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VII Integrated Summary of Safety

VII. Integrated Review of Safety Voriconazole

The safety of voriconazole has been assessed in a clinical program incorporating healthy volunteers, patients with persistent fever and neutropenia on empiric antifungal therapy, and patients with fungal infections in both compassionate use studies and controlled clinical trials. In June 2001, Pfizer submitted an updated Integrated Summary of Safety which encompassed a safety database of 3467 healthy volunteers and patients. Although global safety was assessed as part of this NDA review, selected areas that are characteristic of the safety profile of this new drug such as adverse events involving vision, liver function, cardiac toxicity and skin will be highlighted. Much of the discussion of safety data will focus on results obtained from the comparative trials: Studies 305 (Candida esophagitis), study 307/602 (invasive aspergillosis) and study 603 (empiric antifungal therapy of febrile neutropenia).

Medical Officer Comments: Please see the separate reviews on hepatic and ocular safety. Please also see the Clinical Pharmacology section on drug interactions.

A. Brief Statement of Conclusions

Summary of Risk/Benefit

The safety database for voriconazole was adequate but was often confounded by factors in the severely ill patient that made it difficult to accurately obtain a picture of the events attributable to drug alone.

At present both the Applicant and the Division agree that visual abnormalities occurred at a frequency of between 24% to 33% in the clinical trial database. These changes occur within the first week of therapy and continue during the time they are on therapy. Most patients who used voriconazole for 28 days and developed visual symptoms appeared to have symptoms that were reversible upon discontinuation of the drug. However, it is important to keep in mind, that we do not have complete follow-up data on all of the patients who discontinued voriconazole for visual symptoms. We also do not know if vision may be compromised upon re-challenge with voriconazole or whether it is safe to use this drug in patients who have underlying eye diseases such as CMV retinitis.

Voriconazole has the potential for numerous drug interactions because it is both a substrate and an inhibitor of CYP 2C9, 2C19 and 3A4. The Applicant has evaluated potential drug interactions between voriconazole and several important medications. These should guide precautions intended to minimize potential adverse reaction
This drug is metabolized by the liver and can elevate liver function tests. Although we have data on the use of this drug in patients with chronic liver disease in Child-Pugh classes A and B, we do not have sufficient data to completely ascertain the safety of using this drug in liver transplantation, or in patients with Child Pugh Class C disease or in patients with hepatitis B or hepatitis C disease. Liver function tests should be monitored.

demonstrated a survival advantage. Voriconazole has also demonstrated efficacy in the treatment of infections caused by *Scedosporium apiospermum* and *Fusarium* species. Therefore, in treating patients with *Aspergillus fumigatus*, *Scedosporium apiospermum* and *Fusarium spp.* infection with their attendant high morbidity and mortality, one can reconcile taking the risk of exposing the patient to development of a visual, cardiac, liver function abnormality and/or rash.

B. Description of Patient Exposure

In the therapeutic studies safety database, there were 1493 patients. In the overall pooled safety database there were 2090 patients. The following table depicts the duration of treatment for these two populations.

Table 1 Duration of Treatment*

Duration of treatment (days)	Voriconazole Therapeutic Studies Population (N= 1493)	Voriconazole Overall Pooled (N=2090)
Median (range)	16 (1-326)	21 (1-800)
N (%) subjects receiving randomized treatment for:		
< 7 days	363 (24.3)	440 (21.1)
8-14 days	305 (20.4)	356 (17.0)
15-28 days	289 (19.4)	371 (17.8)
29-84 days	218 (14.6)	365 (17.5)
85-365 days	318 (21.3)	520 (24.9)
>365 days	0	38 (1.8)

*from the Applicant's October 2001 Advisory Committee Briefing Package

Medical Officer Comments: ***The median duration of exposure to voriconazole was 16 days in the therapeutic studies population but there were patients who took voriconazole for greater than 84 days. Please see the section on Long Term Therapy in the Dosing Regimen and Administration Issues section of this safety review. Please also see the Clinical Pharmacology review and the individual clinical study reviews. for additional details on patient exposure.***

Patients

The nature of the study patient population were seriously ill patients who received voriconazole along with numerous concomitant medications.

The following outlines the use of concomitant medications in the 3 major comparative studies. The *Candida* esophagitis trial, study 305, was conducted outside the US mainly in Europe, Africa and Asia. Two hundred patients received voriconazole and 191 patients received fluconazole and the mean number of concomitant medications was

Pharmacokinetics

The pharmacokinetics of voriconazole are non-linear and similar in both immunocompromised adults at risk for infection with aspergillosis and 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 slightly less than 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, if no loading dose is administered.

Medical Officer Comments: ***Plasma accumulation of voriconazole following repeated dosing is extensive and may pose a risk for overdose. Parameters such as liver function should be monitored.***

Analysis of the Phase 1 population pK data indicate that the CYP2C19 genotype plays a significant role in the metabolism of voriconazole. It is the most influential covariate on the clearance and AUC of voriconzole. CYP2C19 genotype alone accounts for 30% of the overall between subject variability in voriconazole pK. This enzyme exhibits genetic polymorphism. Fifteen to 20% of Asian populations may be expected to be poor metabolizers. For Caucasians and Blacks, the prevalence of poor metabolizers is 3-5%. Poor metabolizers have shown that, on average, 4-fold higher voriconazole exposure ($AUC\tau$) occurs when compared to their homozygous extensive metabolizer counterparts. Patients who are heterozygous extensive metabolizers have, on average, 2-fold higher voriconazole exposure than their homozygous extensive metabolizer counterparts.

Medical Officer Comments: ***At present there is no way to easily screen the patient population for the CYP2C19 "poor metabolizer" genotype in order to predict which patient population may require more intensive monitoring on voriconazole.***

Please see the Clinical Pharmacology review for full details on the CYP2C19 genotype and also on the important drug interactions that occur because of voriconazole's hepatic metabolism via CYP2C19, CYP2C9 and CYP3A4. The package insert contains comprehensive information regarding drug interactions.

A patient population in whom additional safety data will be requested includes patients with underlying chronic hepatitis B and C. These are patients in whom it may be difficult to predict the existing degree of hepatic insufficiency unless the patient manifests overt signs of cirrhosis or a liver biopsy has been performed.

C. Methods and Specific Findings of Safety Review-specific studies conducted for safety issues

have been related to prior idarubicin therapy. As a result of this event, cardiac events and the potential for voriconazole to prolong QT interval have been examined in more detail.

In order to include all events that relate to QT prolongation and its possible sequelae, a range of treatment emergent adverse events were examined. The comparison of all causality adverse cardiac events reported during study treatment was similar in patients receiving voriconazole and fluconazole in the Esophageal Candidiasis Study (305).

In the Global Comparative Aspergillosis Study (307/602), there were numerically more events of cardiac arrest and syncope in the voriconazole group (6/196 or 3.1%) than the amphotericin B /other licensed antifungal therapy group (2/185 or 1.1%). While the contribution of voriconazole could not be excluded in every case, clinical review of these cardiac adverse events revealed no obvious pattern within the voriconazole group. In addition, one patient receiving voriconazole in the Empirical Therapy Study (603/MSG42) had an increase in QTc considered by the investigator to be related to loading with amiodarone for ongoing atrial fibrillation.

Non-clinical *in vitro* and *in vivo* data were also gathered to examine the potential for voriconazole to cause cardiac arrhythmia. A recently published study has shown that ketoconazole blocks the HERG (human ether-a-go-go related gene)channel *in vitro* and therefore may have the potential to directly prolong QT interval. (Dumaine, *et. al.*, 1998). The Applicant therefore used a similar *in vitro* approach to define the electrophysiological properties of voriconazole, its N-oxide metabolite and ketoconazole (as a positive control). The approach included a combination of three examinations to identify the potential to cause QT prolongation.

These included:
- effects of voriconazole or ketoconazole on the specific binding of dofetilide to the HERG channel protein
- effects of voriconazole or ketoconazole on HERG current in a patch-clamp assay
- effect of voriconazole or ketoconazole on action potentials recorded from isolated canine Purkinje fibers.

HERG proteins are known to form the channel underlying the cardiac rapidly activating delayed rectifier current IKr. Agents that block HERG delay repolarization and thereby prolong the cardiac action potential, and are seen on the electrocardiogram as a prolongation of the QT interval. The direct effects of voriconazole on HERG can be assessed using both dofetilide-binding and patch-clamp studies of HERG current. The Purkinje fiber preparation allows the effect on action potential duration to be assessed and this preparation is sensitive to agents known to prolong the electrocardiogram QT interval in animals and human beings. The Purkinje fiber is accepted as the preparation of choice to determine the potential of compounds to prolong the QT interval in human beings. Drugs which do not show substantial effects in these tests at appropriate concentrations are unlikely to lead to clinically relevant effects on QT interval.

Voriconazole did not inhibit activated HERG channels or specific radioligand binding of [3 H]-dofetilide to HERG. The highest concentrations of voriconazole and ketoconazole

showed an increase on the duration of the action potential at 90% repolarization (APD90) of less than 10%, which is below the limit of detection of this model. The changes were not significantly different from control values and there was no effect on the duration of the action potential (msec) from the upstroke to 50% repolarization (APD50). In contrast, ketoconazole produced full or partial effects on HERG inhibition and dofetilide binding but not on action potential duration. The N-oxide metabolite of voriconazole was tested on [3 H]-dofetilide binding and Purkinje fibers and there was no effect seen at a concentration of 50 mM. In the non-clinical *in vivo* studies, voriconazole administered up to the maximum tolerated dose of 6mg/kg IV had no effects on the electrocardiogram of either conscious or anesthetized dogs. At higher doses, however, the anesthetized dogs also had inconsistent QT interval changes. One anesthetized animal developed AV nodal premature beats at plasma concentrations well above those observed in the clinical program. The event was not related to dose, continuing unchanged when a higher dose was given. QT prolongation was not observed in dogs in the toxicology program where animals were exposed to peak plasma voriconazole concentrations of up to 62.2 µg/ml, a concentration that is approximately three-fold the maximum plasma concentration observed in any patient. There was no visually apparent relationship between increases in the rate-corrected QT interval (QTc) and either dose or exposure to voriconazole in the Phase 1 healthy volunteer program. This was true for single doses, for absolute values of QTc as well as for increases from baseline. This was also the case regardless of whether Bazett's (QTc=QT/[RR]1/2) or Fridericia's formula (QTc=QT/[RR]1/3) was used to correct for heart rate.

Plasma concentrations up to 9.2 mg/ml were measured in the Phase 1 studies. In the Therapeutic Studies Safety population, 90% of patients had maximum plasma voriconazole concentrations less than 9 mg/ml. Central reading of electrocardiograms collected during the Phase 1 studies was performed and were correlated with plasma concentrations at one hour post-single dose in 119 subjects (116 voriconazole-treated subjects and 35 placebo-treated subjects) from the clinical pharmacology studies population.

To date, analysis of healthy volunteer QT interval data at plasma concentrations likely to be observed in the majority of patients does not indicate an effect on QTc. The *in vitro* data indicate that voriconazole showed no inhibition of activated HERG channels or specific inhibition of radioligand binding of [3 H]-dofetilide to HERG. However, additional studies were undertaken to assess the effect of varying concentrations of voriconazole on QTc.

Medical Officer Comments: ***Please see the Pharmacology Toxicology review for additional details.***

An analysis of grade 3 cardiac events and analysis of CHF cases across the 3 major controlled trials was performed.

Table 2 Frequency of cardiac arrest in the 3 major controlled trials

	Study 305	Study 307/602	Study 603
Voriconazole	1/200 (0.5%)	6/196 (3/1%)	5/421 (1.2%)
Fluconazole	1/191 (0.5%)	-------	--------
Amphotericin formulations	----------	2/185 (1.1%)	5/428 (1.2%)

Medical Officer comments. ***Except for the increased number of cardiac arrests noted in the voriconazole arm in Study 307/602, there were otherwise no major differences in the frequency of these cardiac events across treatment arms in the 3 major controlled clinical trials..***

Negative inotropic effect

Medical Officer comments: ***The information below was taken from the itraconazole package insert.***

When itraconazole was administered intravenously to dogs and healthy human volunteers negative inotropic effects were seen. When itraconazole was administered intravenously to anesthetized dogs, a dose-related negative inotropic effect was documented. In a healthy volunteer study of itraconazole for injection, transient, aymptomatic decreases in left ventricular ejection fraction were observed using gated SPECt imaging and these episodes resolved before the next infusion which was 12 hours later. Cases of CHF, peripheral edema and pulmonary edema have been reported in the post-marketing period among patients being treated for onychomycosis and/or systemic fungal infections.

