CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-266

21-267

MEDICAL REVIEW

Medical Officer's Review

NDA	**21-266 (tablet) and 21-267(for injection)**
Submitted:	**17 November 2000**
Review completed:	**7 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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CLINICAL REVIEW for NDA 21-266 and 21-267

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The basis of evidence to support the treatment of invasive aspergillosis was supported by two clinical trials---study 307/602 and study 304. The study subjects were primarily white males with hematologic malignancies as their underlying disease, and pulmonary sites for their *Aspergillus* infection which was predominantly *Aspergillus fumigatus.*

Study 307/602 was a randomized, controlled, open-label, initial therapy study of voriconazole versus amphotericin B-- both of which could be followed by other licensed antifungal therapy (OLAT). The primary efficacy endpoint was outcome at week 12 as assessed by the Data Review Committee (DRC) and satisfactory response rates of 52.8% for voriconazole and 31.6% for the amphotericin B regimen were seen. The 95% confidence interval for the difference in satisfactory response rates, stratified by protocol, was (9.6, 33.6). Since the lower limit of the confidence interval was greater than –20%, voriconazole is considered to be non-inferior to the amphotericin B regimen and, in this case, the 95% confidence interval does not include zero and, thus, voriconazole met the definition of statistical superiority as well. Voriconazole also demonstrated a survival benefit. The probability of survival at day 84 was (0.708) for the voriconazole arm compared to 0.579 for the amphotericin B regimen.

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

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

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

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

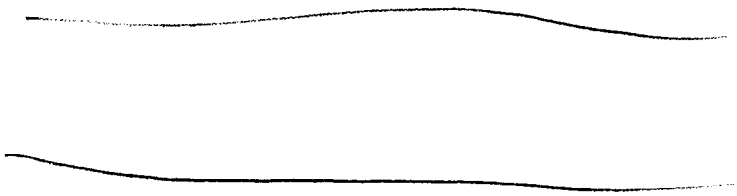
The Applicant has committed to completing an additional oral dose escalation study to ascertain whether voriconazole has a prolonging effect on the QT interval. Despite the aforementioned safety concerns, I believe that voriconazole has demonstrated significant benefit in the treatment of invasive aspergillosis.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

I concur with the present wording of the package insert which states that voriconazole is indicated for use in the "Treatment of invasive aspergillosis". The efficacy of this drug was demonstrated mainly in the treatment of pulmonary *Aspergillus fumigatus* infections.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

Clinical Safety

Cardiac



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

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

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

Clinical Pharmacology

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

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

Microbiology

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

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program and
B. Efficacy

The basis of evidence to support the treatment of invasive aspergillosis was supported by two trials---study 307/602 and study 304. Study 307/602 was a randomized, controlled, open-label, initial therapy study of voriconazole vs amphotericin B-- both of which could be followed by other licensed antifungal therapy (OLAT). Study 304 was a non-comparative study of voriconazole use in primary and salvage patients conducted in Europe. A retrospectively designed historical control study (study 1003) was used as the comparator for study 304. Cases were obtained from both the United States and Europe. In addition, studies 309 and 604 were non-comparative studies which supported the efficacy of voriconazole in the salvage treatment of invasive aspergillosis.

In study 307/602, the modified intent to treat or MITT population (the primary analysis population) consisted of 144 voriconazole subjects and 133 amphotericin B subjects. These subjects were primarily white males, with hematologic malignancies as their underlying disease and pulmonary sites for their *Aspergillus* infection. The studies were designed to allow a switch from randomized therapy to OLAT. More amphotericin B (80.5%) patients switched to OLAT when compared to patients randomized to voriconazole (36.1%) and the major reason for switching to OLAT was elevated serum creatinine. Details of the OLAT regimen were reviewed and felt to represent adequate antifungal therapy (e.g amphotericin B was dosed at 1.0 mg/kg/day and itraconazole was dosed at 200-400 mg daily).

Study 307 and study 602 were identical protocols regarding entry criteria, treatment regimens, study procedures and outcome assessments. The "umbrella analysis plan" was powered to meet specified objectives and preserve study integrity. A blinded Data Review Committee (DRC) was utilized to determine the certainty of diagnosis, global response to treatment and cause of death. The primary efficacy endpoint was outcome at week 12 as assessed by the Data Review

Committee (DRC) and satisfactory response rates of 52.8% for voriconazole and 31.6% for the amphotericin B regimen were seen. The 95% CI for the difference in satisfactory response rates, stratified by protocol, was (9.6, 33.6). Since the lower limit of the confidence interval was greater than –20%, voriconazole is considered to be non-inferior to the amphotericin B regimen and, in this case, the 95% confidence interval does not include zero and, thus, voriconazole is statistically superior.

Medical Officer comments: Please see the Statistical review for a full discussion of the "umbrella analysis plan"

The Division performed 3 additional analyses to assess the robustness of the study 307/602 results. In the Process Plan and Operating Procedures for the Data Review Committee in Study 307/602, it was possible to upgrade investigator assessment of response. Consequently, the Division performed a conservative analysis which did not allow the DRC to upgrade the investigator assessment. The voriconazole arm had a 46.5% satisfactory response rate compared to the 29.3% satisfactory response rate in the amphotericin B arm. In the second analysis, "Modified Week 12" the Division treated voriconazole patients who switched to OLAT as "failures", with the exception of a few patients. These few patients had completed at least 84 days of voriconazole treatment with a satisfactory response and were then placed on prophylaxis. The voriconazole arm had a satisfactory response rate of 45.1% compared to the amphotericin B arm with a satisfactory response rate of 31.6%. Finally, a response at week 16 was assessed. This was an effort to evaluate the number of relapses that occurred in each treatment arm at 4 weeks after the 12 week end of therapy endpoint. The voriconazole arm had a satisfactory response rate of 45.8% and the amphotericin B arm had a satisfactory response rate of 33.1%. Therefore, all of these analyses, demonstrate that the response of voriconazole was consistently greater than the response of the amphotericin B regimen. Finally, survival through day 84 was a secondary endpoint. Voriconazole was shown to have a survival advantage compared to the amphotericin B regimen.

In study 304, the expert evaluable population (the primary analysis population) consisted of 112 voriconazole subjects. The experts classified 58 patients into the primary therapy group and 54 patients as salvage therapy. As assessed by the experts, a patient was considered to be on primary voriconazole therapy if they received less than 10 days of adequate antifungal treatment. All other patients were considered to be on salvage therapy.

Medical Officer comments: As assessed by the experts, patients were descibed as "salvage" if they had received ≥ 10 mg/kg of amphotericin B or 40 mg/kg liposomal amphotericin B or 400 mg/day of itraconazole per day for 10 days and they had a diagnosis of definite aspergillosis. Primary therapy patients received less than the aforementioned doses of amphotericin B, liposomal amphotericn B and itraconazole and had a diagnosis of definite or probable aspergillosis.

