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Voriconazole Hepatic Safety Review Executive Summary

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Medical Officer's Review of the Hepatic Safety of Voriconazole
NDA 21-266 & NDA 21-267

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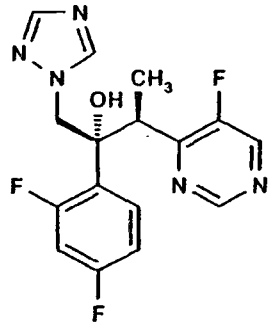
Drug Identification
Generic name: voriconazole
Proposed trade name: VFEND™ (tablets) and VFEND™ I.V. (for injection)
Other names used during development: UK 109,496
Chemical name: (2R, 3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol
Chemical Structure:



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

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Executive Summary

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

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

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

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

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

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

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

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

elevations in alanine aminotransferase and alkaline phosphatase. Data from phase I studies and for dose-ranging phase II studies support a dose or exposure response between voriconazole and transaminases and to a lesser degree alkaline phosphatase. From the phase III studies, elevations in transaminases were more frequent in patients from the esophageal candidiasis study receiving voriconazole than fluconazole. In the aspergillosis study and the empiric antifungal therapy study in febrile neutropenic patients abnormalities of transaminases and alkaline phosphatase were similar between treatment groups. Abnormalities of bilirubin were more frequent among patients receiving comparator (either amphotericin B deoxycholate or AmBisome®) than those receiving voriconazole. Serious liver-related adverse events and discontinuation from initial randomized therapy occurred more frequently in voriconazole than comparator-treated patients. For the hepatic failure cases in the comparative studies, the number of cases and likelihood of association with study drug was similar for voriconazole and comparator. There were four cases of hepatic failure in voriconazole-treated patients (all from non-comparative studies) where the liver abnormalities were considered by at least two of the four expert hepatologists to be at least possibly related to voriconazole. There were three voriconazole-treated patients, all of whom had received a liver transplant, with eosinophilia noted on liver biopsy. The possibility of voriconazole as a contributing factor in these cases cannot be excluded. There was one other notable case of a young woman receiving voriconazole for a corneal infection on few other medications who developed elevated transaminases. She underwent a liver biopsy with the findings of "toxic hepatosis" where voriconazole could not be excluded as a causal factor, and was thought by the investigator to be the likely cause of the patient's liver abnormality. A supplemental review by an expert hepatologist noted that this case could possibly be a drug-related injury.

In the MO's opinion the data support that voriconazole is able to induce elevations in transaminases and to a lesser extent alkaline phosphatase. This effect appears to be somewhat more than what was experienced with fluconazole (based upon the data from the comparative esophageal candidiasis study). The panel of expert hepatologists' assessment of hepatic failure cases identified several cases where voriconazole therapy was considered by at least some of the experts to be either possibly or probably related to the liver event. The case of the young woman with "toxic hepatosis" noted on liver biopsy on few other medications who developed significant transaminase elevations for which a non-study drug cause could not be established also supports that voriconazole may have the ability to cause hepatic toxicity. Taking all of the data into consideration along with its uncertainties, it is likely that voriconazole is associated with hepatic adverse events and possibly associated with infrequent serious hepatic adverse events. The inherent limitations of the available data (because of the populations in whom this drug is intended for use and hence the population in whom this drug was studied) do not allow a more precise estimate of the frequency of less frequent more severe liver events from the NDA database.

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

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

Selected Portions of the Applicant's Proposed VFEND (voriconazole) Label

Portions of the Applicant's proposed label for VFEND (voriconazole) addressing liver-related issues are excerpted below. Note that MO Comments and Recommendations for changes to the Applicant's proposed label are provided in the section of this review titled "Medical Officer's Labeling Recommendations."

The proposed INDICATIONS AND USAGE section of the VFEND™ and VFEND™ I.V. label are as follows:

> VFEND is indicated for use in the treatment of the following fungal infections:
>
> Treatment of invasive aspergillosis.
>
> Treatment of serious fungal infections caused by *Scedosporium* and *Fusarium* patients intolerant of, or refractory to, other therapy.
>
> Specimens for fungal culture and other relevant laboratory studies (histopathology) should be obtained prior to therapy to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, therapy should be adjusted accordingly.

The Applicant's proposed label contains the following as the 2nd and 3rd subsections within the WARNINGS section.