Medical Officer comments: ***Consequently, the Applicant will perform additional phase 4 studies to evaluate whether voriconazole affects cardiac contractility in experimental animals or humans.***

Because of the previously mentioned occurrence of anaphylactoid reactions which surfaced during attempts to perform the QTc study, the following analysis was undertaken. Please see Table 3 below

Table 3 Anaphylactoid reactions in controlled clinical trials:

	Study 305	Study 307/602	Study 603	Study 608
Voriconazole	1/200 (0.5%)	2/196 (1%)	4/421(0.9%)	1/45 (2%)
Fluconazole	1/191 (0.5%)	———	———	1/22 (4.5%)
Amphotericin formulations	-------	6/185 (3.2%)	24/428 (6%)	---------

Medical Officer Comments: ***Cases of "anaphylactoid reactions" were reviewed in the database and the most cases were reported for amphotericin B formulations in study 603. The median day of occurrence of anaphylactoid reactions for patients on amphotericin formulations was day one. The median day for fluconazole was 9 days and it was 24 day for voriconazole.***

RASH

Skin rash was observed in 278/1493 (18.6%) voriconazole patients in the Therapeutic Studies population and 362/2090 (17.3%) voriconazole patients in the Overall Pooled population. The preferred term 'rash' includes event terms such as erythema, erythematous rash, exanthema, redness, and less specific terms such as rash, skin eruption and pimples.

Medical Officer comments: ***The Applicant presented several descriptions of the various types of skin exanthems observed. No specific rash is characteristic of voriconazole exposure. Most rashes were of mild to moderate severity. There were no major differences in the discontinuations for rash between voriconazole and its comparators in the active controlled studies 307/602, 305 and 603.***

We agree with the Applicant that rash is a potential hazard associated with the use of this drug. Patients in the clinical studies were often on concomitant medications that could either cause rash themselves or concomitant medications such as antihistamines and steroids that might affect the type and severity of skin symptoms observed. Conditions such as graft vs host disease (GVHD) can also make it difficult to completely assess a causative role for study drug in the development of rash. The incidence of GVHD was slightly higher in the voriconazole treatment arms (see below):

GVHD incidence :

Voriconazole	4.1 %	in study 307/602	and	2.9% in study 603
Comparator	2.2 %	in study 307/602	and	1.4% in study 603

Medical Officer's comments: ***Only 4 skin biopsy results were submitted on patients with skin exanthems and thus no major conclusions could be drawn from this data.***

The incidence of Grade 3 rashes in the comparative trials are included below.

Voriconazole study 307/602	5/196 (2.6%)	vs	Ampho B/OLAT	1/185	(0.5%)
Voriconazole study 305	3/200 (1.5%)	vs	Fluconazole	1/191	(0.5%)
Voriconazole study 603	12/421 (5.0%)	vs	AmBisome®	15/428	(3.5%)

Medical Officer comments: ***The incidence is of grade 3 rash is higher in the voriconazole treatment arms.***

The Applicant has described 4 cases of non-fatal Stevens -Johnson syndrome which were noted in patients on voriconazole. Two of these cases developed rash, discontinued drug and then re-exacerbated upon re-challenge (304- 01370816 and 604-10346186). Of these, the patients with erythema multiforme and toxic epidermal necrolysis were considered serious and a relationship to voriconazole treatment could not be ruled out. None of these cases was biopsy proven, nor fatal. There was also a case of toxic epidermal necrolysis, TEN, reported on amphotericin B for patient 603-90441462.

Some of the skin reactions appeared to have an element of photosensitivity. In the Overall Pooled population, the Applicant reports that 41 (2.0%) of 2090 patients receiving voriconazole reported events that coded to the preferred term of photosensitivity reaction. Photosensitivity reactions are not normally associated with azoles. Of the 41 events reported in patients treated with voriconazole, only two resulted in discontinuation. Photosensitivity is frequently observed with agents that are likely to be co-administered with voriconazole, such as quinolones or trimethoprim-sulfmethoxazole and are associated with exposure to UV A radiation (320-400nm). Neither voriconazole nor its principal metabolite, UK-121,265, has significant absorption in this region of the spectrum. Outpatients in the voriconazole clinical program were not warned to avoid sunlight during therapy, and the frequency of photosensitivity reaction is still low.

Medical Officer comments: ***There is insufficient information at this time to conclude that photosensitivityis the mechanism for development of rash while taking voriconazole. The package insert includes warnings to avoid sun exposure.***

D. Adequacy of Safety Testing

Overall the safety testing was adequate except for the following areas.
Additional experience will be needed to assess drug interactions for voriconazole with birth control pills, methadone, rifabutin, protease inhibitors such as ritonavir, and non-nucleoside reverse-transcriptase inhibitors such as efavirenz . Additional pediatric studies to further assess the pharmacokinetics and safety of voriconazole use in children have been requested. Data regarding use of voriconazole in patients with chronic hepatitis B and C should be collected. The solid organ transplant population only encompassed about 1% of the database and thus experience with voriconazole in these patients is limited. Voriconazole is contraindicated in translplant patients taking sirolimus and drug levels must be closely monitored in those taking cyclosporine and tacrolimus, as well.

E. Summary of Critical Safety Findings and Limitations Of Data

could not be definitively excluded. The Applicant will perform additional phase 4 studies to evaluate cardiac contractility and QT prolongation.

Please see the tables below which will focus on deaths in the therapeutic studies population. Please also refer to the review on hepatic safety.

Deaths in the Therapeutic Studies population

There were 469 of 1493 (31.4%) patients in the therapeutic studies died and 828 (39.6%) of 2090 in the overall pooled population died.

Table 4 Most Frequently reported cause of Death occurring during therapy or within 30 days of end of therapy*

	Voriconazole Therapeutic Studies (N= 1493) N (%)	**Voriconazole Overall Pooled (N = 2090)** N (%)
Total number of deaths	**469 (31.4)**	**828 (39.6)**
Cause of death		
Septicemia	49 (3.3)	71 (3.4)
Aspergillosis	49 (3.3)	93 (4.4)
Acute myeloid leukemia	42 (2.8)	67 (3.2)
Ill-defined condition	42 (2.8)	70 (3.3)
Respiratory Failure	33 (2.2)	80(3.8)
Shock	31 (2.1)	46 (2.2)
Cardiac arrest	24 (1.6)	32 (1.5)
Pneumonia	22 (1.5)	36 (1.7)
AIDS	19(1.3)	29 (1.4)
Unspecified leukemia	16 (1.1)	23 (1.1)

*from Applicant's 10/01 Advisory Committee Briefing Package

The most common causes of death in the voriconazole-compassionate use patients (occurred in > 2 voriconazole-treated patients) by body system included respiratory failure, acute myeloid leukemia without remission, pulmonary insufficiency, septicemia, ill defined condition causing morbidity or mortality, complications of bone marrow transplantation, intracerebral hemorrhage, unspecified mycoses, CMV disease, acute and subacute necrosis of the liver, pneumonia in aspergillosis and shock.

Table 5 Deaths in the 3 major comparative clinical studies

Medical Officer's Comments: There was no major imbalance across the treatment

	Voriconazole	Amphotericin B /OLAT	Ambisome®	Fluconazole
Study 305	19/200 (9.5%)			15/191(7.5%)
Study 307/602	65/196 (33.2%)	79/185 (42.7%)		
Study 603	62/421 (14.7%)		46/ 428(10.7%)	

arms with regard to the number of deaths in study 305 and study 603. There were more deaths in the amphotericin B/OLAT arm compared to voriconazole in study 307/602. Most patients died due to illnesses such as, but not limited to, sepsis, pneumonia or underlying malignancy. Please see the individual clinical study reviews for additional details.

Discontinuations

Medical Officer's Comments: In the voriconazole treatment arms, one of the most frequent reasons for discontinuation (79/1493 or 5.3%) was liver function abnormalities. This was true for both the therapeutic studies population and the overall pooled patient population (96/2090 or 5%). The package insert contains precautions and warnings that advise the clinician to monitor this laboratory parameter.

Table 6 Most Frequent Adverse Events leading to Discontinuation in the therapeutic studies population*

	Voriconazole Therapeutic Studies Population (N = 1493)	Voriconazole Overall Pooled (N=2090)
Patients with Adverse Events	1437 (96.2%)	1960 (93.8%)
Reasons for discontinuation	———	———
Elevated alkaline phosphatase	25 (1.7%)	29 (1.4%)
Acute kidney failure	23 (1.5%)	28 (1.3%)
Increased hepatic enzymes	19 (1.3%)	20 (1.0%)
Abnormal Liver function tests	13(0.9%)	23 (1.1%)
Rash	13 (0.9%)	20 (1.0%)
Bilirubinemia	12 (0.8%)	14 (0.7%)
Fungal infection	12 (0.8%)	18 (0.9%)
Sepsis	11 (0.7%)	20 (1.0%)
Cholestatic jaundice	10 (0.7%)	10 (0.5%)
Abnormal vision	8 (0.5%)	11 (0.5%)
Respiratory disorder	8 (0.5%)	17 (0.8%)
Fever	8 (0.5%)	10 (0.5%)
Hallucinations	8 (0.5%)	8 (0.4%)

***Applicant's analysis October 2001 Advisory Committee Briefing Package**

Medical Officer Comments: ***Please see tables 7 and 8 below. The rate of discontinuations for the active-controlled trials is higher in the voriconazole treatment arms for studies 305, 603 and 608. The comparators in these arms were fluconazole, AmBisome® and conventional amphotericin followed by fluconazole. The discontinuations were mainly due to abnormalities with liver function, kidney function or rash . In study 307/602 the discontinuations in the amphotericin B followed by other licensed antifungal therapy (OLAT) arm are mainly due to renal dysfunction.***

Table 7 Overall Discontinuations in the active-controlled trials*

	Study 305	Study 307/602	Study 603	608**
Voriconazole	22/200 (11%)	42/196 (21.4%)	55/421(13.1%)	28/45(62.2%)
Fluconazole	8/191 (4.2%)	----------	---------	
Amphotericin formulations	----------	117/185 (63.2%)	42/428 (9.8%)	7/22 (31.8%)

***FDA analysis**
**** 10% interim analysis**

Table 8 Subjects in the therapeutic studies who discontinued from treatment due to adverse events*

	Voriconazole		Ampho B formulations	
	N	%	N	%
# subjects in NDA ISS	1214	100	571	100
Discontinued due to Adverse Events	184	15.2	96	16.8
# subjects in ISS update	1493	100	665	100
Discontinued due to Adverse Events	275	18.4	156	23.4

***Applicant's analysis June 2001 ISS**

Medical Officer's Comments: ***As assessed by the Applicant, the overall discontinuation rate, across the therapeutic studies and focusing on adverse events, was similar for the voriconazole and amphotericin B treatment arms.***

Adverse Events

Serious Adverse Events

Medical Officer's Comments: ***The type of serious adverse events depicted in Table 9 below, reflect the severity of the underlying illnesses in the study patient population.***

Table 9 Most Frequently Reported Serious Adverse Events occurring during therapy or within 30 days of End of Therapy*

Serious Adverse Event	Voriconazole Therapeutic Studies (N= 1493)	
	All causality (n%)	Treatment related** (n%)
Sepsis	135 (9.0)	8 (0.5)
Pneumonia	102 (6.8)	5 (0.3)
Respiratory Insufficiency	92 (6.2)	5 (0.3)
Dyspnea	77 (5.2)	5 (0.3)
Fever	71 (4.8)	0
Fungal Infection	59 (4.0)	0
Acute granulocytic leukemia	58 (3.9)	1 (0.1)
Circulatory failure	56 (3.8)	4 (0.3)
Acute renal failure	53 (3.5)	15 (1.0)
Cardiac arrest	42 (2.8)	2 (0.1)

* Applicant's analysis October 2001 Advisory Committee Briefing Package
**Sponsor or investigator designated "treatment-related"

In addition, it should be noted that in the clinical pharmacology studies there were actually four events of anaphylactoid reactions that occurred in two separate studies i.e. Study A150-1021 and A150-1027. Two anaphylactoid reactions occurred in each study and for study 1021 this included one patient on voriconazle alone and the other patient received voriconazole and the excipient SBECD. Both patients were young females taking contraceptives. The two other patients in study 1027 were on voriconazole alone and in all cases the reactions occurred within a few minutes of initiation of infusion and resolved. Due diligence efforts have not ascertained the cause of these reactions.

Medical Officer comments: ***Cases of tachycardia, flushing and rash occurred both in the voriconazole and comparator arms of the clinical studies, regardless of whether they were receiving steroids, antihistamines and/or immunosuppressants. There was no increase in the rate of anaphylactoid reactions in the voriconazole treatment arms.***

Medical Officer Comments: ***Please see Tables 10 and 11 i.e. the Adverse Events (all causalities)occurring in > 5% of all subjects table and the Treatment Emergent Adverse Event Table which focuses on the active controlled trials that included the conventional and lipid formulations of amphotericin B as the comparators.***

The most frequent adverse events in the voriconazle treatment arms were related to the special senses (visual adverse events) and elevated liver function tests. Appropriate precautions and warnings have been included in the package insert. Clinicians will be advised that patients should not drive while on voriconazole and liver function tests will require monitoring.

