
C. lusitaniae	1/2 (50%)	0/1
C. pelliculosa	0/1	0/0
Candida species	1/5 (20%)	0/2 (0%)

EOT = End of therapy
*The identifications made by the (b) (4) were used for data analysis, except in cases where cultures sent to the (b) (4) failed to grow or no cultures were sent. In such cases, the identification made by the local laboratory was used for data analysis.

The success rates for the different baseline *Candida* species in voriconazole treated patients were higher at EOT compared to 12 weeks after EOT (Tables 2 and 3). Similar observations were made in the ampB → FLZ treated patients. However, the success rates for *C. albicans* and *C. glabrata* at EOT were higher in the ampB → FLZ arm compared to the voriconazole arm, and success rate for *C. tropicalis* at EOT was higher in the voriconazole arm compared to the ampB → FLZ arm.

Table 3: Baseline pathogens (irrespective of mixed infections) in patients with a successful clinical and mycological outcome at **EOT** in study 150-608.

Baseline Pathogen*	**Clinical and mycological success (%)**	
	Voriconazole	**Amphotericin B --> Fluconazole**
C. albicans	74/107 (69%)	51/63 (81%)
C. tropicalis	37/53 (70%)	7/16 (44%)
C. parapsilosis	34/45 (76%)	15/19 (79%)
C. glabrata	19/36 (53%)	16/21 (76%)
C. guilliermondii	3/3 (100%)	0/0
C. inconspicua	2/2 (100%)	0/0
C. kefyr	2/2 (100%)	0/0
C. krusei	2/4 (50%)	1/1
C. lipolytica	0/0	2/2 (100%)
C. lusitaniae	2/2 (100%)	1/1
C. pelliculosa	1/1	0/0
Candida species	3/5 (60%)	0/2 (0%)

EOT = End of therapy
*The identifications made by the (b) (4) were used for data analysis, except in cases where cultures sent to the (b) (4) failed to grow or no cultures were sent. In such cases, the identification made by the local laboratory was used for data analysis.

Relapse was observed in 11/248 (4.4%) voriconazole and 3/122 (2.5%) ampB → FLZ treated patients (Table 4). The pathogens isolated from voriconazole treated subjects were *C. albicans* (6/11), *C. tropicalis* (2/11), and one case each of *C. parapsilosis, C. krusei,* and *C. albicans* plus *C. parapsilosis*. There was no evidence of decrease in susceptibility of these isolates to voriconazole. In

the ampB → FLZ group, relapse occurred in two patients with *C. albicans*, and one patient with *Candida* species.

Table 4: List of patients who relapsed at different time points after end of therapy in study 150-608.

Patient ID	Time point	Site	Species	Voriconazole MIC
Voriconazole				
608 00410354	2 week FU	Blood	*C. albicans*	No change from baseline
608 21700408	2 week FU	Blood	*C. tropicalis*	No change from baseline
608 22710338	12 week FU	Blood	*C. albicans*	No change from baseline
608 23040342	6 week FU	Blood	*C. albicans*	No change from baseline
608 50470311	2 week FU	Blood	*C. albicans* and *C. parapsilosis*	Not available
608 50530206	2 week FU	Blood	*C. albicans*	No change from baseline
608 50640101	2 week FU	Signs of deep tissue infection	*C. tropicalis*	Not available
608 50920427	2 week FU	Blood	*C. albicans*	Not available
608 50940136	2 week FU	Blood	*C. albicans*	No change from baseline
608 66920197	2 week FU	Blood	*C. krusei*	No change from baseline
608 80500062	6 week FU	Signs of deep tissue infection	*C. parapsilosis*	Not available
Amphotericin B-Fluconazole				
608 03980106	2 week FU	Blood	*C. albicans*	No change from baseline
608 52600319	2 week FU	Urine	*Candida* species	Not available
608 80090260	6 week FU	Blood	*C. albicans*	Not available

FU = follow-up

The *in vitro* susceptibility testing of isolates was performed using the National Committee for Clinical Laboratory Standards (NCCLS) method described in the document M27A. The minimum inhibitory concentration (MIC) for azoles was defined as the concentration of the drug that inhibited 80% growth compared to drug free controls. The term MIC_{90} represent the concentration of the drug required for inhibiting 90% of the isolates tested. The voriconazole MIC or MIC_{90} (if ≥ 10 isolates) values of isolates from patients who had a successful outcome and from those who failed therapy with voriconazole overlapped for all *Candida* species except *C. tropicalis* (Table 5). For *C. tropicalis*, there appears to be a trend for voriconazole MICs to be slightly higher in patients failing treatment. However, due to variability of the voriconazole MIC against the *C. tropicalis* isolates, no conclusion can be drawn regarding a correlation between the *in vitro* activity and clinical outcome.

Only few patients had voriconazole MIC data for the pre-treatment, during treatment, and post-treatment study periods (Table 6). All these patients either failed therapy or relapsed. The voriconazole MIC against isolates from these patients were within the voriconazole MIC range for baseline isolates from patients treated successfully with voriconazole. Based on the limited data, breakpoints for voriconazole could not be established and there was no evidence of a decrease in the *in vitro* susceptibility of isolates to voriconazole during therapy.

Table 5: Correlation of voriconazole MIC values against all isolates obtained from invasive candidiasis patients obtained at different time point to the overall clinical and microbiological response at 12 weeks after discontinuation of voriconazole therapy (study 608).

Overall Response / **Species**		**Success**	**Failure**	**Success**	**Failure**	**Success**	**Failure**
		Pre-treatment MIC* µg/ml		**During treatment MIC* µg/ml**		**Post-treatment MIC* µg/ml**	
C. albicans	MIC_{90}	≤ 0.016	≤ 0.016	≤ 0.016	≤ 0.016	-	≤ 0.016
	MIC range	≤ 0.016 – 0.06	≤ 0.016 – 0.25	≤ 0.016	≤ 0.016-0.03	-	≤ 0.016
	n (days isolate collected)	101 (-19 to 0)	182 (-4 to 0)	48 (1 to 14)	118 (1 to 24)	-	10[1R] (12 to 71)
C. glabrata	MIC_{90}	4	2	1	2	-	-
	MIC range	≤ 0.016 – >8.0	0.06 – 4.0	0.25 - 2	≤ 0.016 – 8.0	-	-
	n (days isolate collected)	18 (-4 to 0)	28 (-4 to 0)	13 (1 to 10)	66 (1 to 32)	-	-
C. tropicalis	MIC_{90}	0.125	0.25	-	0.5	-	-
	MIC range	≤ 0.016 – 0.125	≤ 0.016 – ≥8.0	0.06 - 0.125		-	0.06 – 0.25
	n (days isolate collected)	22 (-3 to 0)	70 (-4 to 1)	8 (2 to 8)	49 (2 to 4)	-	3 (50-102)
C. parapsilosis	MIC_{90}	0.125	0.06	0.06	0.06	-	-
	MIC range	≤ 0.016 – 0.125	≤ 0.016 – 0.125	≤ 0.016 – 0.125	≤ 0.016 – 0.06	≤ 0.016 – 0.125	0.03
	n (days isolate collected)	42 (-3 to 0)	30 (-3 to 0)	13 (1 to 24)	15 (1 to 10)	3 (136 to 333)	1 (89)
C. krusei	MIC_{90}	-	-	1.0	-	-	-
	MIC range	0.25	0.5	0.25 – 1.0	0.25 -1.0	-	0.5
	n (days isolate collected)	2 (-1 to 0)	3 (-3 to 0)	14 (2 to 7)	3 (2 to 15)	-	1 (31)
C. lusitaniae	MIC_{90}	-	-	-		-	-
	MIC range	≤ 0.016	≤ 0.016	-	≤ 0.016	-	-
	n (days isolate collected)	1 (-2)	1 (-1)	-	1 (2)	-	-

n = number of isolates tested

*When data for ≥ 10 isolates were available, the MIC_{90} values were reported otherwise the MIC range was reported.

[1R] one of the 10 isolates obtained from patients who relapsed

Table 6: Patients in the voriconazole arm where MIC data were available for all 3 visits.

Patient ID	Pathogen	Clinical outcome at 12 weeks post-therapy	Voriconazole MIC (μg/ml)		
			Pre-treatment	During treatment	Post-treatment
608 00410354	*Candida albicans*	Failed	≤0.016	≤0.016	≤0.016
608 23040342	*Candida albicans*	Failed	≤0.016	≤0.016	≤0.016
608 50710110	*Candida albicans*	Failed	≤0.016	≤0.016	≤0.016
608 51040215	*Candida albicans*	Failed	≤0.016	-	≤0.016
608 22710338	*Candida albicans*	Relapsed	≤0.016	≤0.016	≤0.016
608 66920197	*Candida krusei*	Failed	0.5	1.0	0.5
608 60010177	*Candida parapsilosis*	Failed	0.03	0.06	0.03
608 21700408	*Candida tropicalis*	Failed	0.125 - 0.25	0.125	0.25
608 50920045	*Candida tropicalis*	Failed	0.06	≤0.016	0.06

Voriconazole concentrations in the plasma were obtained by sparse sampling from 162 patients. The mean of the mean voriconazole plasma concentration in patients who failed therapy (3.7 μg/ml) was similar to that observed in patients with a successful outcome (3.1 μg/ml). The mean voriconazole plasma level to MIC ratio for the baseline isolates varied widely from 0.125 to >1024. Other PK/PD parameters such as ratios of area under the concentration time curve to MIC (AUC/MIC) and peak concentration to MIC (C_{max}/MIC), or time the voriconazole concentration remains above MIC (T>MIC) were not measured. The mean voriconazole plasma level obtained by sparse sampling is not sufficient for determination of the PK/PD parameter that correlates with outcome.

The sponsor attempted to assess the activity of voriconazole in patients with baseline *Candida* isolates that were susceptible or resistant to FLZ or ITZ *in vitro*. The interpretative criteria established by the NCCLS for FLZ and ITZ was used for categorizing the *Candida* isolates as susceptible (FLZ MIC ≤ 8 μg/ml, ITZ MIC ≤ 0.125 μg/ml), dose-dependent susceptible (FLZ MIC 16-32 μg/ml, ITZ MIC 0.25-0.5 μg/ml), or resistant (FLZ MIC ≥ 64 μg/ml, ITZ MIC ≥ 1 μg/ml). It is of note that the breakpoints established by NCCLS were derived largely using isolates obtained from patients with mucosal infection due to *Candida*. Please note that these breakpoints have not been established by the Agency nor do the fluconazole or itraconazole labels describe any breakpoints. In the voriconazole and ampB→FLZ groups, a small number of baseline isolates had FLZ MIC ≥ 64 μg/ml or ITZ MIC ≥ 1 μg/ml. All the isolates were identified to be *Candida* species other than *C. albicans* (*C. glabrata, C. tropicalis* or *C. krusei*, see Tables 7 and 8). Voriconazole was active in some of the patients with these isolates. However, the efficacy of voriconazole in patients with invasive candidiasis refractory to FLZ or ITZ remains to be elucidated.

Table 7: Overall (clinical and mycological outcome) of patients stratified by baseline pathogen and fluconazole (FLZ) MIC.

Pathogen	**Outcome**	**Voriconazole**			**Amphotericin B-Fluconazole**		
		FLZ ≤ 8 μg/ml	**FLZ 16-32 μg/ml**	**FLZ ≥ 64 μg/ml**	**FLZ ≤ 8 μg/ml**	**FLZ 16-32 μg/ml**	**FLZ ≥ 64 μg/ml**
C. albicans	CURED	44	0	0	34	0	0
	FAILED	84	0	0	42	0	0
C. glabrata	CURED	7	0	2	6	1	1
	FAILED	11	7	3	9	1	3
C. parapsilosis	CURED	29	0	0	9	0	0
	FAILED	23	0	0	11	0	0
C. tropicalis	CURED	16	0	0	1	0	0
	FAILED	36	0	1	14	0	0
C. krusei	CURED	0	1	1	0	0	0
	FAILED	1	0	3	1	0	0
C. guilliermondii	CURED	2	0	0	0	0	0
	FAILED	0	0	0	0	0	0
C. inconspicua	CURED	0	0	0	0	0	0
	FAILED	1	2	0	0	0	0
C. kefyr	CURED	3	0	0	0	0	0
	FAILED	0	0	0	0	0	0
C. lusitaniae	CURED	1	0	0	0	0	0
	FAILED	2	0	0	2	0	0
C. pelliculosa	CURED	0	0	0	0	0	0
	FAILED	2	0	0	0	0	0
C. lipolytica	CURED	0	0	0	1	0	0
	FAILED	0	0	0	0	0	0

Table 8: Overall (clinical and mycological outcome) of patients stratified by baseline pathogen and itraconazole (ITZ) MIC.

Pathogen	**Outcome**	**Voriconazole**			**Amphotericin B-Fluconazole**		
		ITZ ≤ 0.125 μg/ml	**ITZ 0.25 - 0.5 μg/ml**	**ITZ ≥ 1.0 μg/ml**	**ITZ ≤ 0.125 μg/ml**	**ITZ 0.25 - 0.5 μg/ml**	**ITZ ≥ 1.0 μg/ml**
C. albicans	CURED	44	0	0	36	0	0
	FAILED	85	0	0	42	0	0
C. glabrata	CURED	2	3	4	0	1	5
	FAILED	1	5	12	0	3	9
C. parapsilosis	CURED	25	4	0	9	0	0
	FAILED	23	0	0	11	0	0
C. tropicalis	CURED	11	5	0	0	1	0
	FAILED	30	5	2	11	3	0
C. krusei	CURED	0	2	1	0	0	0
	FAILED	0	3	0	0	0	0
C. guilliermondii	CURED	0	2	0	0	0	0
	FAILED	0	0	0	0	0	0
C. inconspicua	CURED	0	0	0	0	0	0
	FAILED	2	0	0	0	0	0
C. kefyr	CURED	3	0	0	0	0	0
	FAILED	0	0	0	0	0	0
C. lusitaniae	CURED	1	0	0	0	0	0
	FAILED	2	0	0	2	0	0
C. pelliculosa	CURED	0	0	0	0	0	0
	FAILED	0	2	0	0	0	0
C. lipolytica	CURED	0	0	0	1	0	0
	FAILED	0	0	0	0	0	0

Increase in voriconazole MIC was observed with increase in FLZ and itraconazole MICs against clinical isolates, suggesting cross-resistance between azole drugs (Table 9). However, the clinical significance of this finding is not known.

Table 9: Correlation of voriconazole and itraconazole MICs against clinical isolates with fluconazole MIC of ≥ 64 µg/ml.

Voriconazole MIC (µg/ml)	**Number of isolates* with itraconazole MIC (µg/ml)**			
	≤ 0.125	**0.25**	**≥ 1**	**≥ 8**
0.25	0	1	0	0
0.5	0	3	0	0
1	0	0	0	1
2	0	0	1	1
4	0	0	1	3
≥ 8	0	0	0	3

*Please note all isolates were *Candida* species other than *C. albicans* (*C. glabrata*, *C. krusei*, *C. tropicalis*).

Overall, voriconazole was as effective as ampB→ FLZ in the treatment of invasive candidiasis.

4.2. Studies 150-309 and 150-604:

These were open label, non-comparative phase III studies conducted to evaluate the safety and efficacy of voriconazole for the primary or secondary treatment of invasive fungal infections and have been reviewed previously (please see microbiology review dated (b) (4) NDA# 21-266/21-267, N-000, and medical officer's review dated 07-30-01). Patients were treated with 4 mg/kg IV or 200 mg oral voriconazole BID daily, for a maximum of 12 weeks. It should be noted that the endpoints used in these studies are not directly comparable with that of the study 150-608 as there is difference in the time of assessments. In study 150-608, the primary endpoint was the DRC assessment of success at 12 weeks after EOT. In studies 150-309 and 150-604, the primary endpoint was the investigator assessment of patient's response to antifungal therapy at EOT.

(b) (4)

(b) (4)

(b) (4)

5. CONCLUSIONS:

The sponsor is seeking approval of voriconazole for the treatment of candidemia (b) (4) including infections of the abdomen, kidney and bladder wall; (b) (4) wounds; (b) (4) ; and disseminated skin infections.

No new preclinical information was included in this submission. Data reviewed previously suggests that the *in vitro* activity of voriconazole against *Candida* species was variable. *In vivo*, voriconazole was effective in reducing the fungal burden in the tissues of normal and/or immunocompromised guinea pigs infected with *C. albicans*, *C. glabrata,* and *C. krusei*.

Study 150-608, the pivotal study in this submission compared use of voriconazole with a regimen of ampB → FLZ for treatment of (b) (4) candidiasis in nonneutropenic patients. The efficacy of voriconazole was similar to that of ampB → FLZ, at 12 weeks after end of therapy. The most common *Candida* isolate at baseline was C. *albicans* followed by *C. tropicalis*, *C. parapsilosis,* and *C. glabrata*. Other species isolated at low frequencies were *C. guilliermondii, C. inconspicua, C. kefyr, C. krusei, C. lipolytica, C. lusitaniae,* and *C. pelliculosa*. The percentage of favorable responses in the voriconazole and ampB → FLZ arms for patients with baseline *C. albicans*, (voriconazole, 43%; ampB → FLZ, 48%), *C. glabrata* (voriconazole, 33%; ampB → FLZ, 33%), and *C. parapsilosis* (voriconazole, 53%; ampB → FLZ, 53%) was similar. The percentage of successful response in patients with *C. tropicalis* infection was higher in the voriconazole arm (32%, 17/53) than the ampB → FLZ arm (6%, 1/16). A higher percentage of successful outcomes were observed at end of therapy compared to that at 12 weeks after end of therapy. Relapse was observed in 11 patients in the voriconazole arm and 3 patients in the ampB → FLZ arm. There was no evidence of decrease in the *in vitro* susceptibility of isolates from these patients to voriconazole. The voriconazole MIC values did not correlate with clinical outcome. Hence, voriconazole breakpoints could not be established. A decrease in the *in vitro* susceptibility of clinical isolates to voriconazole correlated with decreases in the *in vitro* susceptibilities to FLZ and itraconazole, suggesting cross-resistance between azole drugs.

Supporting data were provided from a subset of (b) (4) candidiasis cases from (b) (4) the salvage therapy study 150-309/604 (b) (4) These studies had a small number of patients (b) (4) . Pooling of data from the pivotal and supportive studies suggests that voriconazole is active against *C. albicans, C. glabrata*, *C. krusei*, *C. parapsilosis,* and *C. tropicalis*. However, the activity of voriconazole against *C. glabrata* appears to be lower than other *Candida* species. Similar observation was made in patients with esophageal candidiasis where 57% patients showed mycological eradication even though a greater percentage had a successful clinical response.

6. LABEL:

6.1. Sponsor's proposed label:

The sponsor's proposed changes to the current approved label are underlined.

3 Pages Immediately Following Withheld - b(4) Draft Labeling

(b) (4)

7. RECOMMENDATIONS:

This NDA supplement is approvable pending an accepted version of the label.

_____
Kalavati Suvarna
Microbiologist, HFD-590

CONCURRENCES:

HFD-590/Deputy Dir. _____Signature _____Date
HFD-590/Micro TL _____Signature _____Date
CC:
HFD-590/Original IND
HFD-590/Division File
HFD-590/MO
HFD-590/Pharm
HFD-590/Chem
HFD-590/Review Micro
HFD-590/CSO/SavilleR

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/s/

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PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-266/S009
NDA 21-267/S009
NDA 21-630/S003

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA:	**21,266 (S-009); 21,267 (S-009); 21,630 (S-003)**
Submission Date:	**15 March 2004**
Drug Product:	**Voriconazole IV, Tablets, Powder for Oral Suspension**
Trade Name:	**VFEND®**
Sponsor:	**Pfizer**
Submission Type:	**Prior Approval Efficacy Supplement (Candidemia)**
OCPB Reviewer:	**Gerlie C. De Los Reyes, Ph.D.**
Team Leader:	**Philip M. Colangelo, Pharm.D., Ph.D.**

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I. Executive Summary

A. Recommendations

The sponsor submitted the findings of clinical studies (Studies 150-608 and 150-309/604) to support the approval of VFEND® for the treatment of candidemia (b) (4) The proposed dosage regimen for this indication is similar to that for the already approved indications including the treatment of invasive aspergillosis i.e., for IV use, 6 mg/kg q12h for the first 24 hours followed by 3 to 4 mg/kg q12h, (b) (4) followed by 200 mg q12h for PO use. The proposed duration of therapy is ≥14 days, following resolution of symptoms or following last positive culture, whichever is longer. In the pivotal Global Candidemia Study (Study 150-608), population PK sampling was conducted but PopPK analysis was not performed. Instead, pooled individual patient mean voriconazole plasma concentration data (without regard to sampling time) was used to explore PK-efficacy and PK-toxicity relationships, as was done in the PK/PD analysis for the original submission (for various indications including aspergillosis). Although voriconazole was non-inferior to the comparator amphotericin B → fluconazole in the treatment of (b) (4) candidiasis (response rates for both groups was 40%), the sponsor's own PK/PD analysis did not show a clear

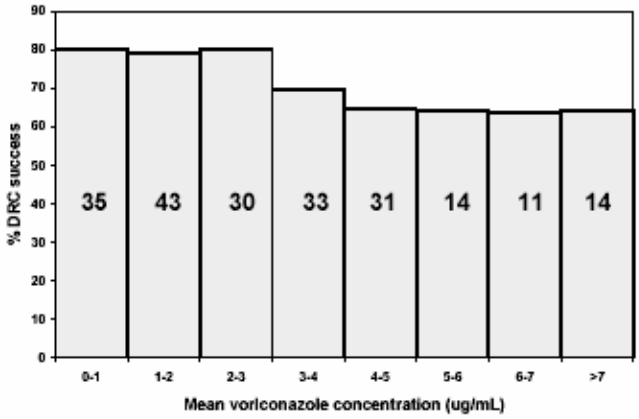
relationship between voriconazole exposure and efficacy. Instead, it appears that this relationship could be best fitted into an umbrella-like plot wherein the region of the curve associated with extremely low concentrations had a positive slope, and the region comprising extremely high exposures had a negative slope. Consequently, a similar curvilinear relationship was found between voriconazole efficacy and mean voriconazole plasma level/MIC ratio. Although mean voriconazole plasma concentration values exceeded the MIC (Concentration/MIC range: 0.125 to 1024) of the infecting baseline *Candida* isolate, the sponsor did not find statistical evidence to support the relationship between %DRC success and this PK-microbiologic parameter. Additionally, although the sponsor found a linear relationship between mean plasma concentration and certain liver function test (LFT) values, a threshold voriconazole plasma concentration value for LFT abnormality had not been identified.

In the following review, only the PK/PD findings of the Global Candidemia Study (150-608) were considered in detail. The PK/PD data from the supportive studies (150-309 and 150-604) were part of the original submission; about 29% of the total patient population in these supportive studies was diagnosed with serious candidiasis, 12.3% of which were candidemia. Because the findings of the current PK/PD study are consistent with that in the original submission, no changes will be recommended for the PK/PD section of the current VFEND® labeling. To improve the chances of finding clear PK-efficacy relationships, future studies should distinguish between failures due to insufficient clinical response and failures related to toxicities (adverse events, laboratory abnormalities, death). In addition, although the use of mean daily or weekly plasma concentration values might reveal trends, for future PK/PD studies, the sponsor should attempt to use more reliable PK endpoints (e.g., Cmax, Cmin, AUC) to improve the chances of identifying threshold voriconazole concentration values for toxicity endpoints. If intensive PK sampling is not feasible, the plasma concentration values should be looked at in relation to the actual sampling/dosing times or time interval to ensure that meaningful PK/PD correlations are obtained. Refer to Appendix E for the Pharmacometrics Consult review of Dr. Jenny J. Zheng.

B. Phase IV Commitments
None.

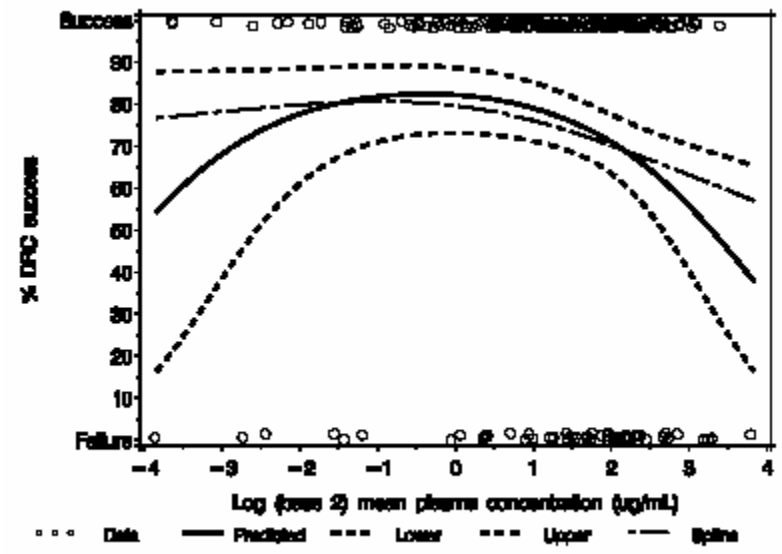
C. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings
The sponsor explored PK/PD relationships based on individual patient mean voriconazole plasma concentrations without consideration of actual dosing/sampling times. Figure 1 shows the relationship between therapeutic outcome (as % Data Review Committee (DRC) success) and mean voriconazole concentration. The total number of subjects in each plasma voriconazole concentration category is indicated in each bar. Figure 2 shows the curvilinear relationship between log mean voriconazole plasma concentration and efficacy for MITT subjects, as revealed by logistic regression analysis.

FIGURE 1
Summary of Success by mean plasma voriconazole concentration bands



Source: 150-608 PK/PD Statistical report Figure 0.8

FIGURE 2
Binomial data and logistic fit for DRC therapeutic success versus log plasma concentration



Source: 150-608 PK/PD Statistical report Figure 0.9

Linear modeling of mean LFTs in the safety population of Study 150-608 revealed statistically significant relationships for AST, AP and bilirubin. Logistic modeling of abnormal LFTs only showed statistical significance for bilirubin only.

_____
Gerlie C. De Los Reyes, Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation 3

RD/FT signed by Philip M. Colangelo, Pharm.D., Ph.D. (TL)_____

II. Question-Based Review

A. General Clinical Pharmacology

1. *What is the relationship between the <u>mean</u> plasma voriconazole concentration and therapeutic outcome?*

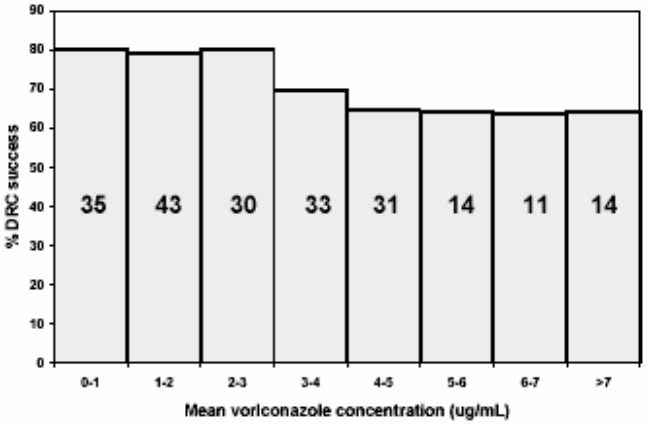
Using mean plasma concentration values obtained in the Global Candidemia Study (150-608), the sponsor failed to identify a clear positive PK/PD relationship for efficacy. Table 1 provides the summary statistics of mean plasma voriconazole concentrations associated with the type of therapeutic outcome (failure or success). Figure 1 provides the success rate associated with each mean plasma voriconazole concentration band. In addition, using a multivariate logistic modeling technique, the sponsor found a statistically higher success rate associated with mean plasma voriconazole concentrations of ≤2 mcg/mL (79.5%) and 2-4 mcg/mL (74.6%) compared to >4 mcg/mL(64.3%).

TABLE 1
Summary statistics of mean plasma voriconazole concentrations by therapeutic outcome

Therapeutic Outcome	No. of Subjects	Range (µg/ml)	Median (µg/ml)	Geometric Mean (µg/ml)
DRC success	154	0.07 – 10.05	2.45	2.16
DRC failure	57	0.07 – 14.19	3.89	2.72
Investigator success	165	0.07 – 10.05	2.40	2.08
Investigator failure	46	0.16 – 14.19	4.34	3.32

Source: 150-608 PK/PD Statistical report Table 0.6

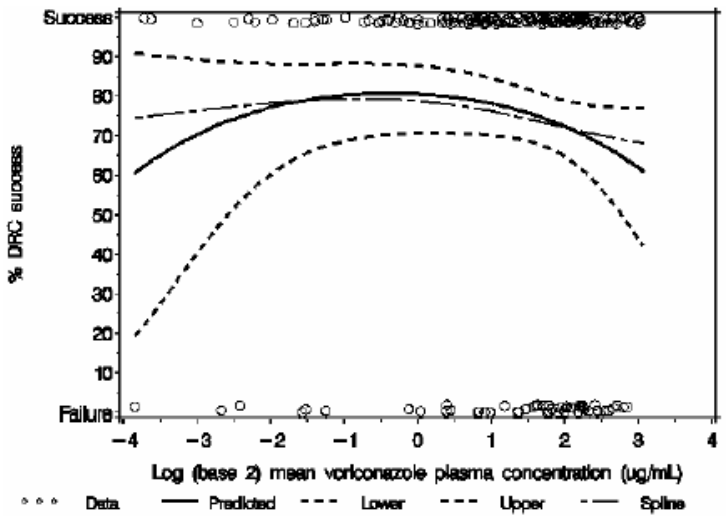
FIGURE 1
Summary of success by mean plasma voriconazole concentration bands



The total number of subjects in each plasma concentration category is indicated in each bar.