As seen in study 307/602, these subjects were primarily white males, with hematologic malignancies as their underlying disease and pulmonary sites for their *Aspergillus* infection. This study was conducted solely in Europe.

The primary endpoint was the expert's global response at end of treatment. The overall satisfactory response rate for patients on voriconazole was 49.1%. A satisfactory response of 60.3% was seen in the primary patients and a satisfactory response of 37% was seen in the salvage patients. Global response was defined as follows:

Complete response - resolution of attributable signs and symptoms, negative cultures and complete or nearly complete resolution of radiographic abnormalities (scar only),
Partial response- nearly complete resolution in attributable signs and symptoms, negative cultures if obtained and at least 50% improvement in radiographic abnormalities,
Stable –minor or no improvement in attributable signs, symptoms and x-ray abnormalities or early discontinuation due to abnormal liver function tests or adverse drug events or lack of clinical data without determinants, or death due to another cause,
Failure – deterioration in attributable signs, symptoms or x-ray abnormalities necessitating alternative antifungal treatment or resulting in death

Since study 304 was a non-comparative study, the Division requested that a retrospective historical control study be performed to act as the comparison group for the primary treated patients in study 304. It should be noted that for this comparison, the definition of primary therapy was less than 5 days of prior antifungal therapy. In order to provide the most comparable population, patients were matched on a 2:1 basis by the prognostic factors of: certainty of diagnosis, underlying disease and site of infection.

The best matched, less than 5 day prior antifungal therapy population, consisted of fifty study 304 voriconazole subjects and ninety-two historical control patients. Satisfactory global response rates were 52% for study 304 voriconazole patients and 25% for the historical control patients. The probability of survival was 0.554 for voriconazole and 0.417 for the historical control.

Even though the Applicant took substantial efforts in the design of the historical control, all of the inherent potential biases were not adequately controlled. Differences in patient populations can impact the success rate of treatment, if patient care and support differ across countries. Study 304 was conducted exclusively in Europe, whereas the historical control included both European and US patients. Satisfactory global response and probability of survival were lower in the US historical control population. This may be due to the fact that the majority of the US historical control patients had bone marrow transplants or other underlying diseases. Whereas the majority of the European historical control patients and the study 304 voriconazole patients had hematologic malignancies as their underlying disease. When these US historical patients are removed, the difference in global response remains but the difference in survival between the European historical controls and the study 304 voriconazole group becomes smaller.

Additional issues regarding the historical control included:
Differences in the total days of treatment---- with the voriconazole treated group having a longer duration of therapy. Differences in the inclusion and exclusion criteria which could possibly allow for sicker patients to be included in the historical control. All in all, these differences in study populations could act to predispose the historical control to lower success rates and the voriconazole treated group to have higher success rates----- independent of treatment with voriconazole. In summary, the historical control trial, study 1003, was a good effort ---but concerns still persisted regarding the comparability of study populations. Study 304 results are

analysis in 45 patients included: no documented infections (n = 19) and entered after the cut-off date (n = 26).

Medical Officer comments: ***Please see Dr. Alivisatos' review on study 309 and study 604 patients who had rare underlying fungal diseases such as Scedosporium and Fusarium species.***

Evaluation of patients with invasive aspergillosis in studies 309 and 604:
The evaluable efficacy population for aspergillosis included: 16 patients in study 309 and 55 patients in study 604. The primary endpoint for studies 309/604 was satisfactory global response at End of Therapy. A satisfactory global response was a 'complete' or 'partial' global response as assessed by the investigator. Time to death was a secondary endpoint. The only analysis population was the Modified Intention to Treat population, defined as patients who had received at least one dose of study drug and had a diagnosis of definite or probable fungal infection that was considered to be systemic or invasive at baseline as determined by the Applicant.

Examples of the major underlying diseases of refractory or intolerant patients with invasive aspergillosis in study 309 and study 604 included the following: 41 patients had hematologic malignancies and 30 of these patients received bone marrow transplants (BMT), 6 patients were listed as BMT patients without an underlying disease, 5 patients had HIV infection and two of these patients also had non-hematologic malignancies,1 solid organ transplant recipient, 7 patients with non –hematologic malignancies and one of these patients was listed as having a non-hematologic and hematologic malignancy and required bone marrow transplantation.

In study 309 (Refractory/Intolerant patients with invasive aspergillosis) there were 16 evaluable patients. The overall satisfactory response rate for voriconazole was 8/16 or 50%. There were 12/16 patients with *A. fumigatus* and 4/16 patients with species of *Aspergillus* other than *A. fumigatus*. One patient had a single isolate of A. *nidulans*. Two patients each had a single isolate of *A. flavus and* 1 patient had both *A. flavus* and *A. terreus* isolated.

The satisfactory response rate for patients with *A. fumigatus* was 5/12 or 42%. The satisfactory response rate for patients with species of *Aspergillus* other than *A. fumigatus* was 3/ 4 or 75%. Failures included the one patient with a mixed *A. flavus* + *A. terreus* infection and 7 patients with *A. fumigatus* infection.

In study 604 (Refractory/Intolerant patients with invasive aspergillosis) there were 55 evaluable patients. Eighteen patients had infection with species of *Aspergillus* other than *A. fumigatus*. One patient had a mixed infection with 3 species of *Aspergillus* (*A. flavus, A. nidulans* and *A. terreus*) and one patient had a mixed infection with 2 species i.e. *A. flavus* and *A. niger*. The patients with mixed infections both had unsatisfactory responses. 16 patients had a single species of *Aspergillus* other than *A. fumigatus* isolated. The satisfactory response rate for *A. terreus* was 2/6, *for A. flavus* was 3/6, *for A. versicolor* 0/1, for *A. nidulans* was 0/2, for *A. niger* 1/1. The overall satisfactory response rate for single species of *Aspergillus* other than *A. fumigatus* in study 604 was 6/16 or 37.5% and for *A. fumigatus* was 16/37 or 43.2%. The overall satisfactory response rate for salvage patients with invasive aspergillosis (mixed and

single species, fumigatus and non-fumigatus species of *Aspergillus*) in studies 309 and 604 was 30/71 or 42.3%.