> **Hepatic toxicity**: In clinical trials, there have been uncommon cases of serious hepatic reactions during treatment with VFEND (including clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities). Instances of hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly hematological malignancy). hepatic reactions, including hepatitis and jaundice, have occurred among patients with no other identifiable risk factors. Liver dysfunction has usually been reversible on discontinuation of therapy.
>
> **Monitoring of hepatic function:** liver function tests during VFEND therapy should be monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of VFEND must be considered if clinical signs and symptoms consistent with liver disease develop that may be attributable to VFEND (see

PRECAUTIONS — DOSAGE AND ADMINISTRATION-Dosage Adjustment, ADVERSE EVENTS-Clinical Laboratory Tests).

Within the PRECAUTIONS section of the Applicant's proposed label a subsection entitled "Laboratory tests" states the following:

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

The PRECAUTIONS section contains the following information regarding voriconazole administration in patients with hepatic insufficiency.

> **Patients with Hepatic Insufficiency**
> It is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B) receiving VFEND (see CLINICAL PHARMACOLOGY- — DOSAGE and ADMINISTRATION,]
>
> VFEND has not been studied in patients with severe cirrhosis (Child-Pugh Class C). VFEND has been associated with elevations in liver function tests and clinical signs of liver damage, such as jaundice, and should only be used in patients with severe hepatic insufficiency if the benefit outweighs the potential risk. Patients with hepatic insufficiency must be carefully monitored for drug toxicity.

The ADVERSE REACTIONS section contains a subsection entitled Overview, which includes the following statement:

> The treatment-related adverse events which most often led to discontinuation of voriconazole therapy were elevated liver function tests, rash, and visual disturbances (see hepatic toxicity under WARNINGS and discussion of Clinical Laboratory Values and dermatological and visual adverse events below).

Later in the ADVERSE REACTIONS section is a table of treatment-emergent adverse events of all causalities. Events with a rate > — adverse events of concern — the "All Therapeutic Studies"; the — and the "Aspergillosis" study populations. Only the portion of the table involving hepatic adverse events follows.

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	All Therapeutic Studies	Empirical Therapy Protocol —	Aspergillosis Protocols 307/602

Under the subsection entitled "Less Common Adverse Events" within the ADVERSE EVENTS section, the paragraph with the heading of "Digestive" includes the following liver-related adverse events: "...cholecystitis, cholelithiasis, GGT/LDH elevated, hepatic coma, hepatic failure, and hepatitis"

The ADVERSE EVENTS section also contains a subsection entitled "Clinical Laboratory Values", that contains the following information regarding liver function tests abnormalities, serious hepatic toxicity, and monitoring liver function tests.

Clinical Laboratory Values

The overall incidence of clinically significant transaminase abnormalities in the voriconazole clinical program was 13.4% (200/1493) of patients treated with voriconazole. Liver function test abnormalities may be associated with higher plasma concentrations and/or doses. The majority of abnormal liver function tests either resolved during treatment without dose adjustment or following dose adjustment, including discontinuation of therapy.

Voriconazole has been infrequently associated with cases of serious hepatic toxicity — cases of jaundice and rare cases of hepatitis and hepatic failure leading to death.

liver function tests during VFEND therapy should be monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of VFEND must be considered if clinical signs and symptoms consistent with liver disease develop that may be attributable to VFEND (see WARNINGS).

The subsection entitled "Clinical Laboratory Values" also contains two tables which show the number of patients with clinically significant changes in liver function tests in either study [redacted] or protocol 307/602 (invasive aspergillosis).

[redacted]

PROTOCOL 307/602
Clinically Significant Laboratory Test Abnormalities

	Criteria*	VORICONAZOLE	AMPHOTERICIN B**
		n/N (%)	n/N (%)
T. Bilirubin	>1.5x ULN	35/180 (19.4)	46/173 (26.6)
AST	>3.0x ULN	21/180 (11.7)	18/174 (10.3)
ALT	>3.0x ULN	34/180 (18.9)	40/173 (23.1)
Alk phos	>3.0x ULN	29/181 (16.0)	38/173 (22.0)

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

The DOSAGE AND ADMINISTRATION section contains the following information on voriconazole dosing:

[redacted]

Dosage Adjustment

If patient response is inadequate, the maintenance dose of [redacted] may be increased to [redacted] 300 mg every 12 hours [redacted] For patients less than 40 kg, the oral dose may be increased to 150 mg every 12 hours.