The statistical significance of this curvilinear realtionship between plasma voriconazole exposure and efficacy disappeared upon the exclusion of five subjects with extremely high mean voriconazole plasma concentrations (>9 mcg/mL), four of whom were failed cases, as shown in Figure 2A. A similar relationship was observed when response (as assessed by the investigator) and the mean plasma voriconazole concentrations were modeled, as well as when modeling was based on the primary DRC endpoint of response at 12 weeks after end of treatment, suggesting that the model was not dependent on the efficacy endpoint. It was also noted that the curvilinear relationship observed for the primary DRC endpoint disappeared when the mean plasma concentration data were determined using the first 8 days of treatment only.

FIGURE 2A
Binomial data and logistic fit for DRC therapeutic success versus log plasma concentration – MITT subjects excluding subjects with mean voriconazole plasma concentration >9µg/ml



Reviewer's comments:

1. The data in Table 1 above reveal a higher median and geometric average of the mean plasma voriconazole concentrations in failed cases compared to that in successful cases. In the original PK/PD submission, resulting data from Phase II/III patients showed that indeed, higher voriconazole plasma concentrations were significantly associated with lower success rates.

2. Figure 1 suggests that relatively higher (>3 mcg/mL) mean plasma concentration values were associated with a greater frequency of failed therapeutic outcome in the Global Candidemia study. It appears that the success rate in voriconazole therapy of Candidemia patients could be improved if <u>mean</u> plasma levels (or Cmax, if majority of these levels were taken at voriconazole Tmax) do not exceed 3 mcg/mL. In the original PK/PD submission, particularly in the Global Aspergillosis study, the proportion of successes in patients with mean voriconazole plasma levels below 6 mcg/mL was about 58% compared to about 26% of success in patients with a mean plasma voriconazole concentration >6 mcg/mL.

3. Figure 3 provides the frequency of patients achieving a particular mean voriconazole plasma concentration band, categorized based on therapeutic outcome (success or failure). For mean concentration bands between 1.0 and 6.0 mcg/mL, the failure rate was generally greater than the success rate. This observation is consistent with the findings of the original PK/PD submission. Within this concentration range, the greatest failure rates were seen for voriconazole plasma concentrations exceeding 4.0 mcg/mL. Outside of this concentration range, high failure rates were also observed for plasma concentrations >9 mcg/mL. Candidemia patients with mean voriconazole plasma concentration values around <u>3.1 to 4.0 mcg/mL</u> comprised the majority of patients with successful outcomes. There were also smaller subsets of the success population with either a relatively lower (<1 mcg/mL) or higher (around 7.01 to 8.0 mcg/mL) mean plasma concentration. Because all (N=5) of the PK/PD patients who failed therapy due to insufficient clinical response did not also achieve sterilization of blood (baseline *Candida* species were either *glabrata* or *albicans*)

despite sufficient or even extremely high blood levels of voriconazole, a small percentage of therapy failures in this study could probably be attributed to microbial resistance to voriconazole. In the area curve representing failed outcomes (all causality), patients with mean plasma concentrations around 4.01 to 6 mcg/mL and >9 mcg/mL occurred with the greatest frequency in the PK/PD population. Figure 3A shows that PK/PD patients with mean plasma voriconazole concentration <3 mcg/mL had a higher success rate than those with higher mean plasma concentrations.

FIGURE 3
Frequency of patients within specific voriconazole plasma concentration ranges: success versus failure

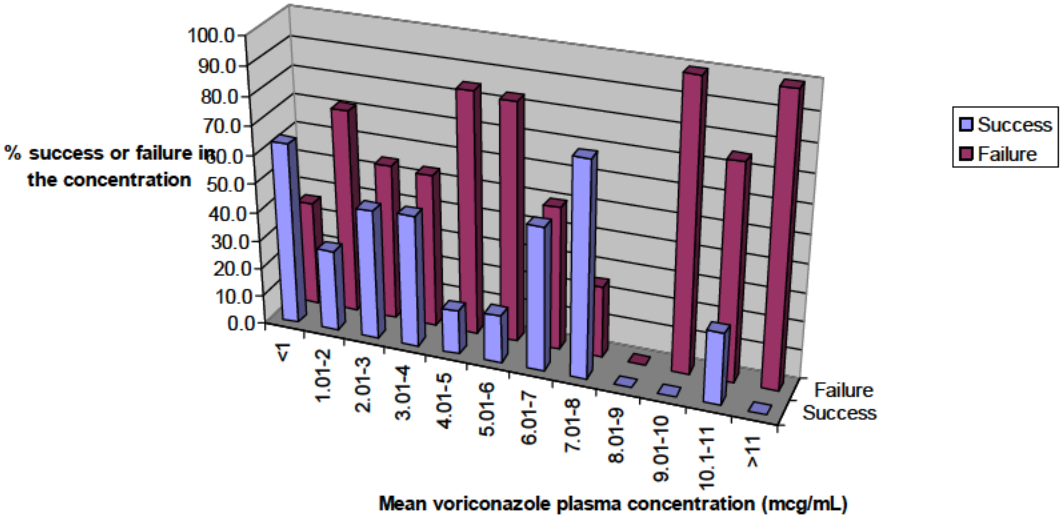
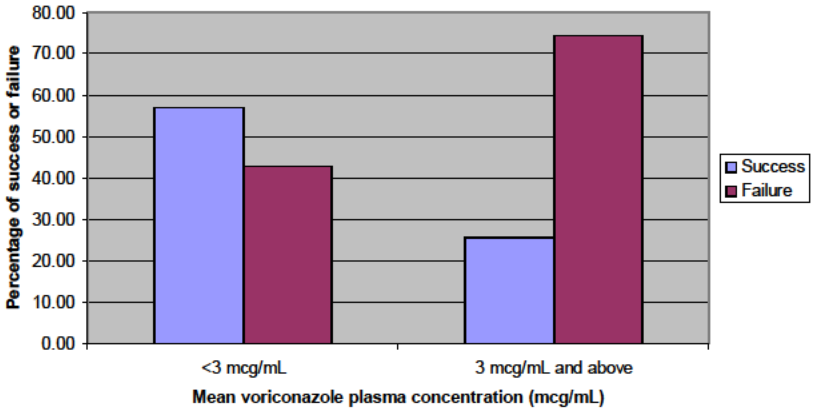


FIGURE 3A
Percentage of success in patients based on mean voriconazole plasma concentration



2. *What is the relationship between the mean voriconazole plasma concentration and the cause of subject withdrawal and/or therapy failure?*

Of the MITT patients in the Global Candidemia study with paired mean voriconazole plasma concentration and DRC therapeutic outcome data at End-of-Therapy Visit (EOT), about 59% were classified as therapeutic failures. Table 2 summarizes the reasons for withdrawal of failed patients during active/DB treatment. Majority (78.3%) of the

discontinuations were attributed to adverse events, laboratory abnormalities, and subject death. Half of the failed cases were from discontinuations associated with adverse events; an additional 9% of these failed cases resulted in laboratory abnormalities. Of the 46 total subjects who were withdrawn from the study and had PK data at EOT, only 13% were attributed to insufficient clinical response. Other causes of subject withdrawal include subject death, withdrawn consent, protocol violation, and underlying illness.

Of all the groups in Table 2, the patients who were withdrawn from the study due to laboratory abnormalities demonstrated the highest median voriconazole plasma concentrations whereas those patients who died had the highest mean plasma concentrations. Compared to these 2 groups, patients who experienced adverse events had relatively lower mean plasma concentrations of voriconazole (3.84 mcg/mL). It is interesting to note that in the original PK/PD submission, the incidence of visual adverse events (VAEs) in Phase II/III patients were approximately doubled when the median plasma voriconazole concentrations were higher, i.e., ≥ 3 mcg/mL.

About 13% of the failed cases were due to insufficient clinical response, even though the average mean and median voriconazole plasma concentrations in this group were relatively high. These patients represented a subset of the study population who probably harbored *Candida* species that were refractory or resistant to voriconazole therapy.

TABLE 2
Voriconazole Plasma Concentrations of MITT Patients Who Failed Therapy in Study 150-608 Due to Various Causes

CAUSE OF WITHDRAWAL FROM STUDY 150-608	N	% OF TOTAL N	VORICONAZOLE PLASMA CONCENTRATIONS (mcg/mL)		
			Mean	Median	Range
Adverse events	23	50.0	3.84	3.89	0.157 – 9.553
Death	9	19.6	5.32	4.54	1.841 – 14.188
Laboratory Abnormality	5	8.7	5.27	5.27	2.601 – 9.495
Withdrawn consent	2	4.3	3.12	3.12	0.941 – 5.302
Protocol violation	1	2.2	4.20	-	-
Insufficient clinical response	6	13.0	4.72	4.33	0.343 – 9.755
Other	1	2.2	1.72	-	-
TOTAL	48	100.0			

3. *What is the relationship between the mean voriconazole plasma concentration and the frequency of Liver Function Test (LFT) Abnormalities?*

Logistic modeling performed by the sponsor revealed no significant relationships between plasma voriconazole concentrations and the rate of subjects experiencing abnormalities for AST, ALT or AP. However, a statistically significant linear relationship was observed for bilirubin. The frequencies of LFT abnormalities were 6.7% (15/223), 6.3% (14/223), 4.0% (9/223) and 7.2% (16/223) for AST, ALT, AP and bilirubin, respectively. Linear modeling revealed significant linear relationships between log mean plasma concentration and AST and AP, as well as a significant quadratic relationship with log mean voriconazole plasma concentration and bilirubin.

Reviewer's comments:
In the original PK/PD submission, modeling showed that voriconazole Cmax and AUC were strongly associated with two LFT indices (ALT and AST) in healthy volunteers (Phase I). The threshold values for increases in ALT and AST appeared to be at Cmax values of approximately 5.0 and 6.0 mcg/mL and at AUC values starting at approximately 40 to 50 mcg*hr/mL. It appeared that the risk of LFT abnormalities was greater after longer duration of therapy (≥7 days). On the other hand, PK/PD analyses of data from 1053 patients in 10 Phase II/III studies

did not identify a threshold concentration value for LFT value increases but reported maximum frequencies of LFT abnormalities at the highest mean voriconazole concentration bands, i.e., 8 to 9 mcg/mL and ≥9 mcg/mL. The maximal reported occurrences of abnormalities in AST, ALT, ALKP, and total bilirubin over the 12-week evaluation period were approximately 10%, 8%, 5%, and 14%, respectively.

Based on Table 3 below, PK/PD patients in the Global Candidemia Study with abnormal LFT values had substantially higher (mean, median, and range) voriconazole plasma concentrations than those who had normal LFT values. It appears that a mean voriconazole plasma concentration of about 3.0 mcg/mL is desirable; the mean plasma levels should not approach 6.5 mcg/mL to minimize abnormal LFTs in Candidemia patients.

TABLE 3
Breakdown of Abnormal and Normal LFT Subjects in Study 150-608
(MITT patients with plasma concentration data at EOT)

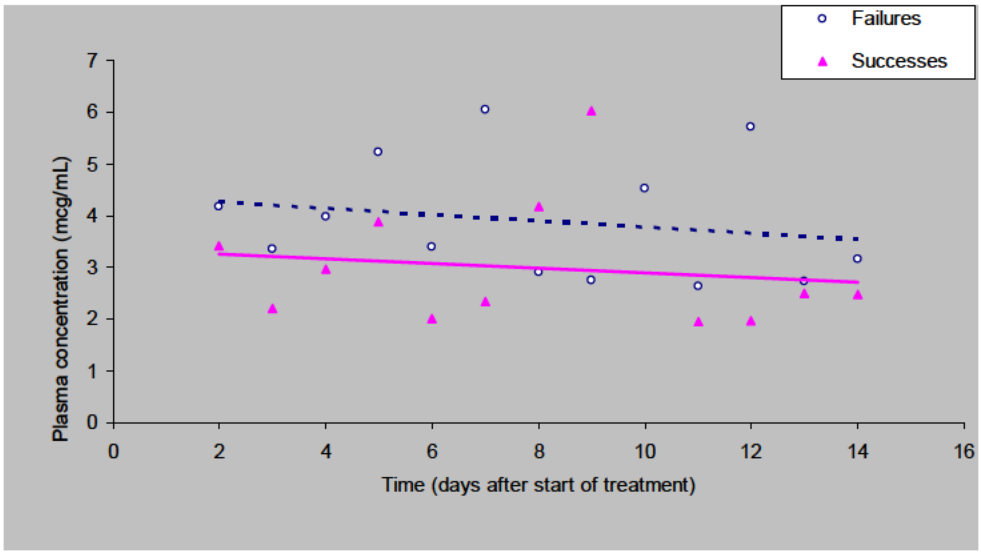
Voriconazole Concentration (mcg/mL)	Abnormal LFTs (N=16 subjects)				Normal LFTs (N=59 subjects)
	AST (n=6 cases)	ALT (n=2 cases)	AP (n=2 cases)	Bilirubin (n=11 cases)	
Mean	6.61				3.31
Median	6.42				3.22
Range					
Lower Limit	2.34				0.16
Upper Limit	14.19				9.76

4. *How do failed cases and successful cases compare in terms of the average daily mean voriconazole plasma concentration values over the treatment duration of at least 14 days? Is it possible to identify an optimum voriconazole plasma concentration range over a definite time interval in the treatment of Candidemia patients?*

Based on Figure 4, the average daily mean voriconazole plasma concentrations were in general, higher in the failed group than in the successful group of patients. Because these concentrations represented the average exposure within a treatment day regardless of time, the optimum plasma concentration range for Candidemia patients could not be accurately determined for any given time point, time interval within the 12-hour dosing interval, or within the entire treatment interval (≤14 days). It appears that in successful cases, there was a greater number of days where the daily mean concentration values were ≤3 mcg/mL On the other hand, failed cases exhibited a greater frequency of days where mean plasma concentration values were >3 mcg/mL; in some days the daily mean plasma levels approached 6 mcg/mL. It is interesting to note that in the original PK/PD submission that analyzed data from 10-Phase 2/3 studies, logistic regression modeling predicted a negative association between mean plasma voriconazole concentration and treatment success in those subjects with mean plasma concentrations exceeding 6 mcg/mL. Thus, if future PK/PD studies could identify threshold concentration values, and find that the trends as observed above (using mean concentration data) still hold true, close PK and/or PD monitoring may benefit high-risk patients that are likely to show higher voriconazole exposure (e.g., patients with underlying hepatic disease, severe illnesses, poor CYP2C19/2C9 metabolizer genotype, are taking concomitant medications that have potential to increase voriconazole exposure, and possess other toxicity risk factors previously identified in PK/PD analyses). Additionally, it appears from the figure below that the highest daily mean concentrations were achieved at or after day 7 of therapy. This observation is consistent with previous PK/PD findings in healthy volunteers that higher voriconazole plasma concentrations and LFT abnormalities may

occur after ≥7 days of therapy. In Phase II/III trials, the incidence of visual adverse events was higher with multiple doses (46%) vs. single dose (24%).

FIGURE 4
Day-to-day voriconazole plasma concentration-time profiles of Study 608 EOT&MITT patients following IV infusion (according to therapeutic outcome-DRC secondary endpoint)



5. *What is the relationship between voriconazole exposure and QT prolongation in the Global Candidemia Study?*

In Study 150-608, the rate for patients with ≥60 msec increase in QTc was 22% in the voriconazole group and 0% in the comparator group. The treatment of several patients were discontinued due to cardiac arrhythmias related to exposure to voriconazole; table 4 provides the corresponding mean voriconazole plasma concentrations for these patients. Majority of these patients were females (6/9), whites (6/8), have BW ≤60 kg (5/8), or were receiving IV (6/8) rather than oral voriconazole. Majority (87.5%, 7/8) of the patients listed in the table had prior history of cardiovascular disease.

Half (4/8) of the patients had documentation of voriconazole levels at the time of the cardiovascular adverse event. Around the time of the reported cardiac AE, the measured voriconazole plasma concentrations in majority (3/4) of these patients were relatively high compared to the average historical values for the same time point under consideration. For example in Patient #608-23010372 (35-year old Asian female), the trough voriconazole level was 6.984 mcg/mL at 11.85 hours post-last dose on the day of the cardiac arrest. This concentration was higher than the expected average voriconazole Cmax as seen in healthy volunteers. This particular patient did not have a history of cardiovascular disease but was taking drugs like diazepam, midazolam and omeprazole at the time if the cardiovascular AE. Additionally, although there is a relatively high frequency of Asians with a CYP2C19/2C9 poor metabolizer genotype, it is unknown whether this patient possessed this genetic predisposition to increased voriconazole exposure. In Patient #608-22710338, the measured voriconazole plasma concentration was not tremendously high for that particular time point but this patient had a history of CHF years prior to the study-related QT prolongation AE. The abnormal liver function and renal function test findings, the relatively low creatinine clearance (24 mL/min on Day 1), as well as the use of pantoprazole (an omeprazole-like drug) could help explain the relatively higher voriconazole Cmax in this patient.

TABLE 4
Voriconazole plasma concentration in patients around the time of their cardiovascular adverse event

Patient ID	Voriconazole exposure (mcg/mL)	Clinical findings
60430309	ND	*intermittent Torsade de Pointes starting day-9 (time after last dose unknown)*
22710338	4.743 (1 h post-dose, Day 11)	*↑ QT starting day-11 (2hr 20 min after last dose)*
23010372	6.984 (11.83 hours post-dose, Day 7)	*Cardiac arrest on day-7 (time after last dose unknown)*
50860086	ND	*ventricular tachycardia onset day-2 (time after last dose unknown)*
50940157	3.222 (23.25 hours post-dose, Day 2)	*atrial & ventricular arrhythmias started day-2 (1 hr 30 min after last dose)*
60130119	ND	*atrial fibrillation started day-2 (time after last dose unknown)*
60130128	2.364 (sampling time not known, Day 2)	*worsening premature atrial contraction -day 2 (time after last dose unknown)*
60130180	4.49 (8.5 h post-dose, Day 4)	*atrial fibrillation -day 4 (time after last dose unknown)*

*ND- not determined

6. *How do the cardiovascular safety findings in the current submission compare with that in the original submission?*

In the Global Comparative Aspergillosis study (307/602), there were numerically more events of cardiac arrest and syncope in the voriconazole group (6/196 or 3.1%) than the amphotericin B/other licensed antifungal group (2/185 or 1.1%). In the Global Candidemia study, 8/40 or 20% of the voriconazole patients were discontinued due to arrhythmia, 3 of these cases occurred within the first or second infusion dose whereas 1 of 9 patients in the A→F discontinued due to ventricular premature beats during amphotericin B infusion. Refer to the review of Dr. Sary Beidas (Medical Officer) for a complete assessment of the cardiovascular and other safety data from Study 150-608.

Reviewer's comment: The voriconazole dosing regimen for Candidemia is the same as that already approved for the treatment of invasive aspergillosis. Except for esophageal candidiasis, none of the previously approved indications specified a minimum duration of therapy. In the proposed label, the recommended duration of voriconazole therapy for the treatment of candidemia is ≥14 days. The mean accumulation index of voriconazole over 14 days dosing in poor metabolizers is approximately 5-fold. Based on PK data from healthy volunteers, the accumulation profile beyond 14 days therapy is not expected to increase further because 14 days would have been enough time to achieve voriconazole steady state, unless hepatic and/or renal function worsens. The relatively higher incidence of arrhythmia in the voriconazole group of the Global Candidemia study could be attributed, at least in part, to confounding factors (e.g., previous history of cardiovascular disease, severity of illness, concomitant medications that altered the voriconazole levels, CYP2C19/2C9 poor metabolizer genotype, hepatic and/or renal dysfunction).

B. Intrinsic Factors

Note: From this point of the review and onwards, the findings of additional analyses performed on a PK/PD database excluding 16 patients with extremely low or high mean voriconazole plasma concentrations will also be discussed. Majority of these excluded patients were using or have just recently discontinued drugs that have the potential to alter voriconazole plasma concentrations. Appendix A summarizes the demographic data of these excluded patients.

1. *Did gender affect the pharmacokinetics of voriconazole and therapeutic outcome of the pivotal study (Study 150-608)?*

In the entire MITT population, males in the voriconazole treatment group achieved 46% success rate compared to females who had a 38% success rate (Table 5). According to the sponsor, the median voriconazole plasma concentrations in subjects failing treatment were similar in both male (4.2 mcg/mL) and female (4.3 mcg/mL) subjects in the PK/PD subset of this population.

TABLE 5

Voriconazole candidemia : Summary of DRC assessment of response to antifungal therapy at 12 week follow up by sex primary candidemia (MITT)

	Voriconazole			A→F			
	Male N=145 (%)	Female N=103	(%)	Male N=71	(%)	Female N=51	(%)
Cured	67 (46.2)	34	(33.0)	27	(38.0)	22	(43.1)
Improved	0	0		1	(1.4)	0	
Failed	78 (53.8)	69	(67.0)	43	(60.6)	29	(56.9)

All subjects not categorized by the DRC as cured or improved at 12 week follow-up are counted as failures.

Adapted from Dr. Sary Beidas' review.

The sponsor's multivariate logistic modeling showed a slightly higher success rate in males compared to females (68.3 versus 61.2%) but this difference was not statistically significant.

Reviewer's PK/PD analysis:

In contrast to the findings for the entire MITT population, in the PK/PD subset, the males on voriconazole therapy demonstrated success/failure rates similar to those reported in females. However, for both gender subgroups, the failure rate was about 1.5-fold higher than the success rate. For the failed cases, there was a small difference between males and females in terms of the mean voriconazole plasma concentrations (≥4.0 mcg/mL). On the other hand, it appears that females who had successful therapy had a slightly (about 38%) higher voriconazole plasma concentrations compared to their male counterparts (Table 6), an observation that is somewhat in agreement with the clinical pharmacology information in the labeling of VFEND®.

When 16 patients with exceedingly high or exceedingly low mean plasma concentrations (>10 mcg/mL or <1.0 mcg/mL) were excluded from the analysis, the difference in success/failure rates between genders was slightly greater than that observed when the entire PK/PD subset was considered (Table 6A). Compared to females, the success rate in males was 11% higher whereas the failure rate was 9% lower. In the failed cases, there was no difference between genders in voriconazole plasma concentrations; in the successful cases, the average mean voriconazole plasma concentration was 32% higher in females than in males.

TABLE 6
SUCCESS AND FAILURE RATES OF MALES AND FEMALES IN STUDY 150-608 (PK/PD SUBSET ONLY)

INCLUDING ALL PATIENTS WITH DRC ASSESSMENT AND PK DATA AT EOT		
THERAPEUTIC OUTCOME		
	Males	Females
Success	19 (40.4%)	12 (38.7%)
Failure	28 (59.6%)	19 (61.3%)
EXCLUDING 16 PATIENTS		
THERAPEUTIC OUTCOME		
	Males	Females
Success	15 (39.5%)	8 (34.8%)
Failure	23 (60.5%)	16 (66.7%)

TABLE 6A
AVERAGE VORICONAZOLE PLASMA CONCENTRATIONS OF MALES AND FEMALES IN STUDY 150-608 (GROUPED ACCORDING TO THERAPEUTIC OUTCOME; PK/PD SUBSET ONLY)

INCLUDING ALL PATIENTS WITH DRC ASSESSMENT AND PK DATA AT EOT		
THERAPEUTIC OUTCOME	AVERAGE VORICONAZOLE PLASMA CONCENTRATIONS (mcg/mL)	
	Males	Females
Success	3.16 (N=19)	4.35 (N=12)
Failure	4.51 (N=28)	4.04 (N=19)
EXCLUDING 16 PATIENTS		
THERAPEUTIC OUTCOME	AVERAGE VORICONAZOLE PLASMA CONCENTRATIONS (mcg/mL)	
	Males	Females
Success	3.86 (N=15)	5.11 (N=8)
Failure	4.46 (N=23)	4.44 (N=16)

2. *Did age affect the pharmacokinetics of voriconazole and therapeutic outcome in the pivotal study (Study 150-608)?*

In the MITT population, there were no clinically significant differences in rates by age groups ≤65 or >65 years.

TABLE 7

Summary of DRC assessment by age at the primary endpoint: Primary Candidemia MITT population. Source: clinical. PDF, Table 10.1.1

Voriconazole (n=248)		A→F (n=122)	
≤65 (n=174) N (%)	>65 (n=74) N (%)	≤65 (n=82) N (%)	>65 (n=40) N (%)
78 (44.8%)	23 (31.1%)	35 (42.7%)	14 (35.0%)
0	0	1 (1.2%)	0
96 (55.2%)	51 (68.9%)	46 (56.1%)	26 (65.0%)

All subjects not categorized by the DRC as cured or improved at 12 week follow-up are counted as failures.

Adapted from Dr. Sary Beidas' review.

The sponsor evaluated the effect of age on voriconazole efficacy for the PK/PD subjects in the pivotal study. For subjects >65 years old, there was a lower success rates (55.4%) than those 45-65 (67.8%) or ≤45 (71.4%) years old. However, the differences were not statistically significant.

Reviewer's PK/PD analysis:
In the PK/PD subpopulation, age did not appear to have a clinically significant effect on therapeutic outcome. Success rates were 43% and 39% in patients <65 and >65 years old, respectively. The average mean voriconazole plasma concentrations of young and elderly patients associated with successful and failed therapies are provided in Table 8.

FIGURE 5
Percentage of patients with successful and failed therapeutic outcomes (according to age and gender)---excluding 16 patients

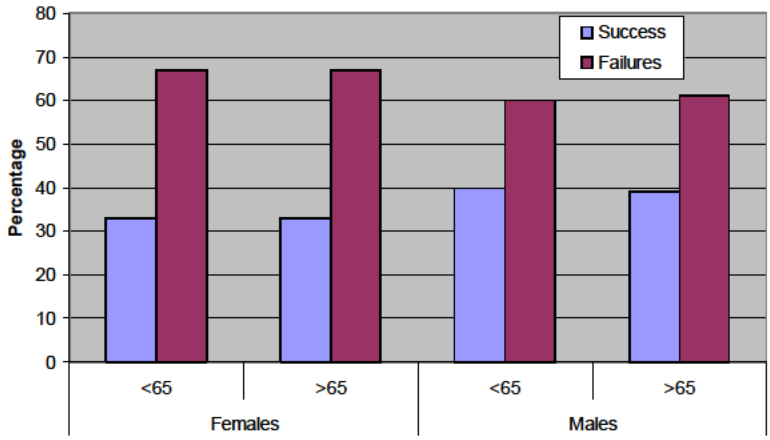


TABLE 8
AVERAGE VORICONAZOLE PLASMA CONCENTRATIONS OF YOUNG AND ELDERLY MALES AND FEMALES IN STUDY 150-608 (GROUPED ACCORDING TO THERAPEUTIC OUTCOME)

INCLUDING ALL PATIENTS WITH PAIRED PK DATA AND DRC THERAPEUTIC OUTCOME AT EOT		
THERAPEUTIC OUTCOME	**AVERAGE VORICONAZOLE PLASMA CONCENTRATIONS (mcg/mL)**	
	< 65 y.o.	> 65 y.o.
Success	3.270 (N=20)	4.711 (N=12)
Failure	4.488 (N=27)	3.789 (N=19)

EXCLUDING THE 16 PATIENTS				
THERAPEUTIC OUTCOME	**AVERAGE VORICONAZOLE PLASMA CONCENTRATIONS (mcg/mL)**			
	Females		Males	
	< 65 y.o.	> 65 y.o.	< 65 y.o.	> 65 y.o.
Success	3.86 (N=8)	6.37 (N=7)	3.83 (N= 4)	3.89 (N=4)
Failure	4.53 (N=12)	3.72 (N=11)	4.17 (N=8)	3.84 (N=8)

When 16 patients with extremely high (≥10 mcg/mL) or extremely low (<1.0 mcg/mL) voriconazole plasma concentrations were excluded from the analysis, the success rates were 37% and 63%, for patients <65 and >65 years old, respectively. This increase in the success rate (and the corresponding decrease in the failure rate) of >65 year old patients is because all 16 of the excluded patients were <65 years old. However, when gender was included as a covariate in the analysis of the age effect, the age-dependent difference in success/failure rates disappeared. Both young and elderly subjects had similar success rates, when their gender was taken into consideration (Figure 5). Table 8 compares the average voriconazole exposures in young and elderly gender groups. Of all 4 age/gender groups of patients with successful therapeutic outcomes, the elderly female patients had the highest average mean voriconazole plasma levels (> 6 mcg/mL).

3. *Did race affect the pharmacokinetics of voriconazole and therapeutic outcome in the pivotal study (Study 150-608)?*

In the MITT population, no notable difference in success rates by ethnicity was observed.

TABLE 9

Summary of DRC assessment by race at the primary endpoint: Primary Candidemia MITT population
Source: clinical. PDF Table 10.1.2 , p:115/900

	Voriconazole (n=248)				A→F (n=122)			
	White n=151 N (%)	Black n=36 N (%)	Asian n=50 N (%)	Other n=11 N	White n=61 N (%)	Black n=20 N (%)	Asian n=33 N (%)	Other n=8 N
Cured	59 (39.1%)	18 (50.0%)	17 (34.0%)	7	25 (41%)	9 (45.0%)	12 (36.4%)	3
Improved	0	0	0	0	1 (1.6%)	0	0	0
Failed	92 (60.9%)	18 (50.0%)	33 (66.0%)	4	35 (57.4%)	11 (55.0%)	21 (63.6%)	5

Adapted from Dr. Sary Beidas' review.