Medical Officer comments: ***The package insert will provide a table which summarizes the combined response data in salvage patients with invasive aspergillosis with a single Aspergillus species from the non-comparative studies 304, 309 and 604. The Applicant reports a combined satisfactory response rate of 44% for salvage patients with invasive aspergillosis due to Aspergillus fumigatus and this rate is consistent with the FDA analysis.***

C. Safety

In study 307/602, the subjects randomized to voriconazole were treated with the intravenous formulation for at least 7 days, followed by oral voriconazole for up to 12 weeks. Patients randomized to conventional amphotericin B (CAB) were to be maintained on this therapy for two weeks but could extend CAB theray to 12 weeks. Patients in either arm could discontinue initial randomized therapy (IRT) because of toxicity, intolerance or clinical failure and could then receive other licensed antifungal therapy (OLAT). The median duration of IV therapy for voriconazole was 10 days and the median duration of oral therapy was 76 days. The median duration of therapy with CAB was 12 days. Therefore, patients receiving voriconazole had a higher exposure to study drug due to the fact that many more subjects discontinued IRT in the amphotericin B treatment arm. The majority of patients in study 307/602 were white (90.3% voriconazole and 94.7% CAB) males (68.1% voriconazole and 66.9% CAB) with underlying hematologic malignancies (56.3% voriconazole and 63.2% CAB). The main pathogen was *Aspergillus fumigatus* and the primary site of infection was pulmonary (82.6% voriconazole and 84.2% CAB). One hundred ninety-six patients received voriconazole and 185 patients received amphotericin B therapy. The Modified Intent to Treat population included 144 patients who received voriconazole and 133 patients who received amphotericin B. MITT patients had received at least one dose of their IRT and had confirmation of definite or probable primary invasive aspergillosis using baseline information as assessed by the Data Review Committee (DRC).

The main reasons for the MITT populations discontinuing IRT included :

Table 1 Discontintuations from IRT (MITT population)*

Reason for discontinuation from IRT	Amphotericin B (n=133)	Voriconazole (n=144)
Completed Treatment	8 (6.0)	69 (47.9)
Patient Died:	13 (9.8)	16 (11.1)
Death by *Aspergillus*	9	7
Indeterminate	-	4
Unrelated to *Aspergillus*, but infection present	3	2
Unrelated to *Aspergillus*, no infection present	1	2
Insufficient Clinical Response	20 (15.0)	14 (9.7)
Adverse Event	35 (26.3)	27 (18.8)

Laboratory Abnormality	42 (31.6)	5 (3.5)
Other	10 (7.5)	7 (4.9)
Lost to Follow-Up	-	2 (1.4)
Protocol violation	2 (1.5)	-
Withdrawn Consent	3 (2.3)	4 (2.8)
Total	133	144

*FDA analysis

Medical Officer comments: The analysis above was performed by our FDA statistician and focuses on the MITT population i.e. the primary analysis population. The adverse events and laboratory abnormalities were mostly related to creatinine increases and renal insufficiency in the amphotericin B group. The laboratory abnormalities for voriconazole were mostly liver function test abnormalities. "Other" reasons for discontinuation for amphotericin B included the patient switching from IV amphotericin B to therapy with an alternative oral antifungal agent. "Other" reasons for discontinuation in the voriconazole arm included the patient not being able to take oral antifungal therapy.

Table 2 Discontinuations in the ITT population in Study 307/602

Reason for discontinuation	Amphotericin B (n=185)	Voriconazole (n=196)
Adverse event	46	33
Completed	14	96
Did not meet entrance criteria	0	1
Insufficient clinical response	25	23
Laboratory abnormality	57	7
Lost to follow-up	0	2
Other	17	9
Subject died (on active treatment)	19	21
Withdrawn consent	5	4
Total discontinuations	186	196

Medical Officer comments: Six of the seven laboratory abnormalities in the voriconazole group that prompted discontinuation were for liver function test abnormalities which occurred anywhere from day 7 to day 64 of therapy. The other patient on voriconazole discontinued because of a low neutrophil count. The adverse events that prompted discontinuation on voriconazole included: 2 rashes, 1 hepatocellular insufficiency, 3 cases of mucormycosis, 3 worsening Aspergillus infections, 2 visual disturbances, 1 sepsis, 2 renal failure, 1 mult-iorgan failure, 2 worsening of underlying disease, 1 bone marrow aplasia, 2 seizures (1 with hypoglycemia), 1 Guillain-Barre, 2 nausea, , 1 metabolic acidosis, 1 worsening fever, 1 pancreatitis, 1 case of vancomycin resistant enterococcal (VRE) infection, 1 pancreatitis, 1 episode of hemoptysis and asthenia, sinusitis and hallucination were the other adverse events that prompted discontinuation . The "other reasons" and "withdrawn consent" categories for voriconzole discontinuation were reviewed and no patterns of concern were detected. The

main adverse events that prompted discontinuation for the amphotericin B arm were related to renal dysfunction.

Deaths and Serious Adverse Events for the ITT (safety) population (these are patients who received at least one dose of IRT).

There were a total of 79 deaths which occurred on amphotericin B and 65 deaths which occurred on voriconazole in the ITT population.

Table 3 Deaths in the ITT population of study 307/602

Cause of Death	**Amphotericin B/OLAT (n=185)**	**Voriconazole (n=196)**
Death caused by aspergillosis	41	23
Death unrelated to *Aspergillus* and no evidence of residual *Aspergillus* infection	11	11
Death unrelated to *Aspergillus* but evidence of residual infection was present	9	14
Indeterminate	18	17
Total	**79**	**65**

Medical officer comments: ***The indeterminate deaths were reviewed and no particular patterns of events were noted in either treatment arm.***

Table 4 Treatment emergent adverse events Study 307/602

Treatment emergent Adverse Events by body system	**Amphotericin B (n =185))**	**Voriconazole N= 196)**
Body as a whole	157	165
Cardiovascular	92	90
Digestive	137	142
Endocrine	2	3
Hemic and lymphatic	84	87
Metabolic and nutritional	135	114
Musculoskeletal	34	33
Nervous	84	102
Respiratory	129	138
Skin and appendage	**72**	**91**
Special senses	**37**	**97**
Urogenital	**165**	**66**

Table 5 Severe Treatment Emergent Adverse Events Study 307/602

Treatment emergent Adverse Events by body system	Amphotericin B (n =185)	Voriconazole (n= 196)
Body as a whole	103	155
Cardiovascular	40	55
Digestive	41	59
Endocrine	1	2
Hemic and lymphatic	54	70
Metabolic and nutritional	66	43
Musculoskeletal	3	6
Nervous	30	33
Respiratory	118	104
Skin and appendages	4	7
Special senses	-	12
Urogenital	33	16

Medical Officer Comments: The above Tables 4 and 5 represent the numbers of treatment emergent adverse events reported for patients in the ITT population and please note that one patient may have had several events over the course of the study period.

Study drug was listed as the cause of rash in 10 patients receiving amphotericin B/OLAT and 18 patients receiving voriconazole. Discontinuations for rash occurred in one patient on amphotericin B and 3 patients on voriconazole. In study 307/602 there were more grade 3 (severe) cardiac events in the voriconazole arm (13) vs the amphotericin B arm (7) and there were more cardiac arrests with voriconazole (3) when compared to amphotericin B (1). Discontinuations for cardiovascular adverse events occurred in patients who were on IV therapy and two patients were on amphotericin B/OLAT (thrombophlebitis and tachycardia) and 3 patients on voriconazole (extrasystoles, heart arrest and hypotension). Discontinuations for renal dysfunction occurred mainly in the patients on amphotericin B/OLAT (75 patients) vs in 2 patients on voriconazole who were also receiving concomitant aminoglycosides and/or cyclosporine. There were no discontinuations on amphotericin B for visual adverse events. Two patients had visual adverse events and permanently discontinued on voriconazole and another patient on voriconazole temporarily discontinued for visual adverse events.

