CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-266

21-267

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDAs:	21-266 and 21-267
Submission Date:	3/22/02; 5/2/02
Drug:	Voriconazole (Vfend™) oral tablets and lyophilized powder for reconstitution
Applicant:	Pfizer Global Research and Development
Type of Submission:	NDA Resubmission
OCPB Reviewers:	Joette M. Meyer, Pharm.D. Philip M. Colangelo, Pharm.D., Ph.D.

BACKGROUND

The applicant has submitted a complete response to the Approvable Letter of December 17, 2001. The resubmission consists of revised labeling, minor re-analyses and clarifications.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

The Biopharm group forwarded the following comments to the applicant during the review process. The comments were concerning: (1) the initial absorption statement in the label; (2) oral loading of voriconazole which is also in the label; (3) the requirement for an oral contraceptive drug interaction study as a Phase IV commitment; and (4) adolescent pharmacokinetic data in the label.

Reviewer's Comment: The first three comments were incorporated into a fax to the applicant on April 29, 2002. The fourth comment was the topic of a later fax on May 10, 2002.

(1) Absorption Statement in the Clinical Pharmacology Section of the Label

We cannot accept the phrase We are proposing to reword the first paragraph under **CLINICAL PHARMACOLOGY, Absorption** to read similar to the fluconazole label. The paragraph has been revised into two paragraphs as follows:

> 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%).
>
> 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_t are reduced by 34% and 24%, respectively (see **DOSAGE AND ADMINISTRATION**).

(2) Oral Loading Doses of Voriconazole

For the indication of invasive aspergillosis, we do not accept your proposal to recommend both] doses of voriconazole. Although the oral bioavailability is estimated to be 96%, the results were variable and the range was as low as 60%. In the clinical studies used to support approval of this regimen, physicians were not given the option of oral loading with voriconazole. Therefore, we do not know the clinical outcome of patients initiated on voriconazole with oral drug. In addition, we believe due to the severity of this disease, it is likely that most physicians will not opt for using oral therapy when initiating voriconazole.

Please modify the **DOSAGE AND ADMINISTRATION** section of the label to delete reference to

(3) Drug Interaction Study with Oral Contraceptives

Although the *in vitro* metabolism data suggest an interaction between oral contraceptives (i.e., ethinylestradiol) is unlikely, the potential still exists for a non-metabolic interaction between the two drugs. Due to the risk of teratogenic effects in fetuses of female patients who become pregnant while taking voriconazole, we are recommending an interaction study with voriconazole and oral contraceptives as a Phase IV commitment.

Reviewer's Comment: Voriconazole will be labeled as Pregnancy Category D.

On May 23, 2002 the applicant noted in a letter that they do not believe the oral contraceptive study should be a requirement for voriconazole. Since the current indication under review is for a serious and life-threatening disease, we are willing to defer the oral contraceptive study. The need for such a study will be revisited upon reviewing subsequent submissions for additional and less serious indications.

Reviewers' Comment: The applicant was also informed in the approvable letter of December 17, 2001 that they would be asked to perform a two-way drug interaction study between voriconazole and rifabutin. The applicant stated in the May 23, 2002 letter that they are considering performing another rifabutin drug interaction study, but that they may choose not to perform such a study. They recognize that this means co-administration of rifabutin with voriconazole will remain a contraindication in the label. We accept their decision for the same reasons as the oral contraceptive interaction study and will revisit the request in the future.

(4) Adolescent Pharmacokinetic Data from Patients in a Compassionate Use Study with Invasive Aspergillosis and other Serious Fungal Infections

On May 10, 2002 the following comment was faxed to the applicant:

At this time we can not accept the final paragraph under the Pediatric subsection of the **CLINICAL PHARMACOLOGY, Pharmacokinetics in Special Populations** section. The other steady-state plasma concentration values in the label were calculated by a

population pharmacokinetic analysis. The new values from the resubmission are medians of geometric means from each patient.

We would be willing to reconsider the data on 12-18 year olds at a later date, if a population pharmacokinetic approach was used, similar to what was used for the adult healthy volunteers and pediatric (2 to < 12 year olds) patients.

In a follow-up teleconference on May 14, 2002, the applicant clarified that the data in this paragraph was derived in a similar manner to the data presented under the **CLINICAL PHARMACOLOGY, Pharmacokinetic-pharmacodynamic Relationships** and that a formal population pharmacokinetic approach was not possible to due to missing data collection times and lack of information on the patients' CYP2C19 genotype.

The Agency expressed concern about having the data located next to the paragraph on pediatric pharmacokinetics, which were derived using a formal population pharmacokinetic analysis.

Therefore, it was agreed between the Agency and the applicant that the information would remain in the label, but would be moved to the **CLINICAL PHARMACOLOGY, Pharmacokinetics,** General Pharmacokinetic Characteristics subsection and would follow Table 2, which contains pharmacokinetic parameters from patients at risk for aspergillosis.

RECOMMENDATION

The proposed label contained in the resubmission of NDAs 21-266 and 21-267 for voriconazole oral tablets and lyophilized powder for reconstitution has been reviewed. Comments were conveyed to the applicant during the review process and the sections of the final label pertaining to clinical pharmacology and biopharmaceutics issues have been found to be acceptable. The final label can be found in Appendix 1.

_____

Joette M. Meyer, Pharm.D.
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Division of Pharmaceutical Evaluation III

_____

Philip M. Colangelo, Pharm.D., Ph.D.
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RD/FT signed by Barbara Davit, Ph.D. (Team Leader) _____

Appendix 1 – Final Voriconazole IV/Oral Label (May 22, 2002)

57 page(s) of revised draft labeling has been redacted from this portion of the review.

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

/s/

Joette Meyer
5/24/02 01:57:31 PM
BIOPHARMACEUTICS

Phil Colangelo
5/24/02 02:45:54 PM
BIOPHARMACEUTICS

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5/28/02 04:58:07 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLCOGY / BIOPHARMACEUTICS REVIEW

NDAs:	21-266 and 21-267
Submission Dates:	11/17/00; 4/6/01; 4/16/01; 6/21/01
Drug:	Voriconazole (Vfend™) oral tablets and lyophilized powder for reconstitution
Applicant:	Pfizer Global Research and Development
Type of Submission:	New NDA, NME
OCPB Reviewers:	Joette M. Meyer, Pharm.D. Philip M. Colangelo, Pharm.D., Ph.D.

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EXECUTIVE SUMMARY

I. BACKGROUND

Voriconazole is a triazole anti-fungal agent with broad antifungal activity against yeasts and molds, in particular *Candida* and *Aspergillus* species. Other approved azole anti-fungal agents include ketoconazole, itraconazole, and fluconazole. Voriconazole was designed to retain the parenteral and oral formulation advantages of fluconazole while extending its spectrum. Systemic fungal infections caused by *Aspergillus* are difficult to treat and are associated with a high mortality rate. The availability of an agent in both an intravenous (IV) and oral formulation to treat *Aspergillus* infection potentially represents a significant therapeutic contribution to the management of this disease.

II. INDICATIONS AND DOSAGES

Indications
The applicant is seeking approval of voriconazole for six indications: treatment of invasive aspergillosis; empiric antifungal therapy of febrile neutropenic patients; treatment of candida eosophagitis; treatment of serious candida infections; treatment of serious fungal infections caused by *Fusarium* and *Scedosporium* spp.; treatment of serious fungal infections in patients refractory or intolerant to other therapy.

Dosage and Administration
The proposed dosage and administration of intravenous and oral voriconazole for adults is shown in the table below.

	INTRAVENOUS	ORAL	
		Patients 40kg and above	Patients less than 40kg
Loading Dose Regimen (first 24 hours)	Two doses of 6 mg/kg 12 hours apart	Two doses of 400 mg 12 hours apart	Two doses of 200 mg 12 hours apart
Maintenance Dose (after first 24 hours)			
Serious *Candida* infections Empirical Therapy	3 mg/kg every 12 hours	200 mg every 12 hours	100 mg every 12 hours
Invasive aspergillosis/ *Scedosporium* and *Fusarium* infections/ Other serious mold infections	4 mg/kg every 12 hours	200 mg every 12 hours	100 mg every 12 hours

The proposed dosage and administration of intravenous and oral voriconazole for pediatrics is shown in the table below. Voriconazole is not recommended for children less than 2 years of age. Adolescents (12 to 16 years of age) should be dosed as adults.

	Intravenous	Oral*
Loading dose regimen (first 24 hours)	Two doses of 6 mg/kg 12 hours apart	Two doses of 6 mg/kg 12 hours apart
Maintenance dose (after first 24 hours)	4 mg/kg every 12 hours	4 mg/kg every 12 hours

*Oral administration has not been studied in children. If the child is able to swallow tablets, the dose should be administered to the nearest mg/kg dose possible using whole 50 mg tablets.

III. CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS SYNOPSIS

The pharmacokinetics of voriconazole are characterized by high inter-individual variability, non-linear pharmacokinetics, and extensive hepatic metabolism by cytochrome P450 enzymes.

In general, the Phase I pharmacokinetic studies show the inter-subject variability in the estimates of C_{max} and AUC following multiple dosing of 3 mg/kg IV bid and/or 200 mg bid orally is high. Inter-subject variability (expressed as %CV) ranges from approximately 20% to greater than 100%. In the population pharmacokinetic analysis of 11 Phase I studies, the between subject variability (expressed as %CV) in the predicted steady state estimates of voriconazole AUC following multiple oral (200 mg Q12 hr) or IV (3 mg/kg Q12 hr) administration is 90-100%. As a consequence of this high variability, different patients treated with voriconazole at the same dose can exhibit a wide range of drug concentrations in plasma.

Voriconazole exhibits non-linear pharmacokinetics in the clinical dosing range due to saturable metabolism. Exposure, in terms of peak plasma concentration (C_{max}) and AUC_{τ}, increases in a disproportionate manner with dose. For IV dosing a 1.6 fold increase in dose from 3 mg/kg to 5 mg/kg results in a 2.4 and 3.1 fold increase in C_{max} and AUC_{τ}, respectively. For oral dosing, a 2-fold increase in dose from 200 mg to 400 mg results in a 2.8 and 3.9 fold increase in C_{max} and AUC_{τ}, respectively.

With repeated dosing, plasma accumulation of voriconazole is substantial due to the non-linear pharmacokinetics. Following multiple dosing with 3 mg/kg IV bid, AUC_{τ} and C_{max} values are about 2.4 and 1.5 times, respectively, that seen after single dosing.

Voriconazole undergoes extensive hepatic metabolism, with less than 2% excreted in the urine as unchanged drug. Hepatic metabolism is primarily by three cytochrome P-450 enzymes: CYP2C19, 2C9, and 3A4. *In vitro* metabolism studies using human hepatic microsomal preparations show that voriconazole is both a substrate and inhibitor of these three enzymes.

A population pharmacokinetics (Pop PK) analysis was performed using a non-linear mixed effects modeling approach on voriconazole plasma concentration-time data combined from 11 Phase I studies in healthy subjects. Data from a total of 236 subjects were used in the analysis. Overall, the analysis of the Phase I data shows that the CYP2C19 genotype is the most influential covariate on the clearance and AUC of voriconazole. CYP2C19 genotype alone accounts for approximately 30% of the overall between subject variability in voriconazole PK. Secondary covariates identified by the Pop PK analysis are gender and age of the subjects. Adding gender and age to the Pop PK model with CYP2C19 genotype accounts for additional variability in PK of approximately 10%.

Overall, the Pop PK analysis of the Phase I data indicates that CYP2C19 poor metabolizers (PM) have the highest plasma voriconazole concentrations/systemic exposure, followed by heterozygous extensive metabolizers (HEM), then extensive metabolizers (EM). Following oral and IV doses of 200 mg and 3 mg/kg Q12 hr, respectively, average steady state plasma concentrations and AUC estimates in PM subjects are approximately 4-times those of EM subjects, while in HEM subjects they are approximately 2-times those of EM subjects.

The variability in plasma concentrations/systemic exposure between subjects of varying genotype is quite high. The between subject variability (expressed as %CV) in the predicted steady state estimates of voriconazole AUC following oral (200 mg Q12 hr) or IV (3mg/kg Q12 hr) administration is >90%. This implies that the range of plasma exposures to voriconazole will show considerable overlap between subjects.

As mentioned, plasma accumulation of voriconazole following repeated dosing is extensive. The Pop PK analysis also shows that the magnitude of this accumulation is dependent on CYP2C19 genotype. As might be expected, plasma accumulation following 200 bid orally is highest for PM subjects

(approximately 6-times vs. single dose), intermediate for HEM subjects (approximately 3-times vs. single dose), and lowest for EM subjects (approximately 2-times vs. single dose).

Special Populations

Hepatic Impairment
In patients with mild to moderate hepatic impairment (Child-Pugh Class A and B) a standard loading dose of voriconazole should be given, but the standard maintenance dose should be reduced by one-half . The pharmacokinetics of voriconazole in patients with severe hepatic impairment (Child-Pugh Class C) have not been studied.

Renal Impairment
No dosage adjustment of oral voriconazole is necessary in patients with renal impairment.

