discontinued due to toxicity, keeping in mind the previously-mentioned limitations of a non-blinded trial. In the voriconazole arm, there were 5.3% (22/415) patients discontinued due to lack of efficacy compared to 1.2% (5/422) in the L-AMB arm. More failures due to lack of efficacy were due to persistent fever in the voriconazole group (14/22) than the L-AMB group (2/5). In the voriconazole arm, 4.6% (33/421) of subjects were permanently discontinued due to toxicity compared to 5.5%% (23/422) of subjects in the L-AMB arm. Of note, 5 patients in the voriconazole group were discontinued due to renal toxicity compared to none in the L-AMB group. This observation is complicated by the lack of specific criteria in the protocol for defining renal insufficiency and the absence of specific laboratory criteria for discontinuation of study drug. There were 14 patients temporarily discontinued from therapy in the voriconazole arm compared to 59 patients temporarily discontinued in the L-AMB arm. However, only permanent discontinuations were included as part of the overall composite endpoint. Again, the study was not powered to determine differences in the individual components of the composite endpoint and the small numbers in each group make definitive conclusions difficult.

Other FDA-Approved Drugs for Empiric Antifungal Therapy in Febrile Neutropenic Patients

Two other drugs are FDA-approved for the indication of empiric antifungal therapy of febrile neutropenic patients; intravenous liposomal amphotericin B (Ambisome, L-AMB) and the intravenous and oral solutions formulations of itraconazole (Sporanox). Both L-AMB and itraconazole presented a single study in support of the indication of empiric antifungal therapy in febrile neutropenia patients. The study with L-AMB was a double blind randomized controlled prospective study compared to amphotericin B deoxycholate (AMB-D). The itraconazole study was an open label study comparing intravenous itraconazole followed by itraconazole oral solution versus AMB-D. The important details of the three studies of empiric antifungal therapy in febrile neutropenic patients are presented in the following table.

Details of Empiric Antifungal Therapy Trials

Trial	Trial design	Comparator	Dates
Ambisome N=343 (ITT)	Double blind, randomized	Amphotericin B deoxycholate N=344	January 29, 1995 – July 10, 1996
Itraconazole N=179	Open, randomized	Amphotericin B deoxycholate N=181	March 22, 1996 – December 4, 1997
Voriconazole N=415	Open, randomized	Ambisome N=422	March 7, 1998 - September 9, 1999

The basic study design of the studies used for registration of these two drugs was similar to that used in the current trial with voriconazole. The studies with L-AMB and the itraconazole both used a composite endpoint composed of the same 5 variables used in

Study 603. Two multi-disciplinary workshops held in 1994 and 1995 discussed the endpoints for trials of empiric antifungal therapy in febrile neutropenic patients. At these meetings, the participants agreed that the composite endpoint would be most appropriate for studies in this indication.

When one compares results across various trials, one must take into account differences in details in study design and patient demographics as well as secular trends in the care of neutropenic patients over time. Although the basic study designs of all three trials in empiric antifungal therapy of febrile neutropenic patients are similar, there are important differences in the details and demographics of the trials. The itraconazole study excluded patients who received allogeneic bone marrow transplants. The current voriconazole study included patients who received peripheral stem cell transplants that may result in shorter durations of neutropenia. The inclusion criteria for Study 603 also specified that patients have a WBC less than 250 cells/mm^3 in the 24 hours prior to randomization. The other two trials included patients with WBC less than 500 cells/mm^3 but did not include the more stringent criteria in the 24-hour pre-randomization time window. This may also have contributed to the shorter duration of neutropenia after randomization in the voriconazole trial.

There were also some differences in the statistical requirements for the trials. The lower bound of the 95% confidence interval used to define non-inferiority for the itraconazole trial was –15%. The lower bound of the 95% confidence interval used to define non-inferiority in the L-AMB and voriconazole trial was –10%. As the lower bound of the 95% confidence interval specified prior to initiation of a trial impacts on the planned sample size necessary to demonstrate non-inferiority, this in part explains the lower number of patients in the itraconazole trial compared to the L-AMB and voriconazole trials.

Most importantly for the purposes of comparison to Study 603, the definition of defervescence prior to recovery from neutropenia was different in the L-AMB and itraconazole trials. The voriconazole Study 603 required that patients be afebrile for 48 continuous hours prior to recovery from neutropenia. The L-AMB and itraconazole trials did not specify an associated time requirement defervescence prior to recovery from neutropenia.

Although the duration of neutropenia prior to randomization to antifungal study drug was similar in all three trials, the duration of neutropenia after randomization was shorter in the voriconazole trial compared to patients in the L-AMB and itraconazole trials. The shorter duration of neutropenia after randomization in the voriconazole trial resulted in less opportunity for patients to deferevesce. The data on duration of neutropenia in the three trials is presented in the following tables.

Duration of Neutropenia Prior to Randomization

Drug	Study Drug Mean	Range	Control Mean	Range
Ambisome	10	N.A*.	10	N.A.*
Itraconazole	8.9	0,7	9	-5 - 39
Voriconazole	10.7	2.4 - 71.5	9.7	2.4 - 59.7

*data not available

Duration of Neutropenia After Randomization

Drug	Study Drug Median	Range	Control Median	Range
Ambisome	10	N.A.*	10	N.A.*
Itraconazole	10	0 - 35	8	0 - 29
Voriconazole	5.46	0.042 - 57.838	5.52	0.033 - 63.121

*data not available

The combination of the time requirement for defervescence in Study 603 and the shorter duration of neutropenia in this study may explain the lower number of patients in the voriconazole trial who experienced fever resolution prior to recovery from neutropenia in compared to the previous trials with L-AMB and itraconazole. As the failure to defervesce during the period of neutropenia was also the most common reason for failure in Study 603, this may explain the lower overall success rates in Study 603 compared to the previous trials and the failure of voriconazole to meet the statistical definition of non-inferiority in this trial. The following tables present the data on fever resolution and overall success rates in the three trials.

Fever resolution during period of neutropenia

Trial	Study Drug	Comparator
Ambisome	58% (199/343)	58% (200/344)
Itraconazole	73% (131/171)	70% (127/181)
Voriconazole	33% (135/415)	36% (154/422)

Success Rates for Trials in Empiric Antifungal Therapy in Febrile Neutropenic Patients

Drug	Comparator	Success Rate	Comp Success	Delta	95% CI
Ambisome	AMB-D	49.9% (171/343)	49.1% (169/344)	-10%	-6.8%,+8.2%
Itraconazole	AMB-D	47% (84/179)	38% (68/181	-15%	-1%, +20%
Voriconazole	L-AMB	26.0% (108/415) – raw 23.7% - stratified	30.6% (129/422) 30.1%	-10%	-10.6%, 1.6% -12.0%, -0.1%

Background on Empiric Antifungal Therapy in Febrile Neutropenic Patients

To determine whether a drug can be considered non-inferior to a control regimen for a give indication, one must first consider the relative advantage of any drug therapy over placebo in that indication. The lower bound of the 95% confidence interval of the difference between the mean efficacy rates of two drug therapies used to define statistical non-inferiority should not be greater (more negative) than the advantage of the control regimen over placebo. In other words, if a control regimen is 10% more effective than placebo then the lower bound of the 95% confidence interval used to define non-inferiority when this control is compared to a new therapy would have to be less negative than −10%. With this in mind, it is worth examining the rationale for empiric antifungal treatment of febrile neutropenic patient and the previous placebo controlled or no-therapy controlled trials in this indication.

Empiric antifungal therapy for febrile neutropenic cancer patients has evolved as the standard of care over the past 20 years. Autopsy studies of leukemia and bone marrow transplant patients performed in the 1980's and early 1990's showed that fungal infections were identified in 25% of each of these patient groups post-mortem[1]. Many patients with invasive fungal infections at autopsy had no pre-mortem evidence of invasive fungal infections. The greatest risk of fungal infection was in patients with neutropenia, especially the group with neutrophil counts less than 100 cells/mm^3. This laid the groundwork for studies of empiric antifungal therapy in neutropenic patients.

This standard of care for empiric antifungal therapy in febrile neutropenic patients was based on several studies from the 1970's and 1980's, which showed a lower incidence of fungal infections in patients receiving empiric antifungal therapy compared to those receiving no antifungal therapy. In the first trial by Pizzo et al.[2] performed between 1975 and 1979, patients who were receiving cephalothin, gentamicin and carbenicillin were randomized after 7 days of such therapy to discontinue the antibacterial therapy or continue the same antibacterial therapy with or without the addition of AMB-D. The group that received empiric AMB-D in addition to continued antibacterial therapy had 1 breakthrough fungal infection in 18 patients. This one infection was a fatal pulmonary infection due to *Petrillidium* (now *Pseudoallescheria*) *boydii* documented at autopsy. In the group receiving continued antibacterial therapy alone, there were 5 breakthrough fungal infections in 16 patients. Two of these patients died, one with disseminated *Aspergillus* infection and one with a disseminated *Candida* and *Aspergillus* mixed infection. The other 3 infections were severe necrotizing *Candida* mucositis, *Candida* esophagitis (with no mention of documentation by endoscopy) and *Candida* pneumonia. Whether there is a true clinical entity of *Candida* pneumonia remains debatable even today. The small number of patients in each group, the very small numbers of breakthrough infections, and the questionable diagnoses in several of the patients make comparison of the groups difficult. In this trial, the median duration of neutropenia after

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[1] Bodey G etal. Fungal infections in cancer patients: An international autopsy survey. Eur J Clin Microbiol Infect Dis 1992;11:99-109

[2] Pizzo PA et al. Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. Am J Med 1982; 72: 101-110.

randomization was 24 days, considerably longer than that seen in more contemporary studies of this indication.

In a second study performed by the European Organization for Research and Treatment of Cancer (EORTC)[3], patients receiving various antibacterial regimens were randomized after 4 days of antibacterial therapy to receive AMB-D or no antifungal therapy. Among the 68 patients randomized to receive AMB-D, there was a single documented fungal infection, a fungemia due to *Candida tropicalis*. In the group that did not receive antifungal therapy, there were 6 fungal infections among 64 patients (two fatal candidemias, one caused by *C. tropicalis* and one by *C. albicans*; two severe oropharyngeal *C. albicans* infections; one fatal pulmonary *Aspergillus fumigatus* infections and one fatal disseminated *Mucor* species infection). Although there was no difference between the groups in terms of overall survival at 30 days, there were no deaths attributed to fungal infections in the patients who received AMB-D compared to 4 deaths due to fungal infection in the patients who did not receive empiric antifungal therapy. Again, the number of breakthrough fungal infections in this trial was small.

It is difficult to determine a numerical value for the benefit of empiric antifungal therapy over no therapy based on these two studies. However, despite the statistical limitations of these trials, empiric antifungal therapy in febrile neutropenic patients became the standard of care over the succeeding decades. Although AMB-D became the standard of treatment, the drug was never FDA –approved for this indication. AMB-D, however, was approved in 1956, prior to the current regulations used in drug approval.