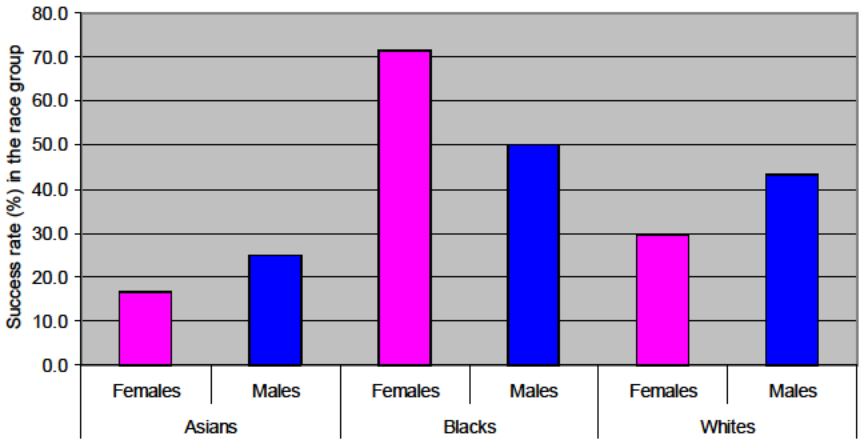
The sponsor evaluated the effect of race on the relationship between log voriconazole plasma concentration and efficacy for the MITT subjects. Asians had the lowest success rate (56%). However a specific comparison of Asians (n=50) with non-Asians (n=198) was not statistically significant (p=0.13). Similarly, there was no significant difference between whites (n=151) and non-whites (n=97) (success rates 62.9 and 69.1% respectively, p=0.32).

Reviewer's PK/PD analysis:

Whites comprised the majority (about 70%) of subjects included in the PK/PD analysis. Asians and Blacks comprised the remainder of the analysis population. The success rates of voriconazole therapy for Asians, Blacks and Whites with Candidemia were 21.5%, 67% and 39%, respectively. The average mean voriconazole plasma concentrations associated with each type of therapeutic outcome in each ethnic group are summarized in Table 10. Black patients (N=3) with candidemia who failed therapy had the highest mean voriconazole plasma concentrations.

Stratification of these ethnic groups based on their gender did not alter the trends observed regarding success/failure rates of voriconazole therapy (Figure 6A). Both Black males and females demonstrated the highest success rates compared to other ethnicities within their own gender group whereas both the Asian males and females had the lowest success rates in their respective gender subgroups. In contrast to Asians and Whites, black females had a higher success rate compared to their male counterparts. When both gender and race were considered as co-variates, it became evident that the high average mean voriconazole plasma concentration in blacks (N=3) was strongly influenced by data from the lone male patient who had a plasma concentration (Cp) of 14.19 mcg/mL; the average Cp for black females was 4.63 (Table 10).

FIGURE 6A
Success rates in different race/gender groups (PK/PD Dataset)



When 16 patients with extremely high (≥ 10 mcg/mL) and extremely low (< 1.0 mcg/mL) voriconazole plasma concentrations were excluded from the analysis, the trends in success rates observed for Asians, Blacks and Whites were similar to that observed using the complete PK/PD dataset (Figure 6B). When the gender of the patients was included as a second co-variate in the analysis, the following observations were made: (1) Because the excluded patients were either Black or White, the average mean voriconazole plasma concentrations for Asians were not different from that obtained using the complete PK/PD dataset. (2) In Asians and Whites, the failure rate was greater than the success rate, and the success rate was slightly higher in males than in females. (3) Of all the Race/Gender groups, Black females with candidemia showed the most benefit from voriconazole therapy. (4) Because there were no Black male patients with paired PK/PD information in this data subset, the therapeutic outcome in this group could not be determined. (4) A comparison of success rates in all female patients in this study suggests that Asian females with candidemia have the least potential for therapeutic benefit from voriconazole. The PK data summarized in Table 10 indicate that the Asian females who failed therapy possessed the highest mean voriconazole plasma concentrations (compared to other ethnic/gender groups who also failed therapy). Among the different groups with successful treatment outcome, the Asian females demonstrated the lowest mean voriconazole concentration in the plasma. Because Asians comprise an ethnic group with the highest frequency (12-23%) of CYP2C19 poor metabolizer genotype compared to Blacks and Whites, the tandem finding of relatively poor therapeutic outcome and relatively high mean voriconazole plasma concentrations in Asian females suggest the importance of CYP2C19 metabolizer genotyping in at least the Asian patients. In contrast, Black and White female patients in the success group had higher mean drug levels compared to their failed counterparts

FIGURE 6B
Success rates in different race/gender groups (excluding 16 patients)

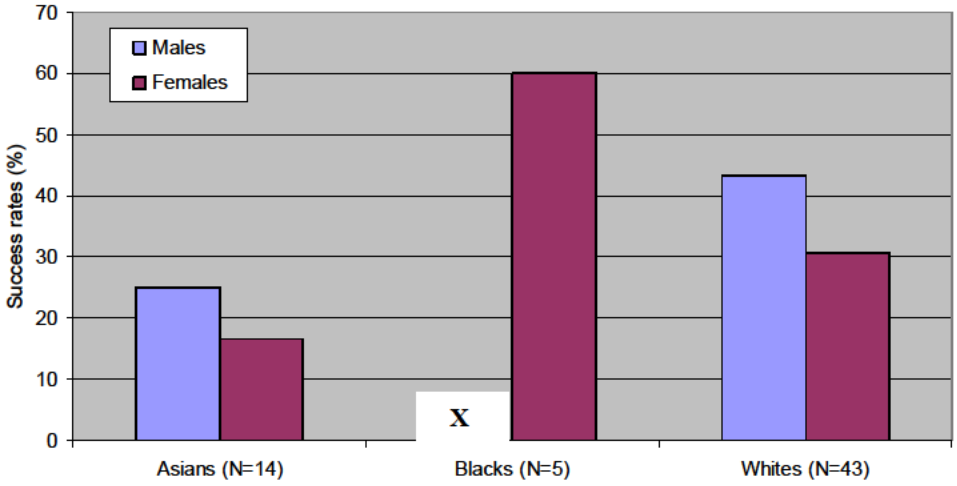


TABLE 10
MEAN VORICONAZOLE PLASMA CONCENTRATIONS ACCORDING TO PATIENT RACE AND RACE/GENDER

INCLUDING ALL PATIENTS WITH PAIRED PK AND THERAPEUTIC OUTCOME DATA AT EOT			
Therapeutic outcome	Mean voriconazole plasma concentrations (mcg/mL)		
	Asians	Blacks	Whites
Success	4.437 (N=3)	4.439 (N=6)	3.243 (N=21)
Failures	4.462 (N=11)	7.817 (N=3)	3.951 (N=35)

Therapeutic outcome	Mean voriconazole plasma concentrations (mcg/mL)					
	Asians		Blacks		Whites	
	Males	Females	Males	Females	Males	Females
Success	4.24 (N 2)	3.634 (N=1)	4.554 (N=1)	5.25 (N=5)	3.12 (N=16)	3.638 (N=5)
Failures	3.96 (N=6)	5.07 (N=5)	14.19 (N=1)	4.63 (N=2)	4.20 (N=21)	3.51 (N=12)
EXCLUDING 16 PATIENTS						
Therapeutic outcome	Mean voriconazole plasma concentrations (mcg/mL)					
	Asians		Blacks		Whites	
	Males	Females	Males	Females	Males	Females
Success	4.24 (N=2)	**3.63** (N=1)	- (N=0)	5.28 (N=3)	3.71 (N=13)	5.36 (N=4)
Failures	3.96 (N=6)	**5.07** (N=5)	- (N=0)	4.63 (N=2)	4.03 (N=17)	3.5 (N=9)

Based on the above observations, race (or perhaps more accurately, CYP2C19 metabolizer genotype) is an important influential covariate of voriconazole efficacy and safety in the treatment of Candidemia.

4. *Did body weight (BW) affect the pharmacokinetics of voriconazole and therapeutic outcome in the pivotal study (Study 150-608)?*

In the MITT population, body weight did not appear to exert an influence on the therapeutic outcome of voriconazole therapy in patients enrolled in the Global Candidemia Study. The success rates were similar between patients with BW <60 kg and patients with BW ≥60 kg. The success rates were 41.7% versus 40.3% for the low BW and the high BW groups, respectively. (Refer to the review of the statistician, Dr. Cheryl Dixon.)

Multivariate logistic modeling conducted by the sponsor revealed that candidemia patients with BW <60 kg (59.1%) had the lowest success rate although this rate was not statistically significantly different from that in those with BW 60-75 kg (70.6%) or those with BW >75 kg (67.8%). In addition, the current labeling recommends administration of ½ the usual dose of voriconazole for patients with BW <40 kg.

Reviewer's PK/PD analysis:
Contrary to the findings of the analysis with the entire MITT population, analysis based on the PK/PD subset of the same study population seems to suggest that body weight (BW) had an influence on therapeutic outcome, in line with sponsor's own finding that patients with BW <60 kg had the lowest success rate, although the difference with the other BW groups were not statistically significant.

Table 11 compares the success/failure rates, as well as the mean voriconazole plasma concentrations of the two BW patient groups in the PK/PD subset of Study 150-608. The success rate in heavier subjects (BW ≥60 kg) was about 25% higher than that for the lighter ones (BW <60 kg). The average mean voriconazole plasma concentrations were relatively lower in the <60 kg group than the ≥60 kg group. Additionally, the failure rate was 100% and 40% higher than the success rate in the same BW group, for the <60 kg and ≥60 kg groups, respectively. It is interesting to note that this is about the only covariate in this analysis that revealed a more or less positive relationship between efficacy and mean voriconazole concentration in the Global Candidemia study.

An inspection of the BW profile of the group of 16 excluded patients indicates that there was an approximately equal proportion of low BW and high BW patients with extremes of voriconazole concentration. Thus, even with the exclusion of these patients, the success/failure rates were found to be similar to those obtained when considering the entire PK/PD dataset for analysis, i.e., there was a slightly (26%) higher success rate and a slightly higher plasma concentration in the ≥60kg group than in the <60 kg group. The failure rates were 125% and 58% higher in the <60 kg group and the ≥60 kg group, respectively. The mean voriconazole plasma concentrations were also slightly higher in the ≥60 kg group compared to the <60 kg group, regardless of therapeutic outcome.

TABLE 11
Mean Voriconazole plasma concentrations
(according to patient body weight and therapeutic outcome)

INCLUDING ALL PATIENTS WITH PAIRED PK AND DRC THERAPEUTIC OUTCOME DATA AT EOT				
Therapeutic outcome	Patients in the Therapeutic outcome group (%)		Mean voriconazole plasma concentrations (mcg/mL)	
	< 60 kg	≥ 60 kg	< 60 kg	≥ 60 kg
Success	33.3	41.7	2.82	3.81
Failure	66.7	58.3	2.96	4.78
EXCLUDING 16 PATIENTS				
Therapeutic outcome	Patients in the Therapeutic outcome group (%)		Mean voriconazole plasma concentrations (mcg/mL)	
	< 60 kg	≥ 60 kg	< 60 kg	≥ 60 kg
Success	30.8	38.8	4.04	4.35
Failure	69.2	61.2	3.78	4.14

5. *Did the CYP2C19/CYP2C9 genotype of the patients affect the pharmacokinetics of voriconazole and therapeutic outcome in the pivotal study (Study 150-608)?*

The relationship of CYP2C19/2C9 genotype of the patient to voriconazole PK is already established. The influence of metabolic genotype on the outcome of Study 150-608 could not be directly assessed because the patients in this study were not genotyped.

C. Extrinsic Factors

1. *Were any of the patients in this study on any concomitant medications that might have contributed to any unusual plasma voriconazole concentration values?*

Historically, in healthy volunteers, the voriconazole steady state Cmax is 2.08 mcg/mL (after 400 mg Q12h loading dose on Day 1 and 200 mg Q12h as maintenance dose) and 3.06 mcg/mL (after 6 mg/kg IV Q12h as loading dose and 3 mg/kg IV Q12h as maintenance dose). Furthermore, according to the label: In ten clinical trials, the median values for the average and maximum voriconazole plasma concentrations in individual patients across these studies (N=1121) was 2.51 mg/mL (inter-quartile range 1.21 to 4.44 mg/mL) and 3.79 mg/mL (inter-quartile range 2.06 to 6.31 mg/mL), respectively.

In Study 150-608, there were at least 16 patients who were reported to have end-of-therapy (EOT) day-to-day mean plasma concentrations either as low as 0.070 mcg/mL or as high as 14.188 mcg/mL. Because the potential of voriconazole to interact with drugs is well-recognized, at least some of these extremely high (>>historical Cmax values) or extremely low mean voriconazole plasma concentrations could probably be attributed to drug-drug interactions. Appendix B provides a list of drugs taken concomitantly by these patients who had unusual mean voriconazole plasma concentrations. Drugs in the list that were highlighted are known to or suspected to have the potential to interact with voriconazole possibly, via mechanisms involving either inhibition or induction of drug metabolism.

2. What PK-PD relationship, if any, exists in this group of 16 excluded patients?

The failure rate was higher in those patients with ≥9.5 mcg/mL mean voriconazole plasma concentration than in those with <1 mcg/mL plasma concentration group (80% versus 33%). The average mean voriconazole plasma concentrations associated with each therapeutic outcome group is given in Table 12 below.

TABLE 12
Therapeutic outcome and average mean voriconazole plasma concentrations in 16 patients with extreme voriconazole day-to-day plasma drug levels

DRC Therapeutic outcome	Percentage of patients		Mean voriconazole plasma concentrations (mcg/mL)	
	<1.0 mcg/mL	≥ 9.5 mcg/mL	<1.0 mcg/mL	≥ 9.5 mcg/mL
Failure	33.3 (N=4)	80.0 (N=4)	0.41	10.7
Success	66.7 (N=8)	20.0 (N=1)	0.48	10.1

Based on Table 12 above and Appendix B below, the following hypotheses could be made regarding the influence of concomitant medications on the therapeutic and PK outcomes of the Global Candidemia Study:

(1) The concurrent use of multiple CYP450 inhibitors (e.g., co-trimoxazole) and/or other drugs that are extensively metabolized (e.g., fluconazole, ondansetron) may have contributed to the unusually <u>high</u> voriconazole plasma concentrations in the first 5 patients of the list in Appendix B. Concurrent use of omeprazole and other proton pump inhibitors is also known to increase voriconazole exposure by about 40%. In addition, because CYP2C19/2C9 genotyping was not performed on these patients, the contribution of a poor-metabolizer (PM) genotype could not be excluded.

(2) CYP450 inducers (e.g., rifampin, phenytoin, fosphenytoin) that were used concomitantly or days shortly before start of voriconazole therapy could have contributed to the unusually <u>low</u> voriconazole plasma concentrations observed in at least 6 patients in the list.

(3) In contrast, the extremely low mean voriconazole plasma concentration in Patient # 608 80090079 could not be readily attributed to drug-drug interaction. One of the two concentrations (<100 ng/mL) reported for this particular patient was taken at 11 hours post-dose (which corresponds to approximately the trough since 12 hours is the dosing interval); the sampling time for the other concentration (0.26 mcg/mL) was not known.

D. Others

1. Is "mean voriconazole plasma concentration over the entire dosing or entire treatment interval" an appropriate PK endpoint for voriconazole PK/PD studies?

No. Voriconazole concentration is a function of time. For example, the mean voriconazole plasma concentration (0.687 mcg/mL) over 14 days for Patient #608 60070235 would lead one to label this patient into a group with rather low voriconazole exposures compared to the rest. A consideration of the voriconazole concentration data obtained by sparse sampling reveals that the 3 blood samples were taken from this patient at times closer to the trough than to the peak, i.e., at 9 to 12 hours post-dose. When these concentrations were compared to those obtained in healthy volunteers at a time point per time point basis, it turns out that the plasma levels were slightly higher yet comparable to historical control values.

Furthermore, voriconazole exposure may likely change over the treatment duration in patients receiving concomitant medications because of its high propensity for drug interactions.

2. Is there justification for the sponsor's proposed maintenance dose and duration of therapy for voriconazole in the treatment of candidemia?

In the proposed label, the sponsor recommends that the maintenance dose for the treatment of candidemia with voriconazole be 3 to 4 mg/kg q12h for at least 14 days, following (b) (4) resolution. Using a multivariate logistic modeling technique, the sponsor observed that the success rate was statistically significantly better in patients who received voriconazole for 13 to 17 days (85.9%) and for ≥18 days (85.5%) compared to when the duration was ≤12 days (22.2%). The dose recommendation was based on the dose used in the pivotal (3 mg/kg q12h for ≥14 days) and supportive (4 mg/kg q12h) trials. The same loading dose (6 mg/kg q 12 h for the 1st 24 hours) was recommended for the treatment of previously approved indications (invasive aspergillosis, scedosporiasis, fusariosis). For the previously approved indications, 4 mg/kg q12h is the recommended IV maintenance dose; (b) (4)

The tables below provide a breakdown of the percentage of MITT patients in Study 150-608 according to therapeutic outcome and the final maintenance dose (Dm). Table 13 was based on the primary efficacy endpoint findings of the study. Based on raw numbers, there was a greater percentage of patients who failed therapy versus those who had successful therapeutic outcomes. Majority of the patients (regardless of therapeutic outcome) received maintenance doses >2.5 to ≤4.5 mg/kg q12h. In this Dm band, there was an almost equal percentage of patients in the failure and success groups. In the success group, none of the patients received a Dm (as Dm on final day of therapy) >4.5 mg/kg q12h. About 10% of the patients in the failure group received >4.5 mg/kg q12h; some of these patients were receiving phenytoin and other drugs known to reduce voriconazole levels.

TABLE 13
Percentage of MITT patients in Study 150-608 grouped according to therapeutic outcome (primary DRC endpoint) and final maintenance dose

	Number (Percentage)	
Maintenance Dose (mg/kg q 12hours	Failed	Successful
≤2.5	12 (7.3%)	20 (18.5%)
>2.5 to ≤4.5	137 (84%)	88 (81.5%)
>4.5	15 (9.1%)	0 (0)
TOTAL	164 (60.3%)	108 (39.7%)

Based on a secondary efficacy endpoint (Table 14), the percentages of MITT patients in each maintenance dose & therapeutic outcome category were similar to when the primary efficacy

endpoint was considered. However, in contrast to the findings based on the primary efficacy endpoint, a greater percentage (65%) of patients had successful outcomes.

TABLE 14
Percentage of MITT patients in Study 150-608 grouped according to therapeutic outcome (secondary DRC endpoint) and final maintenance dose

	Number (Percentage)	
Maintenance Dose (mg/kg q 12hours	Failed	Successful
≤2.5	8 (8.2%)	24 (13.7%)
>2.5 to ≤4.5	78 (80.4%)	146 (83.4%)
>4.5	11 (11.3%)	5 (2.9%)
TOTAL	97(35.7%)	175 (64.3%)

From these findings, it could be speculated that the probability of success in the voriconazole therapy of candidemia patients could be improved if the maintenance dose does not exceed 4 mg/kg q12 h. This seems to be a logical recommendation as it was observed that majority of the failures in the pivotal study were due to adverse events, laboratory abnormalities, death, etc.

Except for esophageal candidiasis, the label does not have a recommended minimum duration of therapy for the previously approved indications. For the current application, the proposed treatment duration for candidemia is at least 14 days following resolution of symptoms or following the lst postivie culture, whichever is longer.

Tables 15 and 16 provide a breakdown of the percentage of MITT patients based on therapeutic outcome and duration of therapy. When the primary efficacy endpoint was considered, majority (93.5%) of the patients who had successful therapies were on voriconazole therapy for at least 14 days. Only about half of the patients who failed therapy were on voriconazole therapy for ≥14 days. Using the secondary efficacy endpoint as therapeutic outcome measure, it was observed that majority (86.1%) of the patients who had successful therapeutic outcome were on voriconazole for at least 14 days; only about 30% of those with failed outcomes were taking the drug for at least 14 days. Thus, it appears that a duration of ≥14 days is desirable provided the voriconazole maintenance dose selected is tolerable for use by the patient for that period of time.

TABLE 15
Percentage of MITT patients in Study 150-608 grouped according to therapeutic outcome (**primary** DRC endpoint) and duration of treatment

	Number (Percentage)	
Duration of therapy (days)	Failed	Successful
≤7	53 (32.3%)	0
>7 to <14	33 (20.1%)	7* (6.5%)
≥14	78 (47.6%)	100 (93.5%)
TOTAL	164 (60.3%)	107 (39.7%)

* at least 10 days

TABLE 16
Percentage of MITT patients in Study 150-608 grouped according to therapeutic outcome (**secondary** DRC endpoint) and duration of treatment

	Number (Percentage)	
Duration of therapy (days)	Failed	Successful
≤7	48 (50%)	6 (3.5%)
>7 to <14	20 (20.8%)	18 (10.4%)
≥14	28 (29.2%)	149 (86.1%)
TOTAL	97(35.7%)	175 (64.3%)

3. *What is the influence of dosage form on the therapeutic outcome of voriconazole therapy in candidemia patients?*

Based on the findings of the multivariate logistic modeling analysis by the sponsor, the success rate after "IV only" therapy was statistically significantly worse (60.7%) compared to "Oral only" therapy (96.4%) and "IV and Oral" therapy (88.1%). A possible explanation for this apparent dosage-form dependence of therapeutic outcome is that patients who could not tolerate the initial/loading IV dose (and thus discontinue therapy) are the ones who do not proceed to the oral phase of the treatment. It is unclear whether excipients in the IV formulation contributed to the lesser tolerability of injectable VFEND®.

4. *How do the overall findings of the Global Candidemia study compare to the findings of the PK/PD analysis in the original submission for VFEND®?*

It appears that the PK/PD findings of cumulative studies in the original submission are similar to the findings of the Global Candidemia study in the current submission, wherein the sponsor failed to find a positive correlation between mean plasma voriconazole concentration and efficacy, despite the favorable efficacy findings in the therapeutic trial. The umbrella-like plot of mean plasma concentrations versus efficacy obtained in both original and current submissions suggests that outside an effective plasma concentration range, therapeutic failure may be due to either lack of sufficient clinical response, or toxicities (represented by the extreme left ascending and extreme right descending portions of the curve, respectively). Thus in future analysis of PK-efficacy relationships, the sponsor should distinguish between failures due to lack of response and failures due to toxicities (e.g., adverse events, laboratory abnormalities, treatment-related deaths). As was the case in the original PK/PD study, a linear relationship was found between mean plasma voriconazole concentration and certain LFT abnormality values. However, the analysis was not able to identify a threshold plasma concentration value possibly because of the inadequacy of the chosen PK endpoint. In future studies, the sponsor should explore alternatives to mean voriconazole plasma concentration as a means to define plasma voriconazole exposure over a prolonged period of time as this could decrease their ability to find a true relationship between efficacy and voriconazole exposure, as well as the ability to identify a target therapeutic concentration value or range that affords optimal safety and efficacy.

III. Detailed Labeling Recommendations

Because the results of the analyses of mean plasma concentrations in the Global Candidemia study for PK/PD relationships were similar to those provided in the original submission, no changes in the PK/PD section of the current VFEND® label will be recommended by the Clinical Pharmacology/ Biopharmaceutics reviewer. Likewise, the sponsor did not propose any changes in the labeling based on the currently submitted information relating to the treatment of candidemia/invasive candidiasis. The pharmacometrics consult review of Dr. Jenny J. Zheng provides a more thorough consideration of the PK/PD findings.

APPENDIX A
Demographic data of the study population (Study 150-608)

A. Including all patients with paired PK/PD data at End of Therapy (EOT)

N=78
Gender – 31 Females; 47 Males
Age - <65 years old (47); ≥ 65 years old (31)
Race – 14 Asians; 9 Blacks; 54 Whites; 1 Other
Body Weight - <60 kg (18); ≥60 kg (60)

B. Excluding 16 patients with extreme mean voriconazole plasma concentrations (<1.0 or ≥9.5 mcg/mL)

N=62
Gender – 24 Females; 38 Males
Age - <65 years old (31); ≥65 years old (31)
Race – 14 Asians; 5 Blacks; 42 Whites; 1 Other
Body Weight - <60 kg (13); ≥60 kg (49)

C. Profile of 16 patients excluded from PK/PD analyses

PATIENT ID	MEAN VORICONAZOLE CONCENTRATION (mcg/mL)	GENDER	AGE (years)	BODY WEIGHT (kg)	RACE	DRC OUTCOME (at EOT only)	REMARKS
608 60070261	**0.157**	**male**	**51**	**53.8**	**white**	**failure**	**AE**
608 80090079	0.170	female	50	36.6	white	success	
608 60070366	**0.185**	**female**	**32**	**93.1**	**white**	**failure**	**AE**
608 02690199	0.205	male	44	80	white	success	
608 51990207	0.343	male	57	54	white	failure	insuff.clin. response
608 03470013	0.366	female	50	76.4	black	success	
608 60070120	0.382	male	35	85	black	success	
608 20270070	0.609	male	50	54	white	success	
608 60070235	0.687	female	26	90.5	white	success	
608 04580164	0.909	male	46	70	white	success	
608 50920097	0.941	female	43	52	white	failure	withdrew consent
608 04030005	9.495	male	63	85	white	failure	lab abnormality
608 50470257	9.553	female	58	74.1	white	failure	AE
608 60070228	9.755	male	59	109.1	white	failure	insuff.clin. response
608 03470069	10.05	female	26	64.1	black	success	
608 03470252	14.188	male	42	60	black	failure	death