However, in patients with moderate renal dysfunction (i.e., creatinine clearance of 30 - 50 ml/min), accumulation of the IV vehicle, SBECD, occurs (see section on SBECD pharmacokinetics). The mean AUC and C_{max} are increased by 4-fold and almost 50%, respectively, in the moderately impaired group compared to the control group with normal renal function. Intravenous voriconazole should be avoided in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min), unless the benefit outweighs the risk in an individual patient.

A 4-hour hemodialysis session removes only 8% of the total body load of voriconazole, therefore no dosage adjustment is necessary in patients undergoing hemodialysis.

Pediatrics
A comparison of the pediatric (age 2 to 11 years) and adult pharmacokinetic data from population PK analyses revealed that the predicted AUCτ estimates and the corresponding average steady state plasma concentrations were similar at the IV maintenance dose of 4 mg/kg bid in children and 3 mg/kg bid in adults. Therefore, a maintenance dose of 4 mg/kg every 12 hours is recommended by the applicant for children. This proposed regimen is based on data from two pharmacokinetic studies and analyzed using a population pharmacokinetic approach. The data contained in this submission is adequate to make preliminary dosing recommendation in pediatrics. The applicant has committed to further studying pediatrics and will be submitting a PPSR.

Body Weight
Although not identified as a significant covariate in the Pop PK model, there is a weak relationship between weight and voriconazole AUC following repeated dosing. With repeated dosing for longer periods of time (i.e., > 1-week duration), the AUC estimates show a trend to increase as the subjects' body weights became lower. Subject body weights in the Phase I datasets ranged from approximately 50 kg to 95 kg. Thus, although subjects with body weights < 50 kg were not included in the Pop PK analysis, a decision was made for the Phase III studies to reduce the dose by one-half in patients with body weights < 40 kg. The plasma concentration data obtained from the 10 Phase II/III trials of patients shows similar average steady state plasma concentrations following oral voriconazole administration between patients with body weights < 40 kg who received one-half the recommended dose versus those patients with body weights ≥ 40 kg. The proposed labeling recommends a reduction in the recommended voriconazole dosage by one-half patients with body weights < 40 kg.

Drug Interactions

In Vitro Studies
In vitro hepatic microsomal studies indicate that voriconazole is both a substrate and inhibitor of the CYP2C9, CYP2C19, and CYP3A4 enzymes in the liver. In microsomes of cell lines expressing only one CYP450 enzyme, substrate affinity of voriconazole was greater for CYP2C19 (Km ~4μM) and CYP2C9 (Km ~21μM) than CYP3A4 (Km ~240μM). No appreciable metabolism of voriconazole was apparent with CYP1A2, CYP2D6, or CYP2E1. Inhibition potency of voriconazole was also greatest against CYP2C9 (Ki 7μM) and CYP2C19 (Ki 14μM) compared to CYP3A4 (Ki 22μM). *In vitro* comparisons between

voriconazole and ketoconazole or itraconazole demonstrate that voriconazole is a substantially less potent inhibitor of CYP3A4 metabolism than the other two azoles.

In vitro interaction studies were performed using liver microsomes to evaluate the potential for voriconazole to interact with other drugs that are substrates for or inhibitors of CYP2C9, 2C19, and 3A4. In some studies the reverse interaction was also evaluated, i.e., the effect of the drug substrate / inhibitor on voriconazole metabolism. The results from these studies are summarized in the tables below.

TABLE 1
Effect of Voriconazole on Drug Substrate Metabolism

CYP450 Enzyme	Drug Substrate	Voriconazole IC50 (Ki) (μM)	Study No.
CYP2C9	Phenytoin	9 (Ki 7±0.4)	DM15
	(S)-Warfarin	13	DM28
CYP2C19	(S)-Mephenytoin	32 (Ki 13.5±6.2)	DM15
	Omeprazole	18	DM28
CYP3A4	Midazolam	9.3	DM34
	Amprenavir	13	DM35
	Saquinavir	22 (Ki ~11) 21	DM25 DM35
	Lovastatin	24	DM36
	Cyclosporine	30	DM28
	Nelfinavir	40	DM35
	Felodipine	50 (Ki 21.5±8.2)	DM15
	Testosterone	54	DM34
	Tacrolimus	117	DM36
	Delavirdine	160	DM36
	Indinavir	>100 (Ki ~70*) ~500	DM25 DM35
	Ethinylestradiol	>300	DM28
	Terfenadine	>300	DM28
	Ritonavir	No Inhibition	DM35
*for IC50 = 100μM			

TABLE 2
Effect of Drug Substrate on Voriconazole Metabolism:
Formation of UK-121,265 (N-oxide metabolite) at 25μM Voriconazole

CYP450 Enzyme	Drug Substrate	Substrate IC50 (μM)	Study No.
CYP2C9	(S)-Warfarin	200	DM28
CYP2C19	Omeprazole	37	DM28
CYP3A4	Indinavir	>100, 1.4, 2.4 ~1000	DM25 DM35
	Ritonavir	16	DM35
	Saquinavir	>100, 19.4, 21.4 ~300	DM25 DM35
	Tacrolimus	19	DM36
	Ethinylestradiol	19	DM28
	Delavirdine	27	DM36
	Amprenavir	58	DM35
	Efavirenz	104	DM36
	Terfenadine	>300	DM28
	Lovastatin	>1000	DM36
	Nelfinavir	>1000	DM35
	Cyclosporine	Not Determined	DM28
Non-Specific	Cimetidine	>300	DM28

The results in Table 1 indicated that voriconazole has the potential to significantly inhibit the metabolism of the CYP2C9 and CYP2C19 substrates phenytoin, warfarin, and omeprazole. Voriconazole appeared to have varying potency as a CYP3A4 substrate inhibitor, demonstrating the greatest potential to inhibit the metabolism of the following CYP3A4 substrates: midazolam, amprenavir, saquinavir, lovastatin, cyclosporine, nelfinavir, felodipine, and testosterone. Voriconazole appeared to be a far less potent inhibitor of the CYP3A4-mediated metabolism of tacrolimus, delavirdine, indinavir, ethinylestradiol, terfenadine, and ritonavir.

In the reverse studies (Table 2), omeprazole showed the greatest potential to inhibit voriconazole metabolism of the CYP2C9 and CYP2C19 substrates tested. There were mixed results with the CYP3A4 substrates tested. Indinavir, ritonavir, saquinavir, tacrolimus, ethinylestradiol, delavirdine, amprenavir and efavirenz all showed the potential to inhibit the metabolism of voriconazole. However, terfenadine, lovastatin, nelfinavir, and cimetidine showed little potential to inhibit voriconazole metabolism.

In Vivo Studies
The potential for *in vivo* drug interactions was evaluated using drugs that are most likely to be co-administered with voriconazole in the clinical setting of fungal infections and that are also substrates, inhibitors, and/or inducers of CYP2C9, 2C19, and 3A4. In addition, other studies were conducted where an interaction might be expected on a mechanistic basis.

Effect of Other Drugs on the Pharmacokinetics of Voriconazole
The most significant interactions and recommendations for co-administration are listed in Table 1. All the interacting drugs were chosen to investigate CYP450-based mechanisms of interaction.

TABLE 1
Effect of Other Drugs on the Steady State PK of Voriconazole
Interaction Studies Investigating CYP450-Based Mechanisms

				Results		
Study # Subjects	**Mech.**	**Drug Dose & Duration**	**Vori Dose & Duration**	**Vori Cmax Point Est. (90% CI)**	**Vori AUC Point Est. (90% CI)**	**Reviewer Proposed Recommendations for Co-Administration**
150-228 N=8 healthy young males	CYP450 Induction	**Rifampin** 600mg QD x 23 days	200mg BID x 14 days	0.072 (0.062, 0.095)	0.044 (0.034, 0.057)	Rifampin is **contraindicated** with voriconazole
			400mg BID x 7 days	0.34 (0.22, 0.54)	0.19 (0.15, 0.24)	
150-228 N=8 healthy young males	CYP450 Induction	**Rifabutin** 300mg QD x 23 days	200mg BID x 14 days	0.34 (0.27, 0.42)	0.21 (0.16, 0.28)	Rifabutin is **contraindicated** with voriconazole
			350mg BID x 7 days (N=3)	0.96 (0.45, 2.05)	0.68 (0.46, 1.00)	
150-1024 N=10 healthy young males	CYP450 Induction	**Rifabutin** 300mg QD x 14 days	400mg BID + Rifabutin x 7 days	2.0 (1.6, 2.6) vs. Vori 200mg BID + PBO*	1.87 (1.5, 2.4) vs. Vori 200mg BID + PBO	
150-233 N=10 healthy young males	CYP450 Induction (primarily CYP3A4)	**Phenytoin** 300mg QD x 21 days	200mg BID x 14 days (N=10)	0.51 (0.39, 0.66)	0.31 (0.24, 0.40)	Increase voriconazole maintenance dose to 5mg/kg IV BID or to 400mg PO BID (from 200mg PO BID); for patients <40 kg increase to 200mg PO BID
			400mg BID x 7 days (N=7)	1.34 (0.89, 2.0) vs. Vori 200mg BID Alone	1.39 (0.97, 1.98) vs. Vori 200mg BID Alone	

*PBO = Placebo

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Effect of Voriconazole on the Pharmacokinetics Other Drugs

The most significant interactions and recommendations for co-administration with voriconazole are listed in Table 2. All the interacting drugs were chosen based on their potential for a CYP450-based interaction.

TABLE 2
Effect of Voriconazole on the PK of Other Drugs
Interaction Studies Investigating CYP450-Based Mechanisms

				Results		
Study # Subjects	**Mech.**	**Drug Dose & Duration**	**Vori Dose & Duration**	**Drug Cmax Point Est. (90% CI)**	**Drug AUC Point Est. (90% CI)**	**Reviewer Proposed Recommendations for Co-Administration**
150-239 N=13 healthy young males	CYP2C9 Inhibition	**Warfarin** 30mg Single Dose	300mg BID x 12 days	PT ↑8 sec ↑(5, 12 sec)	AUEC for PT ↑929 sec•hr ↑(574, 1283 sec•hr)	Monitor PT / other suitable anti-coagulation tests; adjust warfarin dosage if warranted
150-241 N=6 healthy young males	CYP2C9 Inhibition	**Phenytoin** 300mg QD x 17 days	400mg BID x 10 days	1.67 (1.44, 1.93) vs. Phenytoin + PBO*	1.81 (1.56, 2.10) vs. Phenytoin + PBO	Monitor phenytoin concentrations and monitor for phenytoin related AEs with co-administration
150-1013 N=16 healthy young males	CYP2C9 / CYP3A4 Inhibition	**Omeprazole** 40mg QD x 7 days	200mg BID x 7 days	2.16 (1.78, 2.64) vs. Omeprazole + PBO	3.81 (3.28, 4.41) vs. Omeprazole + PBO	When initiating therapy with voriconazole in patients already receiving omeparzooe doses of 40 mg or greater, reduce omeprazole dose by ½ 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.
150-1024 N=10 healthy young males	CYP3A4 Inhibition	**Rifabutin** 300mg QD x 14 days	400mg BID + Rifabutin x 7 days	2.95 (2.19, 3.97) vs. Rifabutin + PBO	4.31 (3.47, 5.36) vs. Rifabutin + PBO	**(See also Table 1)** Voriconazole is **contraindicated** with rifabutin

*PBO = Placebo

TABLE 2 (continued)
Effect of Voriconazole on the PK of Other Drugs
Interaction Studies Investigating CYP450-Based Mechanisms

				Results		
Study # Subjects	**Mech.**	**Drug Dose & Duration**	**Vori Dose & Duration**	**Drug Cmax Point Est. (90% CI)**	**Drug AUC Point Est. (90% CI)**	**Reviewer Proposed Recommendations for Co-Administration**
150-1009 N=12 healthy young males	CYP3A4 Inhibition	**Tacrolimus** 0.1 mg/kg Single Oral Dose	200mg BID x 7 days	2.17 (1.86, 2.52) vs. Tacrolimus + PBO	3.21 (2.69, 3.83) vs. Tacrolimus + PBO	Reduce tacrolimus dose by 1/3 when initiating therapy with voriconazole; monitor tacrolimus concentrations frequently. When VFEND is discontinued, tacrolimus concentrations must be frequently monitored and the dose increased as necessary.
150-1015 N=15 healthy young males	CYP3A4 Inhibition	**Sirolimus** 2mg Single Oral Solution Dose	200mg BID x 9 days	6.56 (5.73, 7.52) vs. Sirolimus + PBO	11.14 (9.87, 12.58) vs. Sirolimus + PBO	Sirolimus is **contraindicated** with voriconazole
150-235 N=7 male and female renal transplant patients	CYP3A4 Inhibition	**Cyclosporine** BID x 8 days (patients on stabilized therapy)	200mg BID x 8 days	1.13 (0.90, 1.41) vs. Cyclosporine + PBO	1.67 (1.47, 1.98) vs. Cyclosporine + PBO	Reduce cyclosporine dose by 1/2 when initiating therapy with voriconazole; monitor cyclosporine concentrations frequently. When VFEND is discontinued, cyclosporine concentrations must be frequently monitored and the dose increased as necessary.