Several important changes in therapy have occurred over the intervening years which one should also take into account when comparing current trials of empiric antifungal therapy in febrile neutropenic patients to older studies in this indication. In the EORTC trial a number of patients were receiving off-label antifungal prophylaxis with drug such as ketoconazole and oral AMB-D. The efficacy of these drugs in preventing fungal infections in neutropenic patients was not clear. Today, many bone marrow transplant patients receive therapy with oral triazole drugs such as fluconazole. Fluconazole is indicated to decrease the incidence of candidiasis in patients undergoing bone marrow transplantation who receive cytotoxic chemotherapy and/or radiation therapy. A study of prophylactic fluconazole in neutropenic bone marrow transplantation patients demonstrated a reduction in invasive fungal infections from 18% in the placebo arm to 1% in the fluconazole arms. One must question how the widespread use of fluconazole may change the epidemiology of fungal infections in persistently febrile neutropenic patients receiving antibacterial therapy. It is possible that early Candida infections may become less frequent and later infections with Aspergillus or other filamentous fungi may begin to emerge. Alternately, fungal infections may be limited to high risk patients such as those receiving allogeneic bone marrow transplantation or those who have received several courses of cytotoxic therapy such as patients treated for relapses of leukemia.

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[3] EORTC International Antimicrobial Therapy Cooperative group: Empiric antifungal therapy in febrile granulocytopenic patients. Am J Med 1989;86:668-672.

Another recent development is shortening in the duration of neutropenia in patients receiving cytotoxic chemotherapy. This has the effect of shortening the period during which patients are at greatest risk of developing fungal infections. In the study by Pizzo et al. in the 1970's , the duration of neutropenia after randomization to study drug was 24 days. This is much longer than the 10 days of neutropenia after randomization in the trial supporting the use of itraconazole in febrile neutropenia and even shorter still than the 5.5 days of neutropenia in the current voriconazole trial. The shorter duration of neutropenia may be a consequence of increased use of growth factor therapy to stimulate recovery from neutropenia and/or the advent of peripheral stem cell transplants. -

In summary, assessment of the benefit of any antifungal drug over placebo for the treatment of febrile neutropenic patients should take into account: 1) the lack of statistical power in the original studies of the indication, 2) the widespread use of more effective prophylaxis, 3) the shorter duration of neutropenia in patients currently treated with cytotoxic therapy, 4) the efficacy of the drug in patients with proven infections especially those due to *Candida* species and *Aspergillus* species and 5) the potential limitation of benefit to a specific subset of patients at higher risk of fungal infections.

Many patients who receive an antifungal drug for empiric antifungal therapy while febrile and neutropenic will never develop a fungal infection. In such cases the patient would be exposed to potential adverse effects with no benefit.

Overall, considering the adverse event profile and the fact that in both the raw and stratified analyses, voriconazole did not meet the statistical definition of non-inferiority, both the Advisory Committee and the FDA agreed that voriconazole should NOT be approved for the indication of empiric antifungal therapy of febrile patients with neutropenia.

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/s/

Rosemary Tiernan
6/6/02 10:19:38 AM
MEDICAL OFFICER

Marc Cavaille Coll
6/7/02 04:25:42 PM
MEDICAL OFFICER

Renata Albrecht
6/12/02 08:58:40 AM
MEDICAL OFFICER

Medical Officer's Review

NDA	21-266 (tablet) and 21-267(for injection)
Submitted:	17 November 2000
Review completed:	06 November 2001
Resubmission:	26 March 2002
Action Date:	24 May 2002
Drug name:	Voriconazole
Generic name:	Voriconazole
Proposed trade name:	VFEND™
Chemical name:	(2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1 H -1,2,4-triazol-1-yl)2-butanol
Sponsor:	Pfizer Inc
	Groton Laboratories
	Eastern Point Road
	Groton, CT 06340
Pharmacologic Category :	Antifungal agent
Proposed Indication(s):	Treatment of invasive aspergillosis. Treatment of serious Candida infections (including *C. krusei*), including esophageal and systemic Candida infections (hepatosplenic candidiasis, disseminated candidiasis, candidemia). Treatment of serious fungal infections caused by *Scedosporium spp.* and *Fusarium spp.* Treatment of other serious fungal infections in patients intolerant of, or refractory to, other therapy. Empirical treatment of presumed fungal infections in febrile immunocompromised patients.
Dosage Form(s) and	50 and 200 mg tablets 200 mg /30 ml vial for intravenous infusion
Related Reviews:	Biostatistics Clinical Pharmacology Pharmacology-Toxicology Chemistry

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**APPEARS THIS WAY
ON ORIGINAL**

CLINICAL REVIEW for NDA 21-266 and 21-267

Executive Summary

I.   Recommendations

A. Recommendation on Approvability

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 (approximately 88%) patients with
Candida albicans esophagitis. However, there were more discontinuations for

adverse events (11.5% voriconazole vs 4.2% fluconazole) and laboratory abnormalities (4% voriconazole vs 1.6% fluconazole) in the voriconazole arm when compared to the fluconazole arm. Visual function abnormalities (30.5% voriconazole vs 15.2% fluconazole) and hepatic function abnormalities were more frequent in patients who received voriconazole when compared to 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*. In addition, patient compliance may be less with the twice a day oral voriconazole regimen. This might facilitate the development of resistant strains of Candida, although this was not demonstrated in study 305.

The safety of voriconazole has been assessed in a clinical program incorporating healthy volunteers, febrile neutropenic patients receiving empiric antifungal therapy and patients with fungal infections in both controlled and non-comparative clinical studies. This safety database includes approximately 3400 patients as of June 2001 when the updated Integrated Summary of Safety was submitted. 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 arrhythmia, PVC's and prolonged QT interval.

Consequently, the Division and the Applicant agreed to further investigate by performing the following study: A multi-center, 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 which occurred in patients receiving either SBECD alone or SBECD and voriconazole. Due diligence efforts have not determined the exact cause of these reactions. The Applicant now plans to pursue a third investigation using the oral formulation of voriconazole and the Division will review these results. In addition, the Applicant will examine the effects of voriconazole on cardiac contractility in experimental animals or humans. Consequently, although in study 305, voriconazole was shown to be as effective as fluconazole for the treatment of *Candida albicans* esophagitis, I see more risk and no benefit to using voriconazole over existing alternative therapies such as fluconazole for the treatment of *Candida albicans* esophagitis.

I recommend that voriconazole be given "approvable" status for the treatment of *Candida albicans* esophagitis. Approval may be granted after the Division reviews the QTc study previously described. Although I am concerned regarding voriconazole's potential for drug interactions, and visual and hepatic function abnormalities, I believe that these issues can be identified, monitored and managed by clinicians. However, it will be important to better characterize the voriconazole exposure that may prolong the QT interval and pose a risk for sudden death and this should be addressed prior to approving the indication of treatement of esophagitis.

Finally, while awaiting the completion of additional drug interaction studies, we will include warnings and precautions in the label to ensure that clinicians understand any potential risks that their patient may incur should particular combinations of antiretroviral or other drugs be prescribed that may increase exposure to voriconazole and thus increase the risk for hepatic, cardiac, ocular or other adverse events.

The Applicant is also the manufacturer of fluconazole which was the comparator drug used in study 305.

Recommendation on Phase 4 Studies and/or Risk Management Steps

Clinical Safety

Cardiac
The Applicant will need to complete the following study to further assess cardiac safety and gain FDA approval: A multi-center, 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.

In addition, the following areas will need to be addressed as phase 4 study commitments. However, an "approval" status will not be predicated on completion of these studies.

Ophthalmologic
Stuctures of the eye are not yet 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 non-albicans strains of Candida.

The Applicant should further characterize the cross resistance against voriconazole, itraconazole and fluconazole and determine the frequency of drug resistance development in Candida species.

II.   Summary of Clinical Findings

A. Brief Overview of Clinical Program

Study 305 was conducted to support the indication for the primary treatment of esophageal candidiasis in immunocompromised patients. The study was conducted from 01 September 1995 through 27 January 1999 in Europe, Russia, Thailand, South Africa, Australia and Singapore. The patients were mainly white males with AIDS, 18 years of age and older. The percentage of patients with severe AIDS (CD4 less than 50 cells/mm^3) was 58.5% in the voriconazole group and 59.7% in the fluconazole group).

Study Objectives: The primary objective was to compare the efficacy, safety and toleration of voriconazole and fluconazole in the treatment of Candida esophagitis in immunocompromised patients. Efficacy was evaluated by assessing the non-inferiority of voriconazole to fluconazole.

Study Design: A randomised, double blind, double dummy comparative multi-center trial of voriconazole (200mg bid) versus fluconazole (400mg on Day 1 and then 200mg once a day). Subjects who completed the screening (Day –2 to Day 0) and baseline (Day 1 prior to drug administration) assessments and who fulfilled the inclusion and exclusion criteria were randomised to receive either voriconazole or fluconazole. Safety and efficacy assessments were made on Days 8, 15 and 29 and then on Day 43 or end of therapy (EOT) if this was earlier than Day 43. There was a further follow up visit, four weeks after EOT, to assess efficacy and safety at an interval after voriconazole and fluconazole had been cleared from the body and considered a suitable time to assess for relapse.

Diagnoses and Criteria for Inclusion of Subjects: Male or non-pregnant female patients, aged over 18 years, who were immunocompromised and who had a diagnosis of Candida esophagitis based on clinical symptoms with or without oropharyngeal candidiasis were enrolled in the trial. Subjects must have had typical Candida esophagitis lesions seen on endoscopy and identified by mycology from a brushing or biopsy specimen showing appearances typical of Candida. Subjects who did not have the presence of Candida confirmed by culture were discontinued. The EOT assessment

compared to screening was used to derive success rates where success was defined as cured or improved.

Two populations of patients were thus identified: the Intent to treat (ITT) and Per Protocol (PP) analysis populations.

The ITT population included all subjects who received at least one dose of their randomized study treatment. For the ITT population endoscopy analysis, if the endoscopy assessment at EOT was missing, the EOT symptomatic assessment was used.

To be evaluable for the PP population, the subjects had to have, in addition to no significant deviations from the inclusion/exclusion criteria and planned study conduct: 1) confirmation of Candida esophagitis by endoscopy, including the presence of hyphae on biopsy or brushing and a positive culture, 2) received at least 12 days of treatment, 3) an EOT evaluation including a repeat endoscopy, 4) evidence of adequate compliance, 5) a visit at each assessment time within the $\pm$ 5 day window, and 6) not received a medication which was outlined in the exclusion criteria.

Evaluation Groups:	Voriconazole 200mg bid	Fluconazole 200mg once daily
Entered Study	200	191
Completed Study	131	136
Discontinued from Study	69	55
Evaluated for Efficacy		
Intent to Treat (ITT)	200	191
Per Protocol (PP)	115	141
Assessed for Safety		
Adverse Events	200	191
Laboratory Tests	189	186

A total of 85 patients (42.5%) voriconazole and 50 (26.2%) fluconazole patients were excluded from the PP population. As summarized by the FDA statistical reviewer, most subjects were excluded from the PP population for more than one reason. The most common reason for exclusion for both treatment groups was that the patient had only one endoscopy, (23% voriconazole and 14.7% fluconazole). Other common reasons for exclusions were that the patient received less than 12 days of therapy, the patient received systemic antifungal therapy within less than 3 days prior to baseline, or there was no mycological evidence of esophageal candidiasis at baseline. Since more voriconazole than fluconazole patients were excluded from the PP population, there was concern that perhaps lack of efficacy or an increased number of adverse events might be the reason for differences in exclusion. Consequently, this might impact the results of the

PP efficacy analysis. However, it was determined that the majority of the voriconazole patients (34/85 or 40%) were primarily excluded because only one endoscopy was performed. Lack of efficacy or drug related adverse events could be attributed as the underlying reason for only 7 of these excluded voriconazole patients. In addition, 4 of these excluded patients died and 7 patients had non-related adverse events. The remaining voriconazole patients who were excluded did not have an exclusion reason that could be attributed to the effect of the drug.