APPENDIX B

CONCOMITANT MEDICATIONS OF PATIENTS WITH UNUSUALLY HIGH OR LOW MEAN VORICONAZOLE PLASMA CONCENTRATIONS

PATIENT ID (SUCCESS/ FAILURE)	MEAN VORICONAZOLE CONCENTRATION (MCG/ML)	CONCOMITANT MEDICATIONS
608 03470252 (Failure – Death)	14.188	Cefoxitin, fentanyl**, glycopyrronium, halothane, *neostigmine*, pancuronium, succinylcholine, thiopental Na, gentamicin, amoxiclav, opium, *metronidazole**, furosemide, mercurochrome, K, tropicamide, hetastarch, APAP, heparin, Vit B, VitC, morphine, O_2, piperacillin/tazobactam, *ciprofloxacin**, amikacin, Epinephrine, atracurium, blood transfusion, etomidate, isoflurane, $NaHCO_3$, succinylcholine, imipenem, Zn, midazolam**, Ca salts, TPN, vecuronium, insulin, vancomycin, betaine/K, chloramphenicol, mupirocin, ranitidine
608 03470069 (Success)	10.05	haloperidol, gentamicin, *metronidazole*, benzylpenicillin, *meperidine*, epinephrine, blood transfusion, etomidate, polygeline, halothane, Nitrous Oxide, sulfentanil, succinylcholine, vecuronium, hetastarch/NaCl, sucrafate, amoxiclav, enoxaparin, midazolam**, morphine, O_2, K, TPN, isoflurane, APAP, alfentanil, betaine/K, metoclopramide, **Co-trimoxazole***, glucerin, chlorhexidine, insulin, *ciprofloxacin***, sucralfate, nystatin, amphotericin, heparin, tropicamide, pancuronium, furosemide, piperacillin/tazobactam, dextrose, $NaHCO_3$, meropenem, ceftazidime,
608 60070228 (Failure – Insufficient Clinical Response)	9.755	Oxygen, promethazine, Dakin's solution, papain/urea, celecoxib, famotidine, morphine, digoxin, metoprolol, vancomycin, loperamide, amitriptyline, dicyclomine, Maalox, **pantoprazole***, enoxaparin, *ondansetron***, ASA, phenol spray, *meperidine*, metoclopramide, *droperidol*, levofloxacin**, lipids, Vit K, TPN, propofol, fentanyl, ibuprofen, amphotericin, blood, lorazepam, vecuronium, phenylephrine, tropicamide, *octreotide*, hydrocodone/APAP, diphenhydramine, **fluconazole**, amikacin, dopamine, mupirocin, HAc
608 50470257 (Failure – Adverse Event)	9.553	Lactulose, spironolactone, enoxaparin, APAP, diphenhydramine, **fluconazole***, levofloxacin, cefepime, humulin, vancomycin, linezolid, dolasetron, temazepam**, **lansoprazole****, **co-trimoxazole****, acyclovir**, morphine, APAP/hydrocodone, diphenhydramine, filgastrim, clavulanic/ticarcillin, promethazine, *caspofungin**, tropicamide, furosemide, cyclobenzaprine**, bisacodyl, lorazepam**, zolpidem**, amphotericin, TPA, dalfopristin/quinipristin, K, bumetanide, O_2, albumin, meropenem
608 04030005 (Failure – Laboratory Abnormality)	9.495	Ipratropium, *albuterol***, insulin, dextrose, heparin, nefopam, *nalbuphine*, tropicamide, cefuroxime, $NaHCO_3$, O_2, furosemide, Vitremix, Lipids, propofol, blood, nicardipine**, *nalbuphine***, amoxicillin, atracurium, **fluconazole****, amino acids, tropicamide, Iloprost, amphotericin, bumetanide, dexamethasone, ceftriaxone, ciprofloxacin**, *caffeine***/dihydroergotamine**, fentanyl**, midazolam**, **omeprazole****
608 60070261 (Failure – Adverse Event)	0.157	APAP, *albuterol*, ASA, codeine/guaifenesin, oxygen, Mg salts, Etham, PZA, **rifampicin***, levofloxacin, **pantoprazole****, metoprolol, ipratropium, K/Na phosphate, Captopril, Mg gluconate, K, pyridoxine, **clindamycin****, epinephrine, fentanyl, morphine, mupirocin, vecuronium, propofol, dopamine, midazolam**, lipids, TPN, Vit K, Aquaphor, Eucerin cream, MC, gentamicin, **fluconazole**,

		tropicamide, phenylephrine, ophthalmic lubricant, famotidine, blood transfusion, lidocaine, APAP/Hydrocodone, bisacodyl, *meperidine*, heparin, tropicamide, phenylephrine, fluoxetine, amphotericin, diphenhydramine
608 80090079 (Success)	0.170	*estradiol*, **lansoprasole**,** levothyroxine, **omeprazole**,** acetaminophen/codeine. Maalox, MgCit, blood transfusion, oxygen, piperacillin/tazobactam, famotidine, morphine, *albuterol*, ipratropium, fentanyl**, midazolam**, gentamicin, nystatin, haloperidol**, fluconazole, lorazepam**
608 60070366 (Failure – Adverse Event)	0.185	Cholestyramine**, **clotrimazole**, lipids, loratadine, Mg salts, *meperidine*, mirtazapine, MV, *ondansetron*, midodrine, promethazine, pseudoephedrine, sertraline, trandolapril, ZnO, zolpidem, enoxaparin, TPN, thyroxine, Ultracal, O_2, ibuprofen, vancomycin, pipera/tazobac, sumatriptan, butorphanol, **rifampicin***, **clindamycin****, APAP, diphenhydramine, blood transfusion, **pantoprazole****, morphine, *albuterol*, furosemide, Ca salts, meropenem, phenylephrine, regular insulin, $NaHCO_3$, dopamine, amphotericin, *caspofungin*, ipratropium, midazolam**, naloxone, APAP, *ciprofloxacin***, heparin, metoclopramide, cisatracurium, $NaHCO_3$, citric acid/Na citrate, **fosphenytoin,** diphenhydramine, furosemide, Mg salts, Ca salts, blood transfusion, K, propofol, haloperidol
608 02690199 (Success)	0.205	Undefined Insulin, **omeprazole****, **tacrolimus****, dopamine, NaCl, K, albumin, dextrose/NaCl, AA/Dextrose/Lipids, MPA**, mV, ceftazidime, **clindamycin***, fenoterol/ipratropium, mesna, O_2, furosemide, octreotide, erythropoeitin, lorazepam, enoxaparin, metoclopramide, APAP, dipyrone, captopril, basiliximab, *doxazosin*, atenolol, $NaHCO_3$, Mg salts/papaverine, amlodipine**, benziodarone, Fe/mucoprotease, APAP, ASA, *prednisone***, ganciclovir, pentoxifylline, cyclopentolate, tropicamide, *loperamide*, teicoplanin, Almagate, ketorolac, Vit K, piperacillin, Na_3PO4, Al salts, allopurinol, nifedipine**, prednisone, simethicone, clonidine, pentosan, **co-trimoxazole**,** *ciprofloxacin***, pentoxifylline, lactulose, amoxiclav, **fluconazole****
608 51990207 (Failure – Insufficient Clinical Response)	0.343	Gentamycin, ranitidine, Tazobac, K, vancomycin, **lansoprazole****, thyroxine, *meperidine*, metoclopramide, amylase/lipase/protease, promethazine, **fluconazole**, cilastatin/imipenem, morphine, docusate, gabapentin, hydroxyzine, paroxetine, clonidine, TPN, prochlorperazine, metronidazole**, folic acid, thiamine, dextrose, levofloxacin, lorazepam, **fosphenytoin**,** promethazine, **phenytoin**,** APAP, isosorbide dinitrate, *propanolol*, lidocaine, diphenhydramine, nystatin, tropicamide, phenylephrine, proparacaine, furosemide, alprazolam**, amphotericin, flucytosine**, Mg salts, octreotide, ceftazidime, sulfadiazine
608 03470013 (Success)	0.366	Insulin, amoxiclav, fenoterol, hetastarch, hydrocortisone, ipratropium, nifedipine, pancuronium, epinephrine, midazolam*, cefotaxime, morphine, aminophylline, methylprednisolone**, hexoprenaline, TPN, metoclopramide, betaine/K, diazepam**, beclomethasone, *albuterol**, enalapril**, blood, tropicamide, dextrose, ketamine, amikacin, imipenem, ranitidine, glycopyrronium, vancomycin, theophylline, morphine, APAP, furosemide, acetazolamide, *ciprofloxacin*, haloperidol, Fe, folic acid, amphotericin, cyclopentolate/phenylephrine

608 60070120 (success)	0.382	**Phenytoin*,** midazolam**, morphine**, APAP, bacitracin, bisacodyl, docusate, ranitidine, enoxaparin, xipamide, Fe, meropenem, vancomycin, blood, *albuterol*, metoclopramide, famotidine, fentanyl, hetastarch, isoflurane, *neostigmine*, phenylephrine, K, glycopyrronium, thiopental Na, thrombin, vecuronium, Ca, citaprolam**, diphenhydramine, Mg cit, Na_4PO_3, APAP/Codeine, K, ceftriaxone, K, labetalol, lorazepam**, levofloxacin**, albumin, dopamine, mupirocin, paroxetine, furosemide, heparin, famotidine, gelatin, cefotetan, dopamine, *metronidazole**, **fluconazole****, tropicamide
608 20270070 (Success)	0.609	Tinzaparin, sucralfate, cholestyramine, loperamide, Vitrimix, imipinem/*cilastatin***, plasma, gentamycin, ampicillin/sulbactam, blood, amikacin*, *metronidazole***, dalteparine*, atropine eye drops, *adrenaline*, furosemide
608 60070235 (Success)	0.687	Acetaminophen, Ca salts, famotidine, O_2, **phenytoin***, metoclopramide, enteral nutrition, ibuprofen, midazolam, levofloxacin, Tazobac, bisacodyl, docusate, Na_3PO_4, ipratropium, *albuterol***, morphine, gentamicin, meropenem, tropicamide, phenylephrine, nystatin/triamcinolone, ceftriaxone, vancomycin, enoxaparin, nifedipine**, **fluconazole****
608 04580164 (Success)	0.909	Furosemide, TPN, insulin, lipids, electrolytes, metoclopramide, O_2, MV, omeprazole, enoxaparin, dipyrone, sulfentanil, midazolam**, cilastatin/imipenem, **fluconazole**, teicoplanin, NE, ropivacaine, amikacin, famotidine, leucocytes, albumin, alprazolam**, fluoxetine**, blood transfusion, tropicamide, **clindamycin**,** vancomycin, nadroparin, diazepam**, nandrolone, bromazepam**, lactulose, cisapride**, hetastarch, sorbitol, thiethyperazine, APAP, teicoplanin, meropenem, flunitrazepam**, ipratropium, ambroxol, aminophylline, aminoacids/lactic acid, plasma, Al/Mg salts, buprenorphine, ranitidine, theophylline, acetazolamide
608 50920097 (Failure – Withdrawn consent)	0.941	Lorazepam**, *meperidine*, promethazine, cyclobenzaprine, APAP/Codeine, TPN, vancomycin, **fluconazole**, phenol spray, Al/Mg, gentamicin, famotidine, sucralfate, cyanocobalamin, heparin, levofloxacin, K, *ciprofloxacin***, O_2, albumin, plasma, midazolam**, blood transfusion, phenylephrine, tropicamide, dopamine, insulin, cilastatin/imipenem, furosemide, amphotericin, *loratidine***/pseudoephedrine

Legend:
Bold- drug affects voriconazole plasma concentration
Italicized – drug undergoes substantial CYP450-mediated metabolism; may potentially interact with voriconazole
Underscored – Voriconazole affects (or has a strong potential to affect) the metabolism of this drug
Double underscored and in red font color – drug highly suspected to cause the increase/decrease in voriconazole plasma concentration
**- drug concurrently used during PK sampling period
*- drug used days before PK sampling period

33 Pages Immediately Following Withheld - b(4) Draft Labeling

APPENDIX D
Individual Study Reviews

1. Study 150-608

Title: A randomized, open label, comparative multicenter study of voriconazole versus conventional amphotericin B →fluconazole in the treatment of candidemia in non-neutropenic subjects

Objectives:
Primary-
To compare the efficacy and safety of voriconazole and conventional amphotericin B→fluconazole in the treatment of candidemia in non-neutropenic subjects

Secondary-
(1) To examine health care resources utilization in subjects treated with voriconazole and conventional amphotericin B
(2) To examine the population pharmacokinetics of voriconazole.

Study Design:
- This was a randomized, open, comparative multicenter study. Subjects received either voriconazole or amphotericin B→fluconazole. Investigators assessed clinical response at end of therapy (EOT) and at 2, 6 and 12 weeks after EOT. Subjects were assessed for safety, including visual safety testing, throughout the study. Subjects who were considered to be at risk of cardiac arrhythmia were required to be continuously monitored during iv therapy.

Study Population:
Subjects had to have at least 1 positive blood culture for Candida species within 96 hours and signs of infection within 48 hours of randomization. A total of 272 and 131 patients were treated with voriconazole and Amphotericin B→ fluconazole, respectively. In each treatment arm, 55% of these patients were discontinued. Males comprised 58% of the population. The mean age was 53.5 (13 to 90) and was comparable between genders. Males were slightly taller and slightly heavier than the females. There were Whites (57%), Blacks (16%), Asians (22%) and subjects from other ethnic groups (5%).

Dosing and Duration:
Subjects received intravenous (iv) treatment for at least the first three days then they could switch to oral therapy. Subjects were treated for at least 14 days after candidemia resolution up to a maximum of eight weeks.

- *Voriconazole*: A 6mg/kg iv loading dose every 12 hours for 24 hours then 3mg/kg iv every 12 hours. The oral dose was 200mg bid, but this could be reduced to 100mg bid for subjects weighing <40kg. It could be escalated to 300mg mg bid or to 150mg for subjects weighing <40kg.
- *Amphotericin B*: At least 0.7mg/kg iv, daily. *Fluconazole*: 400mg iv or oral, daily.

Endpoints:
- *Efficacy:* Investigator and Data Review Committee (DRC) assessment of response to treatment. In addition: time to death, mycology, eye assessments and vital signs were recorded.

- *Safety:* Adverse events, serious adverse events, laboratory safety tests, visual assessments and cardiac monitoring.

- *Pharmacokinetic:*
  Voriconazole plasma concentrations were obtained from blood samples collected weekly up to EOT.

Sponsor's Findings and Conclusions:

A. Efficacy and Safety

- At the fixed timepoint 12 weeks after EOT, the DRC success rates showed that voriconazole was non-inferior to amphotericin B → fluconazole. The stratified success rates at 12 weeks after EOT were 40.72% and 40.70% in the voriconazole and control groups, respectively.

- The Day 98 all cause mortality in the MITT population was 35.5% and 41.8% in the voriconazole and amphotericin B → fluconazole group respectively; the difference was not statistically significant (hazard ratio 0.822; 95% CI; 0.582 to 1.161).

- In both treatment groups, median time-to-blood-sterilization with over 80% subjects was equal to or less than 1 week.

- The rate of discontinuations due to adverse events was higher in the voriconazole (19.5%) than in the ampho→flu group (9.9%). However, the protocol mandated that a switch to fluconazole due to amphotericin toxicity not be recorded as a discontinuation against the control group.

- The frequency and severity of adverse events and laboratory test abnormalitites were similar in the voriconazole group and ampho→flu group.

- A higher proportion of subjects in the ampho→flu group had renal AEs and laboratory test abnormalities whereas a similar proportion of patients in the two groups had hepatic AEs and laboratory test abnormalities.

B. PK-Efficacy Relationship

- Sparse plasma sampling was performed on about 85% of the patients every week until EOT. The median number of voriconazole plasma concentration samples per subject in both the efficacy and safety populations was 2, with a range of 1 to 24.

- Of the 272 subjects treated with voriconazole, 228 had plasma concentration data with 211/228 in the MITT population. A total of 256/272 had post-baseline LFT data, of whom 233/256 were in the MITT population.

- Patients comprising the efficacy population had median average plasma concentration and median Cmax of 2.89 (range: 0.07-14.19) mcg/mL and 3.37 (range: 0.07-24.3 mcg/mL), respectively. Patients included in the safety analysis had medians of the average and maximum plasma concentrations in individual subjects of 2.85 (0.07-14.19) mcg/mL and 3.69 (0.07-24.3) mcg/mL, respectively.

- Table 1 below summarizes the relationship between plasma voriconazole concentrations (mean, median, range) and therapeutic outcome, as assessed by the DRC and the Investigator. Of the MITT subjects with plasma concentration data, 73% were classified as DRC successes using secondary endpoint; 46.4%,

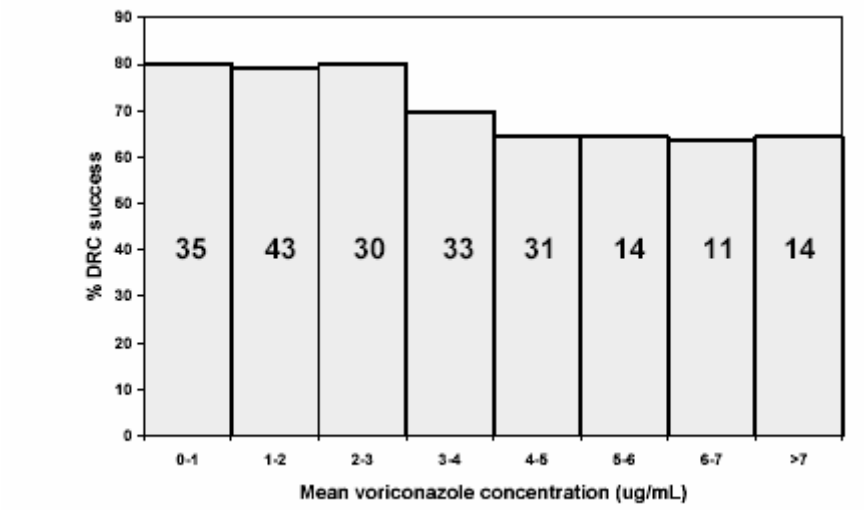
using the primary endpoint. A total of 78.2% of these cases were classified as successes by the Investigator.

TABLE 1
Mean voriconazole plasma concentration summary statistics by therapeutic outcome, MITT subjects

Therapeutic Outcome	No. of Subjects	Range	Median	Mean	Geometric Mean
DRC primary endpoint success	98	0.08 – 8.25	2.32	2.82	2.18
DRC primary endpoint failure	113	0.07 – 14.19	3.54	3.60	2.39
DRC secondary endpoint success	154	0.07 – 10.05	2.45	3.01	2.16
DRC secondary endpoint failure	57	0.07 – 14.19	3.89	3.86	2.72
Investigator success	165	0.07 – 10.05	2.40	2.89	2.08
Investigator failure	46	0.16 – 14.19	4.34	4.48	3.32

- Figure 1 below summarizes the empirical DRC success rate (as secondary endpoint outcome) by mean plasma voriconazole concentration, with the total number of subjects in each plasma concentration categories indicated in each bar.

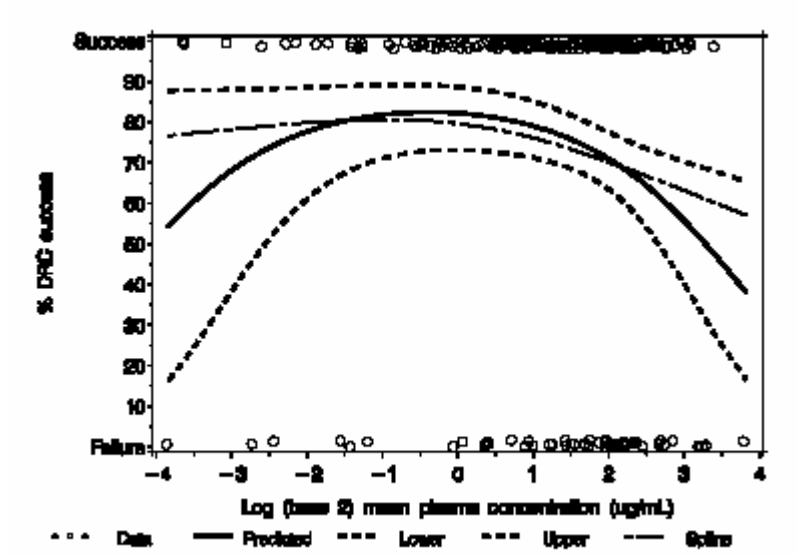
FIGURE 1
Summary of DRC success by mean plasma voriconazole concentration bands ---MITT population



Source: 150-608 PK/PD Statistical report Figure 0.8

- Figure 2 shows the relationship between log mean voriconazole plasma concentration and secondary endpoint efficacy for the MITT subjects, as obtained by logistic regression analysis. The model indicates a curvilinear relationship best fit to a quadratic function. Regardless of efficacy endpoint used (primary or secondary), this curvilinear relationship was observed. However, this relationship disappeared when mean plasma concentration data were determined using the first eight days of treatment only.

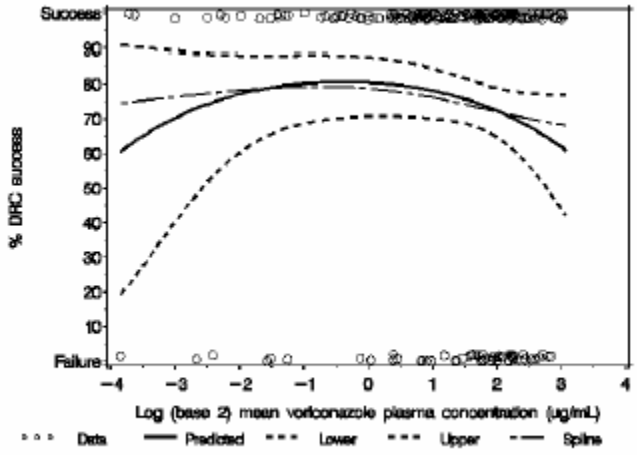
FIGURE 2
Binomial data and logistic fit for DRC therapeutic success versus log plasma concentration --- MITT subjects



Source: 150-608 PK/PD Statistical report Figure 0.9

- Furthermore, the statistical significance of the curvilinear relationship observed (see previous figure) disappeared when the data from five subjects with voriconazole plasma concentrations >9 mcg/mL were excluded (Figure ___).

FIGURE 2A
Binomial data and logistic fit for DRC therapeutic success versus log plasma concentration --- MITT subjects excluding five subjects with voriconazole plasma concentration > 9mcg/mL



Source: 150-608 PK/PD Statistical report Figure 0.10

- Using a multivariate logistic modeling technique, the influence of covariates on DRC therapeutic outcome was assessed. As shown in Table 17, there were statistically significant differences observed for race, days on treatment, log mean plasma concentration ranges, and route of administration.

TABLE 17
INFLUENCE OF COVARIATES ON DRC THERAPEUTIC OUTCOME

Categorical factor	Successful subjects	Total subjects	*p-value* % success
Concentration (µg/mL)			*<0.0001*[4]
≤2	62	78	79.5
2–4	47	63	74.6
> 4	45	70	64.3
Missing	8	37	21.6
Region			*0.2703*
1	90	144	62.5
2	72	104	69.2
Gender			*0.2472*
Male	99	145	68.3
Female	63	103	61.2
Weight (kgs)			*0.2688*
<60	55	93	59.1
60-75	48	68	70.6
>75	59	87	67.8
Race			*0.0231*
Asian	28	50	56.0
Black	30	36	83.3
White	95	151	62.9
Other	9	11	81.8
Race (grouped)			*0.3183*
White	95	151	62.9
Non-white	67	97	69.1
Days on treatment			*<.0001*
≤12	18	80	22.5
13 – 17	73	85	85.9
≥18	71	83	85.5
Age Group (years)			*0.0922*
≤ 45	60	84	71.4
45-65	61	90	67.8
> 65	41	74	55.4
Site of infection			*0.0550*[8]
Candidemia	143	210	68.1
Candidemia/Invasive candidiasis – definite	6	9	66.7
Candidemia/Invasive candidiasis - probable	13	29	44.8
Catheter removal			*0.5183*
All removed	120	188	63.8
Not all removed	19	29	65.5
None to remove	23	31	74.2

C. PK-Safety Relationship

- Table 18 summarizes the relationship between four LFT parameters (AST, ALT, AP, bilirubin) and mean voriconazole plasma concentration, examined using the 223 subjects in the PK/PD safety population (linear modeling approach).

TABLE 18
Summary of significance levels for log mean concentration in models of the four LFT variables, n=222

	Log Mean Concentration			
P-values	**Linear p-value**		**Quadratic p-value**	
Y-variable	**Simple**	**Adjusted**	**Simple**	**Adjusted**
Log AST/ULN	0.0007	0.0017	0.4811	0.3268
Log ALT/ULN	0.9014	0.6902	0.2080	0.2736
Log AP/ULN	0.0105	0.1614	0.4394	0.5044
Log bilirubin/ULN	<0.0001	<0.0001	0.0089	0.0140

- Table 19 summarizes the results of logistic modeling of abnormal LFTs.

TABLE 19
Summary of the significance levels for log mean concentration in logistic quadratic polynomial models for the four LFT variables

Binomial variable per subject	% Yes	Log Mean Concentration	
		Linear p-value	Quadratic p-value
Any AST abnormality?	6.73	0.0788	0.9361
Any ALT abnormality?	6.28	0.7684	0.5605
Any AP abnormality?	4.04	0.8815	0.9018
Any bilirubin abnormality?	7.17	<0.0001	0.9063

- Using Linear Modeling:

  - For AST: there was a statistically significant positive linear relationship between log mean voriconazole plasma concentration and log of AST scaled by ULN, even after inclusion of baseline covariates.

  - For ALT: there was no statistically significant relationships between log mean voriconazole plasma concentration and log of ALT scaled by ULN.

  - For AP: there was a simple statistically significant linear relationship between log mean voricoanzole plasma concentration and log of AP scaled by ULN but this relationship disappeared upon inclusion of baseline covariates in the modeling.

  - For bilirubin: there was a statistically significant linear and quadratic relationship between log bilirubin/ULN and log mean voriconazole concentration, even after inclusion of baseline covariates in the modeling.

- Using Logistic Modeling:

In contrast to the results of linear modeling, no statistically significant relationships were found for AST or AP. The results for bilirubin still showed a statistically significant linear relationship.

Sponsor's Conclusions:

- The MITT population consisted of 248 of 272 subjects treated with voriconazole. PK/PD analysis of efficacy involved 211 MITT patients with both plasma concentration data and therapeutic outcome data. PK/PD analysis of safety involved 223 subjects with both plasma concentration data and complete LFT data, including 15 subjects from the non-MITT population.
- PK-Efficacy: The logistic relationship between log mean concentration and success was curvilinear. However, this curvilinearity disappeared upon exclusion of either 5 patients with voriconazole plasma concentrations >9 mcg/mL or 1 patient with voriconazole plasma concentration of <100 ng/mL. No linear or quadratic relationship was evident when plasma concentration data from the first eight days of treatment were used in the analysis.
- PK-Safety: The PK/PD analyses suggest that there was low absolute risk of LFT abnormalities, with a linear relationship found only for bilirubin. All four LFT variables except ALT were correlated with log mean voriconazole plasma concentration. Modeling confirmed the relationship of AST with concentration but the relationship between bilirubin and concentration was stronger and curvilinear. The relationship with AP was non-significant if the baseline covariates were included in the modeling. When the rate of subjects experiencing abnormalities for each of the four LFTs was modeled a relationship with linear concentration was found only for bilirubin.

- Although there was no clear PK/PD relationship for efficacy, the plasma concentrations achieved with the dose regimen employed were associated with efficacy and exceeded MICs for the majority (96%) of baseline *Candida* clinical isolates encountered. In addition, of all the 4 LFT parameters assessed, only bilirubin was found to have a linear relationship with voriconazole concentration. Thus, these findings support the use of voriconazole at a dose of 6 mg/kg IV every 12 hours for 24 hours then 3 mg/kg IV every 12 hours for ≥ 2 days followed by 200 mg p.o. b.i.d. in the treatment of Candidemia.

REVIEWER'S COMMENTS:

1. Based on the data in Table 1, regardless of whether the investigator or the DRC made the voriconazole efficacy assessment, there was a consistently higher median or mean voriconazole concentration associated with "failure" than that associated with "success". The protocol specified that discontinuations due to voriconazole adverse events would be classified as treatment failures. Thus, it appears that higher adverse event rates would be expected with higher-than-optimal voriconazole concentrations.

2. Based on the relationship between efficacy assessed at EOT (secondary endpoint) and plasma voriconazole exposure (Figure 1 above), it appears that the optimal therapeutic voriconazole concentration for the treatment of candidemia is <3 mcg/mL. That concentration bands >3 mcg/mL mean plasma voriconazole concentration were associated with lower DRC success rates could be explained by the fact that in this study, adverse events (especially those that have led to discontinuations) were considered failures. However, the validity of this assessment is limited because voriconazole exposure data in this submission was based on pooled individual <u>mean</u> plasma voriconazole concentrations regardless of dosing/sampling times.

3. Based on the covariate analyses conducted by the sponsor (Table 17), in order to improve the probability of therapeutic success, voriconazole doses that will produce a >4 mcg/mL <u>mean</u> plasma voriconazole concentration should be avoided (The Cmax corresponding to this mean plasma value was not identified by the sponsor.). In addition, the treatment duration should be ≥12 days. The chances of success also appeared to be greater in patients who tolerated the drug long enough to reach the transition period from the IV to the oral route of administration. Though not shown to be statistically significant, candidemia patients who were females, patients with BW <60 kg, Asians, or patients >65 years old exhibited relatively lower success rates.

4. The clear relationship between voriconazole exposure and Liver Function (LFT) abnormalities, especially bilirubin, was confirmed in the Global Candidemia study.

5. Overall, the PK-PD relationship findings of this particular study involving candidemia patients are similar to those already in the VFEND® label. No changes to the Pharmacokinetics-Pharmacodynamics Relationships section of the current label will be recommended.

2. Study 150-309/604

Title: An open label, non-comparative, multicenter, Phase 3 trial of the efficacy, safety and toleration of voriconazole in the primary or secondary treatment of invasive fungal infections

Objectives:
Primary-
To investigate the efficacy, safety and toleration of voriconazole in the treatment of systemic and invasive fungal infections due to pathogens for which there is no licensed therapy; and in the treatment of systemic or invasive fungal infections in subjects failing or intolerant of treatment with approved systemic antifungal agents.

Secondary-
- To collect random plasma levels of voriconazole to assist population pharmacokinetic modeling in this diverse group of subjects.

Study Design:
Studies 150-309 and 150-604 were open label, non-comparative studies in which all subjects were assigned to receive voriconazole. The maximum total duration of treatment with voriconazole (intravenous and oral) was initially expected to be 12 weeks. However the actual total duration of treatment for each subject was determined by the investigator. Global, clinical, mycological, serological and radiological (imaging) evaluations were carried out at various points throughout the study.

Study Population:
The subjects in these studies had a diagnosis at baseline of a systemic or invasive fungal infection for which there was no licensed therapy or a systemic or invasive fungal infection with evidence of failure and/or intolerance/toxicity to currently approved treatments; about 30% had serious candidiasis but only <u>about 12% of the total patient population was diagnosed with candidemia.</u> There were a total of 236 male and 136 female participants in the two studies. The mean age of males (44.3) was similar to the females (42.0) but on average, the males were slightly of higher BW (68.6 kg) than the females (59.9 kg). Majority of the subjects were Whites.

Dosing and Duration:
- *Voriconazole*: A 6mg/kg iv loading dose every 12 hours for 24 hours then <u>4mg/kg</u> iv every 12 hours for at least 3 days but not exceeding 16 weeks. The oral loading dose was 400 mg every 12 hours for 24 hours, followed by a maintenance dose 200mg every 12 hours. The maintenance dose was adjusted in patients taking rifabutin, nevirapine, or phenytoin concomitantly, due to inadequate clinical efficacy or due to intolerance. Patients weighing <40kg were given ½ the usual maintenance dose.

Endpoints:
- *Efficacy evaluations:*
  - *Primary efficacy variable:* global response (complete, partial, stable or failure) evaluated by the investigator at EOT/Week 16 based on overall clinical, mycological, radiological, and serological responses.
  - *Secondary efficacy variables:* Global response was also assessed four weeks after EOT (and compared with EOT) in subjects who stopped voriconazole therapy at or before Week 16 and whose global response at EOT was complete, partial or stable disease. Clinical, radiological, mycological and serological responses were evaluated at baseline, Weeks 2, 8, 12 or EOT/Week 16 (for those subjects continuing therapy) and at follow up four weeks after EOT. Clinical response was also evaluated at Weeks 1 and 4.

- *Pharmacokinetic evaluations:* Random plasma samples were collected for determination of voriconazole concentrations to assist in population pharmacokinetic analysis

- *Safety evaluations:* Blood and urine for laboratory tests were collected at screening/baseline and Weeks 1, 2, 4, 8, 12, EOT/Week 16 (in subjects continuing therapy) and at any dose level escalation or reduction and at follow up. In females of childbearing potential or up to two years post menopausal, a pregnancy test was obtained at Weeks 4, 8, 12, EOT, 16 and follow up. Ophthalmological safety tests were done at any time up to Week 2 (baseline) and at Weeks 8 and 12, EOT/Week 16 and at the follow up visit.