***PBO = Placebo**

Drugs Not Studied

Voriconazole may be predicted to interact with other drugs based on results from *in vitro* and *in vivo* studies of similar drug substrates/inhibitors/inducers for a given CYP450 enzyme (or enzymes). **Therefore, it is recommended that the following drugs be contraindicated with voriconazole:**

- Terfenadine*, Astemizole*, Cisapride**, Pimozide, and Quinidine
  Inhibition of these CYP3A4 substrates by voriconazole can produce increased plasma levels of these drugs, and potentially, prolongation of the QT interval.
  *no longer marketed in the US
  **restricted distribution in the US

- Carbamazepine and Long Acting Barbiturates: Potent inducers of CYP450 metabolism and likely to significantly reduce voriconazole plasma concentrations/systemic exposure.

- Ergot Alkaloids: Inhibition of metabolism by voriconazole can lead to increased ergot alkaloid concentrations.

Careful monitoring and/or dosage adjustment of the following drugs is recommended with voriconazole co-administration:

- Sulfonylureas, Statins, Benzodiazepines, Vinca Alkaloids, HIV protease inhibitors, and non-nucleoside reverse transcriptase inhibitors (NNRTIs): CYP450 substrates, where increased plasma concentrations are likely when co-administered with voriconazole via metabolic inhibition.

Summary of Pharmacokinetic/Pharmacodyanmic (PK/PD) Analysis for Voriconazole

Exploratory pharmacokinetic/pharmacodyanmic (PK/PD) analyses were performed by the applicant to evaluate the relationship between plasma exposure to voriconazole (i.e., C_{max}, AUC, mean plasma concentrations) and safety and efficacy endpoints. Liver function test (LFT) results and visual adverse events were chosen as the relevant safety endpoints. The efficacy endpoint was an applicant-assessed response at end of treatment. Two separate PK/PD analyses were conducted, one with data from healthy subjects in Phase I studies and the other with data from patients in Phase II/III trials.

Safety - Phase I Studies in Healthy Subjects

Modeling of the PK/PD relationships for ALT and AST using Phase I clinical laboratory test data from 547 subjects indicated that C_{max} and AUC are strongly associated with these two LFT indices. The threshold values for increases in ALT and AST appeared to be at C_{max} values of approximately 5.0 to 6.0 µg/mL and at AUC values starting at approximately 40 to 50 µg•hr/mL. It was difficult to adequately assess the time course of LFT abnormalities with respect to voriconazole dosing, however limited results suggest that LFT abnormalities may occur after longer duration of therapy (i.e., 7 days or more) and may be associated with higher voriconazole doses and/or plasma concentrations.

Visual adverse events (VAE) from the Phase I studies were classified and evaluated as "any VAE" or as "enhanced/altered visual perception". Overall, there was a positive association between C_{max} and AUC and the incidence of any VAE and enhanced/altered visual perception with single dose administration of voriconazole. The association between C_{max} and AUC and visual adverse events was weaker with multiple dose administration. There was considerable overlap in the C_{max} and AUC estimates for those subjects reporting VAE and those who did not report any VAE. Nonetheless, mean estimates of both PK parameters were higher for those subjects reporting VAE versus those who did not.

Safety - Phase II/III Studies in Patients

There were 10 Phase II/III clinical efficacy and safety trials and data from 1053 patients in the PK/PD analyses. The safety population consisted of 1053 patients who had at least one PK sample drawn for determination of voriconazole concentration in plasma. Overall, there was an association between the increase in LFT abnormalities and plasma voriconazole concentrations following multiple dose administration of voriconazole. Unlike the PK/PD analyses for the subjects in Phase I studies, no threshold concentration(s) for the increase in LFT's were apparent for the patients in the Phase II/III trials. However, it should be noted that maximum frequencies of LFT abnormalities occurred at the highest plasma concentration bands, i.e., 8 to 9 µg/mL and ≥9 µg/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. The 95% confidence intervals for the statistical ratios indicate that the odds or risk of an LFT abnormality with every 1 µg/mL increase in plasma voriconazole concentrations may be as low 0% and as high as approximately 30%.

Overall, it appeared that median plasma voriconazole concentrations were higher in those patients with VAE than in those patients without VAE over the majority of the weekly evaluation intervals. The incidence of VAE went from approximately 10% to <20% at plasma concentrations ranging from 0 to 3µg/mL, then increased to approximately 25% to 40% at voriconazole plasma concentration bands starting at 3 to 4µg/mL and up to >9µg/mL. Thus, a threshold concentration of approximately ≥3 µg/mL for VAE in the Phase II/III patients was apparent.

Efficacy

The efficacy population consisted of 453 patients who had a certainty of baseline fungal infection categorized as "definite" or "probable" and were assessed in the applicant's Voriconazole Efficacy Response Assessment database (VERA). The efficacy outcome variable was success or failure at the end of treatment. The VERA was a tool that harmonized the efficacy assessments of patients with the same pathogens, but who were enrolled in different studies. These studies commonly had slightly different entry and evaluation criteria. Patients from all studies contributing to the overall efficacy analysis were assessed according to standardized criteria which included the primary underlying condition, hematological risk factors, infecting organism, certainty of infection and outcome at end of therapy.

An interesting observation of the resulting data from 280 patients from 6 Phase II/III trials was that higher voriconazole plasma concentrations were significantly associated with lower success. Further exploration of this effect was conducted by the applicant and hepatic impairment, poor prognosis and early dose escalation, were identified as confounding clinical factors. Therefore, no definitive conclusions may be made from these 6 Phase II/III studies regarding the relationship between plasma concentrations of voriconazole and efficacy.

Biopharmaceutics

Voriconazole is formulated in a 50 mg and 200 mg tablet. The 50 mg tablet contains one-quarter of the amount of all the ingredients in the 200 mg tablet and is prepared using the same blend.

Voriconazole exposure is lower and C_{max} occurs later in the fed state as compared to the fasted state. Therefore, it is recommended that oral voriconazole be administered either one hour before or one hour after meals. This is how oral voriconazole was dosed in Phase III clinical trials.

IV. GENERAL COMMENTS

1. Upon review of the oral and IV voriconazole NDAs, the Clinical Division has determined that voriconazole is approvable for the treatment of (1) invasive aspergillosis and infections due to *Fusarium* spp. and *Scedosporium apiospermum* and (2) esophageal candidiasis. The indication of empiric antifungal therapy was determined to be not approvable.

2. In the clinical trials for invasive aspergillosis, patients randomized to voriconazole were initiated on an IV regimen and then allowed to switch to oral therapy at the discretion of the investigator. The applicant did not study the clinical efficacy of oral voriconazole when used as initial therapy. The exposure following oral and IV loading doses and after maintenance dosing are compared in the three tables below. It can be concluded that exposure to voriconazole is lower with oral than comparable IV doses. Therefore for the indication of invasive aspergillosis, patients should be limited to IV-to-oral switch therapy.

Mean PK Parameters Following Loading Dose(s)

	6 mg/kg IV x 2	400mg po Q12h x 2	
	1st dose	1st dose	2nd dose
C_{max} (ng/mL)	4812	2305	2329
AUC_{0-12} (ng*h/mL)	13508	9305	16290

Mean PK Parameters on Day 10
(following loading dose x 1 day, then maintenance dosing)

	3 mg/kg IV Q12h	200mg po Q12h
C_{max} (ng/mL)	3175	2389
AUC_{0-12} (ng*h/mL)	15136	15033

Mean PK Parameters on Day 7* or 14**
(following loading dose x 1 day, then maintenance dosing)

	4 mg/kg IV Q12h*	3 mg/kg IV Q12h*	200mg po Q12h**
C_{max} (ng/mL)	5402	3006	1885
AUC_{0-12} (ng*h/mL)	29467	13919	9765

3. The applicant is currently recommending that the oral voriconazole maintenance dose (MD) be reduced by 50% in those adult patients weighing <40 kg. However, during the review, the issue was raised of whether both the intravenous and oral maintenance doses of voriconazole need to be reduced in patients weighing <40 kg. The impetus for dose reduction for patients weighing <40 kg apparently came from the Pop PK analyses of the Phase 1 PK data in healthy subjects where an increase was observed in the predicted AUC estimates (based on simulated data) in subjects <40 kg vs. subjects >40 kg after 1 week of 3 mg/kg IV, then repeat dosing with 200 mg or 300 mg PO BID for an additional 12 weeks. The increase in the predicted AUC estimates was more pronounced for the 300 mg PO BID regimen vs. the 200 mg PO BID regimen. From these results, the applicant then decided to reduce the oral maintenance dose by 50% in those patients <40 kg. An analysis of the plasma voriconazole plasma concentrations from the Phase 2/3 clinical trials in those patients <40 kg (16/552 - 3%) who received the reduced oral MD showed similar voriconazole levels vs. those patients >40 kg who received the usual oral MD of 200 mg BID (350/552 - 64%). Thus, plasma voriconazole concentration data for adult patients weighing <40 kg only exists for the oral MD regimens and not for any of the IV regimens from either pharmacokinetic studies or in the clinical trials.

V. COMMENTS FOR THE APPLICANT

1. Based on the data provided in Studies 150-228 and 150-1024 evaluating the interaction between voriconazole and rifabutin, the reviewer recommends **contraindicating** the coadministration of rifabutin and voriconazole. Additional clinical studies to further evaluate this interaction are recommended so that the labeling for voriconazole may be adequately revised regarding the coadministration of these two drugs. The sponsor may want to consider studies designed to evaluate the interaction with a reduced dose of rifabutin (150mg QD) so that the induction of voriconazole metabolism may be less than what was observed at the usual rifabutin dose of 300 mg QD, and/or evaluate the interaction with lower oral voriconazole maintenance doses, other than 400mg BID, in larger numbers of subjects.

2. It is recommended that additional drug interaction studies be performed in humans with voriconazole and the following drugs / drug classes. These studies should be designed to evaluate the two-way interaction potential for each combination.
   - Oral Contraceptives
   - Methadone
   - Representative HIV Protease Inhibitor (e.g., Ritonavir)
   - Representative Non-Nucleoside Reverse Transcriptase Inhibitor (e.g., Efavirenz)

3. Although the effect of coadministration of voriconazole on the pharmacokinetics of cyclosporine was evaluated in healthy subjects (Study 150-235), it is recommended that the potential for the reverse interaction be also evaluated. That is, the effect of coadministered cyclosporine on the pharmacokinetics of voriconazole.

VI. LABELING COMMENTS

See the attached labeling in Appendix 1, which incorporates the Clinical Pharmacology and Biopharmaceutics reviewer comments. The label has been restricted to information pertinent to only the indication of invasive aspergillosis and infections due to *Fusarium* spp. and *Scedosporium apiospermum.*

VII. RECOMMENDATION

The information contained in Item 6: Human Pharmacokinetics and Bioavailability of NDAs 21-266 and 21-267 for voriconazole oral tablets and lyophilized powder for reconstitution has been reviewed and was found to be acceptable and adequate to support approval. The dissolution method using USP Apparatus 2 (paddle) in HCL at 50 rpm and the specification of Q= at 30 minutes was reviewed and found to be acceptable. Please forward the comments in Sections V and VI on to the applicant.

Joette M. Meyer, Pharm.D.
Office of Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III

Philip M. Colangelo, Pharm.D., Ph.D.
Office of Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III

RD/FT signed by Funmi Ajayi, Ph.D. (Team Leader) _____

OCPB Briefing October 30, 2001 (attendees): Shiew-Mei Huang, John Lazor, Arzu Selen, Funmi Ajayi, Jooran Kim, Joette Meyer, Phil Colangelo

cc: HFD-590: /NDA 21-266
/NDA 21-267
/PM/SalibaJ
HFD-880: /BiopharmTL/AjayiF
/Biopharm/MeyerJ
/Biopharm/ColangeloP
HFD-205: FOI

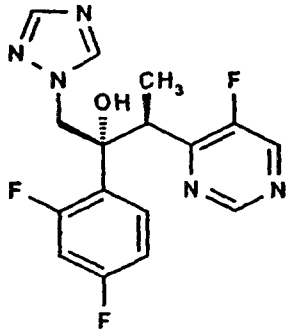
APPEARS THIS WAY
ON ORIGINAL

SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

I. DRUG CHARACTERISTICS AND FORMULATIONS

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

Chemical Structure



Molecular Formula
$C_{16}H_{14}F_3N_5O$

Molecular Weight of Voriconazole
349.3 grams/mole

Formulation – Oral Tablets
The composition of voriconazole film-coated tablets, 50 mg and 200 mg are as shown below in the table. The 50 mg tablet contains one-quarter of the amount of all the ingredients in the 200 mg tablet and is prepared using the same blend.

Component	Grade	Function	50 mg Tablet (mg/tablet)	200 mg Tablet (mg/tablet)
Voriconazole	Pharm	Active	50.000	200.000
Lactose Monohydrate (spray dried)	NF			
Pregelatinised Starch	NF			
Croscarmellose Sodium	NF			
Povidone	USP			
Magnesium Stearate	NF			
Purified Water[a]	USP			
Total Weight			153.750	615.000

developed. Linearity was confirmed over the calibration ranges of [redacted] for voriconazole and [redacted] for the N-oxide metabolite.