The Applicant has presented a table in the NDA that depicts the frequency of treatment emergent adverse events, all causalities, with >5% difference between voriconazole IRT and the amphotericin B regimens. Regarding voriconazole, abnormal vision occurs more frequently (33.2%) than in the amphotericin B group(4.3%) and renal dysfunction(including kidney failure and increased creatinine) occurs more frequently in the amphotericin B/OLAT arm (44%) than in the voriconazole arm (9%). The incidence of rash was similar in both groups occurring in 23% of voriconazole subjects and 21.6% of amphotericin B subjects.

When hepatic laboratory abnormalities (SGOT, SGPT, alkaline phosphatase, and total bilirubin) were compared between the two IRT groups, without regard to baseline, the only major difference identified was that voriconazole had an 11.7% incidence of elevated SGOT compared to 5.1% for amphotericin B.

Please see Dr. Cox's review for additional discussion regarding hepatic safety and Dr. Chambers review regarding ocular safety.

D. Dosing

Medical Officer comments: Fifteen of 24 patients who dose escalated developed severe adverse events and had to discontinue voriconazole. I do not believe that we have voriconazole levels on these patients. In addition, this population is quite confounded because they were very ill. The reason for dose escalation was generally related to difficulty in the treatment of their fungal infection.

E. Special Populations

Please refer to the ISS for a discussion on effectiveness and safety in the elderly, hepatic and renal impairment, gender and pediatric issues.

APPEARS THIS WAY
ON ORIGINAL

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:	**21 June 2001**
Date Review Completed:	**7 November 2001**
Resubmission:	**26 March 2002**
Action Date:	**24 May 2002**
Drug Name:	**Voriconazole**
Proprietary Name:	**VFEND ™ Film coated Tablets** **VFEND ™ IV for Infusion**
Chemical name:	**(2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-l-(l H -1,2,4-triazol-l-yl)2-butanol**
Pharmacologic Category :	**Triazole Antifungal agent**
Dosage Form(s) and	**50 and 200 mg tablets** **200 mg/30 ml vial for intravenous infusion**
Proposed Indication(s):	**Treatment of invasive aspergillosis.**
Materials Reviewed:	**NDA submission for June 21, 2001 which included the 307/602 study report, case report forms , JMP datasets an updated integrated summary of safety (ISS) with updated ISS JMP datasets. Additional analyses were requested to further explore adverse events such as hepatotoxicity and rash as well as analyses regarding the exact dose and duration of therapy for the amphotericin B comparator/other licensed antifungal therapy (OLAT) arm of the study. A resubmission was filed on March 26, 2002 which included additional adolescent pK data and data on satisfactory response rates in patients with species of *Aspergillus* other than *A. fumigatus* and material to support a claim of fungicidal activity was also included.**

B. State of Armamentarium for Indications:

The *Aspergillus* species of mold may cause devastating infections in immunocompromised hosts such as AIDS patients, bone marrow transplant and solid organ transplant recipients, patients with hematologic malignancies and patients with autoimmune disease that require immunosuppressant medication. Current antifungal products that are approved for the treatment of aspergillosis include:

amphotericin B (IV) and **AmBisome®, ABELCET®, AMPHOTEC®, itraconazole** and **Cancidas®** were approved for the treatment of invasive aspergillosis in patients refractory or intolerant of conventional amphotericin B.

C. Important Milestones in Product Development

Medical Officer comments:
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.***

In August 1995, the initial IND-opening study 95CK39-0673 with the oral formulation was submitted. The study 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."

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 included:

- 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

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.

Protocol 150-606, entitled "An Open-Label, Non-Comparative Protocol for the Emergency Use of Voriconazole (UK-109,496) in Patients with Life-Threatening Invasive Mycoses Who are Failing on Currently Available Antifungal Agents", was filed on July 25, 1997. The purpose of this protocol was to reduce the need for emergency INDs. It was agreed that patients would be considered for entry into emergency use/compassionate protocols only after possible entry into the controlled trials had been ruled out.

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 to demonstrate equivalence to amphotericin B Interim analyses were planned by the Mycoses 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 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 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.

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 Products 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 action 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 December 2001 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 Clinical Pharmacology review regarding the adequacy of the adolescent pharmacokinetic data.***

D. Other Relevant information

This product 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 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, Biopharmaceutics, Statistics and/or Other Consultant Reviews

A. Chemistry

Medical Officer comments: 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

Medical Officer comments: 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 cyclosporine 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: ***This product will be classified as pregnancy category D.***

C. Microbiology

Medical Officer comments: ***Please see the Microbiology review and the Microbiology Team Leader's memorandum of May 21,2002 for a full discussion of the mycologic issues including claims regarding fungicidal activity. The following are some key points from the Microbiology review.***

Summary of voriconazole activity against *Aspergillus* species isolated from MITT patients in study 307/602

In vitro studies show that voriconazole has some killling activity against conidia of *Aspergillus fumigatus* and *Aspergillus flavus* (fungicidal activity of 99.9% was not achieved). Voriconazole breakpoints have not been established for *Aspergillus* species. Voriconzole MICs are comparable to those of itraconazole when using the NCCLS M38-P methodology (please see Table 6 below):

Table 6

	Voriconazole MIC (ug/ml)	Itraconazole MIC (ug/ml)
A. fumigatus	0.12-0.25	0.12-0.25
*A. flavus**	0.25-0.50	0.12-0.25
*A. terreus**	0.25-0.50	0.06-0.25
*A. niger**	0.25-0.50	0.25-0.50

- *Few isolates of these species were recovered and thus the MIC's noted will only represent trends seen in the clinical trial.

Medical Officer's comments: ***Regarding any claims about the potential fungicidal activity of voriconazole, one is referred to the Microbiology Team Leader's Memorandum (dated 5/21/02) for a full discussion of this issue. The FDA consensus was that in the absence of standardized methods and established criteria and definitions, it would be premature to state that voriconazole is fungicidal against Aspergillus species.***

Azole-resistant strains of *Aspergillus* were not seen in this study. The development of drug resistance on therapy was not observed in this study.

Medical Officer's comments: As stated in the Microbiology Team Leader Memo the Applicant has agreed to assess cross-resistance and has stated that a world-wide surveillance study will be conducted to monitor trends in voriconazole susceptibility over time and to detect any changes in fungal species from an epidemiological standpoint.

Overall, the clinical trial data indicated that voriconazole is effective in eradicating pulmonary *Aspergillus fumigatus* infections. However, because the number of species of *Aspergillus* other than *A. fumigatus* in these studies were fewer in number, it was not always possible to draw definitive efficacy conclusions.