Sponsor's Findings and Conclusions:

- The infections treated in these studies were categorized into Aspergillosis, Candidiasis, and Rare/Other Diseases. The last category included rare invasive infections including fusariosis, scedosporiosis, cryptococcosis, chromomycosis, coccidioidomycosis, penicilliosis, histoplasmosis, zygomycosis, mycetoma and others. Majority of the patients were immunocompromised and had failed or were intolerant to treatment with other agents, including itraconazole and amphotericin B (both conventional and liposomal formulations).

- The satisfactory global response rate for subjects with serious *Candida* infection (refractory oesophageal, candidemia or disseminated infection) was approximately 60%. Candidemia patients comprised 12.3% of the total patient population in these studies.

- Of the 21 subjects with candidemia, eight had a complete global response at EOT and seven a response of 'cure' at the four week follow up visit.

- Treatment-related adverse events (mainly reversible visual disturbances, LFT elevations) were 15% and 10% for Study 150-309 and 150-604, respectively.

APPENDIX E
Consult Pharmacometrics Review

PHARMACOMETRIC REVIEW

NDA number:	21-266; 21-267, 21-630 (S009)
Submission date:	March 15, 2004
Product:	voriconazole
Brand names:	VFEND®
Sponsor:	Pfizer
Type of submission:	PM Consult / PK/PD Analysis for Treatment of Candidemia (b) (4)
Primary reviewer:	Gerlie De Los Reyes, Ph.D.
Pharmacometric Reviewer:	Jenny J Zheng, Ph.D.

EXECUTIVE SUMMARY:

A pharmacokinetic/pharmacodynamic analysis was conducted for the data obtained from the Global Candidemia Study to investigate the potential relationship between effectiveness or safety and the drug exposure. The effectiveness endpoints were Data Review Committee (DRC) assessment at the latest most relevant time point at EOT, 2, 6, or 12 weeks after EOT, which is the secondary endpoint, and investigators assessment. The safety measures are liver function tests (LFT) including aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (AP) and bilirubin levels in plasma during treatment. The exposure used in this analysis was the mean plasma concentration calculated from samples collected during treatment regardless of the sampling time. The number of samples used to calculate the mean plasma concentration varied from 1 to 24. The analysis showed that no clear relationship between effectiveness and mean plasma concentration was found. Elevation of AST and bilirubin, but not ALT and AP, were associated with higher voriconazole concentrations.

COMMENTS:

1. The exposure metrics used in this analysis may not be appropriate. A mean plasma concentration regardless of sampling time was calculated for each individual. Given the 6 to 12 hours half-life of the drug after doses, the concentrations within each dosing interval will fluctuate. Hence given the varied number of samples and sampling times for each patient, using the mean concentrations for the exposure-response analysis may not be reliable.
2. For the effectiveness analysis, the "failure" categorization included withdrawals, relapses, indeterminate, and failure (due to lack of effectiveness or occurrence of an adverse event). To include patients who failed or withdrew due to adverse event as failure in effectiveness analysis is not adequate for the purpose of the exposure response analysis. If effectiveness and safety are related to exposure, voriconazole concentrations in individuals who failed treatment due to adverse event may be high but voriconazole concentrations in patients who failed treatment due to lack of effectiveness may be low. Therefore, it is not appropriate to pool failures without considering reasons. It is recommended that in future exposure response analyses, the effectiveness and toxicity endpoints should be considered separately.
3. Since escalation was allowed in the trial, the non-responders may end up receiving higher doses, and subsequently would contribute to the inverse exposure response relationship at these higher exposures. Such data should be analyzed using mixed effects modeling employing the repeated measurements. The titration to effect and analysis of the data using a simple logistic model are the most likely causes for the inverted U-shape exposure-response relationship

RECOMMENDATION:
The PK/PD analysis was reviewed and found not to be adequate for arriving at any definitive conclusion regarding voriconazole exposure-response relationships for the treatment of candidemia (b) (4)
(b) (4)

_____
Jenny J Zheng, Ph.D.
Office Clinical Pharmacology/Biopharmaceutics,
Division of Pharmaceutical Evaluation III

_____
Jogarao Gobburu, Ph.D.
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RD/FT initialed by who_____

TITLE: Pharmacokinetic/Pharmacodynamic (PK/PD) Relationships for Voriconazole Study 150-608

OBJECTIVE: To investigate the relationship between voriconazole exposure (as summarized from plasma concentrations) and effectiveness.
To investigate the relationship between voriconazole plasma concentrations and safety, as represented by the four liver function tests (LFTs): aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (AP) and bilirubin.

DESIGN: This was a randomized, open, comparative multicentre study. Subjects received either voriconazole or amphotericin B → fluconazole.
Voriconazole: A 6mg/kg iv loading dose every 12 hours for 24 hours then 3mg/kg iv every 12 hours. The oral dose was 200mg bid, but this could be reduced to 100mg bid for subjects weighing <40kg. It could be escalated to 300mg mg bid or to 150mg for subjects weighing <40kg.

METHODS: **Pharmacokinetics:**
Plasma samples were collected weekly and each weekly sample was to be drawn within a different time or sample window relative to voriconazole dosing: 0-2 hours, 4-6 hours, 6-9 hours and 9-12 hours. The raw PK data were summarized for each individual as mean plasma concentration for the treatment period, including a 7-day lag period for non-zero values. Values recorded as below the lower limit of quantification of 0.1 µg/ml were replaced by 0.07. The mean plasma concentration was used to represent overall exposure in the subject.

Pharmacodynamic:
Effectiveness: Both the Data Review Committee (DRC) and investigator assessment of therapeutic response were used as effectiveness variables. The assessment time, categories and definition for success or failure are listed in the following table:

Assessment	Assessment time	Categories	Success/failure
DRC	EOT, 2, 6, and 12 weeks after EOT	Cured, Improved, Failure, Indeterminate, Relapsed, Withdrew	Success= cure and improved; Failure= Failure, Indeterminate, Relapsed, Withdrew
Investigator	EOT	Improvement, failure, indeterminate	Success=Improvement Failure=treatment failure or indeterminate

Safety: Four liver function tests were assessed: AST, ALT, AP and bilirubin. Each LFT was recorded on a continuous scale at variable intervals throughout the study, and was investigated as continuous data standardized relative to the upper limit of normal range (ULN) for the corresponding analysis laboratory. Africa/Southern Africa/Asia), predisposing factor to Candidemia, age, race (white, black, Asian, other) site of infection, catheter removal, gender, weight concomitant medication and route of administration.

For the safety analyses of LFT abnormalities, a time-based covariate indicating when the first abnormality occurred was calculated. Baseline values, standardized by the respective ULN's, for each of the four LFTs was also available as baseline covariates. The definitions of abnormality as follows:
AST, ALT and AP: Abnormal if,

- baseline<2xULN and tested result ≥5x baseline

- baseline ≥ 2xULN and <5xULN, test results ≥3x baseline
- baseline ≥5xULN and <10xULN, test results ≥2x baseline

Bilirubin: Abnormal if test result ≥ 3mg/dl and test result >baseline
Continuous LFT data was summarized to per subject values by averaging.

Statistical Analysis: The primary analysis of effectiveness and safety was via logistic modeling of the binomial response, success or failure. For both linear and logistic modeling, results are presented for both full models and parsimonious models (excluding non-significant terms, with the stratifying factor region usually included). All statistical analyses were carried out using SAS (1999-2001) modules SAS/BASE, SAS/STAT and SAS/PLOT. Logistic modeling used PROC GENMOD. The incidence of LFT abnormalities was also assessed.

Covairates: The following factors were identified *a priori* as potential covariates to be explored: voriconazole plasma concentration, time on treatment (days), Region (US/Canada/India/South America, Europe/Northern

RESULTS:

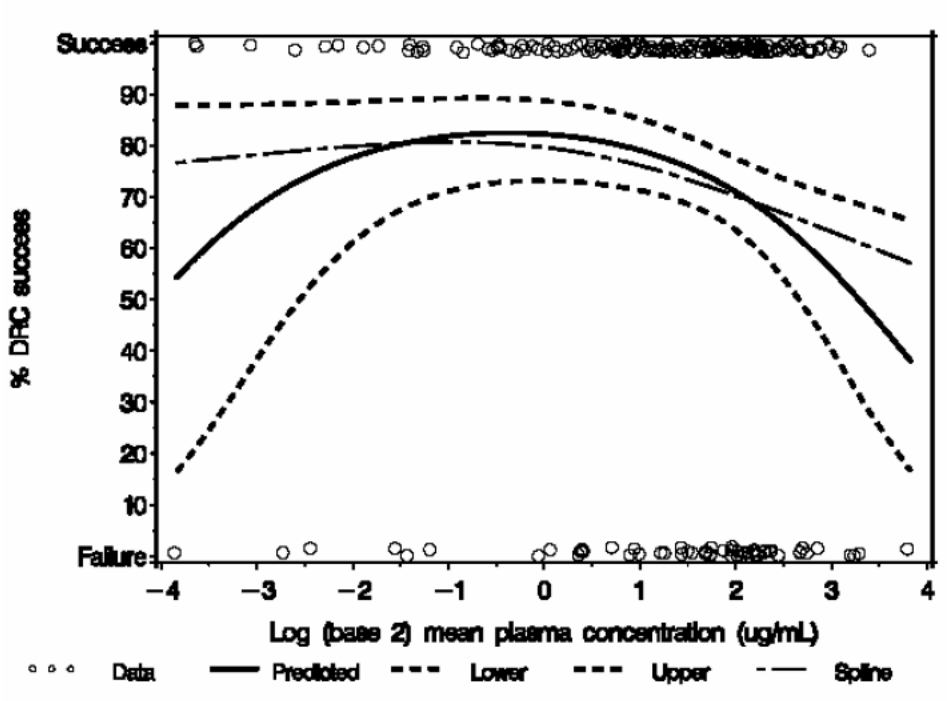
Population: In the Global Candidemia Study, a total of 272 subjects were treated with voriconazole, with 248 being in the MITT population. A total of 211 subjects with plasma concentrations in the MITT population are available for effectiveness analysis. A total of 223 subjects with both plasma concentration and post treatment of LFT values are available for safety analyses.
For DRC assessment in MITT population, 110, 26, 10, and 102 subjects were evaluated at EOT, 2-weeks after EOT, 6-weeks after EOT and 12-weeks after EOT, respectively. For investigator assessment, 248, 134, 106, and 105 subjects were evaluated at EOT, 2-weeks after EOT, 6-weeks after EOT and 12-weeks after EOT, respectively.

PK: One concentration (109.912 μg/mL) was considered outlier and deleted from analysis. The number of samples contributing to the determination of each subject's mean voriconazole plasma concentration was variable, ranging from 1 (n=47) to 24 (n=1).

LFT: Of the 223 subjects, 15 (6.7%) had abnormal AST values averaging 1.33 abnormalities per subject; 14 (6.3%) had abnormal ALT values averaging 1.43 abnormalities per subject; 9 (4.1%) had abnormal AP values averaging 2.11 abnormalities per subject and 16 (7.2%) had abnormal bilirubin values averaging 2.19 abnormalities per subject.

Effectiveness vs Exposure: The relationship between the DRC therapeutic outcome and log mean plasma concentration was investigated using the 211 MITT subjects. The results showed a non-significant linear relationship (p=0.1263), but a significant quadratic relationship (p=0.0300). Graphical presentation of the quadratic relationship is presented in Figure 1.

Figure 1. Binomial data and logistic fit for DRC therapeutic success versus log voriconazole plasma concentration, MITT subjects



Further investigation of the curvilinear relationship indicates that there are 5 subjects with mean voriconazole plasma concentrations above 9 µg/ml who are influential for the quadratic term and that 4 out of the 5 subjects are DRC therapeutic failures. Omission of the 5 subjects removes the statistical significance of the quadratic relationship. In addition, there is a subject with a low mean concentration who is influential for the quadratic term. Omission of this subject also results in the loss of the statistical significance of the quadratic relationship. Thus the curvilinear relationship observed in Figure 1 appears to be due to a few influential observations and is not robust to their omission.
Similar results were found using primary endpoint (DRC assessment at 12 week after EOT) and investigator assessment.

Covariates: The further effect of other explanatory variables on the relationship between outcome and log mean plasma concentration was examined. Each variable was first investigated singly to see what relationship it had with DRC outcome, and to provide an indication of what variables were most likely to be influential in a multivariate model. The analyses were conducted based on the 248 MITT subjects. Mean concentration is presented with a missing concentration category, to give a consistent total of 248 MITT subjects.
Statistically significant differences are observed for race, days on treatment, log mean plasma concentration categories and route of administration.
Asians appear to have the lowest success rate (56%) when compared with non-Asians although not statistically significant (p=0.1258). In addition, whites and non-whites do not appear to respond differently (p=0.3183).
The significant difference in response rates between the different log mean plasma concentration categories is almost entirely due to the missing category having a low success rate. This is probably because subjects failing within the first few days are less likely to have had plasma samples taken as specified in the protocol. The majority of the 37 MITT subjects with missing concentration data are either failed to respond (20) or withdrew (6). Timing of the samples is also likely to be related to the lower failure

rate observed for subjects whose samples were taken after IV administration only (39.3%).
Subjects with shorter treatment durations have a lower success rate, which is reflective of the fact that subjects who do fail tend to do so early in their course of therapy, whereas subjects classified as successes complete the treatment and thus have longer therapy durations. Furthermore, since therapy was initiated with IV administration, subjects who remained on treatment longer are also more likely to receive oral therapy and to respond.
Similarly, time on treatment also affects mean plasma concentration. Therefore these covariates must be considered cautiously.
Subjects with sites of infection defined as candidemia/invasive candidiasis have a lower response rate (50%) than the other subjects (p = 0.0345), but the difference is likely due to subjects with probable sites of infection (13/29; 44.8%). Those with definite sites (6/9; 66.7%), considered to be subjects with deep tissue *Candida* infection, are not significantly different to all others (p = 0.9310).

Liver Function Test vs Exposure: The relationship between LFTs and mean voriconazole plasma concentration was examined using the 223 subjects in the PK/PD safety population.

Results of models fitted to log LFT parameters scaled by ULN are presented in Table 1. The results are presented with and without a quadratic term in concentration to test for curvature, and with (Adjusted) and without (Simple) consideration of the variables region, MITT status, gender, weight, race, age, site of infection, catheter removal, predisposing factor and exclusion criteria.

Table 1. Summary of the significance levels for log mean concentration in models of the four LFT variables, n=222

	Log Mean Concentration			
P-values	**Linear p-value**		**Quadratic p-value**	
Y-variable	**Simple**	**Adjusted**	**Simple**	**Adjusted**
Log AST/ULN	0.0007	0.0017	0.4811	0.3268
Log ALT/ULN	0.9014	0.6902	0.2080	0.2736
Log AP/ULN	0.0105	0.1614	0.4394	0.5044
Log bilirubin/ULN	<0.0001	<0.0001	0.0089	0.0140

- ALT: no statistically significant relationships between log mean voriconazole plasma concentration and log of ALT scaled by ULN.
- AP: a simple statistically significant linear relationship between log mean voriconazole plasma concentration and log of AP scaled by ULN. However when the baseline covariates are included in the model the relationship is removed (p=0.1614), suggesting confounding effects of between baseline covariates and mean concentration.
- AST: a statistically significant positive linear relationship between log mean voriconazole plasma concentration and log of AST scaled by ULN. This relationship is unaffected by the inclusion of baseline covariates.
- Bilirubin: a statistically significant positive linear relationship, which is unaffected by the inclusion of baseline covariates, there is also a statistically significant quadratic relationship between log mean voriconazole plasma concentration and log of bilirubin scaled by ULN.

The incidences for subjects having any abnormal values are 6.7% (15/223), 6.3% (14/223), 4.0% (9/223) and 7.2% (16/223) for AST, ALT, AP and bilirubin, respectively. With such low percentages, the fitting of large models as described above

was not possible, thus simple quadratic modeling only was performed. The results of the simple quadratic models are presented in Table 2.

Table 2. Summary of the significance levels for log mean concentration in logistic quadratic polynomial models for the four LFT variables

Binomial variable per subject	% Yes	Log Mean Concentration	
		Linear p-value	Quadratic p-value
Any AST abnormality?	6.73	0.0788	0.9361
Any ALT abnormality?	6.28	0.7684	0.5605
Any AP abnormality?	4.04	0.8815	0.9018
Any bilirubin abnormality?	7.17	<0.0001	0.9063

In contrast to the linear model results, no statistically significant relationships were found for AST or AP. However the results for bilirubin still showed a statistically significant linear relationship.

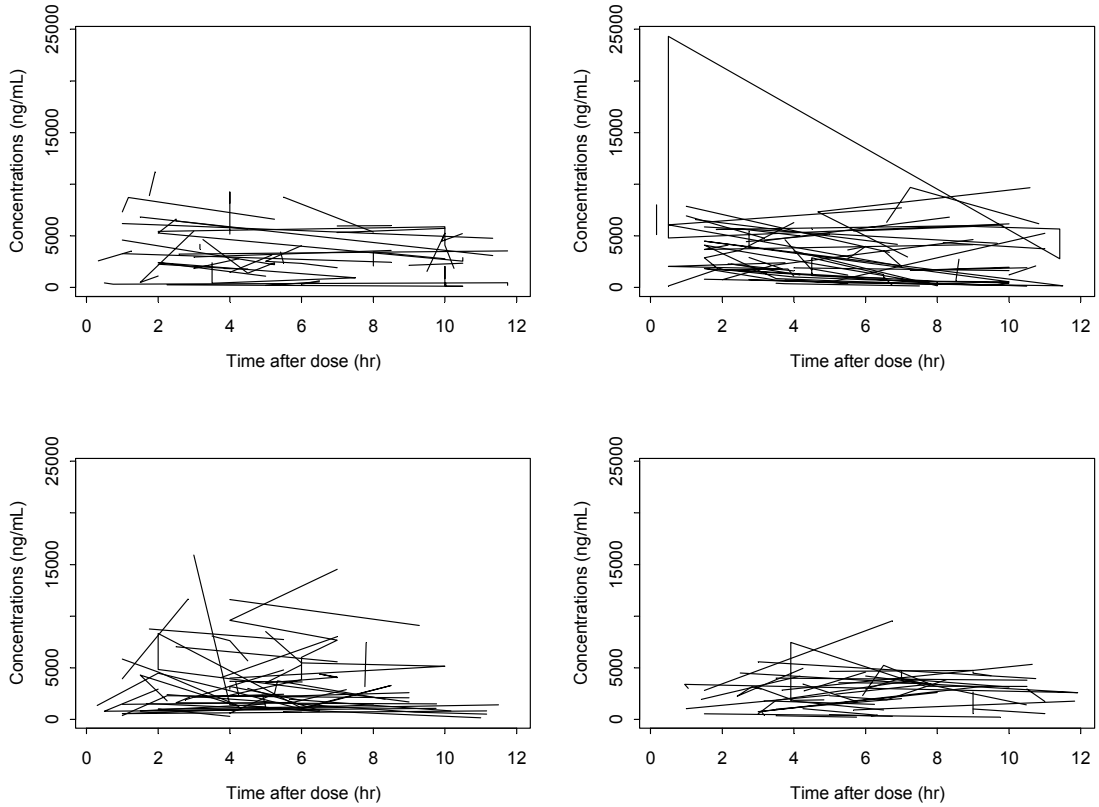
CONCLUSIONS

- No clear PK.PD relationship for effectiveness was identified.
- Among the liver function tests including AST, ALP, AP and bilirubin, elevated AST and bilirubin are associated with voriconazole concentrations.

COMMENTS:

1. The exposure metrics used in this analysis may not be appropriate. A mean plasma concentration regardless of sampling time was calculated for each individual. The elimination half-life of voriconazole is dose dependent. Following a 200 mg single oral dose the half-life is about 6 hours, but increase up to 12 hours after 400 mg. Given the 6 to 12 hours half-life of the drug after the clinical doses, the concentrations within each dosing interval will fluctuate. Hence given the varied number of samples and sampling times for each patient, using the mean concentrations for the exposure-response analysis may not be reliable.
2. Mean concentration would be acceptable only when the expected variation among samples used to calculate the mean concentration are minimal as compared with the variation among expected mean concentrations. The scenarios could be the following:
    a. The half-life of a drug is long as compared with the dose interval, so that the concentration fluctuation within dose interval is minimal,
    b. The between subject variability is substantially higher than expected variation within- and between- dosing interval in each subject and/or
    c. The samples were collected in a relatively narrow sampling window.

    The concentration vs time data for each subject is presented in the following figure, which shows that the samples were collected across the dosing interval instead of a narrow time window. For some subjects, the concentrations used to calculate the mean concentration were very different, most likely due to varied sampling times and number of samples in each patient.



3. For the effectiveness analysis, the failure category included withdrawals, relapses, indeterminate, and failure (due to lack of effectiveness or occurrence of an adverse event). Including subjects who failed or withdrew due to adverse event as failure in effectiveness analysis is not adequate, for the purpose of the exposure-response analysis. If effectiveness and safety are related to exposure, concentrations in an individual who failed treatment due to adverse event may be high but concentrations in the subject who failed treatment due to lack of effectiveness may be low. It is recommended that in the exposure-response analysis, the effectiveness and toxicity endpoints should be considered separately.
4. Since escalation is allowed in the trial, the non-responders may end up receiving higher doses. Such data should be analyzed using mixed effects modeling employing the repeated measurements. The titration to effect and analysis of the data using a simple logistic model are the most likely causes for the inverted U-shape exposure-response relationship.

APPENDIX F
OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-266 (S-009); 21-267 (S-009); 21,639 (S-003)	**Brand Name**	VFEND
OCPB Division (I, II, III)	DPEIII	**Generic Name**	Voriconazole
Medical Division	HFD-590 (DSPIDP)	**Drug Class**	Azole Antifungal
OCPB Reviewer	Gerlie C. De Los Reyes	**Indication(s)**	Treatment of candidemia (b) (4)
OCPB Team Leader	Philip M. Colangelo	**Dosage Form**	IV: 200 mg/vial Oral Tablets: 50, 200 mg Powder for Oral Suspension: 40 mg/mL (when reconstituted)
		Dosing Regimen	IV: 6 mg/kg q12h for the 1st 24 hours, then 3(b)4 mg/kg q 12h PO: (b) (4) 200 mg q12h. Note: Maintenance dose may be adjusted to factor in concomitant therapy and/or low body weight
Date of Submission	15 Mar 2004	**Route of Administration**	IV and Oral
Estimated Due Date of OCPB Review	15 Nov 2004	**Sponsor**	Pfizer
PDUFA Due Date	14 Jan 2005	**Priority Classification**	Standard
Division Due Date	20 December 2004 (?)		

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

Filability and QBR comments		
	"X" if yes	*Comments*
Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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

/s/

Gerlie De Los Reyes
12/16/04 01:00:43 PM
BIOPHARMACEUTICS

Phil Colangelo
12/17/04 11:11:04 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-266/S009
NDA 21-267/S009
NDA 21-630/S003

OTHER REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH	**ODS POSTMARKETING SAFETY REVIEW**	**ODS PID#, DATE:** D040589 October 1, 2004

TO: Renata Albrecht, M.D., Director Division of Special Pathogen and Immunologic Drug Products (DSPIDP), HFD-590	**FROM:** Sarah J. Singer, R.Ph., Safety Evaluator Division of Drug Risk Evaluation (DDRE) HFD-430

DESIRED COMPLETION DATE: October 30, 2004	**REQUESTOR:** Rebecca Saville, Pharm.D., Regulatory Project Manager Division of Special Pathogen and Immunologic Drug Products
DATE RECEIVED BY ODS: September 10, 2004	

DRUG: VFEND® (voriconazole)	**NDA #:** 21-266 21-267 21-630	**SPONSOR**: C.P. Pharmaceuticals International C.V. c/o Pfizer

EVENT:
Cardiac arrhythmias and QT prolongation

EXECUTIVE SUMMARY:
During review of a voriconazole efficacy supplement, DSPIDP became concerned about: 1) arrhythmias closely related temporally to the infusion of voriconazole; and 2) QT interval prolongation seen in patients treated with voriconazole but not in patients treated with comparator drugs. The review division asked DDRE to review cases of QT prolongation and arrhythmias that have been reported to FDA in association with voriconazole administration.

A search of AERS on September 13, 2004 identified 36 unduplicated, nonexcluded cases of arrhythmia, cardiac arrest, sudden death, and/or QT interval prolongation associated with voriconazole. More than half (20/36) of the reports were foreign. Ventricular arrhythmias (14 cases) were the most frequently reported type of arrhythmia; 2 additional patients were reported to have experienced QT prolongation with no mention of arrhythmia.

Although most of the reports were confounded or poorly documented, voriconazole could not be ruled out as the cause in any of the cases. DDRE therefore recommends that the **PRECAUTIONS** sections of the VFEND labeling, which currently addresses only QT prolongation and torsade de pointes, be amended. Proposed wording based on the current labeling is provided below, with deletions indicated by strike-through and additions underlined.

PRECAUTIONS

~~**General**~~ **Arrhythmias and QT prolongation**

Some azoles, including voriconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During clinical development and post-marketing surveillance, there have been rare cases of arrhythmias, (including ventricular arrhythmias such as torsade de pointes), cardiac arrests, and sudden deaths in patients taking voriconazole. These ~~reports~~ cases usually involved seriously ill patients with multiple confounding risk factors, such as history of cardiotoxic chemotherapy, cardiomyopathy, hypokalemia and concomitant medications that may have been contributory.

REASON FOR REQUEST/REVIEW:
DSPIDP is reviewing a voriconazole efficacy supplement. The division identified several patients whose voriconazole was discontinued due to atrial and ventricular arrhythmias, most of which occurred in close proximity to infusion of the drug. In addition, 11 of 50 voriconazole patients monitored with EKGs developed a QT interval change from baseline of 60 msec or more, compared with 0 of 13 monitored in the amphotericin B/fluconazole treatment group.

DSPIDP therefore asked DDRE for information on cases of QT prolongation and arrhythmias that have been reported to the FDA in association with voriconazole administration.

RELEVANT PRODUCT LABELING:

The **PRECAUTIONS: General** section of the VFEND labeling states:

> Some azoles, including voriconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During clinical development and post-marketing surveillance, there have been rare cases of torsade de pointes in patients taking voriconazole. These reports involved seriously ill patients with multiple confounding risk factors, such as history of cardiotoxic chemotherapy, cardiomyopathy, hypokalemia and concomitant medications that may have been contributory.
>
> Voriconazole should be administered with caution to patients with these potentially proarrhythmic conditions.
>
> Rigorous attempts to correct potassium, magnesium and calcium should be made before starting voriconazole (see CLINICAL PHARMACOLOGY - Pharmacokinetic-pharmacodynamic Relationships - Electrocardiogram).

Under **ADVERSE REACTIONS**, tachycardia is listed in a table of treatment-emergent adverse events as having been reported in 2.5% (37 patients) of 1493 patients in therapeutic studies of voriconazole.

The **ADVERSE REACTIONS** sections also provides a list of less common adverse events, which occurred in <1% of all voriconazole-treated individuals (including healthy volunteers and patients treated under compassionate use protocols). It includes the following events:

> Atrial arrhythmia, atrial fibrillation, AV block complete, bigeminy, bradycardia, bundle branch block, extrasystoles, heart arrest, nodal arrhythmia, QT interval prolonged, supraventricular tachycardia, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia (including torsade de pointes)

The VFEND labeling does not contain a postmarketing adverse events section.

LITERATURE:
PubMed was searched for citations on sudden death, cardiac arrest, or any arrhythmia in association with voriconazole, but no citations were found.

SEARCH DATE:	**DATABASE SEARCHED:**
September 13, 2004	Adverse Event Reporting System (AERS)

SEARCH CRITERIA:
Drug Names: Voriconazole, VFEND
MedDRA Terms: CARDIAC ARRHYTHMIAS (High-Level Grouping Term)
ECG INVESTIGATIONS (High-Level Term)

SEARCH RESULTS:
The broad search for any reported arrhythmia or any electrocardiogram with voriconazole listed as a suspect drug identified 52 cases, all of which were retrieved for hands-on analysis. Eight reports were duplicates, and another 8 were excluded from this analysis for the following reasons: 3 cardiac arrests were due to noncardiac causes (multiorgan failure in 2 cases and pulmonary hemorrhage in the third); 1 cardiac arrest was found on autopsy to have resulted from a myocardial infarction; 2 of the arrhythmias were part of the medical history and should not have been coded; 1 case of AV block occurred almost 3 months after voriconazole had been discontinued; and 1 case had been miscoded.

The remaining 36 unduplicated, nonexcluded cases are summarized below. Cases of cardiac arrest (except for those with demonstrated non-arrhythmic causes as described above) and sudden death were included as potentially relevant to the events of interest.

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SUMMARY OF CASES:
Potentially relevant features of the 36 unduplicated, nonexcluded cases of voriconazole-associated arrhythmia, cardiac arrest, sudden death, and QT interval prolongation are provided below.