III. PHARMACOKINETIC RESULTS SUMMARY

A. What is the proposed mechanism of action of voriconazole?

Voriconazole is a triazole antifungal agent. The mechanism of action is the same as for the other approved antifungal azoles (i.e., fluconazole and itraconazole). Voriconazole has been shown to inhibit the cytochrome P-450 dependent 14α-lanosterol demethylase enzyme that is responsible for the removal of the methyl group on the C14 site of lanosterol. Inhibition of this enzyme results in the depletion of ergosterol, a major component necessary for the integrity of the fungal cell wall, and the accumulation of the sterol precursor compounds.

B. What are the proposed indications?

The applicant has submitted a new drug application (NDA) for voriconazole for the indications of: treatment of invasive aspergillosis; empiric antifungal therapy of febrile neutropenic patients; treatment of candida eosophagitis; treatment of serious candida infections; treatment of serious fungal infections caused by *Fusarium* and *Scedosporium* spp.; treatment of serious fungal infections in patients refractory or intolerant to other therapy.

C. What are the proposed dosing regimens for voriconazole?

The proposed dosage and administration of intravenous and oral voriconazole for adults is shown in the table below.

	INTRAVENOUS	ORAL	
		Patients 40kg and above	**Patients less than 40kg**
Loading Dose Regimen (first 24 hours)	Two doses of 6mg/kg 12 hours apart	Two doses of 400mg 12 hours apart	Two doses of 200mg 12 hours apart
Maintenance Dose (after first 24 hours)			
Serious *Candida* infections Empirical Therapy	3 mg/kg every 12 hours	200 mg every 12 hours	100 mg every 12 hours
Invasive aspergillosis/ *Scedosporium* and *Fusarium* infections/ Other serious mold infections	4 mg/kg every 12 hours	200 mg every 12 hours	100 mg every 12 hours

The proposed dosage and administration of intravenous and oral voriconazole for pediatrics is shown in the table below. Voriconazole is not recommended for children less than 2 years of age. Adolescents (12 to 16 years of age) should be dosed as adults.

	Intravenous	Oral*
Loading dose regimen (first 24 hours)	Two doses of 6 mg/kg 12 hours apart	Two doses of 6 mg/kg 12 hours apart
Maintenance dose (after first 24 hours)	4 mg/kg every 12 hours	4 mg/kg every 12 hours

*Oral administration has not been studied in children. If the child is able to swallow tablets, the dose should be administered to the nearest mg/kg dose possible using whole 50 mg tablets.

D. What are the exposure-response relationships for efficacy and safety?

As discussed previously, the pharmacokinetics of voriconazole in humans are characterized by non-linearity due to saturable metabolism, wide intersubject variability, and extensive hepatic metabolism by CYP450 enzymes, namely CYP2C19, which exhibits genetic polymorphism. Because of these features, patients treated with voriconazole at a given dose can be exposed to a wide range of drug concentrations in plasma. Therefore, exploratory pharmacokinetic/pharmacodyanmic (PK/PD) analyses were performed by the applicant to evaluate the relationships between plasma exposure to voriconazole (i.e., C_{max}, AUC, mean plasma concentrations) and safety and efficacy endpoints. Liver function test (LFT) results and visual adverse events were chosen as the relevant safety endpoints. The efficacy endpoint was an applicant-assessed response at end of treatment. Two separate PK/PD analyses were conducted, one with data from healthy subjects in Phase I studies and the other with data from patients in Phase II/III trials. The applicant's analyses included graphical and tabular presentations as well as multiple linear and logistic regression, and survival analyses (for time-to-event data).

Exposure-Safety Results from Phase I Studies in Healthy Subjects

Twenty-nine (29) Phase I studies were used in the analyses and included PK and PD (i.e., clinical laboratory test) data from 547 subjects treated with single and/or multiple doses (PO and/or IV) of voriconazole and 55 subjects with placebo (PBO). Of the 547 voriconazole-treated subjects, multiple doses were administered to 402 subjects. Doses ranged from 0.9 mg/kg to 6 mg/kg IV and from 100 mg to 400 mg PO.

Relevant PK parameters from the Phase I studies are summarized in the tables below.

Voriconazole C_{max} and AUC after Single and Multiple IV and Oral Doses
Pooled Phase I Data

	Single Dosing (N=300)		Multiple Dosing (N=457)	
Subject Demographics	**Mean C_{max} (µg/mL)**	**Mean AUC (µg•hr/mL)**	**Mean C_{max} (µg/mL)**	**Mean AUC (µg•hr /mL)**
All Young Healthy Subjects*	2.43 ± 2.40 (99%)	10.6 ± 14.3 (135%)	2.33 ± 1.73 (74%)	15.6 ± 16.7 (107%)
Young Healthy Males	2.06	8.7	2.19	14.4
Young Healthy Females	5.09	24.3	3.93	29.5
Renal Impairment / Hepatic Impairment (Cirrhotic)	1.17	11.0	Not Reported	Not Reported

*Mean ± SD (%CV); [Maximum Value]

Voriconazole Average Plasma Concentrations and C_{max} at Steady State after Multiple IV and Oral Doses
Pooled Phase I Data

	Average Steady State Conc. N=402 (µg/mL)	Maximum Conc. (C_{max}) N=402 (µg/mL)
Minimum		
25th Percentile	**0.58**	**1.58**
Median	**0.95**	**2.25**
75th Percentile	**1.91**	**3.30**
Maximum		

Exposure – LFT Relationships from Multiple Dose Studies in Healthy Subjects
Increases in both ALT and AST from baseline were related to the increases in the C_{max} and the AUC of voriconazole. Modeling the PK/PD relationships for ALT and AST indicated that C_{max} and AUC are strongly associated with these two LFT indices. Increases in ALT and AST appeared to be most pronounced starting at C_{max} values of approximately 5.0 to 6.0 µg/mL and at AUC values starting at approximately 40 to 50 µg•hr/mL. In the few subjects with the greatest changes in ALT or AST from baseline, the C_{max} and AUC values were also the highest at approximately 8.0 µg/mL and 80 µg•hr/mL and higher, respectively. The greatest changes in ALT and AST were approximately a 1700% and 700% increase from baseline, respectively, at C_{max} and AUC of approximately 8.5 µg/mL and 85 µg•hr/mL, respectively. From the relationships of ALT and AST with C_{max}, it would appear that maximum plasma concentrations of voriconazole should not exceed ——— following multiple dose administration.

C_{max} and AUC of voriconazole were also positively associated with the increase in alkaline phosphatase (ALKP), but the relationships were not as strong as with ALT and AST. Unlike the relationships with ALT and AST, there appeared to be no clear threshold values for C_{max} or AUC of voriconazole with ALKP. The greatest increase in ALKP from baseline was approximately 85% at a C_{max} and AUC of approximately 8.5 µg/mL and 85 µg•hr/mL, respectively.

For total bilirubin, there was little or no relationship with C_{max} or AUC of voriconazole.

It was difficult to adequately assess the time course of LFT abnormalities with respect to voriconazole dosing. This was mainly because the majority of abnormalities were associated with one study. In this study subjects received multiple dose voriconazole that were higher than those usually recommended (i.e., 5 mg/kg IV and 400 mg bid orally) for 14 days duration. Other repeat dose studies employed lower doses (i.e., 3 mg/kg IV and 200 mg bid orally) for a shorter duration of 7 days. Nonetheless, the results from this study suggested that LFT abnormalities may occur after longer duration of therapy (i.e., 7 days or more) and may be associated with higher voriconazole doses and/or plasma concentrations.

Exposure – Visual Adverse Events (VAE) Relationships in Healthy Subjects
Visual adverse events (VAE) from the Phase I studies were classified and evaluated as "any VAE" or as "enhanced/altered visual perception". The overall incidences of these two classifications were higher following multiple doses than with single dose administration. The incidence of any VAE was 46% with multiple doses vs. 24% with single doses; for enhanced/altered visual perception, the incidence was 23% vs. 11%.

Overall, there was a positive association between C_{max} and AUC and the incidence of any VAE and enhanced/altered visual perception with single dose administration of voriconazole. The association between C_{max} and AUC and visual adverse events was weaker with multiple dose administration. It is important to note that there was considerable overlap in the C_{max} and AUC estimates for those subjects reporting VAE and those who did not report any VAE. Nonetheless, mean estimates of both PK parameters were higher for those subjects reporting VAE versus those who did not.

<u>Exposure-Safety Results from Phase II/III Studies in Patients</u>
There were 10 Phase II/III clinical efficacy and safety trials included in the PK/PD analyses. The safety population consisted of 1053 patients who had at least one PK sample drawn for determination of voriconazole concentration in plasma.

Plasma voriconazole concentrations were determined from blood samples collected at various time points during treatment. More than one blood sample may have been collected during a specific dose interval or on different days of treatment. The PK data were summarized as weekly mean plasma concentrations, with one plasma concentration per weekly window that was 7 days in duration. The median number of weekly mean plasma voriconazole concentrations per subject ranged from 1 to 5 across the studies. The concentration data for voriconazole are summarized in the table below.

Summary Statistics for Voriconazole Plasma Concentrations at Steady State from Phase II/III Studies

	N	Average Conc. (µg/mL)	Maximum Conc. (C_{max}) (µg/mL)
Minimum	**1053**		
25th Percentile	1053	1.17	1.80
Median	**1053**	**2.49**	**3.40**
75th Percentile	1053	4.38	5.83
Maximum	**1053**		

Mean plasma voriconazole plasma levels summarized for all Phase II/III patients over bands of 1.0µg/mL (i.e., 0-1, 1-2, 2-3 µg/mL, etc.) are as follows:

Concentration Bands (µg/mL)	Approximate Frequency (Total N=1053)	Approximate Cumulative Frequency
0 (<0.1) to 1.0	22%	22%
1.0 to 2.0	20%	42%
2.0 to 3.0	17%	59%
3.0 to 4.0	13%	72%
4.0 to 5.0	9%	81%
5.0 to 6.0	7%	88%
6.0 to 7.0	4%	92%
7.0 to 8.0	3%	95%
8.0 to 9.0	3%	98%
>9.0 to 21.0	3%	~100%

As can be seen, the majority of patients (80-90%) have mean plasma levels of 6 µg/mL and less, with about half of the patients with levels of 3 µg/mL and less. Approximately 10-15% of patients had mean concentrations greater than 6 µg/mL.

Exposure – LFT Relationships from Multiple Dose Studies in Patients
Overall, there was an association between the increase in LFT abnormalities and plasma voriconazole concentrations. Median voriconazole plasma levels were generally higher in those patients with increased ALT, AST, alkaline phosphatase (ALKP), and total bilirubin levels than those patients with normal values at weekly intervals from 1 to 12 weeks of voriconazole therapy. The results of the longitudinal logistic regression (odds ratio) and time to event (Cox proportional hazard ratio) modeling analyses are shown in the tables below.

Summary Statistics from Longitudinal Logistic Regression for LFT Abnormalities

	Odds Ratio per 1.0 µg/mL Increase in Voriconazole Plasma Conc.	Lower 95% Bound	Upper 95% Bound
ALT		0.97	1.19
AST		1.06	1.20
Alkaline Phosphatase		1.08	1.25
Bilirubin		1.08	1.27

Summary Statistics from Time to Event Analyses for LFT Abnormalities

	Hazard Ratio per 1.0 µg/mL Increase in Voriconazole Plasma Conc.	Lower 95% Bound	Upper 95% Bound
ALT		1.02	1.17
AST		1.07	1.20
Alkaline Phosphatase		1.06	1.25
Bilirubin		1.07	1.25

In the longitudinal regression analyses, the model predicted odds of approximately 7%, 13%, 16%, and 17% in abnormalities of these LFT's for every 1.0 µg/mL increase in plasma voriconazole levels. These odds were statistically significant for AST, ALKP, and total bilirubin ($p<0.001$); the ALT odds ratio was not significant. The time to event analyses showed similar results with respect to the relative risk of LFT abnormalities occurring for every 1.0 µg/mL increase in plasma voriconazole levels. In addition, plasma voriconazole levels and the hazard ratio/relative risk of all LFT abnormalities were significantly associated ($p<0.01$).

Unlike the PK/PD analyses for the subjects in Phase I studies, no threshold concentration(s) for the increase in LFT's were apparent for the patients in the Phase II/III trials. However, it should be noted that maximum frequencies of LFT abnormalities occurred at the highest plasma concentration bands, i.e., 9 µg/mL and ≥9 µg/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. The 95% confidence intervals for the statistical ratios shown in the tables above indicated that the odds or risk of an LFT abnormality with every 1 µg/mL increase in plasma voriconazole concentrations may be as low 0% and as high as approximately 30%.

Exposure – Visual Adverse Events (VAE) Relationships from Multiple Dose Studies in Patients
The frequency of visual adverse events varied from approximately 11% to 52% in the 10 Phase II/III trials. Overall, it appeared that median plasma voriconazole concentrations were higher in those patients with VAE than in those patients without VAE over the majority of the weekly evaluation intervals. The incidence in VAE went from approximately 10 to <20% at plasma concentrations ranging from 0 to 3 µg/mL, then increased to approximately 25% to 40% at voriconazole plasma concentration bands starting at 3 to 4 µg/mL and up to >9 µg/mL. Thus, a threshold concentration of approximately ≥3 µg/mL for VAE in the Phase II/III patients was apparent.