Table 10 Most Frequently Reported Adverse Events (Therapeutic Studies Population) *

	Voriconazole Therapeutic Studies (N=1493)	Voriconazole Overall Pooled(N=2090)
Abnormal vision	358 (24)	422 (20.2)
Fever	324 (21.7)	430 (20.6)
Rash	268 (18.0)	362 (17.3)
Vomiting	259 (17.3)	327 (15.6)
Nausea	229 (15.3)	269 (12.9)
Diarrhea	215 (14.4)	282 (13.5)
Headache	191 (12.8)	233 (11.1)
Sepsis	175 (11.7)	259 (12.4)
Peripheral Edema	176 (11.8)	211 (10.1)
Respiratory Disorder	159 (10.6)	229 (11.0)

*Applicant's analysis October 2001 Advisory Committee Briefing Package

Table 11 Adverse Events (all causalities) occurring in > 5% of all subjects*

	Voriconazole		Amphotericin B Formulations	
	N	%	N	%
Subjects				
Total Treated	1493		665	
No. with Adverse Events	1437	96.2	657	98.8
Adverse Events[1]				
Abnormal vision	363	24.3	28	4.2
Fever	330	22.1	225	33.8
Rash	278	18.6	133	20.0
Vomiting	264	17.7	139	20.9
Nausea	233	15.6	149	22.4
Diarrhea	220	14.7	142	21.4
Headache	193	12.9	65	9.8
Sepsis	180	12.1	80	9.0
Peripheral Edema	179	12.0	111	16.7
Resp Disorder	165	11.1	95	14.3
Abdominal Pain	164	11.0	130	19.5
Dyspnea	137	9.2	129	19.4
Pneumonia	134	9.0	50	7.5
Chills	131	8.8	220	33.1
Hypotension	126	8.6	87	13.1
Hypokalemia	123	8.2	155	23.3
Tachycardia	119	8.0	109	16.4
Hypertension	112	7.5	69	10.4
Asthenia	111	7.4	56	8.4
Cough Inc	106	7.1	71	10.7
Epistaxis	106	7.1	67	10.1
Constipation	100	6.7	40	6.0
Resp tract Infection	94	6.3	28	4.2
Confusion	90	6.0	60	9.0
Alk phos increased	90	6.0	12	1.8
Hallucinations	88	5.9	21	3.2
Pain	87	5.8	66	9.9
Insomnia	82	5.5	36	5.4
Urinary tract infection	78	5.2	16	2.4
Arthralgia	77	5.2	40	6.0
Graft vs Host Reaction	76	5.0	24	3.6

No = Number

[1]Numbers refer to subjects with the adverse event; thus, the event is counted once, even if there were multiple occurrences of the event.

*Applicant's analysis June 2001 ISS

APPEARS THIS WAY ON ORIGINAL

<u>Medical Officer comments</u>: Table 12 below was included in the package insert. FDA requested the Applicant to present the safety data for protocols 305 (comparator drug fluconazole) and protocol 307/602 (comparator drug amphotericin B) and all therapeutic studies. The increased adverse event reporting for visual abnormalities in

the voriconazaole treatment arms and for renal function abnormalities in the amphotericin formualtion arms is consistent across the studies. However, this particular presentation of safety data in Table 11 demonstrates voriconazole's higher frequency of liver function abnormalities and rash when compared to fluconazole.

Table 12 (from the approved package insert)

TREATMENT- EMERGENT ADVERSE EVENTS
Rate ≥ 1% or Adverse Events of Concern in All Therapeutic Studies
Possibly Related to Therapy or Causality Unknown

	All Therapeutic Studies	Protocol 305 (oral therapy)		Protocol 307/602 (IV/ oral therapy)	
	Voriconazole N=1493	Voriconazole N = 200	Fluconazole N =191	Voriconazole N =196	Ampho B** N = 185
	N (%)	N (%)	N (%)	N (%)	N (%)
Special senses*					
Abnormal vision	307 (20.6)	31 (15.5)	8 (4.2)	55 (28.1)	1 (0.5)
Photophobia	36 (2.4)	5 (2.5)	2 (1.0)	7 (3.6)	0
Chromatopsia	20 (1.3)	2 (1.0)	0	2 (1.0)	0
Eye hemorrhage	3 (0.2)	0	0	0	0
Body as a Whole					
Fever	93 (6.2)	0	0	7 (3.6)	25 (13.5)
Chills	61 (4.1)	1 (0.5)	0	0	36 (19.5)
Headache	48 (3.2)	0	1 (0.5)	7 (3.6)	8 (4.3)
Abdominal pain	25 (1.7)	0	0	5 (2.6)	6 (3.2)
Chest pain	13 (0.9)	0	0	4 (2.0)	2 (1.1)
Cardiovascular system					
Tachycardia	37 (2.5)	0	0	5 (2.6)	5 (2.7)
Hypertension	29 (1.9)	0	0	1 (0.5)	2 (1.1)
Hypotension	26 (1.7)	1 (0.5)	0	1 (0.5)	3 (1.6)
Vasodilatation	23 (1.5)	0	0	2 (1.0)	2 (1.1)
Digestive system					
Nausea	88 (5.9)	2 (1.0)	3 (1.6)	14 (7.1)	29 (15.7)
Vomiting	71 (4.8)	2 (1.0)	1 (0.5)	11 (5.6)	18 (9.7)
Liver function tests abnormal	41 (2.7)	6 (3.0)	2 (1.0)	9 (4.6)	4 (2.2)
Diarrhea	16 (1.1)	0	0	3 (1.5)	6 (3.2)
Cholestatic jaundice	16 (1.1)	3 (1.5)	0	4 (2.0)	0
Dry mouth	15 (1.0)	0	1 (0.5)	3 (1.5)	0
Jaundice	3 (0.2)	1 (0.5)	0	0	0
Hemic and lymphatic system					
Thrombocytopenia	7 (0.5)	0	1 (0.5)	2 (1.0)	2 (1.1)
Anemia	2 (0.1)	0	0	0	5 (2.7)
Leukopenia	4 (0.3)	0	0	1 (0.5)	0
Pancytopenia	1 (0.1)	0	0	0	0
Metabolic and Nutritional Systems					
Alkaline phosphatase increased	54 (3.6)	10 (5.0)	3 (1.6)	6 (3.1)	4 (2.2)
Hepatic enzymes increased	28 (1.9)	3 (1.5)	0	7 (3.6)	5 (2.7)
SGOT increased	28 (1.9)	8 (4.0)	2 (1.0)	1 (0.5)	0
SGPT increased	27 (1.8)	6 (3.0)	2 (1.0)	3 (1.5)	1 (0.5)
Hypokalemia	24 (1.6)	0	0	1 (0.5)	36 (19.5)
Peripheral edema	16 (1.1)	1 (0.5)	0	7 (3.6)	9 (4.9)
Hypomagnesemia	16 (1.1)	0	0	2 (1.0)	10 (5.4)

	All Therapeutic Studies	Protocol 305 (oral therapy)		Protocol 307/602 (IV/ oral therapy)	
	Voriconazole N=1493	Voriconazole N = 200	Fluconazole N =191	Voriconazole N =196	Ampho B** N = 185
	N (%)	N (%)	N (%)	N (%)	N (%)
Bilirubinemia	12 (0.8)	1 (0.5)	0	1 (0.5)	3 (1.6)
Creatinine increased	4 (0.3)	1 (0.5)	0	0	59 (31.9)
Nervous system					
Hallucinations	37 (2.5)	0	0	10 (5.1)	1 (0.5)
Dizziness	20 (1.3)	0	2 (1.0)	5 (2.6)	0
Skin and Appendages					
Rash	86 (5.8)	3 (1.5)	1 (0.5)	13 (6.6)	7 (3.8)
Pruritus	16 (1.1)	0	0	2 (1.0)	2 (1.1)
Maculopapular rash	17 (1.1)	3 (1.5)	0	1 (0.5)	0
Urogenital					
Kidney function abnormal	8 (0.5)	1 (0.5)	1 (0.5)	4 (2.0)	40 (21.6)
Acute kidney failure	7 (0.5)	0	0	0	11 (5.9)

* See WARNINGS – Visual Disturbances, PRECAUTIONS – Information For Patients
**Amphotericin B followed by other licensed antifungal therapy

Laboratory Abnormalities

Medical Officer Comments: ***Liver enzyme elevations were reported more frequently in voriconazole-treated subjects when compared to amphotericin and fluconazole -treated subjects. Renal function abnormalities (elevated BUN and creatinine) were reported more frequently for amphotericin-treated subjects. Please see Table 12 above and the review on hepatic safety.***

VIII Dosing, Regimen, and Administration Issues

Medical Officer Comments: ***Please refer to the Clinical Pharmacology and Chemistry reviews for additional details regarding the pharmacokinetics of the voriconazole N-oxide metabolite and excipient sulphobutyl ether ß -cyclodextrin (SBECD). The following section includes salient points from both the Applicant's NDA submission and the Clinical Pharmacology section in the FDA October 2001 Advisory Committee Briefing Package.***

Voriconazole exhibits non-linear pharmacokinetics due to saturable metabolism. Exposure, in terms of C_{max} and AUC, increases in a non-linear 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, 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

respectively. There islarge inter-subject variability. With repeated dosing, plasma accumulation of voriconazole is substantial due to the non-linear pharmacokinetics.

Medical Officer Comments: ***The pharmcokinetic characteristics of voriconazole could pose a potential risk for overdose. However, few overdoses occurred in the clinical trial setting.***

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

Absorption
The T_{max} of voriconazole occurs 1-2 hours after dosing in fasted state.
The oral bioavailability is estimated to be 96%. 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 pharmacokinetics of voriconazole. It is recommended that oral voriconazole be administered either one hour before or one hour after meals. Alterations in gastric pH do not appear to affect the absorption of voriconazole.

Medical Officer's Comments: ***The package insert will state that voriconazole tablets should be taken at least one hour before or one hour after a meal.***

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 of CYP450 enzymes 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.

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

Medical Officer's Comments: ***Please see the Clinical Pharmacology review and package insert which outline the numerous drug interactions for voriconazole. It may be challenging for clinicians to safely manage critically ill patients on voriconazole and numerous concomitant medications, outside the setting of a controlled clinical trial. However, the package insert will serve as a useful guide and clearly outlines problematic drug interactions.***

Elimination
Following IV administration, a mean of 80% of the voriconazole dose is excreted in urine. 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 a 400 mg dose.

Level of confidence about the dose recommendations

Dose response for efficacy
Following the completion of therapeutic studies, exploratory pharmacokinetic and pharmacodynamic analyses were conducted to assess the appropriateness of the dose regimens used. Plasma voriconazole concentrations observed in therapeutic studies were compared with MICs from clinical isolates. Given the wide inter-individual variability in voriconazole pharmacokinetics, analyses were also conducted to assess whether the risk benefit ratio could be optimized by plasma concentration monitoring.

Medical Officer Comments: ***Because of this high variability, different patients treated with the same dose of voriconazole can manifest a wide range of plasma drug concentrations.***

For pharmacokinetic and pharmacodynamic analyses of efficacy, mean plasma voriconazole concentration from start to end of therapy was calculated for each patient. A combined pharmacokinetic and pharmacodynamic analysis of all patients with definite or probable infections was conducted on data for Studies 303, 304, 309, 603, 604 and 608 (n=280) from the NDA Clinical Pharmacology Studies. This efficacy analysis was conducted omitting Study 305 because esophageal, rather than systemic, fungal infection was being treated and the study had an overall high success rate (≥90% in voriconazole-treated patients in the primary efficacy analysis). The pharmacokinetic and pharmacodynamic relationship for efficacy in the Global Comparative Aspergillosis Study (307/602) was explored separately.

The logistic regression analysis of the primary study population (N =280) demonstrated 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 successful outcome was greatest at the 0.5 ug/ml threshold ratio. The proportion of treatment successes in patients with mean plasma voriconazole concentration below 0.5 mg/ml was approximately 46% compared to approximately 56% of successes in patients with mean plasma concentrations above 0.5 ug/ml.

However, reduced efficacy was observed in patients with the highest plasma voriconazole concentrations.The proportion of successes in patients with mean voriconazole plasma levels below 6.0 ug/ml was about 58% compared to about 26% of successes in patients with a mean plasma level above 6 ug/ml. Review of the patients with the higher plasma voriconazole concentrations (>6 mg/ml) provided evidence that the patients had hepatic impairment and severe underlying medical conditions that influenced clinical outcome. Therefore the pharmacokinetic and pharmacodynamic relationship between plasma voriconazole exposure and clinical outcome was significantly confounded by complicating medical factors.

Medical Officer Comments: ***Thus, due to confounding factors, no definitive conclusions can be made from these Phase 2/3 studies regarding the relationship between plasma concentrations of voriconazole and efficacy. No correlation has also been established between efficacy and the level of the N-oxide metabolite.***

Plasma Voriconazole Concentrations, MIC and Clinical Outcome
Over 95% of all clinical fungal isolates tested had MICs at or below 1.0 mg/ml. In therapeutic studies, 86.8% (914/1053) of patients with plasma samples attained a plasma voriconazole concentration over 1.0 mg/ml. In the Global Comparative Aspergillosis Study (307/602), 81.01% (94/116) of patients with plasma samples had all plasma voriconazole concentrations greater than the MIC90 (0.5 mg/ml) for *Aspergillus spp.* These data from therapeutic studies confirmed that the dose regimens used achieved the desired plasma voriconazole concentrations relative to the MICs in clinical isolates. Investigations of the relationship between MIC or mean plasma concentration/MIC ratio and clinical outcome, did not reveal any obvious relationships. A Cured or Improved clinical outcome was recorded for 7 of 11 patients with *Candida* isolates for which the isolates' voriconazole MICs exceeded the *Candida* species MIC90. The MICs of some of these isolates even exceeded the mean plasma voriconazole concentration (notably in some patients with *C. tropicalis* infection) and yet these patients had successful outcomes. This was also observed for other fungi, most notably the *Fusarium* isolates.