Total cases:	**N=36**		
U.S.:		N=16	
Foreign:		N=20	
Serious[1]:	**N=25**		
Death[2]:		N=12	
Life-threatening:		N= 8	
Hospitalization[3]:		N= 5	
Event(s)[4]:	**N=36**		
Ventricular arrhythmia[4]:		N=14	
Torsade de pointes:			N=4
Ventricular fibrillation:			N=7
Ventricular tachycardia:			N=6
Ventricular bigeminy:			N=2
Cardiac arrest/asystole:		N=12	
Sudden death:		N= 3	
Other tachycardia:		N= 2	
Sinus tachycardia:			N=1
Unspecified tachycardia:			N=1
Bradycardia[5]:		N= 7	
W/ right bundle branch block:			N=1
Resulting in asystole:			N=2
Atrial fibrillation:		N= 4	
Unspecified arrhythmia:		N= 1	
QT prolongation[5]:		N= 5	
Gender:	**N=34**		
Female:		N=17	
Male:		N=17	
Age (years):	**N=31**		
Range:		3-82	
Median:		54	
Weight (kg):	**N=18**		
Range:		41-136.4	
Median:		60.5	

[1] By regulatory definition, in decreasing order of severity. Each case is counted only once, starting at the top.
[2] Not all of the deaths were clearly associated with the reported arrhythmia. Some appeared more likely to have resulted from underlying disease progression or another reported adverse event. See **DEATHS** on page 9.
[3] Initial or prolonged.
[4] Each case can have more than one.
[5] Pfizer has a waiver allowing them not to submit the case report forms for cases containing only nonserious labeled events. The periodic reports for VFEND were reviewed, and one case each of bradycardia and QT prolongation have not been submitted to the FDA because they were not serious by regulatory definition.

SUMMARY OF CASES, cont'd.

Route of administration: N=32

Intravenous only:	N=13
Intravenous, then oral:	N= 6
Oral only:	N=12
Oral, then intravenous:	N= 1

Daily dose (mg) at event: N=28

Intravenous only:	N=11	
Range:		120-800
Median:		400
Intravenous, then oral:	N= 6	
Range:		355-800
Median:		500
Oral only:	N=10	
Range:		200-800
Median:		400
Oral, then intravenous:	N= 1	
Dose:		600

Highest daily dose (mg): N=28

Intravenous only:	N=11	
Range:		120-800
Median:		400
Intravenous, then oral:	N= 6	
Range:		400-1200
Median:		500
Oral only:	N=10	
Range:		200-800
Median:		500
Oral, then intravenous:	N= 1	
Dose:		900

Time to onset (days): N=20

Intravenous only:	N= 9	
Range:		<1-11
Median:		3
Intravenous, then oral:	N= 4	
Range:		2-56
Median:		9.5
Oral only:	N= 7	
Range:		2-30
Median:		10

Timing related to iv infusion: N=3

Times: During the infusion
6.5 hours after the infusion
7.5 hours after the infusion

SUMMARY OF CASES, cont'd.

Voriconazole status after event: N=20

- Discontinued: N=11
  - Recovered: N=7
  - Outcome not stated: N=2
- Not discontinued: N= 9
  - Arrhythmia treated: N=7
  - Event resolved anyway: N=1
  - Outcome not stated: N=1

Medical history provided[6]: N=34

Arrhythmia:	N= 4	Fluid overload:	N=3
Other cardiac disease:	N= 9	Burns:	N=1
No cardiac history:	**N= 5**	Hypothyroidism:	N=1
Electrolyte abnormality:	N=11	Hyperthyroidism:	N=1
Malnutrition:	N= 3	Renal dysfunction:	N=7
Acidosis:	N= 2	Liver dysfunction:	N=8

Concomitant medications listed: N=29

- Number of drugs:
  - Range: 1-28
  - Median: 7
- Drugs labeled for event[6,7]:

Ciprofloxacin:	N=3	Fluoroquinolone unspecified:	N=1
Digoxin:	N=3	Haloperidol:	N=1
Esomeprazole:	N=3	Lopinavir/ritonavir:	N=1
Levofloxacin:	N=3	Omeprazole:	N=1
Amsacrine:	N=1	Ondansetron:	N=1
Clarithromycin:	N=1	Pentamidine:	N=1
Fentanyl:	N=1	Quinupristin/dalfopristin:	N=1

Indication[6]: N=28

Aspergillosis unspecified:	N=6	Miscellaneous (one case each):	N=6
Pulmonary aspergillosis:	N=6	*Aspergillus flavus*	
Candida sepsis/Candidemia:	N=4	*Candida* pneumonia	
Candida glabrata:	N=2	Esophageal candidiasis	
Candida krusei:	N=2	Fever	
Empiric therapy of febrile neutropenia:	N=2	Fungal pneumonia unspecified	
Invasive/systemic mycosis unspecified:	N=2	Pulmonary *Scedosporium*	

[6] Each case can have more than one.

[7] Other patients may have been given the same drug but were not tallied if they experienced a different event which is not labeled for that drug.

TEMPORAL RELATIONSHIP TO IV INFUSION (N=1):
The DSPIDP consult request indicated that the majority of the voriconazole-associated arrhythmias occurred in close proximity to the drug infusion in the efficacy supplement being reviewed.

The 14 AERS cases in which voriconazole was being administered intravenously at the time of the event were reviewed. Only 3 of the case narratives provided specific details on the timing of both the infusion and the event. Of those, only 1 indicated that the events occurred in close proximity to (actually during) the infusion. In the 2 other cases, the events occurred 6.5 and 7.5 hours after the infusions, respectively.

The case in which the events (bradycardia and asystole) occurred during infusion is presented below.

AERS # 4365727-9, Mfr # 2004021021, United Kingdom.

A 26-year-old female ICU patient, weighing 46 kg, with a medical history significant for past unspecified cardiac surgery and multiple organ failure, received intravenous voriconazole for an unknown indication. The patient experienced bradycardia and brief episodes of asystole (5-10 seconds) **during the first infusion of the drug**. Voriconazole was immediately discontinued and the patient was treated with atropine, but she experienced further episodes of asystole for 24 hours. Concomitant medications were stated to be unknown.

The 14 AERS cases did provide enough information to determine that, in general, arrhythmic events occurred sooner after starting intravenous administration than oral administration of voriconazole. The median time to onset in the cases involving only intravenous voriconazole was 3 days, versus 10 days in the cases involving only oral administration. None of the patients receiving voriconazole orally experienced an arrhythmia in the first day of therapy, but there were two such cases (including the case described above) among patients receiving the drug intravenously.

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QT INTERVAL CHANGES OF 60 MSEC OR MORE (N=2):
The DSPIDP consult request indicated that 11 of 50 voriconazole trial patients being monitored with EKGs experienced QT interval changes of 60 msec or more.

The 5 AERS cases of voriconazole-associated QT prolongation were reviewed. Only 3 of the narratives provided information on specific QT intervals. One of the 3 did not include a baseline interval, so no assessment of the change could be made.

The 2 AERS cases in which specific QT interval changes were reported are presented below. Both patients experienced ventricular arrhythmias[8]. Although both patients had QTc interval changes of more than 60 msec, the role of voriconazole in the etiology of the QT prolongation in the 1st case is unclear.

AERS # 4102137-3, Mfr # 2002068081, United States.

A 62-year-old female patient with acute myeloid leukemia received chemotherapy which included daunorubicin; her QTc interval around the time chemotherapy was started was 430 msec. The patient developed febrile neutropenia and was treated with unspecified antibiotics. Approximately 10 days later she was diagnosed with *Aspergillus flavus* and began treatment with liposomal amphotericin B. Intravenous voriconazole was later added, and the doses of both amphotericin and voriconazole were subsequently increased. Twelve days after starting voriconazole, congestive heart failure was diagnosed and amphotericin B was discontinued. Two days later the patient was discharged on oral voriconazole. Four days after that, she fainted while sitting after a long walk. She had another episode of syncope later that day and was readmitted; her QTc interval at that time was stated to be 400 msec. Her oral voriconazole was continued; her other admission medications were esomeprazole, phenytoin, furosemide, potassium chloride, ondansetron, lorazepam, hydroxyzine, and possibly magnesium gluconate. Phenytoin was later discontinued but metoprolol and captopril were started. The patient's ECG was monitored and her QTc interval 3 days after admission was noted to be 507 msec. She then experienced several episodes of **torsade de pointes** which were successfully treated with overdrive pacing. She was "slightly hypokalemic" and "slightly hypomagnesemic" (lab values provided ranged from 3.0 to 3.4 for potassium and 1.5 to 1.8 for magnesium around the time of the event). Voriconazole was switched to liposomal amphotericin B plus caspofungin, but QT prolongation lasted more than one week; 3 days after the event the QTc interval was stated to be 670 msec. The patient received an automatic implantable cardioverter/defibrillator (AICD). Voriconazole was later reintroduced but resulted in elevated alkaline phosphatase levels and was discontinued. However, given the life-threatening nature of the patient's fungal infection, voriconazole was rechallenged a second time. Alkaline phosphatase levels then remained normal and there were no arrhythmic triggers to the patient's AICD.

Pfizer consulted a cardiologist on the case and he indicated that it was difficult to evaluate the QT interval during the event due to the rapid heart rate; however, he stated that the tracings demonstrated "typical" or "classic" torsade de pointes. "The persistent profoundly abnormal QT interval 4 days after the event [*FDA note: and discontinuation of voriconazole*] makes it less likely that voriconazole played a large role. The patient may now have an acquired long-QT syndrome secondary to chemotherapy-related cardiomyopathy." The cardiologist stated that it was impossible to rule out voriconazole as a cause for the patient's torsade de pointes, but she was highly susceptible due to the two "very strong predisposing factors" of cardiomyopathy and hypokalemia.

AERS # 4038370-9, Mfr # 2002067191, United States.

A 53-year-old female patient with acute myeloid leukemia received high-dose cytarabine as salvage chemotherapy and developed neutropenia and a necrotic lesion on her breast. The pathology report on the lesion indicated that it was consistent with invasive aspergillosis; she also had 3 pulmonary nodules. She was treated with antibiotics and liposomal amphotericin B but did not improve. She was then started on voriconazole and her QTc interval was closely monitored. On admission it had been 447 msec and just prior to the initiation of voriconazole it was 460 msec. She was treated with intravenous voriconazole 300 mg BID for one day, then switched to oral drug at a dose of 200 mg BID. During that time her QTc interval stayed "about the same". Then the voriconazole dose was increased to 300 mg BID PO because the patient's necrotic lesion had progressed. Her QTc interval rose to 480 msec, then 490 msec, and finally 525 msec (on day 5 of the higher dose) and voriconazole was switched to caspofungin. The QTc interval returned to normal (460 msec) 3 days later. Voriconazole was reintroduced at a later date, approximately the same time as a peripherally inserted central cather (PICC) line was inserted. A prolonged QT interval was noted again and patient experienced a ventricular arrhythmia interpreted as **ventricular tachycardia**. Voriconazole was again discontinued and the PICC line was pulled. The patient did not experience any further arrhythmias.

ADDITIONAL ANALYSES:
The DSPIDP consult request mentioned only the temporal relationship of the arrhythmias to the voriconazole infusions, and QT prolongations of 60 msec or more. DDRE review of the 36 AERS cases (see **SUMMARY OF CASES**) showed that 12 had an outcome of death, 12 patients experienced cardiac arrest/asystole, and 14 developed ventricular arrhythmias. These life-threatening events were analyzed in greater detail.

[8] In 2 of the 3 remaining cases, the narratives did not indicate that the patients experienced any arrhythmias.

DEATHS (N=12):

Twelve of the 36 AERS cases had an outcome of death, but the role of voriconazole in the arrhythmias and/or the relationship of the arrhythmias to the deaths is unclear in most of the cases.

The case that appears the least confounded is summarized below.

AERS # 4048898-3, Direct report, United States.

A 32-year-old, 95-lb ("thin and wasted appearance") female patient had primary pulmonary proteinosis of 6 years' duration and longstanding heavy smoking and alcohol use. She received oral voriconazole 400 mg BID for one day, followed by 200 mg BID, for biopsy-proven pulmonary aspergillosis. On the second day at the lower dose, the patient suddenly collapsed with a nonshockable rhythm and had CPR for 35 minutes before return of a spontaneous heartbeat. She then showed signs of anoxic brain death and multiorgan failure. She required CPR on two more occasions that day and eventually could not be resuscitated. Her only reported concomitant medications were benzonatate, intravenous dexamethasone, intravenous potassium, and ipratropium; moxifloxacin had been discontinued the day voriconazole was started.

In 6 cases, voriconazole attributability in the reported events is difficult to determine.

One patient received an overdose of bortezomib and developed fever, chills, and hypotension followed by coma, metabolic acidosis, disseminated intravascular coagulation, liver dysfunction, anuria, electrolyte abnormalities, and ventricular fibrillation, leading to cardiac arrest and death. Voriconazole and 4 other co-suspect drugs were thought to be possibly responsible for the patient's hypotension, liver function abnormalities and/or ventricular fibrillation, but the report noted that death occurred "48 hours after administration of Velcade overdose".

Another patient had a potassium level of 7.4 mmol/L when he went into ventricular fibrillation on day 4 of oral voriconazole.

One patient was hospitalized for possible pneumonia; her blood pressure was 95/60 mm Hg on admission. She had esophageal candidiasis and CMV retinitis and was diagnosed with AIDS. She experienced a generalized tonic-clonic seizure before oral voriconazole (study drug) was started for her esophageal candidiasis. Despite treatment with volume expanders, her blood pressure remained unstable although she did not exhibit signs of sepsis. She died of cardiorespiratory arrest 10 days after admission. No autopsy was performed. The study sponsor considered the patient's arrest related to her underlying AIDS, although her hypotension was thought possibly to have resulted from an interaction between voriconazole and lorazepam.

One of the 3 patients experiencing sudden death had been treated with caspofungin on the same dates as voriconazole. His "significant denutrition" had improved while he was hospitalized, but he was found dead in bed after 10 days of treatment with both drugs. The autopsy did not show evidence of pulmonary or cerebral hemorrhage.

The 2nd sudden death occurred in a patient who had experienced a significant rise in his ALT and AST (from "around 60 U/L to thousands") within days of starting voriconazole. The drug had been discontinued and the patient's LFTs had improved, but he died suddenly of unknown cause before caspofungin could be started. The report did not indicate if an autopsy was performed.

The 3rd sudden death involved a patient who had been treated with voriconazole for 8 weeks. She had begun amiodarone for atrial fibrillation 12 days before voriconazole was started. She had pulmonary overload but no evidence of cardiomyopathy. She had seemed to be doing well and had been transferred to a rehabilitation center 12 days before she was found dead in bed. Autopsy revealed pulmonary edema but no evidence of myocardial infarction or clots. The reporter stated that an interaction between amiodarone and voriconazole could not be ruled out as the cause of death.

The relationship of the reported arrhythmias to the patient deaths is not clear in the 5 remaining cases.

In 4 of the 5 cases, voriconazole had been discontinued when arrhythmias developed; 2 of the reports specifically indicated that the arrhythmias abated after voriconazole discontinuation. The 4 patients later died at periods of from 7 to about 14 days after voriconazole was discontinued. In 3 of the cases the deaths were attributed only to the patients' underlying diseases. The 4th reporter indicated that voriconazole could possibly have been responsible for the fatal multiorgan failure and atrial fibrillation which developed 7 days after voriconazole was switched to caspofungin.

In the 5th case, voriconazole was still being administered when the patient died, but death was not attributed to the drug or the reported arrhythmia. The patient's potassium level was 3.4 (units unspecified) when he was hospitalized due to an irregular heart rate within 2 weeks of starting voriconazole. His potassium was corrected and his voriconazole dose was lowered by a third. He subsequently (exact timing not provided) was found to be in atrial fibrillation with a rapid ventricular rate; his potassium level was 4.1 at that time. Diltiazem was started and the patient experienced no further arrhythmias. However, he died within the same month; the cause of death was stated to be progression of his *Scedosporium* infection.

CARDIAC ARRESTS (N=12):
One of the 12 AERS cases of cardiac arrest/asystole is the case listed as least confounded under **DEATHS** (preceding page). Another relatively unconfounded case is the case presented under **TEMPORAL RELATIONSHIP TO IV INFUSION** on page 7, but concomitant medications were unknown.

Five other cardiac arrest cases are among the cases described under **DEATHS** (preceding page) in which the role of voriconazole is unclear.

The 5 remaining, nonfatal, cases of cardiac arrest/asystole also cannot clearly be attributed to voriconazole. Each case has confounding factors such as hyper-/hypokalemia or the lack of subsequent arrhythmias despite continued treatment with voriconazole.

One patient with acute myelogenous leukemia and suspected pulmonary aspergillosis received oral voriconazole at a dose of 200 mg/day. On day 12 of therapy she experienced ventricular tachycardia followed by cardiac arrest, received CPR, and recovered completely after 3 to 5 minutes. She was found to have hypokalemia and an increased QT interval. Voriconazole was discontinued 3 days later. No other information was provided.

Another patient had been on oral voriconazole for 9 days with no reported problems. Her potassium level was then noted to be 3.1 mmol/L, and potassium was given. Later that day she received a transfusion of 3 units of blood following chemotherapy for acute myeloid leukemia. "When the last blood unit was finished", the patient developed malaise followed by ventricular fibrillation/cardiac arrest. She was resuscitated but experienced persistent cognitive sequelae.

Another patient had been hyperkalemic on hospitalization and had been treated with sodium polystyrene sulfonate. Two days later (on day 3 of intravenous voriconazole) she experienced ventricular fibrillation with cardiorespiratory arrest and was resuscitated. Her potassium level was noted to be 1.7 mEq/L. She was treated with potassium but serum potassium levels were slow to return to normal; amphotericin-associated tubulopathy with urinary potassium leakage was diagnosed. Voriconazole treatment was continued since no acceptable therapeutic alternative was available, and the follow-up report from 2 months later did not mention any subsequent arrhythmias.

Another patient with acute myelogenous leukemia was stated to be receiving more than 10 concomitant medications. She had been treated with intravenous voriconazole (indication not provided) and was switched to oral drug on day 3. That day and the following day she experienced bradycardia leading to asystole and was resuscitated. Voriconazole was continued and no further arrhythmias developed, but the reporting physician indicated that there was no cause other than voriconazole for the events.

An 82-year-old patient with a complicated history including heart failure, coronary disease, hypertension, and unspecified arrhythmia was diagnosed with pulmonary aspergillosis. The report did not indicate that voriconazole treatment began while he was hospitalized, but stated that on discharge he was told to take the drug for 4 weeks. Six days later he was readmitted with dehydration, acute on chronic renal failure, elevated liver function tests, and hyperkalemia (K=6.5 mmol/L). He developed asystole with a hypoxic generalized seizure and was successfully resuscitated.

VENTRICULAR ARRHYTHMIAS (N=14):
The **PRECAUTIONS** section of the VFEND labeling addresses QT interval prolongation and torsade de pointes but does not mention other types of ventricular arrhythmia.

AERS contains only 4 cases of documented torsade de pointes in voriconazole-treated patients. Three of the patients each had at least 2 of the "multiple confounding risk factors" listed in the VFEND labeling. Such risk factors were not listed in the 4th case, but it appears to have been rather scantily reported. The case is presented below.

AERS # 4089192-4, Mfr # 2003006178, United States.

A 72-year-old, 220-lb female patient, whose only relevant history was listed as abdominal surgery one month prior, was started on intravenous voriconazole 400 mg BID for a resistant *Candida glabrata* peritoneal infection. She was also receiving aztreonam, vancomycin, metronidazole, and hydrocortisone; no other concomitant medications were listed on the report. Four days after starting voriconazole, the patient experienced torsade de pointes and was treated with amiodarone. The torsade resolved the same day. Voriconazole therapy was continued at the same dose; the report did not indicate if amiodarone was also continued.

In addition to the torsade cases, AERS contains 10 cases of other types of ventricular arrhythmia associated with voriconazole treatment.

One (ventricular tachycardia) was the 2nd case described under **QT INTERVAL CHANGES OF 60 MSEC OR MORE** on page 8. It was fairly unconfounded, with a positive dechallenge and positive rechallenge.

Two cases (both cases of ventricular fibrillation) were listed under **DEATHS** on page 9 as being among the cases in which voriconazole attributability in the events was difficult to assess. Two additional cases of ventricular fibrillation/cardiac arrest and one of ventricular tachycardia/cardiac arrest were described under **CARDIAC ARRESTS** on page 10. All 3 cases were confounded by hypokalemia. The timing in one case seemed to implicate blood transfusion as a possible cause, and another patient did not experience any further arrhythmias despite continued treatment with voriconazole.

The 4 remaining cases all had confounding factors such as pre-existing cardiac disease or concomitant medications known to cause ventricular arrhythmias.

One patient had congestive heart failure with an ejection fraction of 20% at the time he was hospitalized for recurrent syncope, one month after starting oral voriconazole. He was diagnosed with ventricular tachycardia and experienced 1 episode of ventricular fibrillation. An AICD was placed, because 2 more months of voriconazole therapy were needed.

Another patient had sinus tachycardia with a QTc interval of 463 msec [*FDA note: considered prolonged in a male*[9]] when he began treatment with IV voriconazole (study drug). Quinupristin/dalfopristin (a CYP 3A4 inhibitor) was added for 7 days. Three days after it was discontinued, the patient experienced a near-syncopal episode 7.5 hours after his voriconazole infusion. He had another episode 2 hours later, during which a monitor revealed 32 beats of wide complex ventricular tachycardia. He did not receive any treatment and experienced no further arrhythmias. Voriconazole was discontinued briefly but then restarted. The sponsor could not exclude an interaction between voriconazole and quinupristin/dalfopristin in the etiology of the tachycardia.

One patient was treated with IV voriconazole 600 mg BID (usually a single-day loading dose) for 4 days, then 400 mg BID for 1 day, and then PO at an unstated dose. Before and after starting voriconazole, "electrolyte decompensation with an elevation of sodium and potassium" were noted. The patient also had tachycardia and other unspecified arrhythmias before starting voriconazole. The report stated that "the patient experienced several episodes of non-sustained ventricular tachycardia and sinus tachycardia on unknown dates both caused by treatment with unspecified catecholamines". No other information was provided.

The final case involved a patient who received IV voriconazole and multiple other drugs labeled for various ventricular arrhythmias. He developed visual hallucinations and flashing lights in front of his eyes after 4 days on voriconazole. At an unstated time thereafter he developed abnormal liver function tests, disseminated intravascular coagulation, ventricular bigeminy, and ventricular ectopics. Voriconazole was discontinued after 1 week; 2 weeks later the DIC was stated to have resolved but the hallucinations and flashing lights had not resolved. No mention was made of the outcome of the ventricular arrhythmias.

[9] Liu BA, Juurlink DN. Drugs and the QT interval—Caveat doctor [editorial]. N Engl J Med **2004**;351:1053-4.

SUMMARY AND CONCLUSIONS:
A broad search of AERS for any type of arrhythmia, cardiac arrest, sudden death, or any electrocardiographic finding reported with voriconazole listed as a suspect drug identified 52 cases. After eliminating duplicates and irrelevant cases, this document summarizes 36 cases. More than half (20/36) of the reports were received from foreign countries. Ventricular arrhythmias (14 cases) were the most frequently reported type of arrhythmia; 2 additional patients were reported to have experienced QT prolongation with no mention of arrhythmia.

DSPIDP was especially concerned about the close temporal relationship of arrhythmic events to infusion of voriconazole in the efficacy supplement being reviewed. Few postmarketing reports had enough information to ascertain the exact temporal relationship. Only 3 of the AERS cases provided enough detail, and in 2 of the cases the events occurred more than 6 hours after the voriconazole infusions. A summary has been provided of the case which was stated to have occurred in close temporal relationship; the patient experienced bradycardia and asystole during her 1st infusion of voriconazole. The median time to onset in the cases involving intravenous voriconazole was 3 days, versus 10 days in the cases involving only oral administration. In addition, none of the patients receiving voriconazole orally experienced an arrhythmia during the first day of therapy, but there were two such cases among patients receiving the drug intravenously.

Another DSPIDP concern was the fact that 11 of 50 patients who had EKG monitoring while being treated with voriconazole developed QT interval prolongation of 60 msec or more. The FDA has only received 5 postmarketing reports of voriconazole-associated QT interval prolongation, and only 2 of them had baseline QT intervals reported. In both cases the QTc interval increased by more than 60 msec. However, the role of voriconazole in 1 of the cases was unclear; QT prolongation lasted more than a week after the drug was discontinued, and there were no arrhythmic triggers to the patient's AICD when it was reintroduced.

In addition to the specific concerns raised by DSPIDP, the AERS cases resulting in death, the cardiac arrests, and the cases of ventricular arrhythmia were reviewed in detail. Although there were 12 deaths among the 36 cases, the relationship of the deaths to the reported arrhythmias was unclear in 5 cases, and voriconazole relationship to the arrhythmias/arrests/sudden deaths was difficult to determine in 6 additional cases. Similarly, among the 12 cases of either fatal or nonfatal cardiac arrest, only 2 appeared relatively unconfounded and 1 of those was incompletely reported.

Among the 14 reported cases of ventricular arrhythmia, 4 were cases of torsade de pointes. Three of the 4 cases definitely had at least 2 of the "multiple confounding risk factors" currently mentioned in the VFEND labeling, and the information in the 4th case may not have been complete. One report of ventricular tachycardia was relatively unconfounded. The 9 remaining cases of ventricular arrhythmia all had confounding factors such as hypokalemia, pre-existing cardiac disease, or concomitant medications known to cause ventricular arrhythmia, making the role of voriconazole difficult to assess.

However, voriconazole cannot be ruled out as the cause in any of the 36 AERS cases. DDRE therefore recommends that the **PRECAUTIONS** sections of the VFEND labeling, which currently addresses only QT prolongation and torsade de pointes, be amended. Proposed wording based on the current labeling is provided below, with deletions indicated by strike-through and additions underlined.

PRECAUTIONS

~~**General**~~ **Arrhythmias and QT prolongation**

Some azoles, including voriconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During clinical development and post-marketing surveillance, there have been rare cases of arrhythmias, (including ventricular arrhythmias such as torsade de pointes), cardiac arrests, and sudden deaths in patients taking voriconazole. These ~~reports~~ cases usually involved seriously ill patients with multiple confounding risk factors, such as history of cardiotoxic chemotherapy, cardiomyopathy, hypokalemia and concomitant medications that may have been contributory.

REVIEWER'S SIGNATURE / DATE:	TEAM LEADER'S SIGNATURE / DATE:
/S/ 10/1/04	/S/ 10/1/04
Sarah J. Singer, R.Ph.	Melissa M. Truffa, R.Ph.
DIVISION DIRECTOR'S SIGNATURE / DATE:	
/S/ 10/1/04	
Mark Avigan, M.D., Director	

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/s/

Sarah Singer
10/1/04 02:38:43 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
10/1/04 04:39:51 PM
DRUG SAFETY OFFICE REVIEWER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21-266/S009
NDA 21-267/S009
NDA 21-630/S003

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY CHECKLIST

Name of Drug Product	NDA	Supplement Number
VFEND® (voriconazole) Tablets, 50 mg and 200 mg	21-266	S-009
VFEND® I.V. (voriconazole) for Injection	21-267	S-009
VFEND® (voriconazole) for Oral Suspension	21-630	S-003

Applicant Name: Pfizer, Inc. HFD # 590

Approval Date If Known: December 21, 2004

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_X_/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

d) Did the applicant request exclusivity?

YES /_X_/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____3_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X_/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

Name of Drug Product	NDA
VFEND® (voriconazole) Tablets, 50 mg and 200 mg	21-266
VFEND® I.V. (voriconazole) for Injection	21-267
VFEND® (voriconazole) for Oral Suspension	21-630

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.) IF “YES” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not

independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain:

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

#1 Study 150-608

#2 Study 150-309/604

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency

to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

Investigation #2 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

#1 Study 150-608

#2 Study 150-309/604

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the

study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # (b) (4) YES /_X_/ ! NO /___/ Explain: _____
IND # 50,410
IND # 66,410

Investigation #2 !

IND # (b) (4) YES /_X_/ ! NO /___/ Explain: _____
IND # 50,410
IND # 66,410

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? N/A

Investigation #1 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X_/

If yes, explain: _____

_____

_____
Rebecca D. Saville, Pharm.D
Regulatory Project Manager, DSPIDP

_____
Renata Albrecht, M.D.
Division Director, DSPIDP

Form OGD-011347 Revised 05/10/2004

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

/s/

Rebecca Saville
12/21/04 12:52:00 PM

Renata Albrecht
12/21/04 05:11:32 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # /Supplement Number: NDA 21-266/S-009, NDA 21-267/S-009, and NDA 21-630/S-003

Supplement Type (e.g. SE5): SE-1

Stamp Date: March 16, 2004 **Action Date:** January 16, 2005

HFD 590

Trade and generic names/dosage form:

Name of Drug Product	NDA	Supplement Number
VFEND® (voriconazole) Tablets, 50 mg and 200 mg	21-266	S-009
VFEND® I.V. (voriconazole) for Injection	21-267	S-009
VFEND® (voriconazole) for Oral Suspension	21-630	S-003

Applicant: Pfizer, Inc. **Therapeutic Class:** Anti-fungal

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 3

Indication #1: Invasive aspergillosis

Is there a full waiver for this indication (check one)?