The longitudinal logistic regression analysis revealed a statistically significant relationship between plasma voriconazole concentration and the odds of a VAE ($p=0.011$). The model predicted approximately a 5% increase in the odds of a VAE occurring for every 1.0 µg/mL increase in plasma voriconazole concentration (95% CI: 1%, 8%).

The percentage of patients with VAE was the highest in the first week of voriconazole dosing ranging from approximately 20% to 40% over plasma concentrations from 0 to >6µg/mL. The incidence decreased by week 2 to approximately 2 to 4% and remained diminished over the subsequent weekly intervals out to week 24.

Exposure – Efficacy Relationship from Multiple Dose Studies in Patients
The efficacy population consisted of 453 patients who had a certainty of baseline fungal infection categorized as "definite" or "probable" and were assessed in the applicant's Voriconazole Efficacy Response Assessment database (VERA). The efficacy outcome variable was success or failure at the end of treatment. The VERA was a tool that harmonized the efficacy assessments of patients with the same pathogens, but who were enrolled in different studies. These studies commonly had slightly different entry and evaluation criteria. Patients from all studies contributing to the overall efficacy analysis were assessed according to standardized criteria which included the primary underlying condition, hematological risk factors, infecting organism, certainty of infection and outcome at end of therapy.

The applicant noted that the primary PK/PD analysis for efficacy was conducted omitting one study because of the very high response rate observed (approximately 90%) compared with other studies. The excluded study enrolled patients with esophageal candidiasis, which has a higher cure rate than the other indications studied by the sponsor. After excluding patient data from this study, 280 patients from 6 Phase II/III trials remained in the primary analysis population.

The logistic regression analysis of the primary population (N=280) revealed a statistically significant negative linear relationship between mean plasma voriconazole concentration and the odds of success (p=0.005). Logistic regression analysis using threshold concentration as the explanatory variable showed that the odds ratio for a successful outcome was greatest at the 0.5 µg/mL threshold (ratio: 1.46; 95% CI: 0.63, 3.41). The proportion of successes in patients with mean voriconazole plasma levels below 0.5 µg/mL was approximately 46% compared to approximately 56% of successes in patients with mean plasma levels above 0.5 µg/mL.

An interesting observation was that the mean plasma voriconazole concentration threshold of 6.0 µg/mL was significantly associated with lower success (p=0.001). The odds ratio was lowest at the 6.0 µg/mL threshold (ratio: 0.16; 95% CI: 0.06, 0.47). The proportion of successes in patients with mean voriconazole plasma levels below 6.0µg/mL was approximately 58% compared to approximately 26% of successes in patients with mean plasma levels above 6.0 µg/mL. Further exploration of this latter effect at plasma levels of 6.0 µg/mL was conducted by the applicant. The finding that treatment failures in these subjects occurred early led to a clinical review that identified hepatic impairment, poor prognosis and early dose escalation as confounding factors.

Overall, due to confounding clincial factors, no definitive conclusions may be made from these 6 Phase II/III studies regarding the relationship between plasma concentrations of voriconazole and efficacy.

E. What are the basic pharmacokinetic characteristics of voriconazole?

Voriconazole exhibits non-linear pharmacokinetics due to saturable metabolism. Exposure, in terms of peak plasma concentration (C_{max}) and AUC_τ increases in a disproportionate manner with dose. For IV dosing a 1.6 fold increase in dose (from 3 mg/kg to 5 mg/kg) results in a 2.4 and 3.1 fold increase in C_{max} and AUC_τ, respectively. For oral dosing, a 2-fold increase in dose (from 200 mg to 400 mg) results in a 2.8 and 3.9 fold increase in C_{max} and AUC_τ, respectively.

With repeated dosing, plasma accumulation of voriconazole is substantial due to the non-linear pharmacokinetics. Following multiple dosing with 3 mg/kg IV bid, AUC_τ and C_{max} values are about 2.4 and 1.5 times, respectively, that seen after single dosing.

Steady state trough plasma concentrations with voriconazole are achieved after 5 days of oral or IV dosing without a loading dose. However, when a loading dose is used, steady state trough plasma concentrations are achieved by Day 3.

Fourteen healthy subjects were administered a loading dose of 6 mg/kg IV bid x 2 doses, followed by 3 mg/kg IV bid x 6 days, followed by 200 mg bid x 6.5 days. The resulting pharmacokinetic parameters of voriconazole are shown below.

Mean (%CV) [Range] Voriconazole Pharmacokinetic Parameters Following Multiple Dosing

Parameter	3 mg/kg (N=14)	200 mg (N=14)
C_{max} (ng/ml)	3006 (21)	1885 (37)
AUC_τ (ng*hr/ml)	13919 (52)	9765 (61)
T_{max} (hr)	1.07 (11)	1.50 (29)

The systemic clearance of voriconazole is calculated to be 8.7 ml/min/kg following a single 3 mg/kg IV dose and drops to 3.7 ml/min/kg after repeated dosing of 3 mg/kg IV bid for 10 days.

In general, the Phase I pharmacokinetic studies show the inter-subject variability in the estimates of C_{max} and AUC following multiple dosing of 3 mg/kg IV bid and/or 200 mg bid orally is high. Inter-subject variability (expressed as %CV) range from approximately 20% to greater than 100%. In the population pharmacokinetic analysis of 11 Phase I studies, the between subject variability (expressed as %CV) in the predicted steady state estimates of voriconazole AUC following multiple oral (200 mg Q12 hr) or IV (3 mg/kg Q12 hr) administration is 90-100%. As a consequence of this high variability, different patients treated with voriconazole at the same dose can exhibit a wide range of drug concentrations in plasma.

Absorption

The peak plasma concentration (C_{max}) of voriconazole occurs 1-2 hours after dosing in fasted state.

From the population pharmacokinetic analysis, the oral bioavailability of voriconazole is estimated to be 96% (60% to 122%). Mean values of C_{max} and AUC_τ following multiple dosing were 37% and 30% lower following oral dosing (200 mg) compared to those obtained following IV dosing (3 mg/kg).

A high fat meal (1000 calories with 50 to 60% of the total caloric content from fat, 25% from carbohydrate and 15% from protein) affects the bioavailability of voriconazole. The exposure after multiple dosing, in terms of mean AUC_τ and C_{max}, is lower (24% and 34%, respectively) in the fed state as compared to the fasted state. Additionally, C_{max} occurs later in the fed state (mean of 2.5 hours fed versus 1.1 hours fasted). It is recommended that oral voriconazole be administered either one hour before or one hour after meals. The applicant conducted Phase III clinical trials using this dosing regimen. However, no pharmacokinetic data were submitted in the NDA to investigate this regimen. Therefore, the effect on absorption caused by administering voriconazole one hour before or after meals has not been characterized.

Alterations in gastric pH do not appear to affect the absorption of voriconazole.

Distribution

The volume of distribution of voriconazole is estimated to be 4.6 L/kg.

Plasma protein binding of voriconazole is approximately 60% and is independent of concentrations achieved following single and multiple doses of 200 mg or 300 mg orally bid (approximate plasma concentration range

Metabolism

Voriconazole undergoes extensive hepatic metabolism, primarily by three cytochrome P-450 enzymes: CYP2C19, 2C9, and 3A4. *In vitro* metabolism studies using human hepatic microsomal preparations

show that voriconazole is both a substrate and inhibitor of these three enzymes. No *in vitro* studies were conducted to evaluate the potential of voriconazole to induce CYP450-mediated substrate metabolism.

A mean of 1.5% of the dose is excreted unchanged in the urine following a single radiolabeled dose in healthy subjects.

The major circulating metabolite in plasma, voriconazole N-oxide, has the potential to inhibit the metabolism of CYP2C9 and CYP3A4 substrates, like the parent voriconazole. The potential for this metabolite to inhibit CYP2C19 substrates appeared to be weaker than that of voriconazole. The inhibition of CYP2C9 and CYP3A4 by voriconazole N-oxide may contribute to the overall inhibitory effect following parent voriconazole administration.

Voriconazole N-oxide has been shown to have minimal anti-fungal activity.

Elimination
Following IV administration of a single radiolabeled dose of voriconazole, a mean of 80% of the dose is excreted in urine (as voriconazole and metabolites) and a mean of 24% in feces. Similarly, following oral administration a mean of 83% of the dose is excreted in urine and a mean of 22% in feces. Eight metabolites of voriconazole have been identified. All of which are present in urine and two are present in feces. The primary route of metabolism involves N-oxidation of the fluoropyrimidine ring to form UK-121,265 (N-oxide metabolite). The N-oxide metabolite accounts for a mean of 72% of the circulating radiolabeled metabolites in plasma. The metabolites and extent of excretion of radioactivity are similar after oral and IV administration of voriconazole.

The apparent elimination half-life of voriconazole is dose dependent. Following a 200 mg single oral dose the half-life is about 6 hours, but increases up to 12 hours after 400 mg. Following single IV dosing the apparent half-life is about 6 hours with doses of 3 mg/kg and 6 mg/kg and about 6 hours after single and multiple doses of 3 mg/kg IV bid.

F. What intrinsic factors influence exposure or response to voriconazole and what is the impact?

Age/Gender
Following a single 6 mg/kg IV dose of voriconazole, elderly subjects have a higher mean C_{max} compared to young subjects (mean ratio 121%, 95% CI: 108 to 135). Female subjects have a lower mean C_{max} compared to male subjects (mean ratio 88%, 95% CI: 79 to 98). Elderly male subjects have the highest plasma concentrations. For AUC_t, elderly males have higher values than the other three groups. Compared to young males the mean ratio is 207% (95% CI: 157 to 273) and elderly females compared to elderly males is 64% (95%CI: 48 to 85). In this study there was a difference in mean weight between males and females, therefore the effect of gender can not be separated from the effect of weight.

Following multiple dosing with 200 mg bid, the mean C_{max} and AUC_t were characterized in young and elderly males and females. The ratios of elderly male:young male are 1.61 (95% CI: 124 to 209) and 1.86 (95% CI: 126 to 273), respectively and those of young female:young male are 1.83 (95% CI: 141 to 238) and 2.13 (95% CI: 145 to 312), respectively. The differences observed in this study between young males and the other three groups were not observed in the single IV dose study.

No dosage adjustment of voriconazole is proposed on the basis of age and/or gender.

Renal Impairment
Following a single 200 mg oral dose of voriconazole, exposure (AUC and C_{max}) is not affected by various degrees of renal impairment from mild to severe.

Moderate renal impairment (creatinine clearance of 30 to 50 ml/min) has no consistent effect on the pharmacokinetics of voriconazole following multiple IV doses. Although mean voriconazole clearance is higher (and mean drug exposure lower) in subjects with moderate renal impairment compared with subjects with normal renal function, inter-subject variability is high and differences between groups are

not statistically significant. This was corroborated by regression analysis, which demonstrated no relationship between voriconazole clearance and the level of renal function.

In subjects with renal impairment and undergoing hemodialysis sessions three times per week, the pharmacokinetic results indicate that exposure, in terms of the concentration at the end of infusion, to voriconazole is 50% lower in dialysis subjects compared with subjects with normal renal function. Voriconazole is dialyzed at a clearance rate of 121 ml/min.

No dosage adjustment of oral voriconazole is necessary in patients with renal impairment. However, in patients with moderate renal dysfunction (i.e., creatinine clearance of 30 - 50 ml/min), accumulation of the IV vehicle, SBECD, occurs (see section on SBECD pharmacokinetics). The mean AUC and C_{max} are increased by 4-fold and almost 50%, respectively, in the moderately impaired group compared to the control group with normal renal function. Intravenous voriconazole should be avoided in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min), unless the benefit outweighs the risk in an individual patient.

A 4-hour hemodialysis session removes only 8% of the total body load of voriconazole, therefore no dosage adjustment is necessary in patients undergoing hemodialysis.

Hepatic Impairment

Following a single 200 mg dose of voriconazole, there is a statistically significant increase in exposure to voriconazole in subjects with mild to moderate hepatic impairment (Child-Pugh Class A and B) compared to healthy normal subjects. The AUC is more than three times higher in the impaired group (Child-Pugh Class A and B) compared to the normal subjects. There is no significant difference in C_{max} between the two groups. When evaluating only the subjects with mild hepatic impairment (Child-Pugh Class A) there is still a 2.3-fold increase in exposure compared to normal subjects.

Administration of a multiple oral doses of 100 mg bid to subjects with moderate hepatic impairment (Child-Pugh Class B) results, on average, in a similar exposure (AUC_τ) to voriconazole to those subjects with normal hepatic function who received 200 mg bid.

In patients with mild to moderate hepatic impairment (Child-Pugh Class A and B) a standard loading dose of voriconazole should be given, but the standard maintenance dose should be halved. The pharmacokinetics of voriconazole in patients with severe hepatic impairment (Child-Pugh Class C) have not been studied.

Patients

The pharmacokinetics of voriconazole in immunocompromised adults at risk for infection with Aspergillosis is similar to that of healthy adult subjects. In patients receiving voriconazole 300 mg bid, the AUC_τ is approximately two fold higher compared to patients receiving 200 mg bid. On the first day of dosing, the mean C_{max} is approximately two-fold higher in patients receiving 300 mg bid compared to patients receiving 200 mg bid. After multiple dosing, the mean C_{max} is approximately two-fold higher in patients receiving 300 mg bid compared to patients receiving 200 mg bid. The accumulation index indicates that there is approximately a five-fold accumulation of voriconazole over 14 days of dosing. There are no apparent differences in accumulation between the 200 mg bid and 300 mg bid doses. On average steady state trough concentrations occurred between 4 and 7 days, but there was no loading dose administered in this study.