Regarding the patients on fluconazole who were excluded from the PP population, fifteen of the 50 (30%) patients were excluded primarily because only one endoscopy was performed. Two of these patients had insufficient clinical response, 2 subjects died and 1 patient had a non-related adverse event.

Medical Officer comments: Overall, it did not appear that patients on voriconazole were disproportionately excluded from the PP population for reasons that could be explained by lack of efficacy or other drug related reasons. The most common reason for exclusion for both treatment groups was that the patient had only one endoscopy, (23% voriconazole and 14.7% fluconazole). Overall, we still felt the quality of the study was acceptable. We do not believe that this high differential discontinuation rate for the voriconazole treatment arm "forced" equivalence. Please see the FDA statistical review for a full discussion of the ITT and PP analyses which will more fully address the robustness of the PP analysis to support non-inferiority.

B. Efficacy

Statistical Methods:
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.

Medical officer comments: Please refer to the Statistical review for a complete description of the statistical methods utilized.

Efficacy Results: 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).

Medical Officer comments: Overall, these results support the claim of non-inferiority of voriconazole compared to fluconazole for the treatment of mainly Candida albicans esophagitis.

Conclusions regarding the efficacy of voriconazole in the treatment of esophagitis due to the non-albicans species of Candida.

The following Table 1 summarizes the non-albicans Candida isolates recovered in the per protocol (PP) and non- per protocol (non-PP) populations in Study 305.

Table 1   Clinical isolates of non-albicans Candida recovered in Study 305

Study 305	Voriconazole PP	Fluconazole PP	Voriconazole Non-PP	Fluconazole Non-PP
C. glabrata	3 /4 cures 1 /4 failure	7/7 cures	1/2 cure 1/2 failure	1/2 cure 1/2 improvement
C. krusei	2/2 cures	-----	1/1 cure	----
C. parapsilosis	1/1 cures	1/1 cures	1/1 cure	-----
C. tropicalis	1/1 cures	1/1 cures	1/1 cure	1/2 cure 1/2 improvement
S. cerevisiase	1/1 cures	1/1 cures	1/1 cure	--------
Total	8/9 successes	10/10 successes	5/6 successes	4/4 successes

Medical Officer Comments:
The success rates were good for both fluconazole and voriconazole in the primary treatment of the non-albicans species of Candida in patients with esophagitis. However, the number of non-albicans isolates in the per protocol group were too few to allow one to draw definitive conclusions regarding voriconazole's efficacy in treating non-albicans Candida.

Refractory Candida Esophagitis

Rare and Refractory Studies (309 and 604)

Brief overview of these two studies:
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). This information was included in
the November 2000 NDA and was also summarized in the Advisory Committee Briefing
Package in October 2001.

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. Most patients had *Aspergillosis* or *Candidiasis.* However some
patients had other fungal diseases such as *Scedosporiosis, Cryptococcosis, Fusariosis,
Chromoblastomycosis, Trichophyton, mycetoma, Paecilomyces, Penicilliosis,
Histoplasmosis, Coccidioidomycosis, Exophiala jeanselmei, Blastomyces, Bipolaris,
Mycoleptidiscus indicus, or mold unspecified.*

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).

In studies 309/604, the mean age was forty three years old. Fifty males/24 females and 98
males/58 females were enrolled in study 309 and 604 respectively. Most patients were
white (72-92%). The categories of immunosuppression included: AIDS (19.9-21.6%),
neutropenia (18.6-23.0%) and other (36.5-46.2%). The median total duration of
voriconazole therapy was 58 days and 56 days for all patients in study 309 and 604,
respectively.

In Study 309, 37 patients were excluded from the Modified Intention to Treat analysis for
the following reasons: no documented infections (n = 6), invalid specimens (n = 7) and
entered after the cut-off date (n = 24). In Study 604, reasons for exclusion from the
Modified Intention toTreat analysis in 45 patients included: no documented infections (n
= 19) and entered after the cut-off date (n = 26).

Medical Officer comments: Please Dr. Alivisatos' review regarding the efficacy of voriconazole treatment of patients who had rare and refractory fungal diseases due to pathogens such as Scedosporium and Fusarium species.

The following comments summarize the findings related to the treatment of refractory Candida esophagitis, and the primary and salvage treatment of disseminated Candidiasis.

There were 29 cases of refractory Candida esophagitis and 3 cases of refractory oropharyngeal candidiasis (OPC) in AIDS patients in studies 309 and 604. The satisfactory response rate for single and mixed infections is as follows:

There were 5/32 mixed infections: 3 mixed *C. albicans/C. glabrata*, 1 *C. albicans/C. krusei* and 1 *C. albicans*/unspecified fungus. All of these mixed infections were esophagitis cases.

Response rate for mixed infections:
C. albicans/C. glabrata   1/3   satisfactory
C. albicans/C. krusei   1/1   satisfactory
C. albicans/unspecified   1/1   satisfactory

There were 27 single species infections and the response rate is listed below:
C. albicans   10/20   satisfactory
C. glabrata   0/1   satisfactory
Candida species   2/5   satisfactory

The overall combined satisfactory response rate for the treatment of refractory OPC and 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.

Medical Officer Comments: 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 considered 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 esophagitis patients in studies 309 and 604. Therefore, it was not possible to draw conclusions regarding the efficacy of voriconazole against these pathogens.

Disseminated Candida Infections and Candidemia: Primary and Salvage Therapy

Medical Officer comments:　Please refer to the reviews done on the primary and salvage treatment of disseminated Candida and Candidemia by Dr. Johann-Liang and Dr. Alivisatos.

Dr. Johann-Liang's review addresses Study 608, "A randomized, open label, comparative multi-center study of voriconazole vs conventional amphotericin B followed by fluconazole in the treatment of candidemia in non-neutropenic subjects". At the time of the November 2001 NDA submission, an interim study report of 10% of the planned enrollment was submitted. Dr. Johann-Liang reviewed this material and discusses the efficacy of using voriconazole in the primary treatment of candidemia. At this time, review of the data does not allow us to grant the indication for the primary treatment of disseminated Candida and Candidemia infections.

Dr. Alivisatos' review addresses the salvage treatment of disseminated Candidiasis and please refer to this for further details.

Medical Officer's comment:　At this time, we will not approve the indication of salvage therapy for invasive Candidiasis.　We believe that it will be important to first evaluate voriconazole's efficacy in the primary treatment of candidemia and disseminated Candida infection.　We await the final report of study 608 .

C.　Safety

The ITT population comprised the safety population i.e. 200 patients on voriconazole and 191 patients on fluconazole.

Medical Officer comments:　A strength of study 305 was that it was a blinded, comparative trial and thus provided a good opportunity to adequately assess safety. However, the incidence of visual adverse events in the voriconazole treatment arm was significantly higher (22.5%) compared to the fluconazole arm (4.2%) and this difference may have impacted the blinding.

Safety assessments were made at screening, baseline, Days 8,15, 29, Day 43/EOT and at follow-up. Ophthalmological examinations were made for visual acuity (Snellen chart), contrast sensitivity (Pelli-Robson chart), color perception (City University Color Vision test) and funduscopy were performed at baseline, EOT/Day 43 and follow up one month later.

Medical officer comments :　Monitoring and follow-up of the ITT population appeared to be adequate.

A total of 159 patients (79.5%) in the voriconazole group and 141(73.8%) patients in the fluconazole group had at least one adverse event. The most common adverse event in the voriconazole group was abnormal vision. The incidence of abnormal vision was statistically significantly higher in the voriconazole group (22.5%) than in the fluconazole

group (7.9%) (p<.0001). Twenty two patients (11%) in the voriconazole group and 8 patients (4.2%) in the fluconazole group discontinued study drug due to adverse events and laboratory abnormalities.

Medical Officer comments: In general, for patients treated with voriconazole visual adverse events may begin after the first day of therapy and persist throughout the treatment period. We did not have complete follow-up data on patients experiencing visual adverse events in the clinical trials. However, data from the 28 day pharmacokinetic study in normal volunteers with normal baseline vision, indicates that after 28 days of therapy with voriconazole, any visual abnormalities that occur are fully reversible.

Data regarding reversibility of visual adverse events is not available for patients on greater than 28 days of voriconazole therapy. Please refer to the Ophthalmology consultation review for additional details.

Treatment related adverse events occurred in 60 patients (30%) in the voriconazole group and 27 patients (14.1%) in the fluconazole group. The most commonly occurring treatment related adverse event was abnormal vision in both treatment groups 15.5% voriconazole and 4.2% fluconazole. As with adverse events overall, abnormal vision related to study treatment was statistically significantly higher in the voriconazole group than in the fluconazole group (p=0.0002).

Medical officer comments: Pre-clinical studies did demonstrate that voriconazole produced mild retinal thinning in female rats at 24 months. Abnormal vision is the most frequent adverse event seen with voriconazole (approximately one in three patients). Symptoms include decreased vision, photophobia, altered color perception, and ocular discomfort. The exact mechanism underlying these visual symptoms is unknown. There is no human histopathology data and slit-lamp examination has not detected ocular lesions in study patients.

Additional issues include: A careful risk benefit assessment will need to be made when considering the use of this drug in patients with underlying eye disease such as CMV retinitis. There is insufficient information to predict what the ophthalmologic effects will be in patients who are either re-challenged or re-treated with voriconazole. We do not have sufficient information to predict the effect of voriconazole on the eye which is not yet fully developed i.e. in children under nine years of age. We can not predict that visual changes will resolve if this drug is used beyond 28 days of therapy. For further details regarding ophthalmologic safety, please see the consultation review submitted by the FDA ophthalmologist.

Most of the adverse events were mild to moderate in severity. Treatment related adverse events were classified as severe in (7/200)3.5% of voriconazole treated patients and (4/191) 2.1% of fluconazole treated patients

Medical officer comments: The severe treatment-related adverse events for
voriconazole were due to elevated liver function tests (elevated alkaline phosphatase
and transaminases and one patient also had jaundice) in 3 patients, renal insufficiency
in one patient , one patient with nausea and vomiting, one patient had a severe pruritic
maculopapular rash and one patient had hypotension that the investigator believed
may have been due to a drug interaction between voriconazole and lorazepam. This
patient with hypotension died and the cause of death was listed as a cardiac arrest. She
was a 25 year old Black woman who had received 11 days of voriconazole therapy. On
the day before her death, she was admitted with hypotension, was described as having
suicidal ideation and was treated with lorazepam. She was described as not showing
any signs of sepsis. No blood cultures or autopsy were done. Her history was
complicated by pulmonary tuberculosis, tonic clonic seizures, CMV retinitis, suicidal
ideation, bilateral chest infiltrates. It is difficult to ascertain the exact etiology of her
demise but a role for voriconazole can not be definitively excluded. The voriconazole
label contains information regarding drug interactions with benzodiazepines.
Voriconazole has been shown to inhibit midazolam metabolism in vitro and thus is
likely to increase the plasma concentrations of benzodiazepines metabolized by CYP
3A4.

Four patients on fluconazole had severe treatment-related adverse events. Two
patients had elevated alkaline phosphatase, one patient had blurred vision and one
patient had throat edema.

It may be difficult to definitively assess the etiology of adverse events in a patient
population which is severely ill and may be on many concomitant medications.
Howwever, the distribution of prior cytotoxics, corticosteroids and antifungal
medication was similar between treatment groups. Antibacterials were the most
common concomitant medications taken by approximately 70% of subjects in the
voriconazole group and approximately 72% of the patients on fluconazole therapy.
Antiviral medications were taken by 34% of subjects in the voriconazole group and
39 % in the fluconazole group.