Medical Officer Comments: ***We concur with the Applicant's statement that consistent with the complex clinical picture of many of the patients treated in the voriconazole program, a clear relationship between MIC and clinical response outcome still needs to be established.***

The recommended voriconazole dosing regimen starts with two loading doses (6 mg/kg) 12 hours apart, followed by a q 12 h maintenance dose regimen.. The intravenous dose should be infused at a maximum rate of 3 mg/kg/hour. The higher maintenance dose of 4 mg/kg IV in aspergillosis and other mold infections is supported by the safety and efficacy results of the randomized open label Global Comparative Aspergillosis Study (307/602). An initial oral maintenance dose of 200 mg q 12 h is recommended rather than 300 mg q 12 h from considerations of hepatic safety from the Multiple Dose Escalation IV/Oral Switch Study .

Doses of voriconazole were chosen for investigation in therapeutic studies on the basis of mycological, pharmacokinetic and clinical data. The intravenous dose regimen of 6mg/kg 12 hours apart for two doses followed by maintenance doses of 3 mg/kg q 12 h rapidly achieved steady state plasma concentrations higher than the MICs for the majority of clinically relevant fungal pathogens. The Dose Ranging Oropharyngeal Candidiasis Study (302) defined the lower end of the dose-response relationship for the treatment of candidiasis. The Multiple Dose Escalation IV/Oral Switch Study (Study 230) showed that the risk of liver function test elevations increased with dose, and supported administration of a maintenance dose of 3mg/kg IV q 12 h or 200mg orally q 12 h, with the option of dose escalation in the face of poor clinical response. Because of the serious nature of the infection, an intravenous maintenance dose regimen of 4 mg/kg q 12 h was used in the Global Comparative Aspergillosis Study (307/602) with a favorable benefit to risk ratio.

Medical Officer comments: ***We concur with the Applicant's conclusions regarding dose justification and discussions regarding dose-efficacy and dose-toxicity relationships. Please see the Clinical Pharmacology review for additional discussion on these issues.***

Dose-response for toxicity

There is a clear relationship between plasma voriconazole concentration and elevated liver function tests and visual abnormalities. However, no such association has been identified for cardiac adverse events, rash or other toxicities. The following points were taken from the FDA Clinical Pharmacology section of the October 2001 Advisory Committee Meeting.

In the Phase 1 multiple dose voriconazole studies, healthy subjects demonstrated that increases from baseline in both ALT and AST were related to the increases in C_{max} and the AUC of voriconazole. This was true also for alkaline phosphatase (ALK PHOS) but the relationship was not as strong as that seen with ALT and AST. For total bilirubin there was little or no relationship with C_{max} or AUC of voriconazole in the phase 1 studies. Data also 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.

In the Phase 1 studies, there was also a positive association between C_{max} and AUC of voriconazole and the incidence of any visual adverse event. The incidence of visual adverse events was higher with multiple doses (46%) vs single dose (24%).

In the Phase 2/3 multiple dose studies 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 and total bilirubin levels than in those patients with normal values at weekly intervals from 1 to 12 weeks of therapy. Longitudinal logistic regression (odds ratio) and time to event (Cox proportional hazard ration) modeling analyses were also conducted. The longitudinal regression analyses predicted odds of approximately 7% (ALT), 13% (AST), 16% (ALK PHOS) and 17% (total bilirubin) in abnormalities for every 1.0 ug/ml increase in plasma voriconazole levels. The odds were statistically significant for AST, ALK PHOS and total bilirubin ($p<0.001$): however the ALT odds ratio was not significant. Likewise, the time to event analyses showed similar results. Plasma voriconazole levels and the hazard ratio/relative risk of all LFT abnormalities were significantly associated ($p<0.01$). However, the PK/PD analyses did not identify a threshold concentration for the increase in LFT's for the patients in the Phase 2/3 trials. The odds or risk of an LFT abnormality with every 1 ug/ml increase in plasma voriconazole concentration may be as low as 0% and as high as approximately 30%.

Medical Officer Comments: ***At this time it does not appear that dosage individualization on the basis of plasma voriconazole concentration measurements will add any value over diligent monitoring of liver function tests.***

In the Phase 2/3 trials, the frequency of visual adverse events varied from approximately 11% to 52%. Overall, it appeared that median plasma voriconazole concentrations were higher in those patients with visual adverse events than in those patients without visual adverse events over the majority of the weekly evaluation intervals. A threshold concentration of approximately ≥3ug/ml for visual adverse events was apparent. The longitudinal logistic regression analysis revealed a statistically significant relationship between plasma voriconazole concentration and the odds of a visual adverse event (p=0.011). The model predicted a 5% increase in the odds of a visual adverse event occurring for every 1.0 ug/ml increase in plasma voriconazole concentration.

Medical Officer comments: ***Please see the ocular safety review for additional details.***

The package insert clearly highlights the visual adverse events and contains precautions and warnings against driving or operating heavy machinery if the patient experiences any visual adverse events while on voriconazole therapy..

Maximum tolerated dose

The maximum tolerated dose regimen was identified in the Multiple Dose Escalation IV/Oral Switch Study. Elevation of liver enzymes was the dose-limiting factor in this study. Voriconazole at 5 mg/kg q 12h IV, followed by 400 mg q 12 h orally, was associated with ALT and AST elevations in 5 of 14 subjects. Therefore, a maintenance dose of 4mg/kg q 12h IV followed by 300mg bid orally represents the maximum tolerated multiple dose regimen of voriconazole.

Long-Term therapy

In the October 4, 2001 Advisory Committee Briefing Package, the sponsor reports that 304 of the 1946 patients therapeutic studies population (as of November 2000) received voriconazole for greater than 84 days. The mean duration of therapy in this long-term voriconazole population was 163 days whereas the median duration of therapy for the NDA all voriconazole population was 14 days. The maximun duration of therapy was 1014 days. Discontinuations and adverse events for patients in the long-term voriconazole therapy population (received greater than 84 days of voriconazole therapy) were examined and the following information was are excerpted from the Applicant's Advisory Committee Briefing package.

Discontinuations due to adverse events included 8.9% (27/304) of the long-term therapy population and 259/1946 (13.3%) of the NDA All-Voriconazole population. Adverse events leading to discontinuation of more than one patient in the long-term therapy population included abnormal liver function tests (1%), fever (0.7%), increased alkaline phosphatase (0.7%), increased hepatic enzymes (0.7%) and rash (0.7%). The incidence of these adverse events was comparable to that seen in the NDA All-Voriconazole population except that fever was more frequent (0.7% long-term vs 0.3% all NDA) and increased alkaline phosphatase was less frequent (0.7% long term vs 1.4% NDA All-Voriconazole.

Serious adverse events included 143/304 (47%) of the long-term therapy population and 882/1946 (45.3%) of the NDA All-Voriconazole population. The frequency and types of serious adverse reporting were similar with the exception of fever (9.2% long term and vs NDA All –Voriconazole 4.2%). Sepsis occurred in 7.2% of the long-term group vs 7.6% in the NDA All-Voriconazole and pneumonia (6.6% long-term vs 5.2% NDA All-Voriconazole).

Rash, fever, pneumonia, diarrhea and sepsis were the most frequently reported adverse events. However, photosensitivity reactions (5.6% vs 1.4%), pneumonia (8.2% vs 7.4%) and increased cough (6.9% vs 5.3%) occurred more frequently in the long term voriconazole population.

Medical Officer comments: ***It will be important to obtain complete safety data, especially regarding visual adverse events, in patients who require long-term therapy with voriconazole. We know that patients who developed visual adverse events while on a 28 day course of voriconazole, had return of normal vision once the drug was discontinued. However, we can not predict the visual sequelae in patients treated with longer courses of voriconazole.***

Dose modification
Dose modifications are required on the basis of weight, impaired renal function and hepatic function. No dose modifications are required based on gender or in the elderly. No firm recommendations for dosing in children can be made at this time, as additional studies are required.

Medical Officer comments: ***The "Pharmacokinetics in Special Populations" section of the label contains a synopsis of pharmacokinetic data in children aged 2 years to <12 years of age. Please see the following section on Special Populations for additional information on gender, age, race, and weight analyses. Information on the pediatric experience with voriconazole and recommendations to avoid use in pregnancy are included.***

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

Medical Officer Comments: ***It will also be helpful to obtain additional safety data on patients receiving voriconazole who have underlying hepatitis B (HBV) and hepatitis C (HCV) disease or have received a liver transplant.***

Renal Impairment
Following a single 200 mg 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, the IV excipient SBECD accumulates in patients with moderate to severe renal failure (i.e., creatinine clearance of $\leq$ 50 ml/min) and thus IV voriconazole is not recommneded unless the benefit outweighs the risk in an individual patient. Oral voriconazole should be used instead, if possible. Since hemodialysis does not remove a significant amount of voriconazole, no dosage adjustment is necessary in patients undergoing hemodialysis.

Over-dosage
In clinical studies there were 3 cases of accidental overdose in pediatric patients who received up to five times the recommended IV dose of voriconazole. A single adverse event of photophobia of 10 minutes duration occurred. There is no known antidote to voriconazole. Voriconazole is hemodialyzed with clearance of 121 ml/min. The intravenous vehicle, SBECD, is hemodialyzed with clearance of 55 ml/min. In an overdose, hemodialysis may assist in the removal of voriconazole and SBECD from the body.

IX. Use in Special Populations

A. Age/ Gender Effects Analyses and Adequacy of Investigation

Medical Officer comments: ***The following information is taken from the Clinical Pharmacology summary in the FDA October 2001 Advisory Committee Briefing Package and from the Applicant's NDA submission.***

The influence of age and gender on the pharmacokinetics of voriconazole was investigated in the Male/Female and Young/Elderly Study . This was an open, parallel group study in which groups of young (18-45 years) and elderly (>65 years) males and females initially received a single intravenous dose of 6 mg/kg voriconazole infused over 60 minutes. After a seven day washout, they were given 400 mg orally q 12 h for one day, followed by 200mg q 12 h for 5.5 days.

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 levels. 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_τ are lower in young males compared to the other three groups. The ratios of elderly male: young male are 161% (95% CI: 124 to 209) and 186% (95% CI: 126 to 273), respectively and those of young female: young male are 183% (95% CI: 141 to 238) and 213% (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.

From the population pK analysis, females appear to have higher plasma exposure than males and greater extent of plasma accumulation than males at the 200 mg q 12 hour dose regimen. A similar trend is apparent for elderly females vs elderly males. However, plasma voriconazole concentration –time data collected from 10 phase 2/3 studies (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.

Medical Officer comments: ***No dosage adjustment of voriconazole is necessary on the basis of age or gender.***

Males and females were comparable with respect to race and mean age. As expected, mean weight for males was greater (71.4 kg) than for females (65 kg). The mean duration of treatment for males and females was similar. The only noteworthy difference in the causes of death between males and females was in the incidence of deaths due to AIDS and this may reflect the demographics of the disease. Discontinuations due to adverse

events that occurred in 1% or more of subjects sorted by gender included events such as the following: alkaline phosphatase elevation in 16% males and 13.8% females. Hepatic enzymes increased in 1.6% males and 1.3% females and acute kidney failure occurred in 1.2% males and 0.9% females. There were no major differences in the numbers of discontinuations due to adverse events when analyzed by gender. All causality treatment emergent adverse events were presented and the most frequent adverse events that occurred in both male and female subjects were abnormal vision, fever, rash, vomiting, nausea and diarrhea. There were also no major differences between males and females in the incidences of any of the most commonly reported adverse events, serious adverse events and laboratory abnormalities.

Medical Officer comments: ***I concur with the Applicant's gender effects analyses. There were adequate proportions of women represented in the clinical studies. There were no major differences in efficacy or safety by gender.***

Weight

Although not identified as a significant covariate in the population 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. greater than 1 week duration), the AUC estimates show a trend to increase as the subject's body weights became lower. Subject body weights in the Phase 1 datasets ranged from 50-95 kg. Thus, although subjects with body weights less than 50 kg were not included in the population pK analysis, a decision was made for the phase3 studies to reduce the dose by one-half in patients with body weights less than 40 kg. The plasma concentration data obtained from the 10 phase 2/3 trials of patients shows similar average steady state plasma concentrations following oral voriconazole administration between patients with body weights less than 40 kg who received one-half the recommended dose versus those patients with body weights greater than or equal to 40 kg.

Several simulations were performed using the population pharmacokinetic model derived from Phase 1 data to explore the relationship between body weight, dosing and AUC. In general, the model predicted that for oral dosing, subjects who weighed less would have higher AUC values than subjects who weighed more. In the therapeutic studies, the oral voriconazole dose was halved for subjects below 40 kg. Exposure in patients less than 40 kg was within the range observed in patients weighing greater than 40 kg. This suggests that the therapeutic strategy to half the oral dose in patients under 40 kg succeeded in achieving plasma voriconazole concentrations comparable to those in patients above 40 kg.