If patients are unable to tolerate treatment [redacted] reduce the intravenous dose [redacted] to 3 mg/kg every 12 hours and the oral dose by 50 mg steps to the 200 mg every 12 hours (or 100 mg every 12 hours for patients less than 40 kg) [redacted]

[redacted] phenytoin may be coadministered with VFEND if the maintenance dose of VFEND is increased to 5 mg/kg I.V. every 12 hours, or from 200mg to 400mg every 12 hours orally (100mg to 200mg every 12 hours orally in patients less than 40kg) (see CLINICAL PHARMACOLOGY, PRECAUTIONS-Drug Interactions).

[redacted] duration [redacted] the patient's clinical [redacted] response.

Also within the DOSAGE AND ADMINISTRATION section the Applicant has included a subsection entitled "Use in Patients With Hepatic Insufficiency", which includes the following regarding dose adjustment.

[redacted] patients [redacted] liver function tests (ALT, AST) (but continued monitoring of liver function tests for further elevations is recommended).

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

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

General Clinical Pharmacology

The pharmacokinetics of voriconazole in humans are non-linear due to saturation of its metabolism. A greater than proportional increase in exposure is observed with increasing dose. The estimated increase in exposure (AUCτ) that results from increasing the oral dose from 200 mg bid to 300 mg bid is 2.5-fold. Increasing the intravenous dose from 3 mg/kg bid to 4 mg/kg bid produces a 2.3-fold increase in exposure.

Voriconazole administered orally is estimated to be over 90% bioavailable, independent of gastric pH. Voriconazole exposure was reduced by approximately 25% when administered with high fat meals.

Voriconazole is metabolized by the hepatic cytochrome p450 isoenzymes CYP2C19, CYP2C9, and CYP3A4. CYP2C19 is significantly involved in the metabolism of voriconazole. CYP2C19 exhibits genetic polymorphisms. Poor metabolizers, on average, have a 4-fold higher voriconazole exposure than homozygous extensive metabolizers. Heterozygous extensive metabolizers have, on-average a 2-fold higher voriconazole exposure than their homozygous extensive metabolizer counterparts. The in vitro affinity of voriconazole for CYP3A4 is 100-fold lower than for CYP2C9 or CYP2C19. Inhibitors or inducers of these enzymes may either increase of decrease levels of voriconazole.

There is considerable interindividual variability of voriconazole pharmacokinetics based upon results from population pharmacokinetics from phase I studies.

Voriconazole is eliminated via hepatic metabolism with less than 2% of the dose excreted unchanged in the urine.

Based upon available data from the therapeutic studies, the median for the average and maximum plasma voriconazole concentrations in individual subjects was 2.5 mcg/mL ( ) and 3.8 mcg/mL ( ), respectively. In a multiple oral dose study, the reported C_{max} and AUCτ were 83% and 113% higher, respectively, in healthy young females than males. In a multiple oral dose study the reported C_{max} and AUCτ were 61% and 86% higher, respectively in healthy elderly males than in young males.

After a single oral dose of voriconazole 200 mg in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B), the reported AUC was 233% higher compared to subjects with normal hepatic function. Multiple oral dose study found that AUCτ was similar between subjects with Child-Pugh Class B (moderate hepatic impairment) receiving a maintenance dose of voriconazole 100 mg bid compared to normal subjects receiving 200 mg bid.

Pharmacokinetic and pharmacodynamic analyses of data from clinical trials identified a positive association between plasma voriconazole concentrations and transaminase and alkaline phosphatase abnormalities.

> **MO Comment:** For more details on the Clinical Pharmacology of voriconazole, please refer to the Dr. Colangelo's Biopharmaceutics Review.

Preclinical Studies and Hepatic Effects

Repeat-dose studies in rats and dogs demonstrated that the liver is a target organ for toxicity for voriconazole. A summary of the findings from preclinical studies with liver-related findings is provided in Table 1. The table provides abnormal findings that were noted in at least one of the animals in the dose group. In rat studies, oral voriconazole was associated with increased liver weights associated with centrilobular hypertrophy. Single cell hepatic necrosis was observed in the high dose group of the 24-month study in mice (96018) and in the 12-month study in dogs (96107). In addition liver adenomas were observed in the female animals in the 24-month oral study in rats (969631). Liver-related serum chemistry changes noted in some studies included increased alkaline phosphatase and alanine aminotransferase as well as decreased albumin and cholesterol. The calculated human equivalent dose (HED) at which these changes were observed to occur in some of the animals in the studies is provided. As noted in the accompanying table, the HED for many of the effects is within the range of the recommended clinical dose in terms of mg/kg/day.