There were 61 (30.5%) voriconazole patients and 52 (27.2%) fluconazole patients with
serious adverse events. Fifteen voriconazole patients and 19 fluconazole patients died
during therapy or within 30 days of EOT. There were 6 additional deaths in the
voriconazole and 10 additional deaths in the fluconazole group that occurred more than
30 days after EOT. All of the deaths were reported as unrelated to study treatment see
Table 2 below.

TABLE 2   Summary of Deaths which occurred on therapy or within 30 days of
            therapy in Study 305

Cause of Death	Voriconazole	Fluconazole
Pneumonia	5	4
Lympho-proliferative disease	1	0

HIV	4	7
Cardiac arrest	3	2
Sepsis	1	2
PCP	1	2
Endocarditis	0	1
CMV	0	1
Total	15	19

Medical Officer Comments: I concur with the Applicant's assessment that voriconazole did not appear to have directly caused the death of any patient in study 305. However, please note the aforementioned patient death that may have been due to a voriconazole-lorazepam drug interaction.

Five patients in the voriconazole group had a serious adverse event reported as related to study treatment and discontinued drug. The events were elevated creatinine, elevated alkaline phosphatase, elevated alkaline phosphatase and transaminases, nausea/vomiting and jaundice.

There were 69 (34.5%) patients on voriconazole and 55 (29%) patients who discontinued fluconazole.

Pharmacology/Toxicology studies demonstrated that voriconazole affects the liver and increases transaminase activity. Toxicity increased with total dose and these findings were more common and more severe at higher doses or with longer treatment duration. In the clinical studies, no threshold plasma concentration has been identified above which the risk of an elevated liver test abnormality was higher compared with plasma concentrations below the threshold.

Three patients on fluconazole (1.3%) had elevated liver functions tests and discontinued study drug. Eight (4.0%) patients developed elevated liver function tests due to voriconazole and discontinued study drug. Three of the eight patients on voriconazole had overt jaundice and most had transaminases and alkaline phosphatase values greater than 3.5 times the upper limit of normal (ULN).

Medical Officer Comments: Patients on voriconazole will need to have their liver function tests monitored. This study was not designed to capture data on hepatitis B and hepatitis C status and these patients may require more intensive monitoring for liver dysfunction, if treated with voriconazole.

Voriconazole is both a substrate and inhibitor of three cytochrome P450 enzymes: CYP 2C9, CYP 2C19 and CYP 3A4. The applicant has evaluated representative substrates/inhibitors /inducers of the three CYP enzymes both *in vitro* and *in vivo*. However, of the protease inhibitors, only indinavir was studied both *in vitro* and *in vivo* and found not to interact with voriconazole. In the study 305 safety population, there was data on antiviral use in 212 patients i.e. in 105 patients on fluconazole and in 107 patients on voriconazole. Eighty- two patients on fluconazole and eighty-nine patients on

voriconazole were taking anti-retrovirals in study 305. Twenty-three patients on voriconazole were taking two anti-retroviral medications, 2 patients were taking three antiretroviral medications and the 64 remaining patients were on one antiretroviral drug. This is not representative of the current US HIV patient population who may have better access to highly active anti-retroviral therapy (HAART) which includes at least 3 antiretroviral drugs The use of voriconazole consequently poses unique drug interaction challenges for the prescriber. Indeed, the Advisory Committee recommended additional drug interaction studies for voriconazole and ritonavir and nelfinavir.

Finally there was no imbalance between treatment arms in relation to adverse events involving the nervous system, skin or cardiovascular systems.

Medical Officer Comment: Overall, voriconazole was less well tolerated, when compared to fluconazole

D. Dosing/Duration

The oral dose forms of voriconazole and fluconazole were used in this study.

Voriconazole: 200mg bid plus fluconazole placebo (four capsules once daily) on Day 1 and voriconazole 200mg bid plus fluconazole placebo (two capsules once daily) from Day 2 onwards.

Fluconazole: 400mg once daily plus voriconazole placebo (one tablet bid) on Day 1 and fluconazole 200mg once daily plus voriconazole placebo (one tablet bid) from Day 2 onwards.

The protocol allowed for the treatment of subjects with esophageal candidiasis of varying severity and the duration of therapy could vary between two and six weeks. Treatment had to continue for seven days after resolution of all clinical signs and symptoms (but should not have exceeded the maximum of 42 days of therapy). The dose of voriconazole used in study 305 proved effective in the treatment of *Candida albicans* esophagitis.

E. Special Populations

In study 305, the efficacy population consisted of approximately 75% adult male HIV patients and most of the HIV patients had severe AIDS characterized by a CD4 of less than 100. The mean ages of the patients in the voriconazole and fluconazole groups were 36.4 years and 37.4 years respectively. The patients were primarily white (67.5% in the voriconazole group and 65.5 % in the fluconazole group).

Medical officer comments: In study 305, efficacy rates were not calculated with respect to race, gender, age or ethnic group. There were no pediatric or geriatric patients included in this study. However, pharmacokinetic analyses have shown that no dosage adjustment is necessary for the elderly or on the basis of gender. Oral administration has not been well studied in children. Adolescents, age 12-16 years, should be dosed as

adults. Pregnant and lactating females were excluded from study 305. The excretion of voriconazole in breast milk has not been studied . This drug is not recommended for use during pregnancy and women of child bearing age should use effective contraception. Patients with a serum creatinine greater than 3 times the upper limit of normal or with an estimated creatinine clearance <20 cc/min were excluded from the study 305.

Voriconazole is primarily metabolized in the liver and its pharmacokinetics are not affected by renal insufficiency. Consequently no dose adjustments are necessary for oral dosing in patients with mild to severe renal impairment. However, in patients with moderate to severe renal insufficiency (creatinine clearance less than 50 mL/minute), accumulation of the intravenous vehicle, SBECD, occurs and it is recommended that these patients receive only oral voriconazole, unless the benefit of intravenous drug outweighs the risk.

Voriconazole has been studied in patients with mild to moderate cirrhosis (Child- Pugh A and B). It is recommended that if a loading regimen of voriconazole is recommended for a particular indication, this can be used but the maintenance dose should be halved in patients with mild to moderate hepatic insufficiency.

Clinical Review Methods

I.   Introduction and Background

A.   Applicant, Drug, Established and Proposed Trade Names, Drug Class, Sponsor's Proposed Indications(s), Dose, Regimens, Age groups

Applicant: Pfizer Global Research and Development
                                  Eastern Point Road
                                  Groton, CT 06340

Date of Submission: November 17, 2000
Date Review Completed: November 6, 2001

Drug Name: Voriconazole
Proprietary Name: VFEND ™ Film coated Tablets
                                  VFEND ™ IV for Injection

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

Pharmacologic Category :   Triazole Antifungal agent

Dosage Form(s)   50 and 200 mg tablets
                                  200 mg/30 ml vial for intravenous infusion

Proposed Indication(s):   Treatment of candida esophagitis

Dose: 200 mg PO BID
Age groups: 18 years and older

Materials Reviewed: NDA submission for November 17, 2000, which included
                            the study 305 report, case report forms, and JMP datasets.
                            An updated integrated summary of safety (ISS) with
                            updated ISS JMP datasets were submitted with the
                            randomized controlled aspergillosis trial, study 307/602, on
                            June 21, 2001 as a clinical amendment.

B.   State of Armamentarium for the Indication:

Current antifungal products that are approved for the treatment of esophagitis include:
fluconazole, itraconazole, ketoconazole,   amphotericin B (IV) and ABELCET® is
approved for treatement of invasive fungal infections in patients refractory or intolerant
of conventional amphotericin B.

C.   Important Milestones in Product Development

*This is summarized well in the Applicant's submission and excerpts regarding the
clinical development program are included below.* **Arial** *is used for direct quotes from
the Applicant's submission.*

At the time of the original IND submission for voriconazole oral tablets in August
1995, over 230 healthy volunteers had received voriconazole in single and
multiple dose regimens. In addition, approximately 250 patients with fungal
infections had been treated with voriconazole in multiple dose studies.

The initial IND-opening study with the oral formulation was ———————
entitled (after amendment) "A Multicenter, Randomized, Double-Blind, Active-
Controlled Phase I Study to Investigate the Safety,Tolerance and
Pharmacokinetics of Two Increasing Oral Doses of Voriconazole in Patients with
Hematologic Malignancies / Conditions, Solid Tumors or Autologous Bone
Marrow Transplantation at Risk for Aspergillosis."

Shortly after IND ——— was filed in November 1995, Pfizer sought discussion
with FDA regarding the proposed clinical development program. The indications
anticipated at that time as appropriate for voriconazole, based on knowledge
from pre-clinical and early clinical studies, are the indications in the current
proposed labeling for voriconazole:
• Treatment of invasive aspergillosis
• Treatment of Candida spp. infections, including esophageal candidiasis
• Empiric treatment of presumed fungal infections
• Treatment of documented invasive fungal infections caused by rare pathogens

and/or those that have failed to respond to current therapies

Pfizer proposed to support each of these indications with data from one US and one non-US study. Although general aspects of the development program were discussed in February, 1996, Pfizer was encouraged to request a formal End-of-Phase II meeting to obtain more definitive input from the Anti-Viral Division.

On April 23, 1996, Pfizer submitted IND _.̅—̅— for voriconazole intravenous, with Study 602 as the IND-opening study: "An Open, Randomized, Comparative Multicenter Study of the Efficacy, Safety and Toleration of Voriconazole Versus Amphotericin B in the Treatment of Acute Invasive Aspergillosis in Immunocompromised Patients." Based on discussions with the Anti-Viral Division, the analysis plan was revised to require that the global response was to follow the Mycosis Study Group criteria which incorporates clinical and radiological assessments. Mycological response was to be assessed separately. The primary analysis would compare the global responses at two fixed time points: 6 weeks and 12 weeks. The study was to be an equivalence trial using a delta of 25% and would enroll a sufficient number of patients to achieve an 80% power in the evaluable patients analysis. A secondary analysis was to be the global response at the end of therapy: voriconazole vs. amphotericin B alone or followed by other licensed antifungal agents. Due to the life-threatening nature of acute invasive aspergillosis infections, the intravenous maintenance dose of voriconazole in Study 602 was to be 4 mg/kg twice daily. Following review of Protocol 602, the Anti-Viral Division granted permission to initiate dosing at 3 mg/kg/day, but requested additional clinical data to justify dosing at the higher doses for the proposed 12 weeks duration of this study.

On February 3,1997, Pfizer provided information from Study 230, a Phase I study in which subjects received intravenous maintenance doses of 3, 4 or 5mg/kg BID, and data from 18 subjects in European Phase II studies who received 4 mg/kg or 5 mg/kg BID intravenously or 300 mg, 400 mg or 500 mg BID orally. In a teleconference on March 31, 1997, the Anti-Viral Division responded that adequate information had been provided to support the 4 mg/kg BID dose.

On July 18, 1997, Pfizer submitted a proposal for a combined analysis of Studies 307 and 602 when the total enrollment reached approximately 276 subjects, which was discussed with the FDA and found acceptable in a teleconference on August 15, 1997. The Week 12 analysis was to be the primary analysis. The End-of-Therapy timepoint was considered of some value, although it is confounded by the fact that the two drugs are given for different durations. It was also accepted that a radiologic diagnosis of aspergillosis by the "halo" sign would support a diagnosis of "probable" aspergillosis.