Subject disposition and demographics of subjects were further grouped by weight i.e. <40 kg, 40 to<70 kg, 70 to <100 kg and ≥100 kg. Subjects who weighed less than 40 kg had a higher mean cumulative dose and longer mean and median durations of treatment. There was no specific pattern regarding cause of death that emerged among the various weight groups. Regarding treatment emergent serious adverse events, there was no particular pattern that emerged relating to any specific organ system. Regarding discontinuations, the most frequent adverse event was an increase in alkaline phosphatase

levels. (1.4-3.6%). Regarding adverse events, there was no evidence that lighter subjects were overdosed or had more adverse events Finally there were no major differences between the different weight groups regarding the incidence of clinically significant laboratory abnormalities.

Medical Officer Comments: ***The package insert recommends a reduction in the recommended voriconazole dosage by one-half in patients with body weights less than 40 kg.***

Age

The Applicant provides a good summary on safety data analyzed by age. Age groups are broken down by <12 years, 12-15 years, 16-44 years, 45-64 years, 65-74 years and ≥75 years. Subjects in younger age categories <15 years weighed less than older age categories. The majority of subjects in each age category were White and there was an equal or greater proportion of males than females. The median duration of treatment was comparable for all age categories. However, the mean duration of treatment for the younger subjects was longer than that for the older subjects and the oldest subjects had the shortest mean duration of treatment.

Regarding deaths, 20% of 12-15 year olds, 21.8% of 16-64 year olds and 39.6% of subjects older than 64 years of age died. A greater proportion of subjects older than 64 years of age died of septicemia (6.7% vs 1.8% in the 16-64 year old group) and AML (8.2% vs 1.8% in the 16-64 year old group) but the groups were otherwise comparable.

Regarding treatment emergent serious adverse events, sepsis was the most frequently reported serious adverse event in all three age groups and occurred at a higher rate in subjects who were 12 to 15 years of age (7/20 or 35%) and in (20/134 or 14.9%) subjects who were older than 64 years of age. Pneumonia occurred more frequently in the patients aged 64 years and older. Overall there was no major pattern in the occurrence of serious adverse events relating to any specific organ system depending on age.

Regarding discontinuations due to adverse events by age category: subjects who were 75 years of age or older had a higher rate of discontinuations (7/22 or 31.2%) than did other subjects (12.6% to 18%). No one specific adverse event accounted for these discontinuations in the elderly patient. Reasons for discontinuations included fever, cellulites, elevated GGT, acidosis, bilirubinemia, encephalopathy, respiratory tract infection, skin ulcer and acute kidney failure. No specific adverse event pattern emerged for particular age groups.

Finally, treatment emergent adverse events and laboratory abnormalities were examined for the age groups. As expected patients 75 years or older reported a higher incidence of renal adverse events than did younger subjects.

Race

The Phase 1 population pharmacokinetic analysis investigated the effect of race on

voriconazole pharmacokinetics. The analysis included 65 Asians, of whom 64 were Japanese subjects, in the total population of 236 subjects. Only four subjects included in the analysis were Black. After accounting for CYP2C19 genotype and body size, the model used in this population did not identify race as an influence on the pharmacokinetics of voriconazole.

In addition, pharmacokinetic data collected in the therapeutic studies were analyzed by race and are summarized as follows: The highest median average plasma concentration was observed in Asian patients. Although the number of Asian subjects was low, this finding is consistent with the higher prevalence of CYP2C19 "poor metabolizers" in the Asian population. Genotype data was not collected in the therapeutic studies. The plasma voriconazole concentrations in the 103 Black patients did not appreciably differ from the concentrations in the 861 White patients.

In regard to cause of death, there were no specific patterns noted among the race groups (White, Black, Asian, Hispanic and Other). Regarding serious adverse events, it was noted that acute renal failure and cardiac arrest occurred more frequently in Black subjects than in other race groups. Otherwise, there were not other remarkable differences among the races regarding serious adverse events. Regarding discontinuations, with the exception of the White race group, there were too few subjects in the other race categories who discontinued due to adverse events to allow for a meaningful analysis. Regarding adverse events, the incidence of rash was highest in the Hispanic patients and and lowest in the Black patients. Regarding laboratory abnormalities, the incidence of significant increases in creatinine levels was higher in Black patients and the incidence of total bilirubin increases was lower in Black patients than in other groups.

Overall, there were no major differences in the tolerability of voriconazole among subjects in different racial groups.

Pediatric Experience

In the therapeutic studies of this NDA there were 18 children with invasive aspergillosis ages 12 years to 18 years old. These patients were enrolled in studies 303, 304, 309, 602, 604, 309, and 609. Additional pediatric efficacy and pharmacokinetic data was submitted and accepted in May 2002. Efficacy data on 4 children with invasive aspergillosis from study 309 was included.

Medical Officer comments: The satisfactory response rate for the 22 children with invasive aspergillosis, after treatment with a maintenance dose of voriconazole (4 mg/kg Q12h) in the therapeutic studies was 12/22 or 54.55%.

The overall experience of voriconazole use in children was mainly based on two pharmacokinetic studies conducted in immunocompromised children and on safety data collected in the compassionate use programs. The experience was summarized by the Applicant in the Advisory Committee Briefing Package in October 2001. There were 52/1946 patients aged under 12 in the November 2000 NDA (NDA All Voriconazole

population). One of these patients was enrolled into the NDA Therapeutic Studies Population and the other 51 received voriconazole in the compassionate program.

The patient who was less than 12 years of age in the NDA Therapeutic Studies Population had three adverse events (rash, osteomalacia, and vomiting), but completed the study. Of the 51 patients of less than 12 years in the compassionate use program., 35 were male (68.6%) and the majority were white (41/51, 80.4%). The median duration of treatment was 82 days. Eighteen of 51 of the 12 year old patients (35.3%) died. The most frequent cause of death was respiratory failure (7 patients).

Serious adverse events reported by more than two patients less than 12 years old were fever (10/51; 19.6%), sepsis (10/51; 19.6%), respiratory insufficiency (10/51; 19.6%), inflammation at the injection site (4/51; 7.8%), abscess (4/51; 7.8%), respiratory tract infection (4/51; 7.8%), acute renal failure (3/51; 5.9%), cellulitis (3/51; 5.9%), and pneumonia (3/51; 5.9%).

No one adverse event led to the discontinuation of more than one patient.

In the Single Dose Pediatric Study, two of 11 patients experienced serious adverse events, neither of which was considered to be related to treatment. Both patients received a single dose of voriconazole on Day 1. A four year old female experienced moderate neutropenia, mild pyrexia and moderate febrile neutropenia on Day 3 (post-treatment event) for which she was hospitalized. A four-year old male experienced febrile neutropenia on Day 12 for which he was hospitalized. Both events resolved.

The 10 most commonly reported adverse events in the 28 patients enrolled in the Multiple Dose Pediatric Study (1007) and all adverse events in the Single Dose Pediatric Study (249) were vomiting (7%), sepsis (6%), diarrhea (6%), mucous membrane disorder (6%), fever (5%), abdominal pain (5%), epistaxis (5%), rash (4%), hypertension (4%) and hyperbilirubinemia (4%).

In the Multiple Dose Pediatric Study (1007), photophobia was reported in 1% of patients. Regarding elevations in liver function tests: the findings were consistent with a dose response as the total bilirubin was elevated in 3.7% of patients at the 3 mg/kg dose and this increased to 5/27 (18.5%) at the higher 4 mg/kg dose. Serum ALT was elevated in 2/27 (7.4%) of patients at the 3 mg/kg dose and in 3/27 (11.1%)of patients at the higher 4 mg/kg dose. Serum AST was elevated in 3.7 % of patients at both the 3 mg/kg and 4 mg/kg dose. There were no elevations in alkaline phosphatase at either dose.

Overall, there were no new serious adverse events or new adverse events reported in the 51 patients less than 12 years old in the compassionate program of the NDA Overall Safety Population, or in the 39 patients in the pharmacokinetic studies, that were not also reported in adults.

Medical Officer Comments: ***In October 2001, at the Division's request, the Applicant submitted additional pediatric data for review. Dr. Johann-Liang summarized the***

safety experience in 217 children with invasive fungal infections in November 2001 (see below):

Of the 217 children, the majority were male. The ethnicity profile included 79% White, 8% Asian and 5% Black. There were 12 children less than 2 years old, 43 children age 2 years to 6 years, 42 children greater than 6 years to 10 years, 40 children greater than 10 years to 14 years and 80 children greater than 14years to 18 years. Underlying diseases included hematologic malignancies, chronic granulomatous disease, children with allogeneic bone marrow transplant, HIV/AIDS and other immune deficiency diseases. Mean dosage of voriconazole ranged from 8.3 mg/kg/day to 11.1 mg/kg/day and in the 2 to 6 year group this dosage was above the Applicant's proposed dosing . Review of adverse event data demonstrated the following most frequent adverse events:

Eye related complaints occurred in 30/217	(14%) of children	aged	1-17 years.
Liver-related adverse events occurred in 18/217	(8.3%) of children	aged	2-17 years.
Skin –related adverse events occurred in 26/217	(12%) of children	aged	1-17 years.

Medical Officer comments: ***The most frequent adverse events in children were related to the eye, liver and skin. However, there may be "under-reporting" of visual adverse events in the younger children with poorer communication skills and thus reporting bias.***

Overall, the safety and effectiveness of voriconazole in pediatric patients, below the age of 12 years, have not been established.

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

Sparse plasma sampling for pharmacokinetics in adolescents was conducted in the therapeutic studies and no definitive conclusions can be made at this time.

Medical Officer Comments: ***Additional safety and pharmacokinetic studies in children are currently under discussion.***

Pregnancy

Clinical Safety

Cardiac

An "approval" status for the indications of treatment of invasive aspergillosis and treatment of serious fungal infections caused by *Scedosporium apiospermum* (asexual form of *Pseudallescheria boydii*) and *Fusarium* spp.including *Fusarium solani* in patients intolerant of, or refractory to, other therapy will not be predicated on completion of these cardiac safety studies.

In addition, the following areas will need to be addressed as phase 4 study commitments.

Ophthalmologic
Structures of the eye are not fully developed until 9 years of age. Additional studies will be required to assess the safety of this product in children less than 9 years of age.

Clinical Pharmacology
The October 4th, 2001 Advisory Committee recommended that voriconazole drug interaction studies be performed using representative protease inhibitors (ritonavir) and non-nucleoside reverse transcriptase inhibitors(efavirenz). Additional drug interactions studies will also be performed with rifabutin, methadone and oral contraceptives.

Additional information should also be collected regarding the use of voriconazole in patients with underlying hepatitis C and hepatitis B disease.

Microbiology
The Division recommends that the Applicant continue to collect data on the efficacy of voriconazole against strains of Aspergillus other than *A. fumigatus*. The Division also recommends that the Applicant continue to assess patterns of cross resistance between voriconazole, itraconazole and fluconazole from all *Candida, Aspergillus, Fusarium* and *Scedosporium* isolates and continue to monitor drug resistance development in patients with isolates of *Candida, Scedosporium and Fusarium.*

XI. Appendix (Ocular and Hepatic Safety Reviews)

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Rosemary Tiernan
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Marc Cavaille Coll
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MEDICAL OFFICER

Renata Albrecht
6/12/02 10:46:30 AM
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INTEGRATED REVIEW OF EFFICACY

FOR

NDA 21-266 and 21-267 **VORICONAZOLE (Vfend®)**

Study 304 was a non-comparative study of voriconazole use in "primary" and "salvage" patients conducted in Europe. The overall expert global response rate for voriconazole in study 304 was 49.1%. A satisfactory response of 60.3% was seen in the "primary" patients and a satisfactory response of 37% was seen in the "salvage" patients.

A retrospectively designed historical control study (study 1003), which consisted of patients from both the United States and Europe who received a predominantly amphotericin B regimen, was used as the comparator for study 304. In the comparison of a subgroup of study 304 voriconazole subjects to historical control patients, the "best matched, less than 5 days of prior antifungal therapy" study 304 voriconazole group had a satisfactory global response rate of 52% compared to an overall satisfactory global response rate of 25% for the historical control patients. The probability of survival was 0.554 for voriconazole and 0.417 for the historical control. This historical control trial represented a good effort by the Applicant---but concern still persisted regarding the comparability of study populations. Consequently, study 304 results are being used to support the randomized controlled study 307/602.

Finally, studies 309 and 604 were non-comparative studies which enrolled patients who were refractory or intolerant to approved therapy for aspergillosis. The overall satisfactory response rate for voriconazole for the salvage treatment of patients with *Aspergillus fumigatus* in studies 304, 309 and 604 was 44%.

In summary, voriconazole has demonstrated that it is effective for both primary and salvage therapy of invasive aspergillosis. The adverse event profile of voriconazole includes the occurrence of visual adverse events in one in three patients, elevated liver function tests, and cases of skin exanthem with four cases described as Stevens- Johnson syndrome. There were also more cardiac arrests in the voriconazole arm of study 307/602 when compared to the amphotericin B/OLAT group and although a causative role for voriconazle could not be proven, it also could not be definitively excluded.

The Applicant has committed to completing an additional oral dose escalation study to ascertain whether voriconazole has a prolonging effect on the QT interval. Despite the aforementioned safety concerns, voriconazole has demonstrated significant benefit in the treatment of invasive aspergillosis. This benefit outweighs the drug associated safety risks for this indication and voriconazole should be approved. The October 4th, 2001 Advisory Committee also unanimously supported approval for voriconazole for the treatment of invasive aspergillosis.