> **MO Comment:** For more details on the preclinical pharmacology and toxicology of voriconazole, please refer to the Dr. McMaster's Pharmacology / Toxicology Review.

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Table 1. Summary of Liver-Related Findings from the Preclinical Studies

Study	Animal Dose w/ Finding (mg/kg/day)	Calculated Human Equivalent Dose (mg/kg/day)	Liver-Related Finding
14-day Rat IV Study # 90150	20mg/kg/day	3.2	-mild (minimal) centrilobular hypertrophy -proliferation of smooth endoplasmic reticulum -P450 induction (1.5 times control levels)
14-day Dog IV Study # 90149	10 → 6 mg/kg/day	5.5 (for 10) 3.3 (for 6)	-alkaline phosphatase increase in all high-dose animals (females>males) -minimal centrilobular hypertrophy and endoplasmic reticulum proliferation in one high dose male
	A dose-related 2 to 3-fold increase in P450 levels was also noted		
1-month Rat IV Study # 91076	5 mg/kg/day	0.8	-mild increase in liver weights in females
	10 mg/kg/day	1.6	-mild increase in liver weights in females -minimal centrilobular hypertrophy was observed in 3/10 females. -decreased bilirubin (high dose females)
1-month Rat IV with a supplementary 1-month reversibility arm Study # 93096	5mg/kg/day	0.8	Minimal to mild increase in liver weight in females
	10 mg/kg/day	1.6	-minimal to mild increase in liver weights -minimal centrilobular hypertrophy of the centrilobular hepatocytes in 5/10 males and 6/10 females. These changes were not observed after the 1-month reversibility period
1-month Dog IV with a supplementary 1-month reversibility arm Study # 93097	1 mg/kg/day	0.5	-increased liver weights
	3 mg/kg/day	1.6	-increased liver weights -small increases alkaline phosphatase
	6 mg/kg/day	3.3	-increased liver weights -small increases alkaline phosphatase -minimal hepatic centrilobular hypertrophy at the end of the dosing period but not 1-month post dosing
10-day maternal oral toxicity study in rats Study # 91025	40 mg/kg/day	6.5	-increased liver weight, enlargement, and centrilobular hypertrophy
	80 mg/kg/day	12.9	-increased liver weight, enlargement, and centrilobular hypertrophy
	120 mg/kg/day	19.4	-increased liver weight, enlargement, and centrilobular hypertrophy
12-day maternal oral toxicity study in rabbits Study # 919671	Highest dose 100 mg/kg/day	32.3 (no effects noted)	No liver findings noted
12-day teratology study in rats Study # 91111/12	60 mg/kg/day	9.7	-increased liver weights, enlargement, and centrilobular hypertrophy
24-month oral (in-diet) study in mice Study # 96018	30 mg/kg/day	2.4	-dose-related centrilobular hypertrophy and fatty change
	100 mg/kg/day	8.1	-dose-related centrilobular hypertrophy and fatty change -single cell necrosis, pigmentation and cystic changes -increased incidence of hepatocellular neoplasms -increased liver weights
24-month oral (in-diet) study in rats Study # 969631	18 mg/kg/day	2.9	-increased liver weights
	50 mg/kg/day	8.1	-increased liver weights, centrilobular hypertrophy, hepatocellular cystic changes in males, hepatocellular adenomas in females
12-month oral dog study Study # 96107	4 mg/kg/day and 8 mg/kg/day	2.2 and 4.4	-increased liver weights, centrilobular hypertrophy, minimal to moderate increase in plasma alkaline phosphatase and alanine aminotransferase, and decreases in albumin and cholesterol
	12 mg/kg/day	6.6	High grade centrilobular hypertrophy and increase in the number of multinucleated hepatocytes associated with single cell necrosis and subcapsular hemorrhage or fibrosis – findings indicative of hepatotoxicity. More pronounced increases in alkaline phosphatase and alanine aminotransferase.