About this time, AmBisome was approved for empirical therapy, with labeling based on a single, large, randomized controlled trial of empirical treatment which demonstrated equivalence to conventional amphotericin B, supported by two open-label comparative empirical treatment studies and demonstration of

efficacy in candidiasis. Thus, Pfizer proposed to revise the clinical program and the Medical Officer suggested that a second End-of-Phase II Meeting would be appropriate.

On February 4, 1998, Pfizer submitted Protocol 608, "A Randomized, Comparative Multicenter Study of Voriconazole vs. Conventional Amphotericin B in the Treatment of Candidemia in Non-Neutropenic Subjects." Subjects were to be initiated with at least 3 days of iv therapy, after which they could be switched to oral therapy, consistent with earlier protocols. This protocol was amended following discussions with the Division of Special Pathogens: The primary analysis of efficacy will be based on the assessment of a Data Review Committee. Sample size was increased from 207 to 360 subjects todemonstrate equivalence to amphotericin B Interim analyses were planned by theMycoses Study Group, independent of Pfizer, after approximately 10% and 50% of the subjects had completed the study.

At the End-of-Phase II meeting on February 25, 1998, the Pfizer proposal to conduct a single large global trial (603) to support the empirical therapy indication was accepted. The pre-meeting package for the second End-of-Phase II meeting proposed that the filing of the NDA would be linked to the completion of the empirical therapy trial and that the efficacy of voriconazole against Aspergillus would be demonstrated by Study 304, the open label, non-comparative study in 137 immunocompromised patients with acute invasive aspergillosis, and by individual cases from the ongoing Phase III program.

The proposal to support the candidiasis indication (esophageal and invasive) with one completed study in esophageal candidiasis (305) and data from an ongoing study in candidemia (608) was accepted, with the acknowledgement that the strength of the data would be an important factor in evaluating the adequacy of these studies to support the proposed indications.

Pfizer's proposal to support the indication for rare and refractory fungal infections with 5-10 cases for each pathogen was also accepted. These cases were to come from two studies, one US, one non-US, as originally planned.

In response to a pre-meeting request, Pfizer presented draft data from Study 304, the open-label aspergillosis study, at the February 1998 meeting. On March 10, 1999 Pfizer met again with members of the Division of Special Pathogens to share final study results from Study 304 and the data analysis plan for display of these results in the NDA. At this time, the Division indicated the likelihood that Study 304 will have sufficient number of patients to support a first-line indication. A cutoff of five days of prior antifungal therapy was discussed as appropriate for a patient to still be considered a first-line voriconazole patient although Study 304 allows for 10 days of prior therapy and Studies 307/602 for aspergillosis utilize 96 hours as the cutoff for classification of a first-line patient. Safety data from the Phase III aspergillosis trials, Studies 307/602, would also be included in the NDAs.

In response to recommendations by FDA, and following discussions and review by the Division of Special Pathogens, Pfizer submitted Protocol A1501003, "An historical control study of the efficacy of standard therapy in acute aspergillosis to allow comparison with the efficacy of voriconazole in protocol 150-304," on September 3,1999.

Pfizer plans for the Integrated Summary of Effectiveness and the use of the Voriconazole Efficacy Response Assessment Tool (VERA) for classifying and evaluating patients from different trials across the NDA database were found acceptable to the Division of Special Pathogens at the March 1999 meeting.

At the July 26, 2000 pre-NDA meeting, Pfizer shared summary data from the empirical therapy trial, from the aspergillosis study /historical control study (304/ A1501003) and from patients with invasive candidiasis.

In October 2000, due to changing medical practice regarding the diagnosis and preferred treatment of aspergillosis, the European Organization for the Research and Treatment of Cancer (EORTC) met and formally recommended closure of the European aspergillosis study 150-307 . FDA agreed with the closure of studies 307/602 and to the use of the combined "umbrella analysis" as the definitive end-of –study analysis.

The voriconazole NDA was filed on November 17, 2000. In the Spring of 2001, Pfizer was asked to submit all of the data from studies 307/602 in a reviewable format. The clinical amendment for the randomized, controlled aspergillosis(study 307/602) trial was submitted on June 21, 2001. This amendment was submitted in the final three months of the originally targeted action date for a 10 month review. This submission extended the primary review goal date to November 17, 2001.

Part of the application was presented to a meeting of the Antiviral Drug Product Advisory Committee, on October 4, 2001. At that meeting the committee recommended unanimously that VFEND™ should be approved for the treatment of invasive aspergillosis. A majority of the committee (8 No versus 2 Yes) voted that the information presented did not support that voriconazole is safe and effective for the empiric antifungal therapy of febrile neutropenic patients.

At the time of the initial regulatory actions in November 2001, no acceptable commercial intravenous formulation was available, due to compliance issues at a contract site where the final product was manufactured. A subsequent MAJOR AMENDMENT concerning proposed measures to address manufacturing and compliance issues was submitted to the NDAs in November 2001, and extended the primary and secondary review goal date to December 17, 2001. FDA worked with the firm to resolve these issues expeditiously. VFEND™ was intended to be marketed as an intravenous and oral product with a common package insert. The lack of an acceptable intravenous

formulation precluded the full approval of indications that would require such a
formulation.

On March 26, 2002 the Applicant re-submitted data that satisfactorily addressed any
compliance and manufacturing issues. Additional information regarding the efficacy of
voriconazole against species of Aspergillus other than *A. fumigatus* and pharmacokinetic
data on the use of voriconazole in adolescent patients was included.

*Medical Officer comments: Please see the Biopharmaceutical reviewer's comments
regarding the adequacy of the adolescent pharmacokinetic data.*

D.   Other Relevant information

Voriconazole is not yet marketed overseas. There is no post-marketing experience.

Site inspections:

The Applicant submitted clinical study outcome data stratified by investigative site. No
specific study site had outcome data that was remarkably different in terms of success,
failure, deaths, discontinuations or drop-outs.

*Medical Officer comments: Consequently, the Division did not request that any
specific clinical study site inspections be conducted either in the US or abroad.*

E.   Important Issues with other Pharmacologically Related Agents

The other azole antifungals approved for this indication are fluconazole, itraconazole
and ketoconazole. Toxicities of the azoles include hepatotoxicty and ketoconazole has
been found to have a direct prolonging effect on the QT interval. Itraconazole has been
shown to produce negative inotropic effects in patients.

*Medical Officer comments: The Applicant has agreed to perform studies on cardiac
contractility in experimental animals or humans as part of their phase 4 commitments.*

II.   Clinically relevant findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Clinical Pharmacology, Statistics and/or Other Consultant Reviews

A.   Chemistry

Please refer to the Chemistry review for a full description of any issues related to the
excipient sulfobutyl ether beta-cyclodextrin (SBECD)

There is no oral solution or pediatric formulation of voriconazole available for use at the present time.

B.   Pharmacology/Toxicology

Please refer to the PharmacologyToxicology review for full details on the following pertinent pre-clinical issues.

In the pre-clinical evaluation of this drug, pharmacology-toxicology studies have demonstrated that voriconazole produced dose-related effects in the electroretinogram (ERG) of dogs exposed to voriconazole. The voriconazole plasma levels which produced these results in dogs were similar to those plasma levels achieved in human studies. Histopathology results for female rats who received 50 mg/kg voriconazole (equivalent to 8 mg/kg IV) demonstrated mild thinning of the outer layer of retina at 24 months. No preclinical testing is available to accurately evaluate the effects of voriconazole on the developing eye in a young animal.

In vitro studies of this drug, demonstrated no major effects for voriconazole in HERG channel studies or in the dofetilide studies when compared to ketoconazole. *In vivo* data demonstrated that in dogs, high doses of voriconazole produced arrhythmia, PVC's and prolonged QT interval.

Voriconazole effects in the liver included increased transaminase activity, increased liver weight, enlarged, pale or marbled liver, centrilobular hypertrophy, hepatocellular fatty change, single cell necrosis and subcapsular necrosis. Toxicity increased with total dose and these findings were more common and more severe at higher doses or with longer treatment duration. In mice, 24 month administration of voriconazole at 50 mg/kg, based on body surface area conversions, resulted in an increase in the incidence of hepatocellular adenoma in both sexes and an increase in hepatocellular carcinoma in males. In rats, there was an increase in hepatocellular adenomas in high dose females.

The vehicle used with voriconazole, sulpho-butyl-ether-cyclodextrin (SBECD), is associated with toxic effects in the kidney. Specifically, SBECD administration was associated with vacuolation in the epithelium of the renal tubules, renal pelvis and urinary bladder. These effects were seen in both drug and vehicle treated animals. In patients with moderate to severe renal dysfunction (serum creatinine >
2.5 mg/dL) accumulation of the intravenous vehicle, SBECD, occurs. Oral voriconazole should be administered to these patients, unless a risk benefit assessment justifies the use of intravenous voriconazole.

At doses as low as 1 mg/kg (equivalent to a human dose of 0.2 mg/kg based on body surface area conversions), there was an increased incidence of variations and minor anomalies such as supernumerary ribs and major visceral anomalies such as hydronephrosis. At a dose of 60 mg/kg (equivalent to a human dose of 9.5 mg/kg, based on body surface area conversions) cleft palates were observed at a rate greater than that seen with the control animals.

Medical Officer comments: Consequently, voriconazole will be recommended as a pregnancy category D.

C.   Microbiology

Medical Officer comments: Please see the Microbiology review for a complete discussion of the pre-clinical and clinical mycologic data.

At baseline *C. albicans* was isolated in greater than 90% of the subjects enrolled in both treatment arms with documented esophageal candidiasis.

The microbiology data from study 305 adequately show that voriconazole is comparable to fluconazole in the treatment of microbiologically documented esophageal Candidiasis due to fluconazole susceptible *C. albicans*. However, there were too few cases of esophageal candidiasis due to other *Candida* species to effectively determine the activity profile of voriconazole against the various non-albicans species of *Candida*.

D.   Clinical Pharmacology

Medical Officer comments: Please see the Clinical Pharmacology reviews for additional details.

Drug interactions are numerous as this drug is both an inhibitor and a substrate for CYP 2C9 ,CYP 2C19 and CYP 3A4. Liver function test elevations did correlate with higher levels of voriconazole but elevated levels of voriconazole did not necessarily predict who would develop liver toxicity (no positive predictive value).

In vitro metabolism studies performed with human hepatic microsomes and genetically engineered cell lines indicate that voriconazole is both an inhibitor and substrate of three cytochrome enzymes: CYP 2C19, CYP 2C9, CYP3A49. The substrate affinity and inhibition potency of voriconazole is greater for CYP2C19 and CYP2C9 compared to CYP3A4. For comparison, the potency of voriconazole as an in vitro inhibitor of CYP3A4 appears to be weaker than ketoconazole and itraconazole. The in vitro potency of voriconazole to inhibit the metabolism of CYP 3A4 substrates (and for CYP3A4 substrates to inhibit voriconazole) varies among classes of drugs including: HIV protease inhibitors, non-nucleoside reverse transcriptase inhibitors and immunosuppressant drugs.

The Applicant has evaluated representative substrates/inhibitors/inducers of the three CYP enzymes both *in vitro* and *in vivo*. However, it is not possible to evaluate every potential drug interaction.

To illustrate, representative protease inhibitors and non-nucleoside reverse transcriptase inhibitors were studied *in vitro* but not *in vivo*. The exception is indinavir which was studied under both conditions and found not to interact with voriconazole. However,

other protease inhibitors and non-nucleoside reverse transcriptase inhibitors are known inhibitors and/or inducers of CYP3A4 and the clinical significance of an *in vivo* interaction with voriconazole is currently unknown.