Pediatrics

The table below shows the individual plasma concentrations of voriconazole at the end of infusion in pediatrics following single IV doses of 3 mg/kg (N=4) and 4 mg/kg (N=4) doses. From the limited data obtained in pediatrics, it appears that patients from 2 to 11 years of age demonstrate pharmacokinetics consistent with those observed in healthy adults who have received the same dose of IV voriconazole (3 mg/kg or 4 mg/kg) in other studies.

Summary of Plasma Voriconazole Concentrations at the End of a 1-Hour IV Infusion of Single Doses of Either 3mg/kg or 4mg/kg to Pediatric Patients Aged 2 to 11 Years

	3mg/kg Single Dose (N=4)*	4mg/kg Single Dose (N=4)
Mean ± SD (%CV) (Min, Max)	2.22 ± 0.31 µg/mL (14%)	2.64 ± 0.87 µg/mL (33%)

*Includes 2 Homozygous Poor Metabolizers (PM) of CYP2C19

Following multiple IV dosing with 3 mg/kg and 4 mg/kg Q12 hr, mean concentrations of voriconazole at pre-dose and at the end of the infusion in children 6 years to < 12 years are higher than those for younger children 2 years to < 6 years, as seen in the table below. There is a large degree of variability in concentrations both between patients (CV's from 75% to 157%) and between days within a patient. However, voriconazole doses may need to be adjusted further for younger children aged 2 to < 6 years compared to children 6 years and above.

Summary of Plasma Voriconazole Concentrations at Pre-Dose and at the End of a 1-Hour IV Infusion of Repeated Doses to Pediatric Patients Aged 2 to 11 Years
Data Expressed as Mean ± SD (%CV); (Min, Max)

	2 to <6years Conc. (µg/mL)	6 to <12years Conc. (µg/mL)	All Subjects Conc. (µg/mL)
3mg/kg Q12 hr x 3 Days			
Pre-dose	0.60 ± 0.94 (157%)	0.97± 1.22 (126%)	0.80 ± 1.10 (137%)
	(N=12)	(N=14)	(N=26)
End of Infusion	2.86 ± 3.08 (108%)	4.97 ± 4.33 (87%)	4.01 ± 3.87 (97%)
	(N=10)	(N=12)	(N=22)
4mg/kg Q12 hr x 4 Days			
Pre-dose	0.78 ± 1.10 (141%)	1.29 ± 1.47 (114%)	1.04 ± 1.30 (125%)
	(N=11)	(N=11)	(N=23)
End of Infusion	2.83 ± 2.12 (75%)	3.48 ± 2.91 (84%)	3.15 ± 2.50 (79%)
	(N=10)	(N=10)	(N=20)

A population pharmacokinetic analysis of voriconazole plasma concentration data was performed using data from the Phase I single dose study and the Phase I multiple dose study in pediatric patients ranging in age from 2 to 11 years (N = 35). Two single IV doses of voriconazole (3 mg/kg and 4 mg/kg) were evaluated in one study. For the multiple dose study, a loading dose of 6 mg/kg IV bid x 2 doses followed by maintenance IV doses of 3 mg/kg or 4 mg/kg was investigated.

The pediatric subjects were genotyped for CYP2C19 expression. There were 2/35 (6%) homozygous poor metabolizers (PM), 11/35 (31%) heterozygous extensive metabolizers (HEM), and the rest were homozygous extensive metabolizers (EM).

The pediatric Pop PK model predicted that systemic CL in EM pediatric patients is faster compared to the CL estimates predicted by the Pop PK model in the healthy subjects from Phase 1 studies (i.e., CL of 0.4 L/hr/kg in pediatrics vs. 0.25 L/hr/kg in adults). Based on the parameter estimates from the Pop PK model, steady state estimates of AUC were predicted by simulating plasma voriconazole concentrations following IV dosing regimens of 3 mg/kg, 4 mg/kg, 5 mg/kg, and 6 mg/kg Q12 hr for 14 days. The predicted AUC estimates and corresponding average steady state plasma concentrations (C_{ave}) for the pediatric patients was compared to that obtained from the Pop PK model in healthy adult subjects following the IV dose regimen of 3 mg/kg for 14 days. The predicted median AUC and C_{ave} estimates at 4mg/kg Q12 hr in pediatrics were comparable to that of the adults at 3 mg/kg Q 12 hr. From these data it

would appear that IV doses of at least 4 mg/kg Q12 hr are needed in pediatric patients to achieve the same extent of systemic exposure as that in adults receiving IV doses of 3 mg/kg Q 12hr.

G. What are the relavent covariates that influcence the pharmacokinetic variability of voriconazole?

A population pharmacokinetics (Pop PK) analysis was performed using a non-linear mixed effects modeling approach on voriconazole plasma concentration-time data combined from 11 Phase I studies in adult healthy subjects. Subjects included both young and elderly Caucasian males and females, and young Japanese males. Data from a total of 236 subjects were used in the analysis over a range of single and repeated dosing from 1.6 to 6 mg/kg IV (Q12 hr for repeat IV dosing) and from 100 mg to 400 mg orally (Q12 hr for repeat PO dosing).

The primary objectives for the Pop PK analysis were to (1) characterize the PK and the PK variability of voriconazole, and (2) identify the relevant covariates that influence the PK variability of voriconazole.

Voriconazole is extensively metabolized primarily by three hepatic CYP450 enzymes: CYP2C19, CYP2C9, and CYP3A4. CYP2C19 accounts for a large part of voriconazole metabolism and exhibits genetic polymorphism in humans, with approximately 5% of Caucasians exhibiting a deficiency in this enzyme (i.e., poor metabolizers, PM) and approximately 10-20% of Asians with the PM genotype. The importance of the PM genotype for voriconazole is that plasma concentrations/systemic exposure can be significantly increased compared to those individuals who are either not deficient in this enzyme (i.e., homozygous extensive metabolizers, EM) or who have partial expression of the enzyme (i.e., heterozygous extensive metabolizers, HEM). Thus, in the Phase I studies included for the Pop PK analysis, subjects were genotyped for CYP2C19 expression. There were 145/236 (61%) EM subjects, 69/236 (29%) HEM subjects, and 22/236 (9%) PM subjects. As mentioned above, PK data from Japanese subjects (65/236) were included in the analysis to increase the representation of both HEM and PM genotypes.

A two-compartment PK model with non-linear elimination adequately characterized the plasma concentration-time data. The non-linear feature of the model was to be expected since the primary route of voriconazole elimination is by saturable hepatic metabolic pathways. Thus, the model was characterized incorporating the (an affinity constant representing drug concentration at one-half the maximum elimination/metabolic rate) and Vmax (the maximal elimination/metabolic rate).

Effect of CYP2C19 Genotype

Overall, the analysis of the Phase I data shows that the CYP2C19 genotype (i.e., EM, HEM, and PM) is the most influential covariate on the clearance and AUC of voriconazole. CYP2C19 genotype alone accounts for approximately 30% of the overall between subject variability in voriconazole PK. Secondary covariates identified by the Pop PK analysis are gender and age of the subjects. Adding gender and age to the Pop PK model with CYP2C19 genotype accounts for additional variability in PK of approximately 10%.

Overall, the Pop PK analysis of the Phase I data indicates that PM subjects have the highest plasma voriconazole concentrations, followed by HEM subjects then EM subjects. Following oral and IV doses of 200 mg and 3 mg/kg Q12 hr, respectively, average steady state plasma concentrations and AUC estimates in PM subjects are approximately 4-times those of EM subjects, while in HEM subjects they are approximately 2-times those of EM subjects.

The variability in plasma concentrations/systemic exposure between subjects of varying genotype is quite high. The between subject variability (expressed as %CV) in the predicted steady state estimates of voriconazole AUC following oral ($20_{0\ mg}$ Q12 hr) or IV (3mg/kg Q12 hr) administration is >90%. This implies that the range of plasma exposures to voriconazole will show considerable overlap between subjects.

As was mentioned earlier, plasma accumulation of voriconazole following repeated dosing is extensive. The Pop PK analysis also shows that the magnitude of this accumulation is dependent on CYP2C19 genotype. As might be expected, plasma accumulation following 200 bid orally is highest for PM subjects (approximately 6-times vs. single dose), intermediate for HEM subjects (approximately 3-times vs. single dose), and lowest for EM subjects (approximately 2-times vs. single dose).

It is noteworthy to mention that no Pop PK analyses were performed in the Phase III clinical program because the Phase III trials were already ongoing when it was discovered that the CYP2C19 genotype was the major covariate influencing the PK of voriconazole. It was not possible to retrospectively assess the genotype of patients in the Phase III trials.

Effects of Gender and Age

From the Pop PK analysis of the Phase I data, it appears that both gender and age may have some additional influence of the PK of voriconazole. Females appear to have higher plasma exposure than males (i.e., AUC 30% to 100% higher) and greater extent of plasma accumulation than males (i.e., accumulation ratio 20% to 50% higher) at the 200 mg Q12 hr dose regimen. A similar trend is apparent for elderly females vs. elderly males. However, plasma voriconazole concentration-time data collected from 10 Phase II/III studies of patients (N=1053) indicates that plasma concentrations of voriconazole are relatively similar between young females and young males and between elderly females and elderly males. There is a trend for both elderly males and females to have slightly higher plasma concentrations than their younger counterparts.

The proposed labeling recommends no adjustment in voriconazole dosage for either gender or age.

Effect of Body Weight

Although not identified as a significant covariate in the Pop PK model, there is a weak relationship between weight and voriconazole AUC following repeated dosing. With repeated dosing for longer periods of time (i.e., > 1-week duration), the AUC estimates show a trend to increase as the subjects' body weights became lower. Subject body weights in the Phase I datasets ranged from approximately 50 kg to 95 kg. Thus, although subjects with body weights < 50 kg were not included in the Pop PK analysis, a decision was made for the Phase III studies to reduce the dose by one-half in patients with body weights < 40 kg. The plasma concentration data obtained from the 10 Phase II/III trials of patients shows similar average steady state plasma concentrations following oral voriconazole administration between patients with body weights < 40 kg who received one-half the recommended dose versus those patients with body weights ≥ 40 kg.

The proposed labeling recommends a reduction in the recommended voriconazole dosage by one-half patients with body weights < 40 kg.

Race

Influence of race in the Pop PK of the Phase I data was limited to an analysis of Japanese versus Caucasian race. Race has no significant influence on voriconazole PK after accounting for CYP2C19 genotype and body size/weight in the model.

H. What are the extrinsic factors that influence exposure or response to voriconazole?

In Vitro Drug Interactions

In vitro hepatic microsomal studies indicate that voriconazole is both a substrate and inhibitor of the CYP2C9, CYP2C19, and CYP3A4 enzymes in the liver. In microsomes of cell lines expressing only one CYP450 enzyme, substrate affinity of voriconazole was greater for CYP2C19 (Km ~4μM) and CYP2C9 (Km ~21μM) than CYP3A4 (Km ~240μM). No appreciable metabolism of voriconazole was apparent with CYP1A2, CYP2D6, or CYP2E1. Inhibition potency of voriconazole was also greatest against CYP2C9 (Ki 7μM) and CYP2C19 (Ki 14μM) compared to CYP3A4 (Ki 22μM). *In vitro* comparisons between voriconazole and ketoconazole or itraconazole demonstrate that voriconazole is a substantially less potent inhibitor of CYP3A4 metabolism than the other two azoles.

In vitro interaction studies were performed using liver microsomes to evaluate the potential for voriconazole to interact with other drugs that are substrates for or inhibitors of CYP2C9, 2C19, and 3A4. In some studies the reverse interaction was also evaluated, i.e., the effect of the drug substrate / inhibitor on voriconazole metabolism. The results from these studies are summarized in the tables below.