Note: 200 mg q12h in a 70 kg human is 5.7 mg/kg/day
Conversion factors used to calculate human equivalent dose (HED)
Dose in mouse (mg/kg) x 12.3 = HED (mg/kg) Dose in rat (mg/kg) x 6.2 = HED (mg/kg)
Dose in rabbit (mg/kg) x 3.1 = HED (mg/kg) Dose in dog (mg/kg) x 1.8 = HED (mg/kg)
Source: Applicant's Study Reports for each of the study numbers referenced in this table

Clinical Hepatic Safety

The total safety database population for voriconazole at the time the safety update was submitted in June 2001 was 3276 subjects including patients and healthy volunteers from the phase I, II, and III studies conducted by Pfizer. The Applicant prepared analyses examining the results for safety in the following groups of patients:

- The pooled population of healthy volunteers from the clinical pharmacology studies
- Safety results for the three large comparative phase III studies
  - Study 305 – Esophageal Candidiasis
  - Study 603 – Empirical Therapy
  - Study 307/602 – Global Comparative Aspergillosis Study
- Safety results for the pooled safety databases
  - Therapeutic Studies – 8 phase III studies four active-controlled treatment studies (305, 307/602, and 608); one active-controlled empirical therapy study (603); and four non-comparative treatment studies (303, 304, 309, and 604). Note that data for Studies 608, 309, and 604 are interim data with a cut-off of 1 May 2001.
  - Compassionate Use – Includes patients in compassionate use studies and extension studies following therapeutic studies (Studies 301, 303A, 304A, 311, 312, 606, 607).
  - Overall Pooled– includes the Therapeutic Studies subgroup and the Compassionate Use subgroup. Note that a patient could be counted in both the Therapeutic Studies subgroup and the Compassionate Use subgroup if the patient was enrolled in one of the therapeutic studies and then subsequently enrolled in a compassionate use study. There were 145 voriconazole-treated patients that were counted in both the Therapeutic Studies and Compassionate Use subgroups.
  - Non-therapeutic Studies – This group includes a Phase I trial in patients the Multiple Dose Adult Patient Pharmacokinetic Study (673) and an early phase II Dose Ranging Oropharyngeal Candidiasis Study (302). These studies were discussed separately because of the atypical nature of treatment in these studies.

The populations for each of the aforementioned groups are provided in Table 2.

Table 2. Number of Patients and Volunteers in Studies Included in the Safety Subgroups		
Group	**Voriconazole**	**Comparator***
Clinical Pharmacology Studies	N = 443	Placebo N = 135
Phase 3 Comparative Studies*		
Esophageal Candidiasis Study (305)	N = 200	Fluconazole N = 191
Empirical Therapy Study (603)	N = 421	Liposomal amphotericin B N = 428
Global Comparative Aspergillosis Study (307/602)	N = 196	Amphotericin B (+ Other Licensed Antifungal Therapy) N = 185
Single Dose Pediatric Study (249)	N = 11	
Multiple Dose Pediatric Study (1007)	N = 28	
Pooled Safety Databases July 2001		
Therapeutic Studies#	N = 1493	N = 856 Amphotericin B formulations N = 665 Fluconazole N = 191
Compassionate Use	N = 597##	N/A
Overall Pooled**#	N = 2090**	N = 856 Amphotericin B formulations N = 665 Fluconazole N = 191
Non-Therapeutic Studies	N = 185	Fluconazole N = 6
Pooled Safety Databases Nov. 2000 NDA		
NDA Therapeutic Studies	N = 1214	
NDA All Voriconazole	N = 1946	
NDA Long-Term Therapy	N = 304	
Pediatric	N = 52	

N/A = not applicable
*The safety populations presented in this section include the Intention to Treat population for Study 305 and the Safety populations for Studies 307/602 and 603.
**This total includes 145 patients who were previously treated in clinical studies.
#It should be noted that the serious adverse events and deaths tables include 4 serious adverse events and 2 deaths from two studies, Japanese Non-Comparative Deep-Seated Mycoses Study (1001) and the Comparative Paracoccidioides Study (1010). Patients from these studies are not included in the denominators for these tables. Data from these studies are not included in any other safety tables.
##Includes 3 patients treated with compassionate use outside of formal protocols.
Source: Applicant's Table 8-1 from p. 101 of the Applicant's Advisory Committee Briefing Document

The results for liver-related safety will be presented for the patients populations described above within the appropriate sections of this review under the categories of Phase I and Phase II/III studies.