Therefore, the potential for drug interactions with voriconazole presents a therapeutic challenge for the prescriber, when attempting to manage patients on multiple concomitant medications. The Applicant states that these drug interactions are "manageable" but please keep in mind that this is predicated on experience within the setting of a carefully monitored clinical trial. The Advisory Committee recommended additional studies should be performed to explore the drug interactions between voriconazole and nelfinavir and ritonavir.

III.   Human Pharmacokinetics and Pharmacodynamics

The following were copied from the applicant's PK/PD summary in the proposed label:

A. Pharmacokinetics

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

The oral bioavailabilty of voriconazole is estimated to be 96%. In vitro studies indicated that voriconazole is metabolized by the hepatic cytochrome P450 isoenzymes CYP2C19, CYP2C and CYP 3A4. In vivo studies indicate that CYP2C19 is significantly involved in the metabolism of voriconazole and this enzyme exhibits genetic polymorphism. The major metabolite of voriconazole is the N-oxide which accounts for 72% of the circulating radiolabeled metabolites in plasma. Voriconazole is eliminated via hepatic metabolism with less than 2% of the dose excreted unchanged in the urine. of the non-linear pharmacokinetics, the terminal half life is not useful in predicting the accumulation or elimination of voriconazole.

__Medical Officer comments:__ The terminal half life (T_ν) of voriconazole depends on the dose and is approximately 6 hours at 3 mg/kg (intravenously) or 200 mg (oral). This allows for BID dosing but not once daily dosing. Because of the non-linear pharmacokinetics, the terminal half-life of voriconazole is not useful in predicting its accumulation or elimination. One potential complication of non-linear pharmacokinetics is the potential for overdosage. Dosage and administration guidelines outlined in the package insert should be followed. Finally, voriconazole has high bioavailability and switching between intravenous and oral administration can be done when clinically indicated.

B.Pharmacodynamics

A positive association between mean, maximum or minimum plasma voriconazole concentrations and efficacy in therapeutic studies was not found. However, pharmacokinetic and pharmacodynamic analyses of clinical trial data identified positive associations between plasma voriconazole concentrations and both liver function test abnormalities and visual disturbances.

Medical Officer Comments   -

For further detailed information please refer to the Clinical Pharmacology review which will more thoroughly address pharmacokinetic issues in special populations (gender, geriatric, renal and hepatic insufficiency and pediatrics) and also address drug interactions.

IV   Description of Clinical Data and Sources

A.   **Overall Data**

Sources of data used in the review include patients who participated in the clinical trial program (see studies listed in Appendix 1) and one historical control Study 1003 which was used for a comparison against the Study 304 aspergillosis trial.

B.   **Tables Listing the Clinical Trials**

For a complete listing of the clinical trials included in this NDA submission please see Appendix 1.

Medical Officer Comments:
The clinical trials in the NDA submission were representative of the study population for which this drug has intended use except in a few situations. Study 305 included mainly HIV patients with severe AIDS who were taking an average of 1.3 antiretroviral medications as opposed to the typical HAART cocktail of at least 3 antiretroviral medications that is used in the US. In addition, the overall clinical trial database included only 1% solid organ transplant recipients. Finally, these trials were not designed to collect comprehensive data on the hepatitis B and hepatitis C status of patients and it is not possible to accurately predict how voriconazole will be tolerated in this population.

C.   **Post-marketing Experience**

This drug is not marketed at present

D.   **Literature review**

The sponsor has provided a comprehensive collection of articles reviewing the indications for which they are seeking approval.

V   Clinical Review Methods

A.   How the Review was conducted and
B.   Overview of Materials Consulted in Review and
C.   Overview of Methods Used to Evaluate Data Quality and Integrity

The case report forms (CRF's) of the deaths and serious adverse events which occurred in Study 305 were reviewed. JMP datasets submitted by Pfizer were used in both the reviews of safety and efficacy. JMP datasets containing demographic, microbiologic and efficacy/outcome data were merged. The quality and integrity of the data appeared to be good and sufficient to allow the performance of basic descriptive statistics.

The Division did not believe it was necessary to undertake a DSI audit process of any of the clinical investigation sites.

D.   Were Trials Conducted in Accordance with Accepted Ethical Standards

It appeared as if all trials, including overseas trials, were conducted ethically and after IRB approval.

E.   Evaluation of Financial Disclosure

__Medical Officer comments:__ The Applicant has provided adequate financial disclosure information in this NDA.   To date, no major conflicts of interest were identified that could potentially influence the validity or outcome of the indications under review

VI.   Integrated Review of Efficacy

A.   Brief Statement of Conclusions

Voriconazole taken by mouth was as effective as fluconazole for the treatment of *Candida albicans* esophagitis.

The overall satisfactory response rate for the treatment of refractory esophagitis in a non-comparative study was 14/29 or 48.3%

B.   General Approach to Review of the Efficacy of the Drug

For the review of efficacy, SAS/JMP datasets, case report forms, patient profiles and summary tables including Section 13 of the NDA were utilized. The NDA was submitted in electronic and paper forms. Volume 126 was used for the review of study 305 as well as volume 150 which is the original version of the ISS.

VII.   Integrated Review of Safety

Medical Officer comments: Please see the separate integrated summary of safety including the individual summaries on hepatic and ocular safety.

A.   Brief Statement of Conclusions

The safety of voriconazole has been assessed in a clinical program incorporating healthy volunteers, febrile neutropenic patients who received empiric antifungal therapy and in 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 encompasses a safety database of 3467 healthy volunteers and patients.

Although global safety was assessed as part of this NDA review, the following Brief Statement of Conclusions section of this NDA package will focus on selected areas that are characteristic of the safety profile of this new drug. Adverse events involving vision, liver function, cardiac toxicity and skin will be highlighted.

OCULAR SAFETY

Summary of Ocular Findings

1)   Abnormal vision has generally been reported in more than one out of every three subjects. Included in these ocular reports are decreased vision, photophobia, altered color perception and ocular discomfort.

2)   Results from Study 1501004 demonstrated that in subjects dosed with voriconazole 400 mg q12 x 1 day and 300 mg q12h for 27 additional days there were ocular abnormalities throughout the treatment period consistent with a drug effect on both the retinal rods and cones.

These effects were noted in:
   a)   ERG testing (decreased b-wave amplitude, decreased implicit time).
   b)   Farnsworth Munsell testing – increased scores in blue-green
   c)   Humphrey Visual Field Test

3)   Baseline exams were normal, and the control group remained normal. As demonstrated by the mean scores for the group, the decreased visual function was present after the first day of voriconazole and continued through the 28 days of drug administration. Testing 14 days after the end of treatment generally demonstrated a return to normal function.

4)   Farnsworth Munsell testing and Visual Field Testing are well known to have
        learning curves. While the scores in the voriconazole group appear to improve at
        Day 28, this is more likely a reflection of the learning curve.

5)   The number of patients discontinuing due to ocular events has been small (<10)
        and has included the following reasons: decreased vision, altered color perception
        and photophobia. It is not known from the submission whether all of these events
        were completely reversible.

6)   Pupil size was not adequately evaluted since the pupil size was measured after
        pharmacologic dilation.

7)   Human histopathology has not been performed. Ocular biomicroscopy has not
        detected ocular lesions.

8)   Effects on ocular function are not known for therapies extending beyond 28 days
        or for retreatments with voriconazole.

HEPATIC SAFETY

The Applicant fully acknowledges that voriconazole causes clinically significant liver
function test abnormalities.

In the Phase I Pharmacology studies, the Applicant notes that there were no elevations of
alkaline phosphatase in either the voriconazole or placebo patients. The incidence of
elevated AST in the voriconazole arm was 0.9% vs 0.8% in placebo. The incidence of
elevated ALT was 1.2% in the voriconazole arm vs 0% in placebo. The incidence of
elevated total bilirubin was 0.5% in the voriconazole arm vs 1.6% in placebo. The
Applicant notes that any hepatic function abnormalities were reversible upon
discontinuation of study drug.

In the controlled phase 3 clinical studies (studies 307/602, 603 and 305), the frequency
of occurrence of elevated alkaline phosphatase, total bilirubin, AST and ALT, without
regard to baseline, is reported as follows:

Alkaline phosphatase   6.8-16%
Total bilirubin   4.3-26.5%
AST   5.6-20.3%
ALT   7.8-18.9%

It is important to note that full information regarding individual hepatitis C status and
hepatitis B status was not always available.

The Applicant states that liver function test abnormalities (AST, alkaline phosphatase
and total bilirubin) have been associated with plasma voriconazole concentration.
However, no threshold plasma concentrations have been identified above which the risk

of an elevated liver function test abnormality was higher compared with plasma ∹
concentrations below the threshold.

CARDIAC SAFETY

In the pre-clinical studies, there was a single occurrence of nodal extrasystoles in an
anesthetized dog. This rhythm was neither felt to be a pro-arrhthymia, nor was a dose
response relationship demonstrated.

 In the Phase 1 healthy volunteer program, the Applicant also maintains that there was no
apparent relationship between increases in the rate-corrected QT interval (QTc) and
either dose or exposure to voriconazole.

In the phase 3 studies, there was a single cardiac death that was due to ventricular
fibrillation that occurred within 30 minutes of the patient's second infusion of
voriconazole. Although the patient had underlying left ventricular dilatation and
electrolyte abnormalities at the time of the event---voriconazole could not be excluded as
a contributing factor.

In the controlled phase 3 trials (aspergillosis study 307/602, candida esophagitis study
305 and febrile neutropenia study 603), examination of cardiac adverse events and
discontinuations for cardiac events did not detect a trend toward more events in the
voriconazole arm. However, it is also important to remember that these studies do not
fully assess the risk to develop an arrhythmia in a population with underlying heart
disease who may be on multiple medications including anti-arrhythmic drugs.

SKIN

Skin rash was observed in 278/1493 (18.6%) of patients in the Therapeutic Studies
program. It is important to note that this was a population that contained many patients
who were also receiving antihistamines, steroids and immuno-suppressant drugs that
might affect the type or severity of skin exanthem observed. In the controlled
aspergillosis study 307/602, 124 of 196 patients on voriconazole received
immunosuppressants, 134 of 196 patients on voriconazole received steroids and 77 of
196 patients received antihistamines and many patients received combinations of these
three types of drugs.

In addition, in study 307/602 the incidence of graft vs host disease (GVHD) was 4.1% in
the voriconazole arm and 2.2% in the amphotericin B/OLAT arm. In study 603, GVHD
occurred in 2.9 % of patients in the voriconazole arm and in 1.4% of patients in the
Ambisome® arm.

Further examination regarding the incidence of discontinuations for skin rashes across
the controlled studies was made. No significant differences were noted between
voriconazole and the comparator arms.

It is difficult to provide a precise description of skin rash across the studies and no pathognomic type of skin exanthem emerges. The rash was described as "rash", "macular papular exanthem" and a host of other descriptions. The severity of rash (mostly mild and moderate) was similar across treatment arms and the median day of onset was 23 days for voriconazole and 19 days for the rashes that developed in the comparator arms for studies 307/602, 603 and 305. There were skin biopsy results available for only 4 patients. Two patients received voriconazole and two patients received liposomal amphotericin B. One voriconazole patient had GVHD at day 30 and the other patient had a "lichenoid drug reaction compounded by elements of phototoxicity" at day 138 of therapy. The patients on liposomal amphotericin B both had GVHD at day 21 and at day 35, respectively.

Severity of rash was assessed across the controlled trials 307/602, 305 and 603 and no major differences across treatment arms was identified. Many of these patients were on other concomitant medications that could cause also rash.