TABLE 1
Effect of Voriconazole on Drug Substrate Metabolism

CYP450 Enzyme	Drug Substrate	Voriconazole IC50 (Ki) (μM)	Study No.
CYP2C9	Phenytoin	9 (Ki 7±0.4)	DM15
	(S)-Warfarin	13	DM28
CYP2C19	(S)-Mephenytoin	32 (Ki 13.5±6.2)	DM15
	Omeprazole	18	DM28
CYP3A4	Midazolam	9.3	DM34
	Amprenavir	13	DM35
	Saquinavir	22 (Ki ~11) 21	DM25 DM35
	Lovastatin	24	DM36
	Cyclosporine	30	DM28
	Nelfinavir	40	DM35
	Felodipine	50 (Ki 21.5±8.2)	DM15
	Testosterone	54	DM34
	Tacrolimus	117	DM36
	Delavirdine	160	DM36
	Indinavir	>100 (Ki ~70*) ~500	DM25 DM35
	Ethinylestradiol	>300	DM28
	Terfenadine	>300	DM28
	Ritonavir	No Inhibition	DM35

*for IC50 = 100μM

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TABLE 2
Effect of Drug Substrate on Voriconazole Metabolism:
Formation of UK-121,265 (N-oxide metabolite) at 25μM Voriconazole

CYP450 Enzyme	Drug Substrate	Substrate IC50 (μM)	Study No.
CYP2C9	(S)-Warfarin	200	DM28
CYP2C19	Omeprazole	37	DM28
CYP3A4	Indinavir	>100, 1.4, 2.4 ~1000	DM25 DM35
	Ritonavir	16	DM35
	Saquinavir	>100, 19.4, 21.4 ~300	DM25 DM35
	Tacrolimus	19	DM36
	Ethinylestradiol	19	DM28
	Delavirdine	27	DM36
	Amprenavir	58	DM35
	Efavirenz	104	DM36
	Terfenadine	>300	DM28
	Lovastatin	>1000	DM36
	Nelfinavir	>1000	DM35
	Cyclosporine	Not Determined	DM28
Non-Specific	Cimetidine	>300	DM28

The results in Table 1 indicated that voriconazole has the potential to significantly inhibit the metabolism of the CYP2C9 and CYP2C19 substrates phenytoin, warfarin, and omeprazole. Voriconazole appeared to have varying potency as a CYP3A4 substrate inhibitor, demonstrating the greatest potential to inhibit the metabolism of the following CYP3A4 substrates: midazolam, amprenavir, saquinavir, lovastatin, cyclosporine, nelfinavir, felodipine, and testosterone. Voriconazole appeared to be a far less potent inhibitor of the CYP3A4-mediated metabolism of tacrolimus, delavirdine, indinavir, ethinylestradiol, terfenadine, and ritonavir.

In the reverse studies (Table 2), omeprazole showed the greatest potential to inhibit voriconazole metabolism of the CYP2C9 and CYP2C19 substrates tested. There were mixed results with the CYP3A4 substrates tested. Indinavir, ritonavir, saquinavir, tacrolimus, ethinylestradiol, delavirdine, amprenavir and efavirenz all showed the potential to inhibit the metabolism of voriconazole. However, terfenadine, lovastatin, nelfinavir, and cimetidine showed little potential to inhibit voriconazole metabolism.

In Vivo Drug Interactions

The potential for *in vivo* drug interactions was evaluated using drugs that are most likely to be co-administered with voriconazole in the clinical setting of fungal infections and that are also substrates, inhibitors, and/or inducers for these three CYP450 enzymes. In addition, other studies were conducted where an interaction might be expected on a mechanistic basis.

The Effect of Other Drugs on the Pharmacokinetics of Voriconazole

Recommendations for co-administration are listed in Table 1. All the interacting drugs in Table 1 were chosen to investigate CYP450-based mechanisms of interaction. Other drugs selected to evaluate their effect on voriconazole based on non-CYP mechanisms of interaction can be found in Table 3.

TABLE 1
Effect of Other Drugs on the Steady State PK of Voriconazole
Interaction Studies Investigating CYP450-Based Mechanisms

				Results		
Study # Subjects	**Mech.**	**Drug Dose & Duration**	**Vori Dose & Duration**	**Vori Cmax Point Est. (90% CI)**	**Vori AUC Point Est. (90% CI)**	**Reviewer Proposed Recommendations for Co-Administration**
150-228 N=8 healthy young males	CYP450 Induction	**Rifampin** 600mg QD x 23 days	200mg BID x 14 days	0.072 (0.062, 0.095)	0.044 (0.034, 0.057)	Rifampin is **contraindicated** with voriconazole
			400mg BID x 7 days	0.34 (0.22, 0.54)	0.19 (0.15, 0.24)	
150-228 N=8 healthy young males	CYP450 Induction	**Rifabutin** 300mg QD x 23 days	200mg BID x 14 days	0.34 (0.27, 0.42)	0.21 (0.16, 0.28)	Rifabutin is **contraindicated** with voriconazole.
			350mg BID x 7 days (N=3)	0.96 (0.45, 2.05)	0.68 (0.46, 1.00)	
150-1024 N=10 healthy young males	CYP450 Induction	**Rifabutin** 300mg QD x 14 days	400mg BID + Rifabutin x 7 days	2.0 (1.6, 2.6) vs. Vori 200mg BID + PBO*	1.87 (1.5, 2.4) vs. Vori 200mg BID + PBO	
150-233 N=10 healthy young males	CYP450 Induction (primarily CYP3A4)	**Phenytoin** 300mg QD x 21 days	200mg BID x 14 days (N=10)	0.51 (0.39, 0.66)	0.31 (0.24, 0.40)	Increase voriconazole maintenance dose to 5mg/kg IV BID or to 400mg PO BID (from 200mg PO BID); for patients <40 kg increase to 200mg PO BID
			400mg BID x 7 days (N=7)	1.34 (0.89, 2.0) vs. Vori 200mg BID Alone	1.39 (0.97, 1.98) vs. Vori 200mg BID Alone	
150-247 N=17 healthy young males	CYP2C19 Inhibition	**Omeprazole** 40mg QD x 10 days	200mg BID x 10 days	1.15 (1.05, 1.25) vs. Vori 200mg BID + PBO	1.4 (1.3, 1.6) vs.Vori 200mg BID + PBO	No dose adjustment needed for voriconazole with co-administration
150-240 N=8 healthy young males	CYP3A4 Inhibition	**Indinavir** 800mg TID x 10 days	200mg BID x 17 days	1.02 (0.91, 1.14) vs. Vori 200mg BID + PBO	1.07 (0.98, 1.18) vs. Vori 200mg BID + PBO	No dose adjustment needed for voriconazole with co-administration
150-243 N=10 healthy young males	CYP3A4 Inhibition	**E-Mycin** 1g x 7 days	200mg BID x 14 days	1.08 (0.91, 1.28) vs. Vori 200mg BID + PBO	1.18 (0.99, 1.40) vs. Vori 200mg BID + PBO	No dose adjustment needed for voriconazole with co-administration
150-229 N=11 healthy young males	CYP450 Inhibition (Non-Specific)	**Cimetidine** 400mg BID x 8 days	200mg BID 7 days	1.18 (1.06, 1.32) vs. Vori 200mg BID + PBO	1.23 (1.13, 1.33) vs. Vori 200mg BID + PBO	No dose adjustment needed for voriconazole with co-administration

*PBO = Placebo

The Effect of Voriconazole on the Pharmacokinetics Other Drugs

Recommendations for co-administration with voriconazole are listed in Table 2. All the interacting drugs in Table 2 were chosen based on their potential for a CYP450-based interaction. Other drugs selected to evaluate the effect of voriconazole based on non-CYP mechanisms of interaction can be found in Table 3.

TABLE 2
Effect of Voriconazole on the PK of Other Drugs
Interaction Studies Investigating CYP450-Based Mechanisms

				Results		
Study # Subjects	**Mech.**	**Drug Dose & Duration**	**Vori Dose & Duration**	**Drug Cmax Point Est. (90% CI)**	**Drug AUC Point Est. (90% CI)**	**Reviewer Proposed Recommendations for Co-Administration**
150-239 N=13 healthy young males	CYP2C9 Inhibition	**Warfarin** 30mg Single Dose	300mg BID x 12 days	PT ↑8 sec ↑(5, 12 sec)	AUEC for PT ↑929 sec•hr ↑(574, 1283 sec•hr)	Monitor PT / other suitable anti-coagulation tests; adjust warfarin dosage if warranted
150-241 N=6 healthy young males	CYP2C9 Inhibition	**Phenytoin** 300mg QD x 17 days	400mg BID x 10 days	1.67 (1.44, 1.93) vs. Phenytoin + PBO*	1.81 (1.56, 2.10) vs. Phenytoin + PBO	Monitor phenytoin concentrations and monitor for phenytoin related AEs with co-administration
150-1013 N=16 healthy young males	CYP2C9 / CYP3A4 Inhibition	**Omeprazole** 40mg QD x 7 days	200mg BID x 7 days	2.16 (1.78, 2.64) vs. Omeprazole + PBO	3.81 (3.28, 4.41) vs. Omeprazole + PBO	When initiating therapy with voriconazole in patients already receiving omeparzooe doses of 40 mg or greater, reduce omeprazole dose by ½ 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.

*PBO = Placebo

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TABLE 2 (continued)
Effect of Voriconazole on the PK of Other Drugs
Interaction Studies Investigating CYP450-Based Mechanisms

				Results		
Study # Subjects	**Mech.**	**Drug Dose & Duration**	**Vori Dose & Duration**	**Drug Cmax Point Est. (90% CI)**	**Drug AUC Point Est. (90% CI)**	**Reviewer Proposed Recommendations for Co-Administration**
150-1024 N=10 healthy young males	CYP3A4 Inhibition	**Rifabutin** 300mg QD x 14 days	400mg BID + Rifabutin x 7 days	2.95 (2.19, 3.97) vs. Rifabutin + PBO	4.31 (3.47, 5.36) vs. Rifabutin + PBO	**(See also Table 1)** Voriconazole is **contraindicated** with rifabutin
150-1009 N=12 healthy young males	CYP3A4 Inhibition	**Tacrolimus** 0.1 mg/kg Single Oral Dose	200mg BID x 7 days	2.17 (1.86, 2.52) vs. Tacrolimus + PBO	3.21 (2.69, 3.83) vs. Tacrolimus + PBO	Reduce tacrolimus dose by 1/3 when initiating therapy with voriconazole; monitor tacrolimus concentrations frequently. When VFEND is discontinued, tacrolimus concentrations must be frequently monitored and the dose increased as necessary.
150-1015 N=15 healthy young males	CYP3A4 Inhibition	**Sirolimus** 2mg Single Oral Solution Dose	200mg BID x 9 days	6.56 (5.73, 7.52) vs. Sirolimus + PBO	11.14 (9.87, 12.58) vs. Sirolimus + PBO	Sirolimus is **contraindicated** with voriconazole
150-244 N=14 healthy young males	CYP 3A4 Inhibition	**Indinavir** 800mg TID x 7 days	200mg BID x 7 days	0.91 (0.83, 1.01) vs. Indinavir + PBO	0.88 (0.77, 1.00) vs. Indinavir + PBO	No adjustment of indinavir dosage needed with co-administration
150-235 N=7 male and female renal transplant patients	CYP3A4 Inhibition	**Cyclosporine** BID x 8 days (patients on stabilized therapy)	200mg BID x 8 days	1.13 (0.90, 1.41) vs. Cyclosporine + PBO	1.67 (1.47, 1.98) vs. Cyclosporine + PBO	Reduce cyclosporine dose by 1/2 when initiating therapy with voriconazole; monitor cyclosporine concentrations frequently. . When VFEND is discontinued, cyclosporine concentrations must be frequently monitored and the dose increased as necessary.
150-210 N=6 healthy young males	CYP 3A4 Inhibition	**Prednisolone** 60mg Single Dose	200mg BID x 30 days	1.11 (0.94, 1.32) vs. PBO BID	1.34 (1.24, 1.44) vs. PBO BID	No adjustment of prednisolone dosage needed with co-administration

*PBO = Placebo

TABLE 3
Interaction Studies Investigating Non-CYP450 Mechanisms

Effects of Other Drugs on Voriconazole Steady State PK						
Study # Subjects	**Mech.**	**Drug Dose & Duration**	**Vori Dose & Duration**	**Vori Cmax Point Est. (90% CI)**	**Vori AUC Point Est. (90% CI)**	**Reviewer Proposed Recommendations for Co-Administration**
150-243 N=10 healthy young males	Non-Specific	**Azithromycin** 500mg x 3 days	200mg BID x 14 days	1.03 (0.91, 1.16) vs. Vori 200mg BID + PBO*	0.97 (0.89, 1.06) vs. Vori 200mg BID + PBO	No dosage adjustment needed for voriconazole with azithromycin
150-229 N=12 healthy young males	Alteration of gastric pH via H_2-antagonism	**Ranitidine** 150mg BID x 8 days	200mg BID x 7 days	1.04 (0.93, 1.15) vs. Vori 200mg BID + PBO	1.04 (0.96, 1.15) vs. Vori 200mg BID + PBO	No dosage adjustment needed for voriconazole with ranitidine
Effects of Voriconazole on PK of Other Drugs						
Study # Subjects	**Mech.**	**Drug Dose & Duration**	**Vori Dose & Duration**	**Drug Cmax Point Est. (90% CI)**	**Drug AUC Point Est. (90% CI)**	**Reviewer Proposed Recommendations for Co-administration**
150-1014 N=27 healthy young males	Inhibition of Glucuroni-dation of MPA	**Mycophenolic Acid (MPA)** (1g Single Dose MMF**)	200mg BID x 5 days	MPA: 1.02 (0.91, 1.15) MPAG**: 1.08 (0.94, 1.24)	MPA: 1.10 (1.05, 1.15) MPAG: 1.09 (1.06, 1.13)	No dosage adjustment needed for MMF with voriconazole
150-236 N=12 healthy young males	Alteration of P-Glyco-protein Transport	**Digoxin** 0.25mg QD x 20 days	200mg BID x 12 days	1.10 (0.97, 1.24) vs. Digoxin + PBO	1.01 (0.91, 1.11) vs. Digoxin + PBO	No dosage adjustment needed for digoxin with voriconazole

*PBO = Placebo
**MMF = Mycophenolate Mofetil; MPAG = Mycophenolic Acid Glucuronide

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I. Are dose adjustments needed when voriconazole is co-administered with other drugs?