Medical Officer's comments: Additional information submitted by the Applicant in March 2002 did support the efficacy of voriconazole in the treatment of patients with infections due to Aspergillus terreus and A. niger and A. flavus.

Data did not support efficacy against A. nidulans and A. versicolor. The Applicant provided in vitro susceptibility data for a very small number of isolates of A. nidulans. However, none of the clinical A. nidulans isolates were included in this data.

D. Clinical Pharmacology

Medical Officer's comments: ***Please see the Clinical Pharmacology review for additional details.***

Drug interactions are numerous as voriconazole 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 that 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. A 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. [redacted] rapidly and almost completely absorbed following oral administration, with maximum [redacted] 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 radiolabelled metabolites in plasma. [redacted] Voriconazole is eliminated via hepatic metabolism with less than 2% of the dose excreted unchanged in the urine. [redacted] of the non-linear pharmacokinetics, the terminal half life is not useful in predicting the accumulation or elimination of voriconazole.

Medical Officer's comments: ***The terminal half life ($T_{½}$) 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.
Howver, 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. This will also address pharmacokinetics 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

Subjects assessed for the indication of invasive aspergillosis were obtained from two pivotal phase 3 studies: Protocols 150-307 and 150-602. Data from the non-comparative study 304 and from study 309 and 604 was used to support the efficacy of voriconazole in the salvage therapy of patients with invasive aspergillosis.

Study Dates for the pivotal trials:

Protocol 307:	**11 July 1997**	**to**	**16 February 2001**
Protocol 602:	**08 September 1997**	**to**	**25 January 2001**

Study Design: Protocols 150-307 (conducted in Europe, Israel and Australia) and 150-602 (conducted in the United States, Canada, South America and India) were open label, randomised, comparative studies of voriconazole versus amphotericin B in immunocompromised patients with acute invasive aspergillosis. Global, clinical, radiological and mycological evaluations were made at various points during the studies by the investigator and by a single Data Review Committee (DRC). The two protocols had virtually identical inclusion and exclusion criteria, study procedures, assessments and endpoints. Data from both studies were pooled and analyzed together according to the "predefined umbrella protocol" (Please see the Statistical review for further details).

B. Tables Listing the Clinical Trials

Please refer to Appendix 1 in this review.

C. Postmarketing Experience

This drug is not marketed in the US or overseas at the present time.

D. Literature Review

The sponsor has provided a comprehensive review of literature on the treatment of aspergillosis.

V. Clinical Review Methods

A. How the Review was conducted

All death, discontinuation and serious adverse event narratives were reviewed. Selected case report forms for deaths and serious adverse events were reviewed. JMP datasets were provided for studies 307 and 602 and additional information was later added and re-formatted in order to facilitate the analysis of safety questions which arose during the review.

B. Overview of Methods Used to Evaluate Data Quality and Integrity

Sponsor's datasets were re-created using JMP and the statistician used SAS. Case report forms (CRF's) and patient profiles were reviewed as well as narrative summaries on deaths and discontinuations.

C. Were the trials Conducted in Accordance with Accepted Ethical Standards

It appears that all trials were conducted in an ethical manner and after IRB approval. In all of the CRF's reviewed, the investigator attested that the patient had given informed consent.

D. 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

In Study 307/602 voriconazole demonstrated a non-inferior global response and actually met the definition of statistical superiority when compared to a regimen of amphotericin B and other licensed antifungal therapy for the primary therapy of invasive aspergillosis. Voriconazole demonstrated a survival benefit as well. Study 304 results are being used to support the randomized controlled study 307/602 for primary therapy of invasive aspergillosis. Studies 309 and 604 and outcome in the salvage patients in study 304 will support the efficacy of voriconazole in treating patients with invasive aspergillosis who are refractory or intolerant to other antifungal therapy.

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

In Study 307/602, efficacy was evaluated utilizing the Modified Intent to Treat population (MITT) and data was evaluated with regard to gender, race, age, underlying disease, site of infection, certainty of diagnosis and neutropenic status. The primary endpoint was global response at week 12 and survival was also assessed.

Medical Officer comments: ***Please see the Statistical Review for a complete discussion regarding the evaluation of efficacy. The following section will provide some additional details regarding the conduct of the pivotal aspergillosis trial (study 307/602).***

C. Detailed Review of Study 307/602

Acute Invasive Aspergillosis
Studies 150-307 and 150-602 were identical ongoing protocols conducted in Europe, Canada, US, Israel, Australia, South America and India to evaluate the safety and efficacy of voriconazole as initial therapy of acute invasive aspergillosis in immunocompromised patients.

Study Dates:
307: 11 July 1997 to 16 February 2001
602: 08 September 1997 to 25 January 2001

Study Objectives: The primary objective of protocols 150-307 and 150-602 was to evaluate the efficacy, safety, and toleration of voriconazole compared with conventional amphotericin B as initial treatment of acute invasive aspergillosis in immunocompromised subjects. The other objectives were to assess survival and investigate resource utilisation in these subjects and to obtain plasma samples for voriconazole population pharmacokinetics. The primary objective of the umbrella protocol was to demonstrate non-inferiority of voriconazole at Week 12 in the modified intention to treat (MITT) population. The other objectives were to demonstrate superiority of voriconazole at end of randomised treatment (EORT) in the MITT population and to assess the survival through Day 84 from the start of treatment between treatment groups in the MITT population.

Study Design: Protocols 150-307 (conducted in Europe, Israel and Australia) and 150-602 (conducted in the United States, Canada, South America and India) were open label, randomised, comparative studies of voriconazole versus amphotericin B in immunocompromised patients with acute invasive aspergillosis. Global, clinical, radiological and mycological evaluations were made at various points during the studies by the investigator and by a single Data Review Committee (DRC). The two protocols had virtually identical inclusion and exclusion criteria, study procedures, assessments and endpoints. Data from both studies were pooled and analysed together according to the predefined umbrella protocol.

Medical Officer's Comments: ***The DRC performed an independent review of the data generated from the two studies. The studies were open label but the DRC was blinded. The DRC comprised a group of 12 physicians including four radiologists all with expertise in the assessment and therapy of serious fungal infections in immunocompromised patients. The DRC was formed of two subgroups in Europe and the U.S. and the committees were blinded to the treatment and outcomes. See the statistical review for a full description and also Section 11 Item 9 of the NDA.***

The DRC confirmed the investigator's diagnosis of definite or probable aspergillosis in 73% of the ITT subjects. The proportion of subjects with confirmed aspergillosis was similar in each treatment arm with 72.4% of patients in the voriconazole group and 71.9% in the amphotericin group having invasive aspergillosis. However, there were more definite cases in the voriconazole group (34.5% vs 22.2%) and a lower number of probable cases (39.7% vs 49.7%) relative to the amphotericin B group

Diagnoses and Criteria for Inclusion of Subjects: Males or (non-pregnant) females, 12 years or older with a diagnosis of definite or probable acute invasive aspergillosis, based on definitions developed by the Mycoses Study Group, with at least one of the following immunosuppressive conditions: allogeneic or autologous bone marrow/peripheral stem cell transplant; haematological malignancy (including lymphoma); aplastic anaemia and myelodysplastic syndrome; solid organ transplantation; solid organ malignancy (after cytotoxic chemotherapy); human immunodeficiency virus (HIV) infection/acquired immune deficiency syndrome (AIDS); or after high dose prolonged corticosteroid or

other immunosuppressive therapy. The fungal infection at baseline was to be newly diagnosed, and only up to four days of prior systemic anti-fungal therapy was allowed.