Treatment of serious fungal infections caused by *Scedosporium* and *Fusarium* spp

The clinical data in the applicant's NDA submission were derived from 4 phase 2/3 open, multi-center, non-comparative studies (150-303, 150-304, 150-309, and 150-604) as well as from 4 compassionate use studies (150-301, 150-303a, 150-304a, and 150-606). Studies 150-309 and 150-604 (open, non-comparative trials in subjects intolerant or failing other therapies or with infections for which there is no approved therapy (interim analyses) were the primary studies from which data were collected.

The case report forms (CRFs) of all cases identified by the Applicant as having an infection with a rare fungal isolate were reviewed by the medical officer (MO). Subjects were assessed for key elements including (i) primary underlying condition, (ii) hematological risk factor, (iii) previous antifungal treatment, (iv) infection details with pathogen, site and certainty of infection, and (v) outcome. Subjects included in the Applicant's database from studies other than 309 and 604, often did not have baseline or follow-up culture information to document the presence of an infection and were included in the Applicant's database based only on the investigator comments when requesting voriconazole for compassionate use. A review of these protocols (301, 303A, 603, 606) revealed that the submission of culture evidence was not an inclusion criterion, that these studies were not monitored, and that the verification of cases was difficult in the absence of culture information. Therefore, the MO determined to exclude any case from these protocols where culture evidence of a deep fungal infection was not provided. For studies 309 and 604, where the submission of cultures was an inclusion criterion and where the subjects were monitored, the MO accepted all cases.

The MO requested that the Applicant submit any additional cases of *Fusarium* or *Scedosporium* spp. infection not included in the November 2000 submission, but collected since the original cutoff date. This request was made in order to increase the size of the database for these fungal pathogens and thus to allow for a larger sample size on which to base a regulatory decision.

Ninety-eight subjects with 147 isolates were included in the FDA database. The primary efficacy variable was the global response (complete, partial, stable, or failure) evaluated by the investigator at end of therapy i.e. EOT/Week 16 (for subjects continuing with voriconazole therapy), based on their overall clinical, mycological, radiological, and serological responses. Global response was also assessed 4 weeks after EOT (and compared with EOT) in subjects who stopped voriconazole therapy at or before week 16 and whose global response at EOT was complete, partial, or stable disease. Clinical, radiological, mycological, and serological responses were evaluated at Weeks 2, 8, 12, or EOT/Week 16 (for those subjects continuing therapy). Clinical response was also evaluated at Weeks 1 and 4. When available the Applicant's VERA assessments took precedence over the investigators. Those subjects who were in compassionate use protocols did not undergo VERA. Subjects with complete or partial successes were determined to have satisfactory response or a success.

The primary population assessed by the MO was the modified-intent- to treat (MITT), defined as subjects that received at least one dose of voriconazole, had a definite or probable diagnosis of systemic or invasive fungal infection at baseline as confirmed by the review of culture reports by the MO, and were recruited on or before 26 May, 1999 (Study 150-604) or May 31, 1999 (Study 150-309). An additional 10 subjects who were treated after the original cut-off date were also included.

The Applicant's MITT population consisted of 101 subjects not including subjects counted twice because of mixed infections or 111 including such patients. The

Applicant's overall success rate by pathogen was 64/137 (47%) and by patient was 45/101 (45%). The by-pathogen breakdown included a 59% success rate for *Scedosporium apiospermum* and a 40% success rate for *Fusarium* spp. These rates do not take relapses into account. Relapses were counted as failures by the MO but not by the Applicant.

As per the FDA analysis, total by patient success rate was 43/98 (44%) or 38/98 (39%) excluding relapses. Total by pathogen rate was 68/147 (46%) or 60/147(41%) excluding relapses.

Voriconazole appeared relatively effective as salvage therapy in the treatment of fungal infections due to *Scedosporium apiospermum/Pseudallescheria boydii* and in those due to *Fusarium solani/Fusarium* spp. in subjects refractory to or intolerant of conventional antifungal treatments. Success rates were 15/25 (60%) or 12/25 (48%) in a by-patient analysis of *Scedosporium apiospermun* (by-pathogen: 22/33 (67%) or 17/33 (52%) with relapses) and 9/21 (43%) or 7/21 (33%) with relapses in a by-patient analysis for *Fusarium* spp. (by-pathogen 12/32 (38%) or 9/32 (28%) with relapses. Although the success rates are not high, especially for *Fusarium* spp. infections, the mortality associated with these infections can be > 80%, thus the success rates obtained with voriconazole are clearly an improvement and provide an obvious benefit to patients.

The clinical reviewer recommended approval for use of voriconazole in the treatment of serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp. in subjects intolerant of or refractory to other therapy.

B. Summary of Efficacy for Approvable Indications

Treatment of *Candida* Esophagitis

In study 305, voriconazole, at a dose of 200 mg PO BID, proved to be as effective as fluconazole for the treatment of mainly HIV patients with *Candida albicans* esophagitis.

The primary objective of the study was to show that voriconazole was non-inferior to fluconazole. Sample sizes were based on 80% power to show that the lower bound of the two -sided 95% confidence interval for the differences in success rates (voriconazole-fluconazole) was no less than –15%. ITT and PP populations were both used for the efficacy analyses. However, the primary efficacy analysis was based on the PP population while the ITT population was used to test the robustness of the per protocol results. Two-sided 95% confidence intervals, calculated using the normal approximation to the binomial distribution with continuity correction, were used to estimate the difference in the proportion of success between the treatment groups.

The degree of severity of the esophageal candidiasis was determined by endoscopy and was graded on a scale of 0-4. Comparison of Day 43/EOT to screening was used to categorize subjects as cured/improved or failed. The investigator assessed symptoms of esophageal candidiasis and signs plus symptoms of oropharyngeal candidiasis at each

visit as cured/improved or failed. Mycology was also assessed at Day 43/EOT and compared to screening, in order to be classified as eradicated or persisted.
The esophageal success (cured + improved) rate was 98.3% for voriconazole and 95% for fluconazole using the endoscopy assessment at EOT for the per protocol population. These response rates for the per protocol population were similar to those derived by the sponsor. The difference in success rates (voriconazole-fluconazole) was 3.3% (in favor of voriconazole) and the exact 95% confidence interval for the difference between the treatment groups was (-3.6,10.7). Regardless of the method used to calculate the 95% confidence interval about the difference in success rates, the lower limit of the 95% confidence interval is greater than the pre-specified non-inferiority margin of –15%. Finally, for the ITT population, the esophageal candidiasis success (cured + improved) rate was 87.5% for voriconazole and 89.6% for fluconazole. The difference in success rates (voriconazole-fluconazole) was –2.0% (in favor of fluconazole).

Efficacy against *Candida glabrata* and/or *Candida krusei* would be considered a therapeutic advantage for any new antifungal product. However, in study 305, the majority (90%) of the clinical isolates were *Candida albicans* and there were insufficient numbers of non-albicans isolates to support that voriconazole had efficacy against either *Candida glabrata* or *Candida krusei*.

Of note, there were more discontinuations for adverse events and laboratory abnormalities in the voriconazole arm when compared to the fluconazole arm. Blurred vision and hepatic function abnormalities were more frequent in patients who received voriconazole when compared to fluconazole. In addition, there was one sudden death in the phase 3 clinical trials for which a role for voriconazole could not be excluded. *In vitro* studies of voriconazole had demonstrated no major effects for voriconazole in HERG channel studies or in the dofetilide studies when compared to ketoconazole. However, *in vivo* studies had demonstrated that, in dogs, high doses of voriconazole produced arrhthymia, PVC's and prolonged QT interval.

Consequently, the Division and the Applicant agreed to further investigate by performing the following study: A multicenter, double-blind, placebo controlled, 5 way cross-over, dose escalation study with random insertion of an active comparator oral ketoconazole 800 mg and placebo using the excipient, IV sulfobutylether-cyclodextrin (SBECD), to investigate the effect of 3 intravenous doses of voriconazole (4 mg/kg, 8 mg/kg and 12 mg/kg) on QTc interval in healthy subjects aged 18-65 years. The Applicant attempted to perform this study but on two separate occasions had to terminate the study due to the development of anaphylactoid reactions in patients receiving either SBECD alone or SBECD and voriconazole. Due diligence efforts have not yet determined the cause of these reactions.

Consequently, although in study 305, voriconazole was shown to be as effective as fluconazole for the treatment of *Candida albicans* esophagitis, there is no benefit and more risk to using voriconazole for the treatment of *Candida albicans* esophagitis. Therefore, voriconazole will be given "approvable" status for the primary treatment of

Candida albicans esophagitis. Approval will be granted after the Division reviews the QTc study previously described.

Treatment of Refractory Candida Esophagitis

Studies 309 and 604 had identical objectives and designs. Study 309 was conducted in Europe and Australia from July 1998 to October 2000 and Study 604 was conducted in the U.S., Canada, and Thailand from December 1997 to June 2000. The efficacy results were presented as an interim analysis on all patients entered into the study on or before 31 May 1999(Study 309) or 26 May 1999 (Study 604).

The primary objective of each study was to investigate the efficacy, safety and tolerability of voriconazole in the treatment of systemic and invasive fungal infections due to pathogens for which there is no licensed therapy; and in the treatment of systemic or invasive fungal infections in patients failing or intolerant of treatment with approved antifungal agents.

These were open label, non-comparative studies in which all patients received voriconazole, initiated as an intravenous loading dose of 6 mg/kg q 12 h for two doses or an oral loading dose of 400 mg bid for two doses, followed by maintenance dosing with 4 mg/kg q 12 h or 200 mg bid, respectively, for a total duration of 12 weeks. Eligible patients included patients who had been diagnosed with a systemic or invasive fungal infection for which there was no approved therapy and patients with a systemic or invasive fungal infection which was unsuccessfully treated or who had experienced intolerance or toxicity to an approved antifungal agent. Most patients had been treated with prior antifungal therapy within four weeks of starting the study (approximately 95%). The antifungal therapy most frequently used prior to study entry was amphotericin B (62% of study 309 patients and 78% of study 604 patients).

The overall combined satisfactory response rate for the treatment of refractory OPC and refractory esophageal candidiasis was 15/32 or 47%. The overall satisfactory response rate for the treatment of refractory esophagitis was 14/29 or 48.3% and for refractory OPC was 1/3 or 33.3%. There were two neutropenic AIDS patients with *C. albicans* esophagitis and they both had unsatisfactory responses.

Overall, results in 29 patients from these two non-comparative studies demonstrate a satisfactory response rate of 48.3% for the treatment of refractory *Candida* esophagitis. An indication for treatment of refractory *Candida* esophagitis will not be granted until the additional cardiac safety studies have been completed to support the safety of using voriconazole in the primary treatment of *Candida* esophagitis.

There were small numbers of the non-albicans species of *Candida* in refractory OPC and refractory esophagitis patients in studies 309 and 604. Therefore, it was not possible to draw conclusions regarding the efficacy of voriconazole against these pathogens.

D. Summary of Efficacy for Indications which were Not Approved

Treatment of other serious fungal infections in patients intolerant of, or refractory to, other therapy

Voriconazole appeared relatively effective as salvage therapy in the treatment of fungal infections due to *Scedosporium apiospermum/Pseudallescheria boydii* and in those due to *Fusarium solani/Fusarium* spp. in subjects refractory to or intolerant of conventional antifungal treatments. Success rates were 15/25 (60%) or 12/25 (48%) in a by patient analysis of *Scedosporium apiospermun* (by pathogen: 22/33 (67%) or 17/33 (52%) with relapses) and 9/21 (43%) or 7/21 (33%) with relapses in a by patient analysis for *Fusarium* spp. (by pathogen 12/32 (38%) or 9/32 (28%) with relapses. Although the success rates are not high, especially for *Fusarium* spp. infections, the mortality associated with these infections can be > 80%, thus the success rates obtained with voriconazole are clearly an improvement and provide an obvious benefit to patients.

However, voriconazole was ineffective in the treatment of infections due to *Cryptococcus neoformans/Cryptococcus* spp. including CNS infections and is not recommended for such processes (success by patient 4/13 (31%) and by pathogen 6/21 (29%). Although the success rates versus *Cryptococcus* spp. are similar to those attained versus *Fusarium* spp., the rates that are attainable with conventional antifungal therapies are much higher; thus voriconazole would not be beneficial in such a population. Additionally, voriconazole was ineffective in the treatment of zygomycosis (success 0/4).

Conclusions regarding the efficacy of voriconazole in the treatment of infections due to *Scedosporium prolificans/inflatum* and *Paecilomyces lilacinus* could not be drawn due to the small number of isolates. Additionally, no conclusions could be drawn regarding the efficacy of voriconazole in the treatment of a number of other fungal pathogens that did not have an adequate sample size to allow for conclusions.

The total sample size of 98 subjects was too small to draw valid conclusions regarding the efficacy of voriconazole depending on the underlying disease process. It appeared as if subjects with underlying hematologic malignancies had a lower success rate that those with a history of trauma or other underlying diseases.