Finally the Applicant has provided data on the most severe episodes of skin rash that emerged during the clinical trials. At this time, we concur with the company that rash, including severe episodes such as Stevens-Johnson syndrome can occur with voriconazole administration. Although most skin rashes were of mild severity, clinical judgment should always dictate when to discontinue drug. The mechanism of action for the development of this skin exanthem has not been identified. There is insufficient information to conclude that these reactions represent photosensitivity.

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. Most of these visual symptoms appear to resolve with discontinuation of 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 diabetic retinopathy and 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 hepatically metabolized 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.

Regarding cardiac toxicity, the studies to assess the effect of different doses on the QTc in healthy patients have still not been completed. In addition, the use of this drug in patients with underlying heart disease and on anti-arrhythmic drugs should be done with caution and consideration given to cardiac monitoring during the use of the intravenous preparation. Patients should have electrolyte abnormalities corrected before infusion of this drug.

The mechanism for the skin exanthem remains to be clarified but clinical judgment should dictate if and when this drug should be discontinued.

Approved therapy available for *Aspergillus* infections includes drugs such as amphotericin B, lipid formulations of amphotericin B, itraconazole and caspofungin. Voriconazole represents an important new addition to our armamentarium of antifungal agents and, in the controlled aspergillosis study 307/602, the drug has demonstrated a survival advantage. Therefore, in treating patients with *Aspergillus* infection with its attendant high morbidity and mortality, one can reconcile taking the risk of exposing the patient to the development of rash and other adverse events related to visual, cardiac and liver function.

APPEARS THIS WAY
ON ORIGINAL

VII

Appendix I   **Voriconazole Clinical Studies NDA 21-266 and 21-267**
                                   (from the Applicant's Advisory Committee Briefing
                                   Package dated October 4, 2001)

Study Number Title Location of sites	Start/end dates	Design	Treatments	Entered (or randomized and received study drug)/ completed	Efficacy			Safety		
					Efficacy population(s)#		Efficacy endpoints	Safety population(s)		Safety endpoints
Aspergillosis										
307/602 Global Comparative Aspergillosis Study U.S.; Canada; Europe; Israel; Mexico So. America; India; Australia	307: Jul 1997 / Feb 2001 602 : Sep 1997 / Jan 2001	OL, MC, randomized, comparative study of voriconazole versus amphotericin B followed by OLAT in immunocompromised patients with acute invasive aspergillosis	Voriconazole (V) IV 6 mg/kg q 12 h x 2 doses → 4 mg/kg q 12 h x 7 d → voriconazole PO 200 mg bid Dose escalation to 6 mg/kg q 12 h IV and 300 mg bid PO permitted Amphotericin B (A) 1.0-1.5 mg/kg/d x 2 wk Dose adjustment permitted for toxicity Both groups could be switched to OLAT if failed to respond or unable to tolerated IRT Total duration maximum 12 wk	V 196/79* A 185/7	ITT MITT PP	V 194 A 185 V 144 A 133 V 131 A 111	Global success Survival	Safety	V 196 A 185	Adverse events Discontinuations Laboratory analyses
304 Non-Comparative Aspergillosis Study Europe	Jan 1994 / Jul 1996	OL, MC, uncontrolled study of IV and oral voriconazole in immunocompromised patients with acute invasive aspergillosis with or without previous anti-fungal treatment	Voriconazole IV 6 mg/kg q 12 h x 2 doses → 3 mg/kg q 12 h x 7-28 d → voriconazole PO 200 mg bid Total duration 4-24 wk	137/33	ITT PP Expert Eval	137 101 112	Clinical response Mycology Survival	Safety	137	Adverse events Discontinuations Laboratory analyses

Study Number Title Location of sites	Start/end dates	Design	Treatments	Entered (or randomized and received study drug)/ completed	Efficacy		Safety		
					Efficacy population(s)#	Efficacy endpoints	Safety population(s)	Safety endpoints	
1003 Historical Control Study U.S.; Europe	Jan 1993 / Dec 1995	Historical control survey to collect global response and survival data for immunocompromised patients who received standard therapy for invasive aspergillosis	Standard therapy	257	Eval	257	Clinical response Survival	N/A	N/A	N/A
304 vs. 1003		Comparison of matched populations from 304 and 1003 to compare global response and survival in patients with invasive aspergillosis			10pp

5pp | 304 / 72 1003 / 126; 304 / 50 1003 / 92 | Clinical response Survival | N/A | N/A | N/A |
| 303 Chronic Fungal Infection Study Europe | Jul 1993 / Dec 1996 | OL, MC, uncontrolled study of voriconazole in patients with chronic fungal infections . | Voriconazole 200 mg PO bid (100 mg bid if <40 kg). Dose escalation to 350 mg bid permitted based on clinical response | 58/18 | ITT PP | 58 46 | Clinical response | Safety | 58 | Adverse events Discontinuations Laboratory analyses |
| **Empirical Treatment** | | | | | | | | | |
| 603 Empirical Therapy Study; U.S.; Canada; Europe; India | Mar 1998 / Sep 1999 | OL, MC, comparison on voriconazole with liposomal amphotericin B in the empirical treatment of immunocompromised patients with persistent fever and neutropenia | Voriconazole (V) IV 6 mg/kg q 12 h x 2 doses → 3 mg/kg q 12 h x 3 d → 200 mg PO bid Liposomal amphotericin B (A) IV 3 mg/kg/d Total duration up to 12 wk | V 421/310 A 428/335 | ITT

MITT

PP | V 421 A 428 V 415 A 422 V 382 A 368 | Overall response: Survival Absence of BT infections, Defervescence, Lack of discontinuation due to toxicity/lack of efficacy | Safety | V 421 A 428 | Adverse events Discontinuations Laboratory analyses |

Study Number Title Location of sites	Start/end dates	Design	Treatments	Entered (or randomized and received study drug)/ completed	Efficacy population(s)#	Efficacy endpoints	Safety population(s)	Safety endpoints

Rare and Refractory Infections

Study Number Title Location of sites	Start/end dates	Design	Treatments	Entered (or randomized and received study drug)/ completed	Efficacy population(s)#	Efficacy endpoints	Safety population(s)	Safety endpoints
309/604 Global Rare and Refractory Study U.S.; Canada; Europe; Australia; Thailand	Dec 1997 / Oct 2000 309: Efficacy cut-off date: 31 May 1999 604: Efficacy cut-off date: 26 May 1999 309 and 604: Safety cut-off date: 1 May 2001	OL, noncomparative studies of voriconazole in patients with systemic and invasive fungal therapy for which there is no licensed therapy and the treatment of systemic or invasive fungal infections in patients failing or intolerant of treatment with approved anti-fungal agents	Voriconazole IV 6 mg/kg q 12 h x 24 h → 4 mg/kg q 12 h x 3 d Voriconazole PO 400 mg q 12 h x 1 d → 200 mg q 12 h Total duration 12 wk	309: 166 / 73 604: 206 / 94	MITT 37 111	Clinical response	Safety 166 206	Adverse events Discontinuations Laboratory analyses

Candidiasis

| 302 Dose Ranging Oropharyngeal Candidiasis Study Europe | Jan 1993 / Feb 1994 | DB, randomized, MC dose-ranging study of oral voriconazole in HIV positive patients with oropharyngeal candidiasis | Voriconazole 50 mg PO QD Voriconazole 200 mg PO QD Voriconazole 200 mg PO bid Total duration 7 d Post-treatment option to switch to fluconazole 50 mg PO QD for additional 7 d | 167/127 | ITT 167 | Clinical response Mycology Voriconazole plasma levels | Safety 167 | Adverse events Discontinuations Laboratory analyses |
| 305 Esophageal Candidiasis Study Europe; Australia Russia Singapore; South Africa; Thailand | Sep 1995 / Jan 1999 | DB, randomized, MC comparative study of voriconazole vs. fluconazole in the treatment of esophageal candidiasis | Voriconazole (V) 200 mg PO q 12 h Fluconazole (F) 400 mg PO qd x 1 d → 200 mg PO QD Total duration 2-6 wk | V 200/131 F 191/1136 | ITT V 200 F 191 PP V 115 F 141 | Success Esophagoscopy Symptoms | Safety V 200 F 191 | Adverse events Discontinuations Laboratory analyses |

Study Number Title Location of sites	Start/end dates	Design	Treatments	Entered (or randomized and received study drug)/ completed	Efficacy			Safety		
					Efficacy population(s)#		Efficacy endpoints	Safety population(s)		Safety endpoints
608 Comparative Candidemia Study U.S.; Europe; So. America; Canada; Israel; Morocco; So. Africa	Sep 1998 / Safety cut-off date: 1 May 2001	OL, MC, randomized comparative study of voriconazole (V) vs. conventional amphotericin B (A) followed by fluconazole in the treatment of candidemia in non-neutropenic patients.	Voriconazole IV 6 mg/kg q 12 h x 2 doses → 3 mg/kg q 12 h Day 4 or later: Voriconazole 200 mg bid (patients >40 kg) or 100 mg bid (patients ≤40 kg) Dose escalations permitted to 4 mg/kg IV or 300 mg PO bid in case of insufficient clinical response Amphotericin B 0.7 mg/kg/day x 3-7 days → fluconazole IV or oral, minimum dose of 400 mg/day Total duration: dosing to be continued until 2 wks after infection resolved.	V 110/40 A 52/20	N/A	N/A	Clinical response Mycology	Safety	V 110 A 52	Adverse events Discontinuations Laboratory analyses
Compassionate Use and Extension Studies										
301 Non-US Compassionate Program Europe; Australia; Canada; Czech Republic; Iceland; Israel; Saudi Arabia; Singapore	Mar 1997 / Efficacy cut-off date: 20 Sep 1999 Safety cut-off date: 1 May 2001	Named patients program for patients with proven life-threatening invasive fungal infections who are failing or are intolerant of currently available anti-fungal therapies	Voriconazole IV 6 mg/kg q 12 h x 2 doses → 4 mg/kg q 12 h or Voriconazole 400 mg/bid on day 1 → 200 mg/bid (patients > 40 kg) Voriconazole 200 mg/bid on day 1 → 100 mg/bid (patients < 40 kg) Dose escalations were allowed in cases of insufficient clinical response	288/83 7 ongoing at safety cut-off date	ITT	127	Global response	Safety	288	Adverse events Discontinuations Selected laboratory analyses

Study Number Title Location of sites	Start/end dates	Design	Treatments	Entered (or randomized and received study drug)/ completed	Efficacy			Safety		
					Efficacy population(s)#		Efficacy endpoints	Safety population(s)		Safety endpoints
303A & 304A Named Patient Use Of Voriconazole Europe	Jul 1993 / Sep 1997 Cutoff I May 2001	Named patients program for patients with proven life-threatening invasive fungal infections who are failing or are intolerant of currently available anti-fungal therapies	Voriconazole IV 6 mg/kg q 12 h x 2 doses → 3 mg/kg q 12 h x 7-28 d → voriconazole PO 200 mg bid	46/14	ITT	46	Global response	Safety	46	Adverse events Discontinuations Laboratory analyses
311 and 607 Non-Comparative Extension Study of Invasive Fungal Infections US; Canada; Argentina; Europe; Australia	May 1998 / Efficacy cut-off date: 20 Sep 1999 Safety cut-off date: 1 May 2001	OL, extension protocol for patients with invasive fungal infections previously treated with voriconazole in a Phase 3 study requiring more than 16 wks of treatment	Voriconazole 200-300 mg PO bid or 3-4 mg/kg q 12 h IV for patients ≥40 kg and 100-150 mg bid for patients <40kg	91/45 7 ongoing at safety cut-off date	ITT	33	Global response Mycology	Safety	91	Adverse events Discontinuations Laboratory analyses
312 Emergency Use Protocol in Europe	Jul 1998 / Efficacy cut-off date: 20 Sep 1999 Safety cut-off date: 1 May 2001	Emergency use protocol for patients with proven life-threatening invasive fungal infections who are failing or are intolerant of currently available anti-fungal therapies	Voriconazole IV 6 mg/kg q 12 h x 2 doses → 4 mg/kg q 12 h → voriconazole PO 200 mg bid (patients > 40 kg) or 100 mg bid (patients < 40 kg) Dose escalations and reductions were allowed in cases of insufficient clinical response or intolerance, respectively	37/9 6 ongoing at Safety cut-off date	ITT	7	Global response	Safety	37	Adverse events Discontinuations Selected laboratory analyses