Medical Officer's comments: ***Most patients had received and completed antifungal treatment or prophylaxis at least 8 weeks prior to start of study drug. In the voriconazole group 141 (72%) of patients and in the amphotericin group (67%) of patients received prior antifungal therapy. Amphotericin B was the most common drug used for prior antifungal therapy (66% voriconazole and 61% in the amphotericin group). Approximately 30% of patients in each group had not received any prior antifungal therapy at study entry because they had just been diagnosed with acute invasive aspergillosis. Overall, the use of prior systemic antifungal therapy was balanced across treatment arms.***

The mean duration of diagnosis of invasive aspergillosis was similar for subjects in each treatment arm with a mean duration of 5 days for the voriconazole group and 4 days for the amphotericin B group. Two subjects (one in each treatment arm) were included despite having a duration of aspergillosis diagnosis over 28 days

Inclusion criteria

Males and females 12 years of age with any of the following conditions:

- allogeneic or autologous bone marrow/peripheral stem cell transplant
- haematological malignancy (including lymphoma)
- aplastic anaemia and myelodysplastic syndromes (currently on immunosuppressive treatment)
- solid organ transplantation
- solid organ malignancy (after cytotoxic chemotherapy)
- human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS)
- high dose prolonged corticosteroid therapy [20mg daily of prednisolone or equivalent for at least three weeks; or prolonged therapy with other immunosuppressive agents (eg azathioprine, methotrexate)]

Subjects with a diagnosis of definite or probable acute invasive aspergillosis (based upon the Mycoses Study Group criteria), as defined below were enrolled in study 307/602:

Definite aspergillosis

This was defined as either:

- Positive histopathologic evidence (acutely branching septate hyaline hyphae with evidence of tissue invasion) in tissue specimens obtained by aspiration or biopsy with isolation of *Aspergillus* species from the same site;
- Isolation of *Aspergillus* species from an otherwise sterile tissue or body fluid obtained by an invasive diagnostic procedure, such as transbronchial biopsy, biopsy/brushing of tracheobronchial lesions, percutaneous or fine needle aspiration (including liver biopsy, brain biopsy, bone or sinus aspiration), but not bronchoalveolar lavage (BAL), in the presence of clinically compatible illness

· In subjects with allogeneic bone marrow/peripheral stem cell transplant, or any of the following conditions with recent neutropenia (defined as an absolute neutrophil count <500cells/mm within 14 days prior to enrollment): autologous bone marrow/peripheral stem cell transplant, haematological malignancy (including lymphoma), aplastic anaemia, or myelodysplastic syndrome the following findings supported a diagnosis of definite aspergillosis:

(a) New infiltrates, nodules, or cavities on chest radiography and/or Computed Tomography (CT) scan that were not attributable to other infection, lymphoma, or post operative changes, AND
(b) One BAL positive for *Aspergillus* by culture or positive cytology or microscopy positive for hyphae AND
(c) No other clinically significant pulmonary pathogen identified.

Probable Aspergillosis
This was defined as either:
· Positive histopathologic evidence (acutely branching septate hyaline hyphae with evidence of tissue invasion) in tissue specimen obtained by aspiration or biopsy without isolation of *Aspergillus* species from the same site;
· In subjects with allogeneic bone marrow/peripheral stem cell transplant or any of the following conditions with recent neutropenia: autologous bone marrow /peripheral stem cell transplant, haematological malignancy (including lymphoma), aplastic anaemia, or myelodysplastic syndrome, the following findings were to support a diagnosis of probable aspergillosis:

(a) Positive 'halo' or 'air-crescent' sign on CT scan of the chest
(b) No other clinically significant pulmonary pathogen was identified. OR

(a) New infiltrates, nodules, or cavities on chest radiography and/or CT scan that were not attributable to any other infection, lymphoma, or post operative changes AND
(b) At least one sputum positive for *Aspergillus* by culture, AND
(c) No other clinically significant pulmonary pathogen was identified.

· In subjects with allogeneic bone marrow/peripheral stem cell transplant or any of the following conditions with recent neutropenia: autologous bone marrow/peripheral stem cell transplant, haematological malignancy (including lymphoma), aplastic anaemia or myelodysplastic syndrome, the following findings were to be used to support a diagnosis of probable sinus aspergillosis:
(a) opacification of one or more sinuses on CT or Magnetic Resonance Imaging scan AND
(b) clinical evidence of infectious sinusitis AND
(c) biopsy/culture from nose or other local lesion positive for *Aspergillus spp.*

In subjects with HIV infection/AIDS, solid organ transplantation (except lung transplant, or prolonged corticosteroid/immunosuppressive therapy, the following findings were used to support a diagnosis of probable aspergillosis:

(a) new infiltrates, nodules, or cavities on chest radiography and/or CT scan that were not attributable to any other infection, lymphoma, or post operative changes AND
(b) one BAL positive for *Aspergillus* by culture or cytology [Note: a positive sputum culture was not adequate.] AND
(c) no other clinically significant pulmonary pathogen identified.
[Note: All diagnostic procedures, including histopathology, mycology, and radiological investigations were to be performed within 14 days prior to study enrollment.]

The fungal infection at baseline must have represented a new episode of acute invasive aspergillosis. Any course of systemic therapy for aspergillosis with amphotericin B (conventional or lipid formulation) or itraconazole must have been completed at least eight weeks prior to study entry.

Signed informed consent was to have been obtained prior to study participation (subject, relative, or legal representative). For subjects aged 12-17 years, the written informed consent of the parents or legal guardian was also obtained.

Women of child-bearing potential must have had a negative pregnancy test at entry and had to agree to use barrier methods of contraception throughout the study.

Medical Officer's Comments: ***The most common underlying disease was hematologic malignancy (55% in the voriconazole arm and 61% in the amphotericin arm) and the distribution of other underlying diseases was similar across treatment arms. The most common site of infection was pulmonary (61% in the voriconazole and 61% in the amphotericin treatment arms) and the most common species of Aspergillus was A. fumigatus.***

Ninety two patients (47%) in the voriconazole group and 84 patients(45%) in the amphotericin group had a baseline neutrophil count of <500/mm^3. All others had baseline neutrophil counts ≥500/mm^3.