Eighty of ninety-eight (82%) of the FDA subjects were classified as requiring salvage treatment for a variety or reasons and had received varying amounts of previous antifungal treatment. Fourteen of these subjects were classified as complete successes (18%) and 25 (25%) were classified as partial successes as compared to 1/18 (6%) and 4/18 (22%) respectively of subjects who received voriconazole as primary treatment. 43% of salvage subjects as compared to 28% of primary therapy subjects were successes. As noted in other analyses, the sample size was too small to draw valid conclusions.

Twenty-eight of ninety-eight (29%) subjects had a documented risk factor. This number was too small to allow for valid conclusions. As expected, it appeared as if those subjects with profound neutropenia had the worst outcomes.

The clinical reviewer did NOT recommend approval for the following requested indication:
"VFEND™ is indicated for use in the treatment of other serious fungal infections in patients intolerant of, or refractory to, other therapy".

This non-approval is recommended because of the non-comparative nature of the studies, and the small sample size, not only of the total population but of each specific pathogen. The issuance of such a generalized approval is not feasible given the vastly different clinical responses (depending upon underlying disease and presence or absence of risk factors) that can be seen, as well as the varying mycological efficacy rates not only of different pathogens but also within the same species.

Treatment of Candidemia

Study 608 was the Applicant's administrative interim analysis for the regulatory submission, which descriptively summarized data after approximately 10% of the total number of subjects to be enrolled had completed the study. Study 608 was an open-label, comparative, multicenter, randomized study to compare voriconazole and conventional amphotericin B followed by fluconazole in the treatment of non-neutropenic subjects with candidemia. The Randomization ratio was 2 (voriconazole):1 (amphotericin B-to-fluconazole) . Subjects received the study treatment for at least two weeks following the complete resolution of all clinical findings of an active infection or at least two weeks after the last positive culture was collected, whichever was later. The total maximum duration of therapy for the two treatment arms was to be eight weeks.

Subjects were required to have had a diagnosis of *Candida* or *Torulopsis* infection, based on blood cultures within 96 hours of study entry, and clinical evidence of infection within 48 hours prior to study entry. Intravenous voriconazole was administered at a loading dose of 6mg/kg Q12 hrs for the first 24 hours, with a maintenance dose thereafter of 3mg/kg Q12 hrs. Oral voriconazole treatment was initiated at 200mg BID (or 100 mg BID for subjects weighing less than 40kg). For subjects who failed to demonstrate prompt improvement, the voriconazole dose could be escalated to 4mg/kg Q12 hrs for the IV formulation and 300mg BID for the oral formulation (or to 150 mg BID for subjects weighing less than 40 kg). Subjects whose doses were escalated but who were unable to tolerate the increased dose could be considered for dose reduction. Voriconazole was administered intravenously for a minimum of three days. Amphotericin B was to be administered at a minimum average daily dose of 0.7mg/kg. Amphotericin B was to be administered for a minimim of three days and a maximum of seven days. Subjects who could not tolerate amphotericin B or had baseline isolates that, based upon the available data, were thought to be more appropriately treated by extended amphotericin B therapy or fluconazole therapy beginning earlier than Day 4 were permitted to deviate from this regimen.

Clinical assessments (blood pressure, pulse, temperature, signs and symptoms of infection) were made by the investigator daily during therapy, at the end of therapy (EOT), as well as at two, six, and 12 weeks following EOT. Mycological assessments (blood cultures, other cultures, histopathology) were as follows. Blood cultures were performed on Days 1 through 4, and Day 7, at EOT, two weeks following EOT, and if clinically indicated, at 6 and 12 weeks following EOT. Histopathology was performed if clinically indicated.

Imaging tests (i.e. radiographic, sonographic, MRI) were also conducted if clinically indicated. In addition to the investigator's assessment, the Data Review Committee (DRC) assessed each completed subject's response to antifungal therapy. To make the assessment, the DRC was provided with a blinded, monitored, and corrected copy of the case report form (CRF) of each subject as well as other relevant documentation. The possible classifications were cured, improved, failed, indeterminate, withdrew from study, relapsed, or not a study subject. The primary efficacy endpoint was derived from the DRC assessment of each subject's response to antifungal therapy as follows. Subjects with a DRC assessment of cured or improved at the 12-week follow-up visit were cured or improved in the analysis; all other subjects were considered to have failed.

The Applicant clearly stated that this data represented an administrative interim analysis for the regulatory submission, summarizing data after approximately 10% of the total number of subjects to be enrolled had completed the study. No formal statistical analyses were carried out. The primary efficacy endpoint analysis is summarized descriptively only.

The mean duration of therapy for subjects in the voriconazole treatment group in days $\pm$ SD (range) was 10 days $\pm$ 5 (3 –22) for IV therapy and 9 days $\pm$ 5 (1 – 15) for oral therapy. The mean duration in days $\pm$ SD (range) for amphotericin B-to-fluconazole group was 9 $\pm$ 6 (1-21) for IV and 13 $\pm$ 6 (5 – 22) for oral therapy. It is notable that 28 (62%) subjects remained on IV voriconazole for the total duration of treatment. On the other hand, only five (23%) subjects remained on amphotericin B and did not switch to fluconazole. In summary, this study does not compare IV voriconazole head to head with IV Amphotericin B in duration of treatment.

The results of the MITT analysis show that the responses to antifungal therapy in the two treatment groups were equivalent. The 12 week outcomes, classified as cured by the DRC's assessment, were 41.9% for voriconazole subjects and 40% for amphotericin B-to-fluconazole subjects. However, there are several points to note. As mentioned previously, no *C. krusei* has been isolated in this study thus far. All four patients with isolates of *C. glabrata* failed with voriconazole treatment in comparison to 3 out of 5 patients in the amphotericin B-to-fluconazole arm who failed treatment. Voriconazole treated patients with *C. parasilopsis* did well (6/8 patients cured). Overall, the number of *non-albicans* isolates were very small and the MIC data on these isolates was incomplete in the database. The data generated from these isolates may be more meaningful if

combined with results from other systemic *Candida* treatment protocols at this juncture, and should be analyzed in more detail when the full database is submitted.

The Applicant has submitted this interim report of study 608 after 10% patient completion in order to support the global voriconazole NDA application and in particular the treatment of "serious *Candida*" indications. The patient population for this study was an assortment of subjects (many surgical patients after multiple trauma, prolonged central line with total parenteral nutrition, elderly with severe pneumonia) who were non-neutropenic with candidemia. The comparison of treatment was open-label, but with randomized arms of either voriconazole (IV first, then switch to PO at the investigator's discretion) or amphotericin B (short duration: 3 to 7 days IV) followed by fluconazole (IV or PO). Evaluation of efficacy by the MITT population at 12 weeks outcome resulted in the two arms having equivalent results (41.9% cured for voriconazole subjects and 40% cured for amphotericin B-to-fluconazole subjects). The numbers for different non-albicans *Candida* isolates were quite small, but the breakdown from this study suggests equivalent results between the two arms for *C. albicans* and *C. tropicalis,* better response against *C. parasilopsis* for voriconazole, and poorer response against *C. glabrata* for voriconazole. There was no *C. krusei* isolated.

To summarize, forty-five subjects in the voriconazole arm and 22 patients in the amphotericin B-to-fluconazole arm were treated after 2:1 ratio randomization. Baseline characteristics in the two arms were similar. Thirty-one (69%) in the voriconazole arm and 15 (68%) in the amphotericin B-to-fluconazole were evaluated for efficacy by modified intent to treat analysis. The outcome assessment at 12 weeks follow-up was comparable between the two arms with 41.9% cure for voriconazole-treated subjects and 40% cure for amphotericin B-to-fluconazole treated. The voriconazole arm had a poorer safety profile than amphotericin B-to-fluconazole. There were 8 discontinuations from the study in the voriconazole arm due to adverse events versus none in the amphotericin B-to-fluconazole arm. The concerning safety issues were liver function test elevations, visual symptoms, and a patient with blistering rash.

Overall, the 10% interim results from study 608 are considered insufficient to support approval for the indication of treatment of serious *Candida* infections (including *C. krusei*) such as systemic *Candida* infections (hepatosplenic candidiasis, disseminated candidiasis, candidemia).

Treatment of Refractory Candidiasis and Refractory Candidemia

The clinical data in the Applicant's NDA submission pertinent to the refractory candidiasis indication were derived from 3 phase 2/3 open, multicenter, non-comparative studies (150-303, 150-309, and 150-604) as well as from 3 compassionate use studies (150-301, 150-312, and 150-606). Studies 150-309 and 150-604 (open, non-comparative trials in subjects intolerant have or failing other therapies or with infections for which there is no approved therapy (interim analyses) were the primary studies from which data were collected.

The case report forms (CRFs) of all cases identified by the applicant as having a refractory *Candida* infection were reviewed by the MO. Subjects were assessed for key elements including (i) primary underlying condition, (ii) hematological risk factor, (iii) previous antifungal treatment, (iv) infection details with pathogen, site, and certainty of infection, and (v) outcome.

Forty-three subjects with 64 isolates were included in the FDA database. The primary efficacy variable was the global response (complete, partial, stable, or failure) evaluated by the investigator at EOT/week 16 (for subjects continuing with voriconazole therapy), based on their overall clinical, mycological, radiological, and serological responses. Global response was also assessed 4 weeks after EOT (and compared with EOT) in subjects who stopped voriconazole therapy at or before week 16 and whose global response at EOT was complete, partial, or stable disease. Clinical, radiological, mycological, and serological responses were evaluated at weeks 2, 8, 12, or EOT/week 16 (for those subjects continuing therapy). Clinical response was also evaluated at weeks 1 and 4. When available the Applicant's VERA assessments took precedence over the investigators. Those subjects who were in compassionate use protocols did not undergo VERA. Subjects with complete or partial successes were determined to have satisfactory response or a success.

The primary population assessed by the MO was the MITT, defined as subjects that received at least one dose of voriconazole, had a definite or probable diagnosis of systemic or invasive fungal infection at baseline as confirmed by the review of culture or histology reports by the MO, and were recruited on or before 26 May, 1999 (Study 150-604) or May 31, 1999 (Study 150-309). An additional 10 subjects who were treated after the original cut-off date were also included.

The Applicant's and the FDA's MITT populations were the same. Relapses were counted as failures by the MO but not by the Applicant.

Voriconazole appeared relatively effective as salvage therapy in the treatment of refractory *Candida* infections due to *Candida albicans* and *Candida krusei*. Success rates were 5/12 (42%) or 4/12 with relapse (33%) in a by patient analysis of *Candida albicans* (by pathogen: 5/14 (36%) or 4/14 (29%) with relapses) and 6/10 (60%) in a by patient analysis for *Candida krusei* (by pathogen 7/13 (54%). Although the success rates are not high, especially for *Candida albicans* infections, the mortality associated with these infections can be very high and thus the success rates obtained with voriconazole are of significance for patients with these refractory infections.

Voriconazole was marginally effective in the treatment of infections due to *Candida glabrata* with a large number of failure in patients with candidemia (success by patient 4/12 (33%) and by pathogen 6/17 (35%). As the success rates versus *Candida glabrata* are similar to those attained versus *Candida albicans*, a final decision regarding approval can only be made based on the bulk of the evidence of voriconazole's effectiveness versus this pathogen in a population with non-refractory but with disseminated disease.

Conclusions regarding the efficacy of voriconazole in the treatment of infections due to *Candida tropicalis* and *Candida parapsilosis* could not be drawn due to the small number of isolates.

The total sample size of 43 subjects was too small to draw valid conclusions regarding the efficacy of voriconazole depending on the underlying disease process. It appeared as if subjects with underlying hematologic malignancies had a lower success rate that those with a history of trauma or other underlying diseases.

Twenty of forty-three (47%) subjects had a documented risk factor. This number was too small to allow for valid conclusions. Thee of eight (38%) of subjects with profound neutropenia (including 2 with *Candida krusei)* and 19/35 (54%) without neutropenia (including 4 subjects with *Candida krusei)* were treated successfully with voriconazole.

Total by-patient success rate was 22/43 (51%) or 20/43 (46.5%) excluding relapses. Total by-pathogen rate was 30/64 (47%) or 28/64 (44%) excluding relapses.

The sample size was too small to allow for valid conclusions regarding the outcome of refractory *Candida* infections by site of infection. 2/6 subjects with hepatosplenic candidiasis, 10/24 (17%) with candidemia, 4/6 (67%) with skin infections, 2/6 with pulmonary infections, and 9/15 subjects with other sites of infection were treated successfully with voriconazole. All subjects with cerebral disease failed.