See Tables 1-3 above.

J. Are there any medications that should be contraindicated in patients receiving voriconazole?

See Tables 1-3 above.

K. What other drugs, not studied by the applicant, may have a significant pharmacokinetic interaction when coadministered with voriconazole?

Voriconazole may be predicted to interact with other drugs based on results from *in vitro* and *in vivo* studies of similar drug substrates/inhibitors/inducers for a given CYP450 enzyme (or enzymes). **Therefore, it is recommended that the following drugs be contraindicated with voriconazole:**

- Terfenadine*, Astemizole*, Cisapride**, Pimozide, and Quinidine
  Inhibition of these CYP3A4 substrates by voriconazole can produce increased plasma levels of these drugs, and potentially, prolongation of the QT interval.
  *no longer marketed in the US
  **restricted distribution in the US

- Carbamazepine and Long Acting Barbiturates: Potent inducers of CYP450 metabolism and likely to significantly reduce voriconazole plasma concentrations/systemic exposure.

- Ergot Alkaloids: Inhibition of metabolism by voriconazole can lead to increased ergot alkaloid concentrations.

Careful monitoring and/or dosage adjustment of the following drugs is recommended with voriconazole co-administration:

- Sulfonylureas, Statins, Benzodiazepines, Vinca Alkaloids, HIV protease inhibitors, and non-nucleoside reverse transcriptase inhibitors (NNRTIs): CYP450 substrates, where increased plasma concentrations are likely when co-administered with voriconazole via metabolic inhibition.

L. What are the basic pharmacokinetic characteristics of the major metabolite of voriconazole (i.e., voriconazole N-oxide)?

The mean exposure to voriconazole N-oxide, in terms of C_{max} and AUC, achieved after single and multiple oral dosing with 200 mg bid is compared to that of voriconazole in the following table:

Mean (%CV) Plasma Pharmacokinetic Parameters

		Voriconazole	Voriconazole N-oxide
C_{max} (ng/ml)	Day 1 (n=6)	967 (31)	1580 (23)
	Day 10 (n=5)	2704 (59)	2810 (15)
AUC_τ (ng*h/ml)	Day 1 (n=6)	3986 (53)	13290 (21)
	Day 10 (n=5)	18877 (81)	30240 (15)

Following multiple oral dosing with voriconazole 200 mg bid, the C_{max} for voriconazole N-oxide occurs around 2-4 hours, the half-life is about 9 hours, and the mean amount of N-oxide excreted in urine over 12 hours is low (16% of the daily dose).

As with voriconazole, the pharmacokinetics of voriconazole N-oxide do not appear to be affected by renal impairment. Exposure to voriconazole N-oxide following a multiple dose IV voriconazole dosing regimen was similar in subjects with moderate renal impairment (creatinine clearance 30 to 50 ml/min) and subjects with normal renal function.

In subjects with renal impairment and undergoing hemodialysis sessions three times per week, exposure, in terms of the concentration at the end of infusion, to voriconazole N-oxide is 69% lower than in subjects with normal renal function.

The exposure, in terms of mean C_{max} and AUC_{τ}, for voriconazole N-oxide in subjects with moderate hepatic impairment (Child-Pugh Class B) is approximately half that seen in subjects with normal hepatic function. These findings are consistent with an approximately 50% lower mean apparent oral clearance of voriconazole in subjects with moderate hepatic impairment.

M. What are the basic pharmacokinetic characteristics of Sulphobutyl Ether β-Cyclodextrin (SBECD)?

SBECD is a solubilizing excipient used in formulation of IV voriconazole. The exposure to SBECD, in terms of mean C_{max} and AUC_{τ}, following 6 mg/kg voriconazole (96 mg/kg SBECD) IV bid x 2 doses, then 3 mg/kg voriconazole (48 mg/kg SBECD) IV bid x 5.5 days, is 3200 ng/ml and 3600 ng*h/ml, respectively. The C_{max} occurs about 3 hours after dosing.

There is no accumulation of SBECD between Days 1 and 10, the half-life is about 1.6 hours on Days 1 and 10, and the volume of distribution is about 0.2 L/kg.

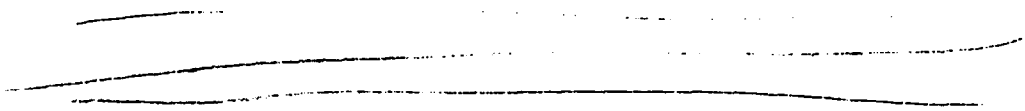
However, renal impairment has a significant effect on the pharmacokinetic parameters of SBECD. In subjects with moderate renal impairment (estimated creatinine clearance of 30 to 50 ml/min) the mean C_{max} and AUC increased by almost 50% and 4-fold, respectively, compared to subjects with normal renal function. There was strong correlation between SBECD clearance and creatinine clearance. SBECD has been associated in animal studies with toxic effects in the kidney, specifically cytoplasmic vacuolation in the epithelium of the renal tubules, renal pelvis, and urinary bladder. Therefore, IV voriconazole (containing SBECD) is not recommended in patients with moderate to severe renal impairment (creatinine clearance ≤ 50 ml/min) unless the benefit outweighs the risk in an individual patient. Oral voriconazole should be used instead, if possible.

In subjects with renal impairment and undergoing hemodialysis sessions three times per week, the pharmacokinetic results indicate that exposure, in terms of the concentration at the end of infusion, to SBECD is higher (455%) in these subjects than in subjects with normal renal function. SBECD is dialyzed at a clearance rate of 55 ml/min.

IV. BIOPHARMACEUTICS RESULTS SUMMARY

A. What are the solubility and permeability data for voriconazole, and the dissolution profile for voriconazole tablets, for the purpose of classification under the Biopharmaceutics Classification System (BCS)?

Solubility



8 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Appendix 1 – Proposed Labeling (12/17/01)

35 page(s) of revised draft labeling has been redacted from this portion of the review.

Appendix 2 – Individual Study Reviews (Available Upon Request)

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Joette Meyer
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Phil Colangelo
1/14/02 09:18:42 AM
BIOPHARMACEUTICS

Funmilayo Ajayif
1/16/02 06:55:38 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

Div. 6

IND: _____

DRUG: Voriconazole
SPONSOR: Pfizer
TYPE: New Protocol

REVIEWER: Kellie Schoolar Reynolds, Pharm.D.
SUBMISSION DATE: 02-04-98
LOG-IN DATE: 02-12-98; 02-19-98
REVIEW DATE: 03-06-98

MAR 6 1998

TITLE: A Randomized, Comparative Multicenter Study of Voriconazole Versus Conventional Amphotericin B in the Treatment of Candidemia in Non Neutropenic Subjects (Protocol 150-608)

OBJECTIVES: Primary: To compare the efficacy and safety of voriconazole and conventional amphotericin B with optional oral fluconazole follow-on therapy, in the treatment of candidemia in non neutropenic subjects.
Secondary: 1. To examine health care resource utilization in subjects treated with voriconazole and conventional amphotericin B.
2. To examine the population pharmacokinetics of voriconazole.

SUBJECTS: This multicenter study at approximately 60 centers worldwide will aim to recruit 198 subjects. Males and nonpregnant females who are at least 12 years of age and have at least one positive blood culture isolation of a *Candida* or *Torulopsis* spp from a specimen drawn within 96 hours prior to study entry are eligible. Exclusion criteria include a diagnosis of AIDS, aplastic anemia, Chronic Granulomatous Disease, or an absolute neutrophil count of less than 500/mm^3 at study entry.

STUDY DESIGN: This is a prospective randomized study. Subjects will be randomized to receive intravenously either voriconazole or amphotericin B in a 2:1 ratio. After a minimum period of intravenous dosing, subjects may be switched to oral therapy, as indicated below.

Voriconazole Arm: Initial IV therapy will be administered as a loading dose of 6 mg/kg q12hr for the first 24 hours, followed by 3 mg/kg q12hr. After at least three days of IV dosing, in the absence of significant nausea, vomiting, mucositis or other events contraindicating oral therapy, the voriconazole can be administered orally at 200 mg bid. Subjects weighing <40 kg will receive 100 mg bid. Voriconazole tablets should be taken at least one hour before or one hour after a meal.

If the clinical situation indicates a need for a dose increase, the IV dose may be increased to 4 mg/kg bid and the oral dose to 300 mg bid (150 mg bid for subjects weighing <40 kg).

Amphotericin B Arm: Amphotericin B will be administered as an IV infusion according to each institution's standard practice, at a minimum average daily dose of 0.7 mg/kg. After at least 5 days of IV dosing with amphotericin B, subjects may be switched to oral fluconazole at a minimum dose of 400 mg/day, at the discretion of the investigator.

Appropriate dose adjustments for amphotericin B and fluconazole are included in the protocol.

End of Therapy is defined as the termination of protocol therapy which can occur at least 2 weeks after the complete resolution of all clinical findings of an active infection OR at least 2 weeks after the last positive site culture was taken, whichever is longer.

Concomitant Therapy: Systemic antifungals other than study medications are prohibited during the study treatment period.

Voriconazole is both a substrate and an inhibitor of 3 hepatic microsomal enzymes: CYP3A4, CYP2C9, and CYP2C19.

Administration of the following drugs is an exclusion criteria for this study: terfenadine, cisapride, astemizole, rifampin, carbamazepine, barbiturates, sulfonylureas.

The following instructions regarding known or potential drug interactions are included in the protocol:

Drugs that alter or that have the potential to alter voriconazole levels;

Rifabutin and phenytoin: Both drugs significantly decrease voriconazole levels. For subjects receiving either drug, voriconazole doses should be increased to 5 mg/kg IV bid or to 400 mg bid po (300 mg bid po in subjects weighing <40 kg).

Nevirapine: This drug has the potential to decrease voriconazole levels and consideration should be given to increasing the voriconazole dose.

Erythromycin, ritonavir, delavirdine, omeprazole: These potent inhibitors of CYP enzymes may significantly increase voriconazole levels.

Drugs known to be affected by voriconazole:

Warfarin: Coadministration increases warfarin induced prothrombin time approximately 2-fold. Close monitoring of prothrombin time is recommended if voriconazole and warfarin are coadministered.

Cyclosporine and tacrolimus: Voriconazole increases cyclosporine AUC by approximately 1.7 fold and is expected to increase tacrolimus AUC. Monitoring of cyclosporine/tacrolimus levels is recommended when voriconazole is coadministered with either agent.

Drugs potentially affected by voriconazole:

Phenytoin levels are likely to be increased and should be monitored.

Lovastatin (and other statins) levels may be increased. The increased levels have been associated with myopathy.

Benzodiazepine levels may be increased. Dose adjustment of the benzodiazepine should be considered.

Ritonavir: Due to the narrow therapeutic index of ritonavir and the likelihood that voriconazole will increase plasma ritonavir levels, switching patients to an alternate protease inhibitor is recommended.

Anticancer agents: consideration should be given to the temporary withdrawal of voriconazole treatment from 48 hours before the scheduled cycle of anti-cancer therapy until 48 hours after its completion.

PHARMACOKINETICS: Weekly plasma samples will be collected for voriconazole analysis during study therapy for subjects randomized to the voriconazole arm. It is recommended that the weekly sample be drawn within a different time or sample

window relative to voriconazole dosing: 0-2 hrs, 2-4 hrs, 4-6 hrs, 6-9 hrs, and 9-12 hrs. The samples will be used for population PK analysis. (Note: the sponsors population pharmacokinetic analysis plan for Phase II studies was previously reviewed by Dr. Barbara Davit and Dr. Ene Ette; IND ——— . review date 05-12-97.)

If an invasive procedure is performed during the administration of voriconazole treatment, a tissue sample should also be obtained for voriconazole tissue concentration assay.

EFFICACY: Efficacy endpoints include: improved, cured, failed, and relapsed. Clinical and culture data will be used to determine the efficacy. Clinical and culture data will be collected out to 12 weeks follow-up.

CONCLUSIONS: The following comments should be relayed to the sponsor. These comments may apply to Phase III Studies other than 150-608. If responses to these comments have been provided previously, it is acceptable to either provide a copy of the previous response or indicate the previous submission number.

1. Please indicate the rationale for the voriconazole dose reduction in subjects that weigh less than 40 kg.

2. Please indicate how the timing of drug administration relative to meals was determined. Will a food effect study be performed with the final tablet formulation?

3. The effect of voriconazole on rifabutin pharmacokinetics should be considered. Other CYP3A4 inhibitors have been shown to increase rifabutin concentrations.

4. The potential for drug interactions with protease inhibitors other than ritonavir should be considered. The approved labeling for the other protease inhibitors indicate the types of interactions that have been observed between the protease inhibitors and other CYP3A4 inhibitors and substrates.

/S/ 3-6-98

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Special Pathogen and Immunologic Drug Products Section, DPEIII, OCPB

Concurrence:

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cc:
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/CSO/EFrank
HFD-880 /Biopharm/KReynolds
HFD-880 /TLBiopharm/FAjayi
HFD-880 /DPEIII
CDR /BMurphy

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