Concomitant antifungals that did not have efficacy against Aspergillus were allowed during the trial. 112 (57%) of the voriconazole patients and 97(52%) of the amphotericin patients received anti-fungal drugs such as non-systemic or oral or inhaled polyenes (amphotericin and nystatin). Other concomitant anti-fungal medications were itraconazole and fluconazole imidazoles and other agents. These medications were reported as "concomitant" because of the sponsor's reporting conventions—e.g. if a patient discontinued a prior antifungal on the day they began voriconazole or amphotericin B the antifungal was listed as a concomitant medication.

Exclusion Criteria
1. Subjects with sarcoidosis, aspergilloma, or allergic bronchopulmonary aspergillosis.
2. Subjects with chronic invasive aspergillosis, with a duration of symptoms or radiological findings for more than four weeks prior to study entry.
3. Subjects who had received systemic anti-fungal therapy at doses greater than

0.5mg/kg/day for conventional or lipid formulations of amphotericin B or greater than 200mg/day of itraconazole, for more than 96 hours during the two week period prior to study entry.
4. Subjects with a diagnosis of Cytomegalovirus (CMV) pneumonia.
5. Pregnant or lactating females.
6. Subjects with a history of hypersensitivity or intolerance to azole anti-fungal agents, including miconazole, ketoconazole, fluconazole, or itraconazole.
7. Subjects with a history of hypersensitivity or severe intolerance (despite supportive therapy) to conventional or a lipid formulation of amphotericin B.
8. Subjects who were receiving or were unable to discontinue the following drugs at least 24 hours prior to randomisation: terfenadine, cisapride, and astemizole (due to the possibility of QTc prolongation), sulphonylureas (these compounds have a narrow therapeutic window and an increase in plasma levels might lead to hypoglycaemia).
9. Subjects who had received the following drugs within 14 days prior to randomisation: Rifampin, carbamazepine, and barbiturates (these compounds are potent inducers of hepatic enzymes and would result in undetectable levels of voriconazole).
10. Subjects who had received or were likely to receive any investigational drug (any unlicensed new chemical entity), except one of the following classes of medications: cancer chemotherapeutic agents, anti-retrovirals, therapies for HIV/AIDS-related opportunistic infections.
11. Subjects who had received or were likely to receive the following medications or treatments during the study period:
· Granulocyte Colony Stimulating Factor (G-CSF) or Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) (for other than treatment of granulocytopenia)
· any systemic anti-fungal medication active against *Aspergillus*
· white blood cell transfusions.
12. Subjects with the following abnormalities of liver function tests (LFTs):
· Aspartate transaminase (AST), alanine transaminase (ALT) >5 x upper limit of normal (ULN)
· Alkaline phosphatase (AP), total bilirubin >5 x ULN
13. Subjects with renal insufficiency that would contraindicate treatment with initial randomised treatment (IRT) (serum creatinine > 2.5mg/dL).
14. Subjects with a life expectancy of less than 72 hours.
15. Subjects on artificial ventilation, unlikely to be extubated within 24 hours of study entry.
16. Subjects for whom written informed consent could not be obtained.
17. Subjects who had already participated in this trial. The inclusion of a subject more than once in this trial was not allowed.
18. Subjects with any condition that, in the opinion of the investigator, could affect subject safety, preclude evaluation of response, or render it unlikely that the contemplated course of therapy could be completed.
19. Protocol 150-307 only: subjects in whom the investigator intended to administer amphotericin B in intralipid solution as study drug, if the subject was randomised to the amphotericin B treatment arm. Amphotericin B was to be administered in a solution of

5% dextrose in water.

Medical Officer's Comments:
The demographic characteristics of voriconazole and amphotericin B- treated patients in the Intention to Treat and Modified Intention to Treat populations were similar (see Table 7 below for gender, age, weight and race demographics).

Table 7 Modified Intent to Treat Population*

Study 307/602	Voriconazole (N = 144)			Amphotericin B/OLAT (N=133)		
Gender	Males (N=98)	Females (N=46)	Total (N=144)	Males (N=89)	Females (N=44)	Total (N=133)
Age range (years)	13-77	20-79	13-79	15-75	12-72	12-75
Mean age (years)	48.9	47.7	48.5	50.4	50.6	50.5
Mean Weight (kg)	72	66.9	70.4	73.5	66	71
Race (n)						
White	88	42	130	84	42	126
Black	5	2	7	0	1	1
Asian	3	1	4	0	0	0
Other	2	1	3	5	1	6

**Taken from the Applicant's study 307/602report.*

Medical Officer's comments: Underlying disease and neutrophil counts were similar for patients in the two treatment arms. The sites of infection were similar between the treatment groups. Most patients in both treatment arms had pulmonary aspergillosis.

In both the ITT and MITT populations there were more patients with definite infections in the voriconazole treatment groups than in the amphotericn B treatment group (ITT: 34.5% vs 22.2% and MITT: 46.5% vs 30.8%). Within each treatment group, there were proportionally more definite infections in the primarily U.S. based Study 602 than in the primarily European-based Study 307.

Overall, the population studied in study307/602 was representative of the US population that would be eligible to receive voriconazole for treatment of invasive aspergillosis.

Removal of Subjects from Treatment or Assessment
A discontinuation was defined as occurring when an enrolled subject ceased participation in the clinical trial, regardless of circumstances, prior to completion of the protocol. The reason for a subject discontinuing was recorded on the CRF and any discontinuations due to serious adverse events (SAEs) were to be reported to the sponsor's clinical research

associate (CRA)/clinical project manager (CPM) immediately. The final evaluation required by the protocol was to be performed just prior to study drug discontinuation if medically acceptable. Otherwise, the final evaluation was performed as soon as possible after study drug discontinuation. If individualized randomized therapy (IRT) was discontinued for any reason, the EORT visit had to be completed. All randomised subjects had to be followed for the full 16 week duration of the study. Voriconazole rechallenge to evaluate possible toxicity could take place only if the investigator, the IRB, and the medical monitor agreed to the rechallenge and if the subject's informed consent for rechallenge was obtained. The investigator was to record the reason for study discontinuation, provide or arrange for appropriate follow up (if required) for such subjects, and document the course of then subject's condition.

The investigator was required to discontinue the IRT (voriconazole or amphotericin B) if any of the following events occurred:
1. Severe elevation of AST or ALT.
· AST and ALT (at study entry <2 x ULN) that rose to >5 x ULN.
· AST and ALT (at study entry >2 x ULN) that rose to >10 x ULN.
2. Severe elevation of serum creatinine.
· Serum creatinine (at study entry <1.5mg/dL) that rose to >2 x baseline.
· Serum creatinine (at study entry >1.5mg/dL) that rose to >3.0mg/dL.
3. Grade 3-4 intolerance to IRT that included:
· infusion-related fever 40°C (Grade 3);
· any severe or life-threatening symptoms (Grade 3-4) (e.g. flu-like symptoms);
· intractable nausea/vomiting (Grade 4).
4. A serious adverse event (SAE) related to study medication.
5. Other treatment related AEs that led the investigator to conclude that withdrawal of the subject from the study medication was in the subject's best interest.