The clinical reviewer recommended approval for use of voriconazole in the treatment of serious fungal infections caused by *Candia albicans* and *Candia krusei* in subjects intolerant of or refractory to other therapy. The clinical reviewer did NOT recommend approval for other *Candida* species as requested by the Applicant as the sample size studied was small and the outcomes inconclusive. The recommendation for approval for *Candida albicans* is based on the bulk of evidence within the NDA that supports the activity of voriconazole versus *Candida albicans* and on the fact there is no other currently approved oral antifungal with a refractory candidiasis indication and that the severity of the infections as well as the underlying diseases in the patients studied indicate the medical need for an oral antifungal for this indication. The clinical reviewer did NOT recommend approval for the following requested indication: "VFEND™ is indicated for use in the treatment of other serious fungal infections in patients intolerant of, or refractory to, other therapy". This non-approval is recommended because of the broadness and the lack of specificity of the proposed indication. The issuance of such a generalized approval is not feasible given the vastly different clinical responses (depending upon underlying disease and presence or absence of risk factors) that can be seen as well as the varying efficacy rates between the different species of *Candida.*

Ultimately, the decision was made NOT to approve the indications for use of voriconazole in the treatment of serious fungal infections caused by *Candia albicans* and *Candia krusei* in subjects intolerant of or refractory to other therapy until the results of study 608 (primary treatment of candidemia) can be reviewed and until the safety study to assess QT prolongation has been completed.

by cancer chemotherapy or bone marrow/ peripheral stem cell transplantation. Subjects had at least 96 hours of neutropenia (defined as a neutrophil count of <500 cells/mm^3 and <250 cells /mm^3 in the 24 hours preceding randomization), temperature of ≥ 38°C, and at least 96 hours of systemic empirical antibacterial therapy prior to randomization. Subjects were randomized to receive either voriconazole or L-AMB in a 1:1 ratio. Randomization was stratified according to risk of fungal infection and previous systemic antifungal prophylaxis. The study defined high-risk patients as those with allogeneic transplants or relapsed leukemia.

This study was not blinded. The Applicant cited the differences in the physical natures of the intravenous formulations of voriconazole and L-AMB and the lack of a suitable oral formulation of L-AMB as reasons for conducting this as an open label trial. The Applicant considered administration of dummy infusions of the excipient for each agent to maintain blinding. However, the Applicant considered it unethical to administer second intravenous infusions to critically ill patients who may have potential difficulties with fluid balance. The absence of blinding in this trial could introduce potential bias into the study. The toxicities of amphotericin B related products, both renal insufficiency and infusion related events, is well known and clinicians may be more likely to discontinue therapy in patients receiving L-AMB. On the other hand, the efficacy of amphotericin B and related products has been well-established over years of use and clinicians may be more likely to discontinue therapy with a new agent if they are concerned about it's efficacy.

Although the administration of study drug was not blinded, a blinded data review committee (DRC) evaluated all subjects with diagnoses of documented baseline and/or breakthrough deeply invasive fungal infections (DIFIs). Reviewers in the DRC were not provided with information on treatment allocation or dosage.

Subjects who were randomized to voriconazole received an intravenous loading dose of 6mg/kg q12h for the first two doses followed by 3mg/kg IV bid. Subjects randomized to voriconazole received intravenous study drug for a minimum of three days. After three days of intravenous voriconazole, further empirical treatment could be given using oral voriconazole (200mg bid for subjects ≥40 kg, 100mg bid for subjects <40 kg). Empirical oral therapy (or continued empirical intravenous therapy) was administered for a maximum of up to three days after recovery from neutropenia (RFN). Subjects diagnosed with baseline or breakthrough DIFI could receive a maximum of 12 weeks of therapy.

L-AMB was administered via intravenous infusion at a dose of 3mg/kg/day, the FDA approved dose for this indication. The protocol specified that L-AMB be infused at a maximum rate of 3mg/kg per hour (i.e. at least 1 hour for a 3mg/kg dose, at least 2 hours for a 6mg/kg dose) if administered through a peripheral vein. Subjects randomized to L-AMB were treated with L-AMB until up to three days after RFN, or resolution of baseline or breakthrough DIFI for a maximum of 12 weeks of therapy, whichever came first.

Empiric Antifungal Therapy of Patients with Febrile Neutropenia

The Applicant is seeking approval of voriconazole (VFEND) injection and tablets for the indication of empiric therapy of febrile neutropenia. The specific wording requested by the applicant in their proposed labeling states that voriconazole is effective in "empirical treatment of presumed fungal infections in febrile immunocompromised patients". In support of this indication, the Applicant submitted data from one non-inferiority study (Study 603) of voriconazole compared to liposomal amphotericin B (Ambisome, L-AMB) in patients with neutropenia secondary to cancer chemotherapy. The results of the study showed an overall response rate of 26% (108/415) in the voriconazole group and 30.6% (129/422) in the L-AMB group using a composite endpoint in a non-stratified analysis. Using this raw data, the difference in the point estimated of the efficacy of the two therapies was -4.5% with a 95% confidence interval of -10.6% to +1.6%. The study was designed to stratify patients by risk of fungal infection and previous use of antifungal prophylaxis. The stratified results yielded an overall response rate using the same composite endpoint of 23.7% in the voriconazole group and 30.1% in the L-AMB group. The difference in the point estimates the two therapies in the stratified analysis was –6.08% with a 95% confidence interval of –12.0% to –0.1%. The pre-specified lower bound of the 95% confidence interval used to define non-inferiority in this trial was –10%. Thus, in both the raw and stratified analyses, voriconazole did not meet the pre-specified statistical definition of non-inferiority.

Statistical considerations are one part of the decision making process used by the FDA in determining whether a drug is safe and effective for a given indication. However, the FDA also considers other potential efficacy and safety issues related to a new drug in the light of currently available therapy for that indication. On October 4, 2001, the Advisory Committee was asked to consider the potential advantage of fewer numbers of breakthrough infections in the voriconazole group and the adverse experience profile of voriconazole compared to other available therapies for empiric antifungal therapy in febrile neutropenic patients. The Advisory Committee was also be asked to consider the adverse experience profile of voriconazole given that many patients will receive empiric therapy who will not have fungal infections.

Two other drugs have been FDA-approved for the indication of empiric therapy of fungal infections in febrile neutropenic patients. The studies in febrile neutropenic patients with both liposomal amphotericin B for injection (Ambisome) and itraconazole injection and oral solution (Sporanox) used similar, although not identical, study designs to the current voriconazole Study 603. However, both the Ambisome and Sporanox trials resulted in higher cure rates and both trials met their pre-specified statistical definitions of non-inferiority.

Study 603 was designed as a prospective, centrally randomized, open label, comparative (non-inferiority), multi-center study. The Applicant conducted the study from March 7, 1998 through September 9, 1999 at 45 centers in the United States and Canada. Eligible subjects were male or female patients 12 years of age or older with neutropenia induced

Dosage of either treatment could be increased in presence of a baseline or breakthrough DIFI, persistence of fever and no improvement in baseline pulmonary infiltrates at least 24 hours after initiation of treatment, or persistence of fever and new pulmonary infiltrates at least 24 hours after initiation of treatment.

For subjects unable to tolerate an escalated dose of intravenous voriconazole, the dose could be reduced by 1mg/kg increments back to the original 3mg/kg q12h. For subjects who were unable to tolerate an escalated dose of oral voriconazole, the dose could be reduced by 50mg decrements to a minimum dose of 200mg bid (subjects weighing ≥40kg) or 100mg PO bid (subjects weighing <40kg).

For subjects randomized to L-AMB unable to tolerate the 3mg/kg/day dose, the dose could be reduced to 1.5mg/kg/day. For L-AMB subjects who were unable to tolerate the escalated 6mg/kg/day dose, the dose could be reduced to 3mg/kg/day and then to 1.5mg/kg/day. Note that the dose of L-AMB could be reduced to less than the original dose but the voriconazole dose could not be reduced below the original dose.

Investigators assessed the overall response to empirical therapy for patients without baseline of breakthrough DIFIs at least seven days after the last dose of study medication. There was no end of treatment (EOT) study assessment for subjects without baseline or breakthrough infections (the empirical therapy only group). The time point for assessment of the overall response for subjects with baseline or breakthrough documented DIFI was at least seven days after the last dose of study medication.

The primary endpoint for this study was the composite variable denoted as overall response. Investigators categorized the overall response as ***SUCCESS*** if all of the following five criteria were met (regardless of whether subjects were treated empirically or for a baseline DIFI):

1) Survival for at least seven days after discontinuation of study medication

2) Absence of breakthrough fungal infection during the period of neutropenia and for at least seven days after discontinuation of study medication

3) Defervescence during the period of neutropenia or prior to EOT, whichever occurred first

4) No discontinuation from randomized study medication due to toxicity or lack of efficacy prior to recovery from neutropenia

5) For subjects with baseline fungal infections only: global response assessed as complete or partial at EOT

Investigators categorized the overall response as ***FAILURE*** if <u>any one</u> of the following criteria was met:

1) Death within seven days after discontinuation of study medication

2) Documentation of breakthrough fungal infection during the period of neutropenia or within seven days after discontinuation of study medication

3) Persistent fever during the period of neutropenia or prior to EOT, whichever occurred first

4) Discontinuation of randomized study medication due to toxicity or lack of efficacy prior to recovery from neutropenia

5) For subjects with baseline fungal infections only: Global Response assessed as Stable or Failure at EOT

The definitions of the various components of the overall response to therapy as defined by the applicant were as follows:

- Recovery from neutropenia was defined as ANC >250 cells/mm^3.
- Time to recovery from neutropenia was defined as the date and time of the first sample with an ANC result of >250 cells/mm^3.
- Defervescence (resolution of fever) during neutropenia was defined as all temperatures of <38.0°C or 100.4°F (excluding those taken within one hour after the infusion of pyrogenic agents) for a continuous period of at least 48 hours preceding recovery from neutropenia (absolute neutrophil count >250 cells/mm^3).
- Time to defervescence was defined as the time from the first dose of study medication until the first time the oral temperature (or equivalent) measured <38.0°C or 100.4°F.
- Baseline infection was defined as any deeply invasive fungal infection that is diagnosed based on results of tests performed at baseline or up to 24 hours after study entry fungal infection.
- Breakthrough infection was defined as any deeply invasive fungal infection diagnosed based on results of tests performed from 24 hours after study entry up to seven days after discontinuation of study medication.

The primary analysis population for this study was the Modified Intent to Treat population (MITT) defined as all patients who had received as least one dose of the stud drug and who had sufficient clinical information available to confirm the investigator's assessment of overall response.

The overall response rate was 26% (108/415) in the voriconazole group and 30.6% (129/422) in the L-AMB group using a composite endpoint in a non-stratified analysis. The difference in the point estimates of the efficacy of the two therapies was -4.5% with a 95% confidence interval of -10.6% to +1.6%. The stratified results yielded an overall response rate using the same composite endpoint of 23.7% in the voriconazole group and 30.1% in the L-AMB group. The difference in the point estimates of the two therapies in the stratified analysis was –6.08% with a 95% confidence interval of –12.0% to –0.1%. The pre-specified lower bound of the 95% confidence interval used to define non-

inferiority in this trial was –10%. Thus, in both the raw and stratified analyses, voriconazole did not meet the statistical definition of non-inferiority.

The applicant calculated the sample size for this trial based on expected success rate of approximately 50%, based on the success rates in the trial of empiric therapy of febrile neutropenic patients used to obtain FDA approval for Ambisome® when compared to conventional amphotericin B deoxycholate (AMB-D). The lower than expected cure rates could have been one reason for the failure of voriconazole to meet the statistical definition of non-inferiority in this trial.

The main reason for failure in this trial was that many patients did not meet the protocol-specified definition for absence of fever prior to resolution of neutropenia. Only 33% (135/415) of voriconazole treated patients and 36%(154/422) of L-AMB treated patients fulfilled this criteria. This is lower than the rate of resolution of fever in previous trials of empiric antifungal therapy of febrile neutropenic patients with itraconazole compared to AMB-D or L-AMB compared to AMB-D (see following section comparing Study 603 to prior studies in febrile neutropenia). Part of the reason for the high numbers of failures in this component of the composite endpoint may be a more stringent criteria used to define defervescence in this trial. In Study 603, a patient was required to be afebrile for no less than 48 hours prior to recovery of neutropenia. In a previous trial of itraconazole versus AMB-D, their was no time requirement attached to resolution of fever i.e. a patient could be afebrile for less than 48 hours prior to recovery from neutropenia and still fulfill the criteria for a successful outcome. Another reason for the lower than expected rate of patients becoming afebrile prior to recovery of neutropenia was that the duration of neutropenia after randomization to study drug was shorter in this trial compared to previous trials. In the trial of itraconazole vs. AMB-D and the trial of L-AMB versus AMB-D, the median duration of neutropenia was approximately 10 days in both the test and control arms of these trials. In Study 603, the median duration of neutropenia after randomization to study drug was 5.5 days in each treatment arm.

Since many patients who receive empiric antifungal therapy will never have an invasive fungal infection it is important to evaluate the numbers of patients with breakthrough infections in patients receiving empiric therapy. Although one of the components of the composite endpoint, this study was not powered to specifically determine a difference in the number of breakthrough infections. The number of breakthrough infections in the voriconazole arm was 1.9% (8/415) and 5.1% (21/422) in the L-AMB arm. Of the eight (8) breakthrough infections in the voriconazole arm, 4 were caused by Aspergillus species. Thirteen (13) of the 21 breakthrough infections in the L-AMB group were caused by Aspergillus species. Although there were fewer numbers of breakthrough infections in the voriconazole arm, the small number of overall breakthrough infections precludes a definitive comparison.

One of the difficulties with composite endpoints in general is that it merges failures due to toxicity and failures due to lack of efficacy of the drug and may mask important differences between drugs. It is useful, therefore, to examine the numbers of patients discontinued from therapy due to lack of efficacy and the numbers of patients