☐ **Yes: Please proceed to Section A.**

☒ **No: Please check all that apply: ____Partial Waiver __X_ Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

0-2 years of age deferred
2-16 years of age deferred

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ☒ **Other:** Studies in the 2-16 year age group are currently being conducted

Date studies are due (mm/dd/yy): 12-31-2007

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2:
Serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* spp., including *Fusarium solani*, in patients intolerant of or refractory to other therapy

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**

X No: Please check all that apply: ____Partial Waiver __x__Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:_____**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

0-2 years of age deferred
2-18 years of age deferred

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☒ **Other:** Studies in the 2-16 year age group are currently being conducted

Date studies are due (mm/dd/yy): 12/31/2007

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

Indication #3: Esophageal Candidiasis

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**

X No: Please check all that apply: ____Partial Waiver _X_Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

0-2 years of age deferred
2-16 years of age deferred

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☒ **Other:** Studies in the 2-16 year age group are currently being conducted

Date studies are due (mm/dd/yy): 12/31/2007

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

This page was completed by:

{See appended electronic signature page}

Rebecca D. Saville
Regulatory Project Manager

cc: NDA 21-266/S-009
NDA 21-267/S-009
NDA 21-630/S-003
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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/s/

Rebecca Saville
5/12/04 07:05:50 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # /Supplement Number: NDA 21-266/S-009, NDA 21-267/S-009, and NDA 21-630/S-003

Supplement Type (e.g. SE5): SE-1

Stamp Date: March 16, 2004 **Action Date:** December 21, 2004

HFD 590

Trade and generic names/dosage form:

Name of Drug Product	NDA	Supplement Number
VFEND® (voriconazole) Tablets, 50 mg and 200 mg	21-266	S-009
VFEND® I.V. (voriconazole) for Injection	21-267	S-009
VFEND® (voriconazole) for Oral Suspension	21-630	S-003

Applicant: Pfizer, Inc. **Therapeutic Class:** Anti-fungal

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Non-neutropenic Candidemia and the following *Candida* infections: disseminated infections in skin (b) (4) and infections in abdomen, kidneys, bladder wall, and wounds

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☒ **No: Please check all that apply: ____Partial Waiver __X_ Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

0-2 years of age deferred
2-16 years of age deferred

Min _____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ☒ **Other:** Studies in the 2-16 year age group are currently being conducted

Date studies are due (mm/dd/yy): 12-31-2007

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Invasive aspergillosis

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☒ **No: Please check all that apply: ____Partial Waiver __X_ Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

0-2 years of age deferred
2-16 years of age deferred

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ☒ **Other:** Studies in the 2-16 year age group are currently being conducted

Date studies are due (mm/dd/yy): 12-31-2007

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Indication #3:
Serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* spp., including *Fusarium solani*, in patients intolerant of or refractory to other therapy

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**

X No: Please check all that apply: ____Partial Waiver __x__Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**

- ❑ **There are safety concerns**
- ❑ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

0-2 years of age deferred
2-18 years of age deferred

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☒ **Other:** Studies in the 2-16 year age group are currently being conducted

Date studies are due (mm/dd/yy): 12/31/2007

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

Indication #4: Esophageal Candidiasis

Is there a full waiver for this indication (check one)?

- ❑ **Yes: Please proceed to Section A.**

X No: Please check all that apply: ____Partial Waiver _X__Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Other:_____**

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**

- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

0-2 years of age deferred
2-16 years of age deferred

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☒ **Other:** Studies in the 2-16 year age group are currently being conducted

Date studies are due (mm/dd/yy): 12/31/2007

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

This page was completed by:

{See appended electronic signature page}

_____
Rebecca D. Saville
Regulatory Project Manager

cc: NDA 21-266/S-009
NDA 21-267/S-009
NDA 21-630/S-003
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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/s/

Rebecca Saville
12/21/04 04:24:42 PM

MEMORANDUM OF TELECON

DATE: **December 15, 2004**
TIME: **2:30 p.m. EST**

APPLICATION NUMBER:

NDA 21-266/S-009 VFEND (voriconazole) Tablets, 50 mg (b) (4)
NDA 21-267/S-009 VFEND I.V. (voriconazole) for Injection
NDA 21-630/S-003 VFEND (voriconazole) for Oral Suspension

BETWEEN:

Pfizer, Inc.
Maureen H. Garvey, Ph.D., Senior Director, Worldwide Regulatory Strategy
Mike Hodges, M.D., Clinical, UK
Iwonka Oborska, M.D., Clinical, UK
Haran Schlamm, Clinical, NY
Bob Swanson, Clinical, NY
Justine King, Regulatory Affairs, NY

AND

Division of Special Pathogen and Immunologic Drug Products
Renata Albrecht, M.D., Division Director
Marc Cavaille-Coll, M.D., Ph.D., Clinical Team Leader
Cheryl Dixon, Ph.D., Biometrics Reviewer, DB-3
Shukal Bala, Ph.D., Microbiology Team Leader
Kala Suvarna, Ph.D., Microbiology Reviewer
Rebecca D. Saville, Pharm.D., Regulatory Project Manager

SUBJECT: Labeling Discussion

Teleconference December 15, 2004

BACKGROUND AND DISCUSSION:
Pfizer submitted efficacy supplements for candidemia (b) (4) on March 15, 2004. The Division proposed text for the labeling, which was sent to Pfizer on December 6, 2004. Pfizer submitted draft labeling and a table summarizing their counter-revisions and corresponding rationale on December 14, 2004. The Division coordinated this teleconference with Pfizer to communicate our comments on each counter-revision. These comments are indicated in a column that has been added to Pfizer's table.

On December 14, 2004, the Division had provided recommendations to Pfizer from ODS to revise the PRECAUTIONS section of the labeling in order to strengthen safety information pertaining to arrhythmias and QT prolongation. Pfizer indicated that the revision of the PRECAUTIONS section was acceptable.

(b) (4)

5 Pages Immediately Follow Withheld - Draft Labeling b(4)

ACTION ITEMS:

- Pfizer agreed to provide a (b) (4)

- Pending the review of the submission from Pfizer on December 17, 2004, the Division will coordinate another teleconference to discuss the findings and to finalize labeling for voriconazole.

_____
Rebecca D. Saville, Pharm.D.
Regulatory Project Manager

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/s/

Rebecca Saville
12/21/04 12:46:20 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: December 14, 2004

To: Maureen H. Garvey	**From:** Rebecca Saville
Company: Pfizer, Inc.	Division of Special Pathogen and Immunologic Drug Products
Fax number: 646-441-5735	**Fax number:** 301-827-2475
Phone number: 212-733-5688	**Phone number:** 301-827-2127

Subject: Draft Labeling for NDA 21-266/S-009, NDA 21-267/S-009, and NDA 21-630/S-003 Voriconazole Candidemia

Total no. of pages including cover: 3

Comments:

Concurrence:

Renata Albrecht, M.D, Division Director
Marc Cavaille-Coll, M.D., Ph.D., Clinical Team Leader

Document to be mailed: YES ☑ NO

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NDA 21-266/S-009
NDA 21-267/S-009
NDA 21-630/S-003

Dear Dr. Garvey,

Please refer to NDA 21-266/S-009, NDA 21-267/S-009, and NDA 21-630/S-003 for VFEND® (voriconazole) Tablets, Injection, and Oral Solution, respectively, submitted March 15, 2004, received March 16, 2004.

As part of the clinical review of these supplements, the Division requested a postmarketing safety review from the Office of Drug Safety addressing cardiac arrhythmias and QT prolongation. Based on this review, we recommend revision of the labeling to strengthen the PRECAUTIONS section. The Division's proposed deletions (~~double strikethrough~~) and additions (double underline) are summarized as follows:

1. Revision of the PRECAUTIONS section as indicated:

~~General~~ Arrhythmias and QT prolongation

Some azoles, including voriconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During clinical development and post-marketing surveillance, there have been rare cases of arrhythmias, (including ventricular arrhythmias such as torsade de pointes), cardiac arrests, and sudden deaths in patients taking voriconazole. These ~~reports~~ cases usually involved seriously ill patients with multiple confounding risk factors, such as history of cardiotoxic chemotherapy, cardiomyopathy, hypokalemia and concomitant medications that may have been contributory.

We are providing these comments via telephone facsimile and email for your convenience. Please acknowledge receipt. Please contact me at 301-827-2127 if you have any questions regarding the contents of this transmission.

Regards,

Rebecca D. Saville, Pharm.D.
Regulatory Project Manager

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/s/

Rebecca Saville
12/14/04 03:50:16 PM
CSO
NDA 21-266/S-009, NDA 21-267/S-009, and NDA 21-630/S-003

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: December 10, 2004

To: Maureen H. Garvey	**From:** Rebecca Saville
Company: Pfizer, Inc.	Division of Special Pathogen and Immunologic Drug Products
Fax number: 646-441-5735	**Fax number:** 301-827-2475
Phone number: 212-733-5688	**Phone number:** 301-827-2127

Subject: Draft Labeling for NDA 21-266/S-009, NDA 21-267/S-009, and NDA 21-630/S-003 Voriconazole Candidemia

Total no. of pages including cover:

Comments:

Concurrence:

Marc Cavaille-Coll, M.D., Ph.D., Clinical Team Leader

Document to be mailed: " YES ☑ NO

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NDA 21-266/S-009
NDA 21-267/S-009
NDA 21-630/S-003

Dear Dr. Garvey,

Please refer to NDA 21-266/S-009, NDA 21-267/S-009, and NDA 21-630/S-003 for VFEND® (voriconazole) Tablets, Injection, and Oral Solution, respectively, submitted March 15, 2004, received March 16, 2004.

Please also refer to your email of December 9, 2004.

Pfizer Question: "Will you please identify the 2 patients with intraabdominal infections and the single patient with kidney and bladder wall infection who were removed from the paragraph about favorable response at various sites of infection? The paragraph begins "In Studies 608 and 309/604 (non comparative study..." Also, will you please share your reasons for deleting these patients?"

Two cases from the mycologically confirmed subset of intraabdominal infections from Study 309/608 were counted as successes by Pfizer; however, we disagree and counted these cases as failures. Patient #604-10716034 was treated with voriconazole for 4 days for *C. albicans* peritonitis then switched to amphotericin B and fluconazole. The patient died on day #10 from multi-organ failure and sepsis. Patient# 604-10916126 grew a mix of *C. glabrata* and *C. albicans* from bile and was withdrawn by the family from study. The patient died during active treatment day #16. Therefore, 2/7 is the corresponding success rate for intraabdominal infection according to the primary clinical reviewer's assessment.

We agree with your assessment of the three cases of kidney and bladder wall infection in study 150-608. Out of the three subjects that you identified, we agree with you that two out of the three cases were successes.

Of the three subjects identified in the group of mycologically confirmed cases from Study 309/604, we agree with two of the cases, one with *C. krusei* invasive bladder infection and one with *C. tropicalis*. However, we do not agree with the third case. The primary clinical reviewer classified this case as indeterminate and not a success, due to what he felt was a lack of clarity in the case report form about further antifungal treatment, presence of fever, elevated white cell count, and abnormal imaging studies of the kidney, meaning that there was possible evidence that the infection had not resolved.

Therefore, we disagree with Pfizer that the three subjects identified in Study 309/604 were successes and conclude that only two of the three were successes.

We totaled the number of successes to be 4 out of a total of 6 cases, and not 5 out of 6. The difference is due to the one subject in Study 309/604 mentioned above. The primary clinical reviewer did not include the patient ID number in his draft review, but the information in the paragraph above should allow you to identify the one patient out of three by process of elimination.

We are providing these comments via telephone facsimile and email for your convenience. Please acknowledge receipt. Please contact me at 301-827-2127 if you have any questions regarding the contents of this transmission.

Regards,

Rebecca D. Saville, Pharm.D.
Regulatory Project Manager

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/s/

Rebecca Saville
12/10/04 03:52:56 PM
CSO
NDA 21-266/S-009, NDA 21-267/S-009, and NDA 21-630/S-003

MEMORANDUM OF TELECON

DATE: December 9, 2004
TIME: 3:30 p.m. EST

APPLICATION NUMBER:

NDA 21-266/S-009 VFEND (voriconazole) Tablets, 50 mg (b) (4)
NDA 21-267/S-009 VFEND I.V. (voriconazole) for Injection
NDA 21-630/S-003 VFEND (voriconazole) for Oral Suspension

BETWEEN:

Pfizer, Inc.

Maureen H. Garvey, Ph.D., Senior Director, Worldwide Regulatory Strategy, US
Iwonka Oborska, M.D., Clinical, UK
Bob Swanson, M.D., Clinical, US
Vera Muzrithas, Regulatory Affairs

AND

Division of Special Pathogen and Immunologic Drug Products

Marc Cavaille-Coll, M.D., Ph.D., Clinical Team Leader
Rebecca D. Saville, Pharm.D., Regulatory Project Manager

SUBJECT: Cardiac Monitoring (Response Dated September 30, 2004)

BACKGROUND:

Pfizer submitted efficacy supplements for candidemia (b) (4) on March 15, 2004. Theses efficacy supplements are supported by Study 150-608, a randomized, comparative trial in patients with candidemia. Pfizer also submitted results from Study 150-309/604, a non-comparative trial in patients with invasive fungal infections who received voriconazole as primary or salvage therapy.

During teleconferences conducted on September 3, 2004 and September 10, 2004, the Division requested that Pfizer address two issues that were identified during the clinical review. One of the review issues pertained to the observed increase in cardiac monitoring that was performed in subjects enrolled in the voriconazole treatment arm as compared to those subjects enrolled in the amphotericin B/fluconazole arm. During the September 10, 2004 teleconference, Pfizer provided an acceptable rationale. The Division requested that Pfizer submit the rationale in

writing and provide a summary of the extent of cardiac monitoring that was performed. On September 30, 2004, Pfizer submitted this information in a clinical amendment.

Upon review of the clinical amendment, the secondary reviewer needed to clarify that his interpretation of the information presented in the clinical amendment dated September 30, 2004 was correct. The Division coordinated this teleconference to provide the opportunity for discussion with Pfizer.

SUMMARY OF DISCUSSION:

Dr. Cavaille-Coll initiated discussion by acknowledging that the rationale and summary of cardiac monitoring information presented in the submission dated September 30, 2004 adequately addressed the Division's concern about the observed increase in cardiac monitoring in subjects enrolled in the voriconazole treatment arm as compared to the subjects in the amphotericin B arm.

The Division and Pfizer discussed that the protocol amendment dated May 6, 1999 to Study 150-608 was intended to address safety concerns associated with subjects at risk for cardiac arrhythmias and QT prolongation. A formal comparative investigation of the effect of treatment drug on QTc was not the purpose. During the teleconference, tables summarizing the cardiac monitoring data were reviewed together by Pfizer and the Division. Dr. Cavaille-Coll was able to verify that he was not incorrectly interpreting the tables in Section 11.Item 11. These tables list the EKG results, and the QTcB, QTcF, heart rate, and RR interval were summarized by day and time. He noted an increase in the number of EKGs performed occurred after the implementation of cardiac monitoring mandated by the protocol amendment.

Dr. Cavaille-Coll indicated he was comfortable that an increased awareness of the cardiac risks associated with the use of voriconazole caused the incorporation of mandatory cardiac monitoring in the study protocol. He felt this was a reasonable explanation for the increased numbers of EKGs that were performed in subjects in the voriconazole treatment arm of Study 150-608.

ACTION ITEMS: N/A

_____

Rebecca D. Saville, Pharm.D.
Regulatory Project Manager

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/s/

Rebecca Saville
12/15/04 02:09:21 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: December 6, 2004

To: Maureen H. Garvey	**From:** Rebecca Saville
Company: Pfizer, Inc.	Division of Special Pathogen and Immunologic Drug Products
Fax number: 646-441-5735	**Fax number:** 301-827-2475
Phone number: 212-733-5688	**Phone number:** 301-827-2127

Subject: Draft Labeling for NDA 21-266/S-009, NDA 21-267/S-009, and NDA 21-630/S-003 Voriconazole Candidemia

Total no. of pages including cover:

Comments:

Concurrence:

Renata Albrecht, M.D, Division Director
Marc Cavaille-Coll, M.D., Ph.D., Clinical Team Leader
Sary Beidas, M.D., Clinical Reviewer
Cheryl Dixon, Ph.D., Statistics Reviewer, DB-3
Shukal Bala, Ph.D., Microbiology Team Leader
Kala Suvarna, Ph.D., Microbiology Reviewer

Document to be mailed: YES ☑ NO

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Dear Dr. Garvey,

Please refer to NDA 21-266/S-009, NDA 21-267/S-009, and NDA 21-630/S-003 for VFEND® (voriconazole) Tablets, Injection, and Oral Solution, respectively, submitted March 15, 2004, received March 16, 2004.

Attached electronically, please find draft labeling for your review. This working version of the labeling incorporates Pfizer's proposals (indicated with single underline) and the Division's proposed deletions (~~double strikethrough~~) and additions (double underline).

The Division's proposed revisions and acceptance of your proposals are summarized as follows:

1. The proposed addition of *C. parapsilosis* and *C. tropicalis* to the **MICROBIOLOGY** section is acceptable.

2. (b) (4)

3. (b) (4)

1 Page Immediately Following Withheld - Draft Labeling b(4)

(b) (4)

We are providing these comments via telephone facsimile and email for your convenience. Please acknowledge receipt. Please contact me at 301-827-2127 if you have any questions regarding the contents of this transmission.

Regards,

Rebecca D. Saville, Pharm.D.
Regulatory Project Manager

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/s/

Rebecca Saville
12/6/04 06:19:19 PM
CSO
NDA 21-266/S-009, NDA 21-267/S-009, and NDA 21-630/S-003

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM:
Iris Masucci, Pharm.D., BCPS Labeling Reviewer DDMAC, HFD-42	Rebecca Saville Project Manager DSPIDP (HFD-590)

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
November 16, 2004		NDA 21-266/S-009 NDA 21-267/S-009 NDA 21-630/S-003	Efficacy Supplement – New Indication (b) (4) Candidiasis	March 15, 2004

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
VFEND (voriconazole)	High	Anti-fungal	December 3, 2004

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☒ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review proposed new text in the voriconazole labeling. I can provide you with a WORD version of the labeling. Please contact me at 301-827-2387 or email (saviller@cder.fda.gov) for anything to facilitate your review. The submission and labeling can be found in the EDR at the following link. Thank you.

The EDR has received an Electronic Document on NT DLT 40/80 GB for division HFD-590:
NDA # N21266
Incoming Document Type: SE1
Incoming Document Type Sequence Number: 009
Supplement Modification Type:
Letter Date: 3/15/2004
The network path location is: \\CDSESUB1\N21266\S_009\2004-03-15

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Rebecca Saville, Pharm.D.	☐ E-MAIL ☐ HAND

SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Rebecca Saville
11/16/04 03:26:41 PM

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV

FACSIMILE TRANSMITTAL SHEET

DATE: September 17, 2004

To: Maureen Garvey, Ph.D.	**From:** Kristen Miller, Pharm.D.
Company: Pfizer	Division of Special Pathogen and Immunologic Drug Products
Fax Number: 212-857-3558	**Fax Number:** 301-827-2475
Phone Number: 212-573-4471	**Phone Number:** 301-827-2127

Subject: Microbiology request

Total no. of pages including cover:

Comments: Concurrence:
Kalavati Suvarna, Ph.D. Microbiology Reviewer

Document to be mailed: " YES ☑ NO

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Please refer to study 150-608. The microbiology reviewer has the following requests for information:

1. The section entitled "Written Summary of Mycology Data from the Global Candidemia Study Protocol 150-608" makes several references to the 608 CSR Mycology Statistical Report. We are unable to locate this report. If the report was submitted to the NDA, please indicate its location in the NDA. Otherwise, please provide a copy of the 608 CSR Mycology Statistical Report.

2. There is discrepancy in the baseline pathogen listed in the "clnmicro.xpt" dataset and the case report form for the patients listed in Table 1. Please indicate whether the pathogen listed in the case report forms or the clnmicro.xpt dataset is the true baseline pathogen in these patients and clarify the reasons for the discrepancy.

Table 1: Patients in study 150-608 with discrepant baseline pathogens.

Patient ID	**Baseline pathogen**	
	clnmicro.xpt	**Case report forms**
608 03470252	*Candida albicans*	*Candida albicans* + *Candida glabrata*
608 03690250	*Candida albicans*	*Candida tropicalis*
608 03690315	*Candida albicans*	*Candida glabrata*
608 23140418	*Candida glabrata*	*Candida glabrata* + *Candida parapsilosis*
608 24440390	*Candida albicans*	*Candida albicans* + *Candida krusei*
608 50470308	Yeast	*Candida glabrata*
608 50940033	*Candida glabrata*	*Candida tropicalis* + *Candida glabrata*
608 51020244	*Candida glabrata*	*Candida guillermondii* + *Candida glabrata*
608 51020376	*Candida parapsilosis*	*Candida parapsilosis* + *Candida lusitaniae*
608 51040141	*Candida tropicalis*	*Candida tropicalis* + *Candida albicans*
608 51050194	*Candida albicans*	*Candida tropicalis*
608 51330149	*Candida* species	*Candida rugosa*+ *Candida* species
60851330152	None	*Candida* species
608 60070362	*Candida albicans*	*Candida albicans* + *Candida glabrata*

We are providing the above information via telephone facsimile for your convenience. Please feel free to contact me at 301-827-2127 if you have any questions regarding the contents of this transmission.

Kristen Miller, Pharm.D.
for Rebecca Saville, Pharm.D.
Regulatory Project Manager

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/s/

Rebecca Saville
9/21/04 10:56:04 AM
CSO
NDA 21-266, NDA 21-267, and NDA 21-630

MEMORANDUM OF TELECON

DATE: September 8, 2004
TIME: 4:00 p.m. EST

APPLICATION NUMBER:

NDA 21-266/S-009 VFEND (voriconazole) Tablets, 50 mg (b) (4)
NDA 21-267/S-009 VFEND I.V. (voriconazole) for Injection
NDA 21-630/S-003 VFEND (voriconazole) for Oral Suspension

BETWEEN:

Pfizer, Inc.

Maureen H. Garvey, Ph.D., Senior Director, Worldwide Regulatory Strategy
Mike Hodges, M.D., Clinical, UK
Iwonka Oborska, M.D., Clinical, UK
Haran Schlamm, Clinical, NY
Fiona Hilton, Statistics, UK
Nolan Wood, Clinical Pharmacology, UK
Peter Troke, Clinical Microbiologist, UK
Justine King, Regulatory Affairs, NY

AND

Division of Special Pathogen and Immunologic Drug Products

Renata Albrecht, M.D., Division Director
Marc Cavaille-Coll, M.D., Ph.D., Clinical Team Leader
Sary Beidas, M.D., Clinical Reviewer
Cheryl Dixon, Ph.D., Biometrics Reviewer, DB-3
Philip Colangelo, Pharm.D., Ph.D., Clin. Pharm. and Biopharm. Team Leader, DPE-3
Gerlie De Los Reyes, Ph.D., Clin. Pharmacology and Biopharmaceutics Reviewer
Jenny Zheng, Pharmacometrician, OCPB
Rebecca D. Saville, Pharm.D., Regulatory Project Manager
Keith Bockhold, Pharm.D. Candidate, Visiting Student, Univ. of Illinois, Chicago

SUBJECT: Information Requests from Clinical and Clinical Pharmacology and Biopharmaceutics

BACKGROUND AND DISCUSSION:

Pfizer submitted efficacy supplements for candidemia (b) (4) on March 15, 2004. Reviews have been progressing without any major issues. The Division coordinated this

teleconference with Pfizer to discuss minor issues that were identified during the clinical review. These issues were presented as requests for information during a teleconference conducted with Pfizer on September 3, 2004. In addition, the Clinical Pharmacology and Biopharmaceutics reviewers addressed deficiencies in the PK evaluation.

Following introductions, the Division proceeded with each issue described below. Discussion points follow each issue:

1. During the evaluation of special populations by gender, females in the voriconazole arm of the study did not respond as well as males (females receiving voriconazole = 33% vs. males receiving voriconazole = 46%, females receiving amphotericin B = 43%, and males receiving amphotericin B = 38%). The Division requested a sensitivity analysis exploring why these women had a decreased success rate at the primary endpoint.

    - Pfizer acknowledged the gender difference and explored several reasons including similar survival rates at day 98, similar two day median time to blood culture clearing, similar voriconazole plasma levels, no obvious differences in baseline demographics, and no differences in investigator response rates. No gender differences were observed in a review of the safety profiles. They concluded that these reasons were unlikely the cause of the observed difference in the response rates between the genders. Pfizer indicated that the difference in the investigator response rates at end of therapy was similar and the differences arose during the 12-week follow up period. They suggested that during the 12-week follow-up period perhaps more females were assessed as treatment failures because of a combination of factors including relapse, loss to follow up, or taking concomitant antifungals.

    - Pfizer agreed to submit this rationale in writing.

2. In Study 150-608, more EKGs were performed in patients enrolled in the voriconazole arm than in the amphotericin B (n = 50 in the voriconazole arm and n = 13 in the amphotericin B arm). The Division requested an explanation. The Division also requested more information about the cardiac monitoring including a description of the process and what risk factors did the monitored patients have.

    - Following the death of a study participant following an incident of ventricular fibrillation, Pfizer indicated that cardiac monitoring was mandatory for all patients at risk of cardiac arrhythmias and was requested for patients receiving regular EKGs as part of their routine clinical care in the hospital. These requirements were incorporated into the protocol with a protocol amendment to Study 150-608 dated May 6, 1999. Upon analysis, Pfizer concluded that patients receiving voriconazole received more cardiac monitoring most likely due to the heightened awareness of the investigators to cardiac safety issues related to the use of voriconazole following the protocol amendment.

    - Pfizer agreed to submit a summary of the extent of cardiac monitoring that was performed before and after the amendment was implemented.

3. The Division indicated that using mean plasma concentration data without appropriate documentation of the timing of PK sample collection to represent the exposure for individual patients in the PK/PD analysis was not appropriate.

   - The apparent difference in the mean plasma concentration between patients may result from the true difference in exposure between patients or the difference in sampling time between patients. The Division indicated that use of the mean plasma concentration data without appropriate documentation of the timing of PK sample collection is not recommended in future analyses.

   - The Division inquired why a population PK study was not performed. Pfizer indicated that they didn't have both end of week 1 and end of week 2 samples and not enough data were derived for a population PK study.

   - Pfizer recognized that not enough data for a correlation was collected (b) (4)

ACTION ITEMS:

- Pfizer will submit a rationale for the observed gender differences in the response rate.

- Pfizer agreed to submit a summary of the extent of cardiac monitoring that was performed before and after the amendment was implemented.

- The Division will request a postmarketing safety review of cardiac arrhythmias and QT prolongation from the Office of Drug Safety.

_____

Rebecca D. Saville, Pharm.D.
Regulatory Project Manager

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/s/

Rebecca Saville
12/17/04 06:21:56 PM
CSO

MEMORANDUM OF TELECON

DATE: September 3, 2004
TIME: 11:00 a.m. EST

APPLICATION NUMBER:

NDA 21-266/S-009 VFEND (voriconazole) Tablets, 50 mg (b) (4)
NDA 21-267/S-009 VFEND I.V. (voriconazole) for Injection
NDA 21-630/S-003 VFEND (voriconazole) for Oral Suspension

BETWEEN:

Pfizer, Inc.

Maureen H. Garvey, Ph.D., Senior Director, Worldwide Regulatory Strategy

AND

Division of Special Pathogen and Immunologic Drug Products

Marc Cavaille-Coll, M.D., Ph.D., Clinical Team Leader
Sary Beidas, M.D., Clinical Reviewer
Rebecca D. Saville, Pharm.D., Regulatory Project Manager
Keith Bockhold, Pharm.D. Candidate, Visiting Student, Univ. of Illinois, Chicago

SUBJECT: Agenda Items (Information Requests) for Upcoming Teleconference

BACKGROUND AND DISCUSSION:

Pfizer submitted efficacy supplements for candidemia (b) (4) on March 15, 2004. Reviews have been progressing without any major issues. The Division coordinated this teleconference with Pfizer to discuss several minor issues that were identified during the clinical review. These issues, as listed below, are requests for information and will also serve as agenda items for a teleconference scheduled to occur at 4:00 p.m. EST on September 8, 2004.

The Division initiated this teleconference, and following introductions, proceeded to provide the following information requests:

- During the evaluation of special populations by gender, females in the voriconazole arm of the study did not respond as well as males. The Division requested a sensitivity analysis exploring why these women had a decreased success rate.

- In Study 150-608, more EKGs were performed in patients enrolled in the voriconazole arm than in the amphotericin B (n = 50 in the voriconazole arm and n = 13 in the amphotericin B

arm). The Division requested an explanation. The Division also requested more information about the cardiac monitoring including a description of the process and what risk factors did the monitored patients have.

ACTION ITEMS:

A teleconference will be conducted between Pfizer and DSPIDP on Wednesday, September 8, 2004 to discuss these requests.

_____

Rebecca D. Saville, Pharm.D.
Regulatory Project Manager

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/s/

Rebecca Saville
12/15/04 02:27:39 AM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**REQUEST FOR CONSULTATION**

TO *(Division/Office)*: **Office of Drug Safety** **Division of Drug Risk Evaluation**	FROM: **Rebecca Saville, Regulatory Project Manager** **Division of Special Pathogen and Immunologic Drug Products** **301-827-2387**

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
September 10, 2004	**n/a**	**21-266, 21-267, 21-630**	**SE-1**	**March 15, 2004**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE
VFEND (voriconazole)	**Standard 1/14/05** **(Division goal 12-22-04)**	**7030410** **(Systemic Antifungal Agent)**	**October 30, 2004**

NAME OF FIRM: **Pfizer, Inc.**

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☒ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☒ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☒ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☒ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☒ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

We are in the process of reviewing an efficacy supplement for (b) (4) candidiasis. Voriconazole was approved in May 2002 for the treatment of invasive aspergillosis and esophageal candidiasis. During review of the submission, we have identified several patients who discontinued voriconazole due to cardiac arrhythmias (atrial & ventricular). In a majority of these patients, these arrhythmias occurred in close proximity to the infusion of the study drug. In addition, a selected group of patients in the study (open-label, comparative, 2:1 randomization, clinical trial) were monitored with EKGs. In 11 of 50 patients in the voriconazole treatment group reported a QT interval change from baseline of ≥60msec compared to 0/13 in the amphotericin B/fluconazole treatment group.