Discontinuations could be categorized in two ways:
-discontinuation from individualized randomized therapy (IRT)and
-discontinuation from study and the two categories are not mutually exclusive.

The MITT population (Voriconazole 144 patients and Amphotericin B 133 patients) was the primary efficacy population and included all patients who:
-had received at least one dose of their IRT and
-had confirmation of definite or probable primary diagnosis of invasive aspergillosis using baseline information as assessed by the DRC

The safety population included all 196 Voriconazole patients and 185 Amphotericin B patients. All treatment emergent adverse events (AEs)which occurred during study treatment or within 7 days of the end of study treatment were coded using COSTART (Coding Symbol Thesaurus of Adverse Reaction Terms) and recorded as mild, moderate or severe.

Schedule of efficacy and safety evaluations

Efficacy assessments occurred at baseline and weeks 1,2,4,6, 12, EORT and week 16 ie. four weeks after the 12 week efficacy endpoint)

Serious Adverse Events were characterized as an event that:
Resulted in death
Was life-threatening
Resulted in in-patient hospitalization or prolongation of hospitalization
Resulted in a persistent or significant disability or incapacity or
Resulted in a congenital anomaly/birth defect

Protocol Deviations
113 patients in protocol 150-307 and 59 subjects in protocol 150-602 deviated from the protocol for one or more reasons. Most reasons involved violations of the inclusion and exclusion criteria or deviations from the dosage prescribed by the investigator.

Medical Officer's Comments: ***I have reviewed these deviations and do not feel that they compromised the validity of the efficacy or safety findings in this study.***

Subject disposition
Of the 391 subjects who were randomized, 11 did not receive study drug treatment (two subjects in the voriconazole and nine subjects in the amphotericin B group. Ten of these 11 were not included in any analyses. One subject in protocol 150-602 was randomized and never received study drug and then was re-randomized and received voriconazole. This patient was included in the safety analysis (subject 80183300) but was excluded from the efficacy analysis as defined in the protocol.

381 subjects received study treatment and 196 were in the voriconazole group and 185 in the amphotericin B arm. This slight imbalance may be partially due to the greater number of patients who withdrew from the study without receiving randomized treatment and partly due to the stratification methods (stratified on protocol, underlying disease, neutropenic status and site of diagnosis). Please see Table 8 below.

Table 8 Patient Disposition

Evaluation groups	**Voriconazole Group**	**Amphotericin B Group**
Entered study and treated	**196**	**185**
Completed study	116	88
Evaluated for efficacy		
ITT	194	185
MITT	**144**	**133**
Evaluated for safety		
Adverse Events (AEs)	**196**	**185**
Laboratory Tests	193	180

Permanent and temporary discontinuations from individualized randomized therapy (IRT) are outlined in Table 9 and 10 below.

Table 9 Summary of permanent discontinuations from IRT

	Voriconazole N =196	Amphotericin N=185
Death	21 (11%)	19 (10%)
Related to study drug		
Insufficient clinical response	23 (12%)	25 (14%)
Adverse Event	15 (8%)	35 (19%)
Laboratory abnormality	5 (3%)	55 (30%)
Not related to study drug		
Adverse Event	18 (9%)	11 (6%)
Laboratory abnormality	2 (1%)	2 (1%)
Other*	16 (8%)	24 (13%)

* Includes protocol violation, lost to follow-up, does not meet entrance criteria, withdrawn consent and other.

Table 10 Summary of temporary discontinuations and dose reductions

	Voriconazole IRT N =196	Amphotericin B IRT N=185
Temporary discontinuations (AE's)	14	24
Dose reductions	4	14

Medical Officer Comments ***Tables 9 and 10 show that the amphotericin B arm had a higher number of permanent and temporary discontinuations and dose reductions and these were mainly due to renal dysfunction.***
Thirty three patients on voriconazole developed adverse events. No particular trends were noted except that laboratory abnormalities were mainly hepatic (6/7). In addition the following adverse events leading to discontinuation were noted in the voriconazole arm: 2 visual adverse events, 2 cardiac events (1 cardiac arrest and 1 arrhythmia), 1 hepatocellular insufficiency, 3 discontinuations due to mucormycosis, 2 renal failure and 1 rash.

Efficacy

Finally, to summarize the efficacy of voriconazole in the treatment of invasive aspergillosis (Please see the statistical review for additional details):

In study 307/602, the modified intent to treat or MITT population (the primary analysis population) consisted of 144 voriconazole subjects and 133 amphotericin B subjects. These subjects were primarily white males, with hematologic malignancies as their

underlying disease and pulmonary sites for their *Aspergillus* infection. The studies were designed to allow a switch from randomized therapy to OLAT. More amphotericin B (80.5%) patients switched to OLAT when compared to patients randomized to voriconazole (36.1%) and the major reason for switching to OLAT was elevated serum creatinine. Details of the OLAT regimen were reviewed and felt to represent adequate antifungal therapy (e.g amphotericin B was dosed at 1.0 mg/kg/day and itraconazole was dosed at 200-400 mg daily).

Study 307/602 was a randomized, controlled, open-label, initial therapy study of voriconazole versus amphotericin B-- both of which could be followed by other licensed antifungal therapy (OLAT). The primary efficacy endpoint was outcome at week 12 as assessed by the Data Review Committee (DRC) and satisfactory response rates of 52.8% for voriconazole and 31.6% for the amphotericin B regimen were seen. The 95% confidence interval for the difference in satisfactory response rates, stratified by protocol, was (9.6, 33.6). Since the lower limit of the confidence interval was greater than –20%, voriconazole is considered to be non-inferior to the amphotericin B regimen and, in this case, the 95% confidence interval does not include zero and, thus, voriconazole met the definition of statistical superiority as well. Voriconazole also demonstrated a survival benefit. The probability of survival at day 84 was (0.708) for the voriconazole arm compared to 0.579 for the amphotericin B regimen.

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, this Brief Statement of Conclusions 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 immunosuppressant 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.

VIII Appendix 1 Voriconazole NDA 21-266 and 21-267 Clinical Trials

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			Safety		
					Efficacy population(s)#		Efficacy endpoints	Safety population(s)		Safety endpoints
Rare and Refractory Infections										
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 PP	V 200 F 191 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 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 → 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

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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 09:50:28 AM
MEDICAL OFFICER

Marc Cavaille Coll
6/7/02 04:23:20 PM
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Renata Albrecht
6/12/02 08:50:29 AM
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INTEGRATED REVIEW OF SAFETY

FOR

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