Study Number Title Location of sites	Start/end dates	Design	Treatments	Entered (or randomized and received study drug)/ completed	Efficacy			Safety		
					Efficacy population(s)#		Efficacy endpoints	Safety population(s)		Safety endpoints
606 Emergency Use Protocol in US & Canada	Sep 1997 / Efficacy cut-off date: 20 Sep 1999 Safety cut-off date: 1 May 2001	Emergency use protocol for patients with proven life-threatening invasive fungal infections who are failing or are intolerant of currently available anti-fungal therapies	Voriconazole IV 6 mg/kg q 12 h x 2 doses → 4 mg/kg q 12 h → voriconazole PO 200 mg bid (patients > 40 kg) or 100 mg bid (patients < 40 kg) Dose escalations and reductions were allowed in cases of insufficient clinical response or intolerance, respectively	134/18 16 ongoing at Safety cut-off date	ITT	52	Global response	Safety	134	Adverse events Discontinuations Selected laboratory analyses

Study Number Title Location of sites	Start/end dates	Design	Treatments	Entered (or randomized and received study drug)/ completed	Efficacy			Safety		
					Efficacy population(s)#	Efficacy endpoints		Safety population(s)		Safety endpoints
606 Emergency Use Protocol in US & Canada	Sep 1997 / Efficacy cut-off date: 20 Sep 1999 Safety cut-off date: 1 May 2001	Emergency use protocol for patients with proven life-threatening invasive fungal infections who are failing or are intolerant of currently available anti-fungal therapies	Voriconazole IV 6 mg/kg q 12 h x 2 doses → 4 mg/kg q 12 h → voriconazole PO 200 mg bid (patients > 40 kg) or 100 mg bid (patients < 40 kg) Dose escalations and reductions were allowed in cases of insufficient clinical response or intolerance, respectively	134/18 16 ongoing at Safety cut-off date	ITT	52	Global response	Safety	134	Adverse events Discontinuations Selected laboratory analyses
Other Studies										
1001 Japanese Non-Comparative Deep-Seated Mycoses Study Japan	Jan. 1999/ ongoing	OL, MC, uncontrolled study of intravenous and oral voriconazole in the treatment of patients with deep-seated mycoses	Voriconazole IV 6 mg/kg q 12 h x 2 doses → 3-4 mg/kg q 12 h → voriconazole PO 200-300 mg bid Voriconazole oral 300 mg bid x 2 doses on Day 1 → 200 mg bid Patients weighing less than 40 kg should have all doses of voriconazole reduced by half. Dose reduction permitted based on adverse events and plasma monitoring Total duration minimum of 3 days and maximum of 12 weeks	N/A		N/A	Not included		N/A	Serious adverse events

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/s/

Rosemary Tiernan
6/6/02 10:31:37 AM
MEDICAL OFFICER

Marc Cavaille Coll
6/7/02 04:24:52 PM
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Renata Albrecht
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Executive Summary for the Medical Officer's Review of the Hepatic Safety of Voriconazole - NDA 21-266 & NDA 21-267

Identifying Information
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Submission/review dates
Date of submission: November 17, 2000
CDER stamp date: November 17, 2000
Date hepatic safety review assigned: August 10, 2001
Date hepatic safety review begun: August 10, 2001
Date of submission of major clinical amendment: June 22, 2001
Date of Advisory Committee Meeting: October 4, 2001
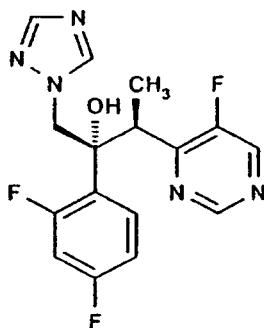Date review completed: December 17, 2001

Drug Identification
Generic name: voriconazole
Proposed trade name: VFEND™ (tablets) and VFEND™ I.V. (for injection)
Other names used during development: UK 109,496
Chemical name: (2R, 3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1*H* -1,2,4-triazol-1-yl)-2-butanol
Chemical Structure:

Molecular formula: $C_{16}H_{14}F_3N_5O$ Molecular weight: 349.3
Pharmacologic category: triazole antifungal agent
Dosage forms:
VFEND™ – film-coated tablet   Strengths: 50 or 200 mg
VFEND™ IV – each single dose vial contains 200 mg of lyophilized voriconazole for reconstitution with water to a concentration of 10 mg/mL for voriconazole and 160 mg/mL of sulfobutyl ether beta-cyclodextrin sodium (a molecular inclusion complex)
Route of administration: oral (VFEND™) and intravenous infusion (VFEND™ I.V.)

Executive Summary

Voriconazole is a triazole antifungal agent. Its mechanism of action involves the inhibition of fungal cytochrome P450-mediated 14 alpha-sterol demethylation, an essential step in fungal ergosterol biosynthesis. In humans, voriconazole is eliminated via hepatic metabolism with less than 2% of the dose excreted unchanged in the urine. It is metabolized in humans by the cytochrome P450 isoenzymes CYP2C19, CYP2C9, and CYP3A4. There are genetic polymorphisms for CYP2C19 and voriconazole exposure can be 4-fold higher in poor metabolizers. Considerable interindividual variability of voriconazole pharmacokinetics was observed in population pharmacokinetics from phase I studies.

In preclinical pharmacology/toxicology studies, the liver was found to be a target organ for voriconazole toxicity. The human equivalent doses at which hepatic findings were noted in the preclinical animal studies are within the range of the recommended human therapeutic doses. In preclinical animal studies the liver-related findings included increases in alanine aminotransferase and alkaline phosphatase, increased liver weights, centrilobular hypertrophy, and in the high dose groups in some studies, single cell necrosis was noted. In the high-dose group of a 24-month mouse study, a higher incidence of hepatic adenomas was noted.

In the phase I and dose-ranging phase II studies in humans, the data support an exposure or dose response relationship with elevations in transaminases and to a lesser extent alkaline phosphatase. In a multiple dose intravenous (IV) to oral (PO) phase I study 2 of 14 patients in the high dose group and one of the 7 subjects in the middle dose group developed clinically significant abnormal liver function tests. (The high dose group received 6 mg/kg/ IV bid on Day 1, then 5 mg/kg IV bid Day 2 to 7, and then 400 mg PO bid Day 8 to 14; the middle dose group received 6 mg/kg/ IV bid on Day 1, then 4 mg/kg IV bid Day 2 to 7, and then 300 mg PO bid Day 8 to 14.) The aforementioned subjects in the high dose group had the following abnormalities; ALT and GGT > 3x the upper limits of normal for one of the subjects, GGT > 3x ULN for the other subject. The aforementioned subject in the mid dose group had ALT > 6x ULN, AST > 3x ULN, GGT > 4xULN. (Elevations of these analytes of >3x ULN meet the protocol criteria for "clinically significant abnormality".)

From the eight phase III therapeutic studies and the compassionate use studies, there were a total of 2090 patients enrolled. (Note that 145 patients were enrolled in a therapeutic study and then also in a compassionate use study and hence are counted twice in the total of 2090.) A total of 1493 of these patients received voriconazole in one of the 8 therapeutic studies (as opposed to compassionate use studies). Because of the differences in the patient populations studied in the phase III studies, the differing comparators used

recipients of liver transplants. There were three cases where eosinophilia was noted on the liver biopsy report. All three patients were liver transplant recipients. One of the three patients also had marked peripheral eosinophilia in the absence of hepatocellular damage noted on biopsy and with normal transaminases. Voriconazole as a possible contributing factor to the findings noted on liver biopsy in these three patients cannot be excluded.

There was one more notable case of what is reported histopathologically as "toxic hepatosis" in a young woman who was treated with voriconazole for a corneal infection. She was treated with voriconazole at doses ranging from 200 to 600 mg per day (either IV or PO) along with voriconazole administered in the form of ophthalmic drops (not a formulation under investigation in these studies). The total duration of voriconazole therapy was 60 days (Day 1 to Day 60). She developed elevations in her ALT and AST beginning around Day 53 of therapy that peaked at Day 146 at levels of 10x ULN for ALT and 8x ULN for AST. She was hospitalized Day 153 to Day 155 for evaluation of her elevated liver function tests. Serologic evaluation for viral causes of hepatitis (including hepatitis A, B, and C, EBV, and CMV) was negative. An anti-nuclear antibody (ANA) was positive at 1:80 and the patient was noted to have unexplained leukopenia, arthralgias, and myalgias. A liver biopsy was performed. The histopathologic reading on the liver biopsy was "toxic hepatosis." A supplemental review by an expert hepatologist noted that this case could possibly be a drug-related injury. The expert hepatologist's review also noted some of the limitations of the information available on this patient, that the recovery following cessation of voriconazole was very slow, and that no other obvious causes for liver disease in this patient had been established.

The limitations of the data from the phase III clinical studies in evaluating the potential hepatotoxic effects of voriconazole deserve mention. Most of the patients had other serious underlying medical conditions, some with conditions affecting the liver (veno-occlusive disease of the liver, graft versus host disease, viral hepatitis, or other active liver disease). Most patients were receiving other medications that could have contributed to hepatic abnormalities (the mean number of concomitant medications recorded for patients in the comparative studies was around 25). In this generally ill population it is difficult to accurately estimate background rates for hepatic events for studies that lack a comparator group. For studies enrolling patients for "compassionate-use," it is quite possible that the background event rates may differ from patients being treated for the same indication in the comparative studies. In addition, in some of the non-comparative studies, concomitant medications were not recorded and serum chemistries were infrequently reported.

In summary, the liver is one of the target organs for voriconazole toxicity. The hepatic findings noted in the preclinical studies occurred at doses that when converted to human equivalent doses are within the range of the recommended human therapeutic doses. The findings noted in the preclinical studies included

of the frequency of less frequent more severe liver events from the NDA database.

Given the mortality advantage shown in the invasive aspergillosis study, the safety and efficacy of alternative therapies, and the lack of approved therapies for the treatment of *Scedosporium apiospermium* and *Fusarium* spp., despite the known and potential risk for hepatotoxic effects, based upon the currently available information, in the MO's opinion for these indications the liver-related effects of voriconazole do not prevent a satisfactory risk-benefit profile from being achieved. For esophageal candidiasis, considering the limited number of approved therapies, it may be possible to achieve a satisfactory risk benefit profile provided the hepatic concerns along with the other safety concerns for voriconazole (visual, cardiac, drug interactions, dermatologic reactions, pharmacokinetic variability) taken in combination, do not present an unsatisfactory constellation of risk when weighed against the benefits of voriconazole therapy. It will be important to provide healthcare providers with appropriate information on the hepatotoxic potential of voriconazole in the product label.

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