We request that you search the relevant databases for cases of QT prolongation and cardiac arrhythmias that may have been reported in association with voriconazole administration. The submission can be found in the EDR (\\CDSESUB1\N21266\S_009\2004-03-15). The Division would be glad to provide further information to assist with your investigation. Thank you.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Rebecca Saville, Pharm.D.	☒ EMAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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Rebecca Saville
9/10/04 10:53:28 AM
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: September 2, 2004

To: Maureen H. Garvey	**From:** Rebecca Saville
Company: Pfizer Global Research & Development	Division of Special Pathogen and Immunologic Drug Products
Fax number: 646-441-5735	**Fax number:** 301-827-2475
Phone number: 212-733-5688	**Phone number:** 301-827-2127

Subject: Request for Information - Clinical Pharmacology and Biopharmaceutics

Total no. of pages including cover: 3

Comments:

Concurrence:

Philip Colangelo, Pharm.D., Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader, DPE-III

Gerlie De Los Reyes, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer, DPE-III

Document to be mailed: " YES ☑ NO

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To: Maureen H. Garvey

Please refer to NDA 21-266/S-009, NDA 21-267/S-009, and NDA 21-630/S-003 for VFEND® (voriconazole) Tablets, I.V. for Injection, and Oral Suspension, respectively. The Division appreciates your responses to the query of our Clinical Pharmacology and Biopharmaceutics reviewers sent in submissions dated July 23, 2004 and August 13, 2004. Our pharmacometrician has additional comments regarding the PK/PD datasets. The Division has the following requests:

1. Mean plasma concentrations of voriconazole for each subject in Study 150-608 was calculated from the concentration values of collected samples regardless of sampling time. This mean concentration was used to represent drug exposure for the subjects in the PK/PD analysis. Because drug concentration values are dependent on the time of sample collection, the lack of information regarding the actual sampling times may result in an inaccurate estimate of voriconazole exposure. Please provide justification for the use of mean concentration values in the PK/PD analysis.

2. Please verify that the column of "PREVDOSD" and DOSLTIME" in dataset "pkdata6" submitted in March 15, 2004 represent the dosing date and time before plasma samples were collected and also verify that the column of "SAMPDATE" and "TESTTIME" represent date and time when plasma samples were collected. Please confirm that the above information can be used to derive the time after dose.

We are providing the above information via telephone facsimile for your convenience. We have coordinated a teleconference at 4:00 p.m. EST on Wednesday, September 8, 2004 to provide an opportunity for discussion. Contact me at 301-827-2127 if you have any questions regarding the contents of this transmission. Please acknowledge receipt of this correspondence. Thank you.

_____

Rebecca D. Saville, Pharm.D.
Regulatory Project Manager

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/s/

Rebecca Saville
9/3/04 09:54:51 AM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: August 12, 2004

To: Maureen H. Garvey	**From:** Rebecca Saville
Company: Pfizer Global Research & Development	Division of Special Pathogen and Immunologic Drug Products
Fax number: 646-441-5735	**Fax number:** 301-827-2475
Phone number: 212-733-5688	**Phone number:** 301-827-2127

Subject: Request for Information - Clinical Pharmacology and Biopharmaceutics

Total no. of pages including cover: 3

Comments:

Concurrence:

Philip Colangelo, Pharm.D., Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader, DPE-III

Gerlie De Los Reyes, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer, DPE-III

Document to be mailed: " YES ☑ NO

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To: Maureen H. Garvey

Please refer to NDA 21-266/S-009, NDA 21-267/S-009, and NDA 21-630/S-003 for VFEND® (voriconazole) Tablets, I.V. for Injection, and Oral Suspension, respectively. The Division has the following request from the Clinical Pharmacology and Biopharmaceutics reviewer regarding the dataset 608pk/fdaic008.xpt of your submission dated July 23, 2004:

1. Please provide the DOSING DATE: TIME corresponding to each entry in the PK SAMPLE DATE: TIME Column.

2. Please provide clarification regarding the meaning of the numbers appearing in the "TYPE OF RECORD" column.

We are providing the above information via telephone facsimile for your convenience. Contact me at 301-827-2127 if you have any questions regarding the contents of this transmission. Please acknowledge receipt of this correspondence. Thank you.

_____
Rebecca D. Saville, Pharm.D.
Regulatory Project Manager

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/s/

Rebecca Saville
8/12/04 04:42:35 PM
CSO
NDA 21-266/S-009, NDA 21-267/S-009, NDA 21-630/S-003

MEMORANDUM OF TELECON

DATE: July 15, 2004
TIME: 11:00 a.m. EST

APPLICATION NUMBER:

NDA 21-266/S-009 VFEND (voriconazole) Tablets, 50 mg (b) (4)
NDA 21-267/S-009 VFEND I.V. (voriconazole) for Injection
NDA 21-630/S-003 VFEND (voriconazole) for Oral Suspension

BETWEEN:

Pfizer, Inc.

Maureen H. Garvey, Ph.D., Senior Director, Worldwide Regulatory Strategy

AND

Division of Special Pathogen and Immunologic Drug Products

Sary Beidas, M.D., Clinical Reviewer
Rebecca D. Saville, Pharm.D., Regulatory Project Manager

SUBJECT: Request for Information – Case Report Forms

BACKGROUND AND DISCUSSION:

Pfizer submitted an efficacy supplement for (b) (4) candidiasis on March 15, 2004. The efficacy supplement is supported by Study 150-608, a randomized, comparative trial in patients with candidemia. Pfizer also submitted results from Study 150-309/604, a non-comparative trial in patients with invasive fungal infections who received voriconazole as primary or salvage therapy. During the filing review period, the clinical reviewer decided to review disseminated cases of candidiasis from the non-comparative trial in order to further evaluate efficacy. He was unable to locate nine of the case report forms (CRFs) from this study. The Division initiated a teleconference with Pfizer to request the following CRFs from Study 150-309/604:

309 01131011

309 01131030

309 20471780

604 10186031

604 10326022

604 10366024

604 10366025

604 10506140

604 10596276

Pfizer agreed to send the CRFs. The teleconference was cordial throughout, and Pfizer expressed appreciation for providing an explanation for the request.

ACTION ITEMS:

Pfizer will submit the requested CRFs.

_____
Rebecca D. Saville, Pharm.D.
Regulatory Project Manager

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/s/

Rebecca Saville
8/3/04 10:33:13 AM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: July 1, 2004

To: Maureen H. Garvey	**From:** Rebecca Saville
Company: Pfizer Global Research & Development	Division of Special Pathogen and Immunologic Drug Products
Fax number: 646-441-5735	**Fax number:** 301-827-2475
Phone number: 212-733-5688	**Phone number:** 301-827-2127

Subject: Request for Information - Clinical Pharmacology and Biopharmaceutics

Total no. of pages including cover: 3

Comments:

Concurrence:

Philip Colangelo, Pharm.D., Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader, DPE-III

Gerlie De Los Reyes, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer, DPE-III

Document to be mailed: " YES ☑ NO

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To: Maureen H. Garvey

Please refer to NDA 21-266/S-009, NDA 21-267/S-009, and NDA 21-630/S-003 for VFEND® (voriconazole) Tablets, I.V. for Injection, and Oral Suspension, respectively. The Division has the following request from the Clinical Pharmacology and Biopharmaceutics reviewer:

1. Several figures such as figure 1.1, 1.2, 3.1 3.2 3.3 are missing in the PK/PD report for Study 150-608. Please provide those figures.
2. Please submit the data set and the files used for PK/PD analysis.
3. Please provide the data set including the following columns:

Study #	Site #	ID	Dose	Time to event	Type of record	Voriconazole Conc.	age	gender	weight	race	Route administration	region

Predisposing factor	Site of infection	MITT	AST value	ALT value	AP value	Bilirubin value	AST abnormal	ALT abnormal	AP abnormal	Bilirubin abnormal	Dose escalation
		0:not MITT 1: MITT					0: No 1: yes	0: No 1: yes	0: No 1: yes	0: No 1: yes	0: No 1: yes

Predisposing factors	Discontinuation	Days on voriconazole treatment	DRC assessment period	DRC outcome

The information for the subjects used in the PK/PD analysis should be included. For the subjects whose plasma samples were collected at different times, all concentrations should be included in the data set. Column 5 should record the time elapsed since the subject's first record to the events. The events include dosing time, plasma sampling, AST, ALT, AP, bilirubin measurements, escalation and discontinuation. The first record for each subject will have a value of "0." Column 6 would be indicator of event at the time (e.g. 1 = dosing record, 2 = concentrations; 3 = AST measuring; 4 = ALT measuring; 5 = AP measuring; 6 = bilirubin measuring; 7 = escalation record, and 8 = discontinuation record).

We are providing the above information via telephone facsimile for your convenience. Contact me at 301-827-2127 if you have any questions regarding the contents of this transmission. Please acknowledge receipt of this correspondence. Thank you.

_____

Rebecca D. Saville, Pharm.D.
Regulatory Project Manager

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/s/

Rebecca Saville
7/1/04 09:32:09 PM
CSO
Voriconazole SE1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-266/S-009
NDA 21-267/S-009
NDA 21-630/S-003

C.P. Pharmaceuticals International C.V.
c/o Pfizer, Inc.
Attn: Maureen H. Garvey, Ph.D.
Senior Director, Worldwide Regulatory Strategy
235 East 42nd Street
New York, NY 10017

Dear Dr. Garvey:

Please refer to your March 15, 2004 new drug applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product	NDA	Supplement Number
VFEND® (voriconazole) Tablets, 50 mg and 200 mg	21-266	S-009
VFEND® I.V. (voriconazole) for Injection	21-267	S-009
VFEND® (voriconazole) for Oral Suspension	21-630	S-003

We also refer to your submissions dated April 9, 2004 (2) and April 26, 2004 (2).

We have completed our filing review and have determined that your applications are sufficiently complete to permit a substantive review. Therefore, these applications will be filed under section 505(b) of the Act on May 15, 2004 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, please call Rebecca Saville, Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Ellen F. Molinaro, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Ellen Molinaro
5/14/04 12:09:35 PM
NDA 21-266/S-009, NDA 21-267/S-009, and NDA 21-630/S-003

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: May 12, 2004

To: Maureen H. Garvey	**From:** Rebecca Saville
Company: Pfizer Global Research & Development	Division of Special Pathogen and Immunologic Drug Products
Fax number: 646-441-5735	**Fax number:** 301-827-2475
Phone number: 212-733-5688	**Phone number:** 301-827-2127

Subject: 1. Request for Information
2. Pre-sNDA Meeting Minutes

Total no. of pages including cover: 7

Comments:

Concurrence: Cheryl Dixon, Ph.D., Biometrics Reviewer
Sary Beidas, M.D., Clinical Reviewer

Document to be mailed: " YES ☑ NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2127. Thank you.

To: Maureen H. Garvey

From: Rebecca D. Saville

Please refer to NDA 21-266/S-009, NDA 21-267/S-009, and NDA 21-630/S-003 for VFEND (voriconazole) Tables, I.V. for Injection, and Oral Suspension, respectively. The Division has the following request from the biometrics reviewer.

- Please submit the data listings for Section 13 of the study report. We would prefer to work from the data listings instead of trying to pull the information from multiple datasets.

We would appreciate receiving the submission of these data listings within a few weeks.

Attached, please find the Memorandum of Meeting Minutes from the Pre-sNDA meeting that occurred on January 13, 2004. I apologize for the delay.

If you have any questions, please contact me. Thank you.

_____

Rebecca D. Saville, Pharm.D.
Regulatory Project Manager

Attachment

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/s/

Rebecca Saville
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CSO

MEMORANDUM OF MEETING MINUTES

MEETING DATE: January 13, 2004

TIME: 10:00 A.M.

LOCATION: 9201 Corporate Blvd., Room S-400
Rockville, MD 20850

APPLICATION: NDA 21-266
NDA 21-267

TYPE OF MEETING: Pre-sNDA

MEETING CHAIR: Renata Albrecht, M.D.

MEETING RECORDER: Rebecca D. Saville, Pharm.D.

SPONSOR ATTENDEES (Pfizer, Inc):
Mike Hodges, M.D., Clinical Team Leader
Maureen Garvey, Ph.D., Director, Worldwide Regulatory Affairs
Justine King, MRPharmS, Regulatory
Iwonka Oborska, Ph.D., Clinical
Haran Schlamm, M.D., Clinical
Nolan Wood, Clinical Pharmacology (UK)
Fiona Hilton, M.Sc., CStat, Biometrics (UK)
Irja Lutsar, Clinical (UK)

FDA ATTENDEES:
Renata Albrecht, M.D., Director, DSPIDP
Steven Gitterman, M.D., Deputy Director, DSPIDP
Marc Cavaille-Coll, M.D., Ph.D., Medical Officer Team Leader, DSPIDP
Sary Beidas, M.D., Medical Officer, DSPIDP
Eileen Navarro Almario, M.D., Medical Officer, DSPIDP
John Powers, M.D., Lead Medical Officer for Antimicrobial Drug Devel. & Resistance Initiatives, ODEIV
Ellen F. Molinaro, R.Ph., Chief, Project Management Staff, DSPIDP
Philip Colangelo, Pharm.D., Ph.D., Clinical Pharmacology & Biopharmaceutics Team Leader, DPE-III
Gerlie De Los Reyes, Ph.D., Clinical Pharmacology & Biopharmaceutics Reviewer, DPE-III
Shukal Bala, Ph.D., Microbiology Team Leader, DSPIDP

Karen M. Higgins, Sc.D., Biometrics Team Leader, DB-III
Cheryl A. Dixon, Ph.D., Biometrics Reviewer, DB-III
Rebecca D. Saville, Pharm.D., Regulatory Project Manager, DSPIDP

BACKGROUND:

VFEND (voriconazole) tablets (50 mg and 200 mg) and I.V. was approved on May 24, 2002 for the following indications: invasive aspergillosis and serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* spp. On November 14, 2003, voriconazole was approved for use in esophageal candidiasis. On December 19, 2003, the oral suspension (40 mg/mL) formulation was approved. Pfizer is planning on submitting an NDA efficacy supplement for a new indication of candidemia (b) (4) infections, which this meeting was coordinated to discuss.

MEETING OBJECTIVES:

1. Describe the patient population evaluated in Study 150-608; to present and discuss the safety and efficacy data from this study.

2. Present efficacy data from Study 150-309/604 that will be submitted as supportive data for the indication of the treatment of candidemia.

3. Discuss administrative issues and Division recommendations.

4. Provide an update of the pediatric IV-to-oral suspension switch study A1501037.

DISCUSSION AND GENERAL RECOMMENDATIONS BASED ON REVIEW OF THE PRE-sNDA MEETING PACKAGE:

<u>Summary of Discussion</u>

Following introductions, Pfizer had a brief presentation that described the patient population evaluated in Study 150-608. They presented data from this study and efficacy data from supportive study 150-309/604. See attached slide presentation. The Division had the recommendations listed below.

Following the candidemia presentation, Pfizer presented an update regarding the ongoing pediatric safety studies. Pfizer will complete studies in the 2 - 11 year old age group and submit a final report including pharmacokinetics results by the end of 2004. These children will have a one-year follow-up with vision tests, but depending on clinical data, the second age group (12 -16 year old) may not have a one-year

follow-up by this time. Pfizer would like to update the package insert to include pediatric information. Pfizer has recently started enrolling individuals in the age 12 – 16 year old age group. They have increased the I.V. dose to 8 mg/kg, which has demonstrated a good safety and efficacy profile and matches most closely with the adult dose. Pfizer does not plan to study voriconazole use in children <2 years old. See attached slide presentation.

Recommendations

Clinical

- The Division noted that 20% of patients were unaccounted for at 12 weeks. Pfizer responded that these patients may be lost to follow-up due to several reasons including death, transfer to nursing homes, withdrawn consent, unknown reasons, etc. Several patients were censored at 12 weeks because of other factors (i.e., use of other antifungals). The Division recommended that Pfizer submit all required CRFs be submitted, including those of participants that resulted in death, serious adverse drug reactions, discontinuation of therapy, and loss to follow-up. The Division suggested that it would be helpful if Pfizer could include, in the CRFs, any information or detailed narratives about the outcome of these patients. Pfizer agreed.

- The Division asked if a list of protocol violators and a chronological list of amendments will be included. Pfizer stated that these lists will be in the study report.

- The Division questioned whether any participants had a blistering rash or vision abnormalities. Pfizer replied that there were cases of non-severe rash reported, but a lower frequency of vision abnormalities were established, since documenting events was difficult due to the severity of illness in these patients. The Division suggested Pfizer provide detailed information on the cases of these adverse events and update the labeling. Pfizer agreed.

- The Division inquired whether APACHE scores were collected. Pfizer stated that they were.

- The Division requested that Pfizer indicate in their study report the frequency of non-blood sites of candida infection.

Clinical Pharmacology and Biopharmaceutics

- The Division questioned if there would be a PK/PD analysis in the submission. The Division also suggested that the genotype/phenotype status for CYP 2C19 be identified for patients enrolled in the candidemia study. Pfizer stated that there was a PK/PD analysis and the genotype/phenotype status was not performed.

Microbiology

- The Division recommended that the microbiological outcome and the clinical outcome data be combined in the SAS Transport files. Pfizer agreed and asked for an example. The Division will forward a sample template to Pfizer.

Statistics

- The Division requested that Pfizer include the text of Section 13 of the study report electronically with the initial submission. Pfizer agreed.

ACTION ITEMS:

- The Division will send to Pfizer an example of a dataset which combines clinical outcome with microbiological outcome. [Note: A sample template was sent to Pfizer on January 25, 2004. Pfizer submitted draft sample datasets on February 23, 2004 and March 3, 2004 for our review. The Division responded via teleconference on March 12, 2004 that the draft dataset was appropriate.]

- Pfizer will submit the efficacy supplement in March or April 2004. [Note: The efficacy supplement was received March 15, 2004.]

Minutes Preparer: _____
Rebecca D. Saville, Pharm.D., Regulatory Project Manager, DSPIDP

Team Leader Concurrence: _____
Marc Cavaille-Coll, M.D., Ph.D., Medical Officer Team Leader, DSPIDP

Chair Concurrence: _____
Renata Albrecht, M.D., Director, DSPIDP

ATTACHMENTS: Slide presentation by Pfizer.

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/s/

Renata Albrecht
5/5/04 06:01:31 PM

MEMORANDUM OF TELECON

DATE: April 29, 2004
TIME: 1:30 PM EST

APPLICATION NUMBER:

NDA 21-266/S-009 VFEND (voriconazole) Tablets, 50 mg (b) (4)
NDA 21-267/S-009 VFEND I.V. (voriconazole) for Injection
NDA 21-630/S-003 VFEND (voriconazole) for Oral Suspension

BETWEEN:

Pfizer, Inc.

Maureen H. Garvey, Senior Director, Worldwide Regulatory Strategy

AND

Division of Special Pathogen and Immunologic Drug Products

Sary Beidas, M.D., Clinical Reviewer
Rebecca D. Saville, Regulatory Project Manager

SUBJECT: Request for Information – Clinical DRC Assessment Folders

BACKGROUND AND DISCUSSION:

Pfizer submitted an efficacy supplement for (b) (4) candidiasis on March 15, 2004. During the filing review period, the clinical reviewer needed to understand how the DRC process functioned and how a final decision was derived. The Division initiated a teleconference with Pfizer to request copies of the DRC assessment folders. Pfizer agreed to send the Division a copy of these patient sample workbooks.

ACTION ITEMS:

Pfizer will submit sample DRC workbooks.

_____
Rebecca D. Saville, Pharm.D.
Regulatory Project Manager

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/s/

Rebecca Saville
5/12/04 09:34:24 PM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # /Supplement # 21-266/S-009 [SE1] SE2 SE3 SE4 SE5 SE6 SE7 SE8
21-267/S-009
21-630/S-003

Trade Name: VFEND®
Generic Name: voriconazole
Strengths: Tablets, 50 mg and 200 mg
I.V., 200 mg (10 mg/ml)
Oral Suspension, 40 mg/ml

Applicant: Pfizer, Inc.

Date of Application: March 15, 2004
Date of Receipt: March 16, 2004
Date clock started after UN:
Date of Filing Meeting: April 28, 2004
Filing Date: May 15, 2004
Action Goal Date (optional): January 14, 2005 User Fee Goal Date: January 16, 2005

Indication requested: Candidemia (b) (4) including infections of the abdomen; kidney and bladder wall; deep tissues and wounds; (b) (4) and disseminated skin infection.

Type of Original NDA: (b)(1) _____ (b)(2) _____
OR
Type of Supplement: (b)(1) ____X____ (b)(2) _____
NOTE: A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S ____X_____ P _____
Resubmission after withdrawal? ____N_____ Resubmission after refuse to file? _____N____
Chemical Classification: (1,2,3 etc.) ____N/A___
Other (orphan, OTC, etc.) ____N/A___

User Fee Status: [Paid] Exempt (orphan, government) _____
Waived (e.g., small business, public health) _____

Form 3397 (User Fee Cover Sheet) submitted: [YES] NO
User Fee ID # NDA 21-266 4707
NDA 21-267 4708
NDA 21-630 4712
Clinical data? [YES] NO, Referenced to NDA # _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

[YES] NO

If yes, explain:
NCE – May 24, 2002 (exp May 24, 2007)
New Indication – EC November 14, 2003 (3 years)

Does another drug have orphan drug exclusivity for the same indication? YES [NO]

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
[N/A] YES NO

Is the application affected by the Application Integrity Policy (AIP)? YES [NO]
If yes, explain.

If yes, has OC/DMPQ been notified of the submission? [N/A] YES NO

- Does the submission contain an accurate comprehensive index? [YES] NO
- Was form 356h included with an authorized signature? [YES] NO
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? [YES] NO
  If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A [YES] NO
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:
- If in Common Technical Document format, does it follow the guidance? [N/A] YES NO
- Is it an electronic CTD? [N/A] YES NO
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?
  The entire supplement except the certifications and forms.

  Additional comments:
- Patent information submitted on form FDA 3542a? [YES] NO
- Exclusivity requested? [YES, ___3___years] NO
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? [YES] NO
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., *"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application."* Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature? [YES] NO
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- Field Copy Certification (that it is a true copy of the CMC technical section)? [N/A] YES NO

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? [YES] NO
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? [YES] NO

- List referenced IND numbers: IND (b) (4) IND 50,410, and IND 66,410

- End-of-Phase 2 Meeting(s)? Date(s) _____ [NO]
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) January 13, 2004 NO
  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  [YES] (to be sent in October, 2004) NO

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? [N/A] YES NO

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? [N/A] YES NO

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  [N/A] YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS?
  [N/A] YES NO

- Has DOTCDP been notified of the OTC switch application? [N/A] YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? [N/A] YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? [YES] NO
  If no, did applicant submit a complete environmental assessment? [N/A] YES NO
  If EA submitted, consulted to Nancy Sager (HFD-357)? [N/A] YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? [N/A] YES NO

- If a parenteral product, consulted to Microbiology Team (HFD-805)? [N/A] YES NO

If 505(b)(2) application, complete the following section: [N/A]

- Name of listed drug(s) and NDA/ANDA #:

- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)
  YES NO

- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).
  YES NO

- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).
  YES NO

- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

  ____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

  ____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

  ____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.
____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.
____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)
____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:

  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

    YES NO

  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

    YES NO

  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

    N/A YES NO

  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

    N/A YES NO

- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

    YES NO

  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

    YES NO

  - EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND # _____ NO

OR

A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

N/A YES NO

- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 28, 2004

BACKGROUND:

Voriconazole tablets (50 mg and 200 mg) and I.V. was approved on May 24, 2002 for the following indications: invasive aspergillosis and serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* spp. On November 14, 2003, voriconazole was approved for use in esophageal candidiasis. On December 19, 2003, the oral suspension (40 mg/mL) formulation was approved. This current NDA efficacy supplement is for a new indication of candidemia (b) (4)

ATTENDEES:

Renata Albrecht, M.D., Division Director
Marc Cavaille-Coll, M.D., Ph.D., Medical Team Leader
Sary Beidas, M.D., Medical Reviewer
Ellen F. Molinaro, R.Ph., Chief, Project Management Staff
Karen M. Higgins, Sc.D., Biometrics Team Leader
Cheryl A. Dixon, Ph.D., Biometrics Reviewer
Philip Colangelo, Pharm.D., Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader
Gerlie De Los Reyes, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer
Shukal Bala, Ph.D., Microbiology Team Leader
Kala Suvarna, Ph.D., Microbiology Reviewer
Rebecca D. Saville, Pharm.D., Project Manager

ASSIGNED REVIEWERS:

Discipline	Reviewer
Medical:	Sary Beidas
Secondary Medical:	Marc Cavaille-Coll
Statistical:	Cheryl Dixon
Pharmacology:	Owen McMaster
Statistical Pharmacology:	N/A
Chemistry:	Gene Holbert
Environmental Assessment (if needed):	N/A
Biopharmaceutical:	Gerlie De Los Reyes
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	Kala Suvarna
DSI:	N/A
Regulatory Project Management:	Rebecca Saville
Other Consults:	Jenny J. Zheng (Pharmacologist – OCPB/DPEIII) DDMAC

Per reviewers, are all parts in English or English translation? [YES] NO
If no, explain:

CLINICAL FILE ___X___ REFUSE TO FILE _____

- Clinical site inspection needed: YES [NO]
- Advisory Committee Meeting needed? YES, date if known _____ [NO]
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  [N/A] YES NO

CLINICAL MICROBIOLOGY NA _____ FILE ___X___ REFUSE TO FILE _____

STATISTICS FILE ___X__ REFUSE TO FILE _____

BIOPHARMACEUTICS FILE ___X___ REFUSE TO FILE _____

- Biopharm. inspection needed: YES [NO]

PHARMACOLOGY NA _____ FILE ___X___ REFUSE TO FILE _____

- GLP inspection needed: [N/A] YES NO

CHEMISTRY FILE ___X___ REFUSE TO FILE _____

- Establishment(s) ready for inspection? [N/A] YES NO
- Microbiology [N/A] YES NO

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

___X__ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

___X__ No filing issues have been identified.

_____ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.

2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

3. Document filing issues/no filing issues conveyed to applicant by Day 74.

_____
Rebecca D. Saville
Regulatory Project Manager, HFD-590

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/s/

Rebecca Saville
5/12/04 06:34:43 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-266/S-009
NDA 21-267/S-009
NDA 21-630/S-003

PRIOR APPROVAL SUPPLEMENTS

C.P. Pharmaceuticals International C.V.
c/o Pfizer, Inc.
Attn: Maureen H. Garvey, Ph.D.
Senior Director, Worldwide Regulatory Strategy
235 East 42nd Street
New York, NY 10017

Dear Dr. Garvey:

We have received your supplemental new drug applications (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product	NDA	Supplement Number
VFEND® (voriconazole) Tablets, 50 mg and 200 mg	21-266	S-009
VFEND® I.V. (voriconazole) for Injection	21-267	S-009
VFEND® (voriconazole) for Oral Suspension	21-630	S-003

Review Priority Classification: Standard (S)

Date of supplements: March 15, 2004

Date of receipt: March 16, 2004

These supplemental applications propose the following changes:

- Addition of candidemia (b) (4) infection to the **INDICATIONS AND USAGE** section.
- Addition of *C. parapsilosis* and *C. tropicalis* to the Activity *In Vitro* and *In Vivo* subsection of the **MICROBIOLOGY** section.
- Addition of information pertaining to candidemia to the **CLINICAL STUDIES** section.
- Revision of the **ADVERSE REACTIONS** section to incorporate updated information.
- Revision of the **DOSAGE AND ADMINISTRATION** section to provide recommended dosing regimens for candidemia and to add information to the Dosage Adjustment subsection.
- Minor editorial adjustments necessary to incorporate these changes.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 15, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be January 14, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are deferring submission of your pediatric studies until December 31, 2007.

All communications concerning these supplements should be addressed as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Special Pathogen and
Immunologic Drug Products, HFD-590
Attention: Document Room N-115
9201 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions, please call Rebecca Saville, Pharm.D., Regulatory Project Manager, at (301) 827-2127.

Sincerely,

{See appended electronic signature page}

Ellen F. Molinaro, R.Ph.
Chief, Project Management Staff
Division of Special Pathogen and
Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Ellen Molinaro
4/14/04 02:54:40 PM
NDA 21-266/S-009, NDA 21-267/S-009, and NDA 21-630/S-003

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE IV

FACSIMILE TRANSMITTAL SHEET

DATE: April 5, 2004

To: Maureen H. Garvey	**From:** Rebecca Saville
Company: Pfizer Global Research & Development	Division of Special Pathogen and Immunologic Drug Products
Fax number: 646-441-5735	**Fax number:** 301-827-2475
Phone number: 212-733-5688	**Phone number:** 301-827-2127

Subject: Request for Information: CRFs for Study 608

Total no. of pages including cover: 3

Comments:

Document to be mailed: " YES ☑ NO

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To: Maureen H. Garvey

From: Rebecca Saville

Please refer to NDA 21-266/S-009, NDA 21-267/S-009, and NDA 21-630/S-003 for VFEND (voriconazole) Tablets, I.V. for Injection, and Oral Suspension, respectively. The Division has the following request from the clinical reviewer. Please submit the CRFs for the following participants in Study 150-608:

01440270	51330152
03470054	52330275
03590002	60070140
03690024	60070145
04160395	60070213
04520075	60070348
21020385	60070361
22510285	60070377
22510318	60380262
23000388	60430310
23010328	66760290
24440390	66920295
50340043	80090188
50610064	80500133
50920012	

If you have any questions, please contact me.

_____

Rebecca D. Saville, Pharm.D.
Regulatory Project Manager

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/s/

Rebecca Saville
4/5/04 05:11:39 PM
CSO