Phase I Studies

There were a total of 1,150 subjects who received voriconazole, placebo, or comparator in the voriconazole clinical pharmacology program. The analysis of safety from the clinical pharmacology program focuses on the Clinical Pharmacology Studies Pooled Safety Population which includes the 443 healthy volunteer subjects who received voriconazole and the 135 subjects who received placebo in studies where voriconazole was given alone (table 3). Data from the drug interaction studies and special population studies were not included in this analysis population.

Table 3. Disposition of Subjects in the Clinical Pharmacology Program

Group	Overall number of subjects	Subjects receiving voriconazole	Subjects receiving placebo[a]
Total*	1150	986	166
Pooled subjects[b]	509	443	135
Special population Patients[c]	150	144	0
Special population Japanese	80	71	12
Subjects in Interaction studies	365	310	0
Subjects in SBECD studies[d]	46	18	19

*Includes subjects receiving placebo and voriconazole in crossover studies.
[b]Primary healthy volunteer pooled safety population.
[c]Includes subjects with hepatic and renal impairment, and children and adults with hematological malignancy in PK studies.
[d]Primarily investigated the safety and PK of vehicle (sulfobutylether-beta-cyclodextrin; SBECD).
*Serious adverse events and deaths discussion includes additional studies: Suspension Bioequivalence Study (1019), Single Dose Comparative QTc Study #1 (1021), Single and Multiple Oral Dose Study in Japan (1022)
Source: Applicant's Table 8-4 from p104 of the Applicant's Advisory Committee Briefing Document

The population of 443 healthy volunteers from the phase I non-drug interaction studies included multiple dose and single dose studies in which patients received IV (n=167) or PO (n=368) voriconazole. Treatment durations were up to 14 days for IV voriconazole and 29 days for PO voriconazole. With the exception of Study 250, which enrolled 36 females and 18 elderly males, all of the 443 voriconazole-treated subjects and 135 placebo recipients were healthy young male volunteers.

Discontinuations due to adverse events in Phase 1 were similar between voriconazole (14/443; 3.2%) and placebo (3/135; 3.2%). Two volunteers in the voriconazole group (2/443; 0.5%) and one volunteer in the placebo group (1/135; 0.7%) discontinued due to abnormal liver function tests (LFTs). There were no deaths in the Clinical Pharmacology Studies Pooled Safety Population (CPSPSP). There were two serious adverse events in the Clinical Pharmacology Studies Pooled Safety Population, possible epileptic seizure in a placebo patient and appendicitis in a voriconazole-treated patient. In the other clinical pharmacology studies not included in the CPSPSP, there were 7 other serious adverse events; none were primary liver AEs. (Results from the clinical pharmacology studies involving pediatric patients are discussed in the section of this review discussing pediatric patients.)

The rate of laboratory abnormalities for liver analytes for the subjects in the CPSPSP is provided in Table 4. In this phase I study population of healthy subjects, abnormalities in liver function tests were reversible after discontinuation.

Table 4. Clinically Significant Renal and Hepatic Laboratory Abnormalities – Clinical Pharmacology Studies				
Laboratory Parameter	**Units**	**Criterion**	**Voriconazole n/N (%)**	**Placebo n/N (%)**
Total bilirubin	mg/dL	>1.5 x ULN	2/431 (0.5)	2/127 (1.6)
AST	IU/L	>3.0 x ULN	4/431 (0.9)	1/127 (0.8)
ALT	IU/L	>3.0 x ULN	5/431 (1.2)	0
Alkaline Phosphatase	IU/L	>3.0 x ULN	0	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = Upper Limit of Normal
Source: Adapted from the Applicant's Table 8-7 from p.107 of the Applicant's Advisory Committee Briefing Document

Study 230

Study 230 was a phase I, parallel group, double blind, randomized, placebo controlled, multiple dose escalation study in which healthy male subjects aged 18 to 42 years received intravenous, followed by oral voriconazole or placebo. The dosing regimens evaluated are outlined in Table 5.

Table 5. Dosing Regimens for Study 150-230				
Dosing	**Study Drug**	**Voriconazole Dose**		
		1st day	**2nd-7th Day**	**8th-14th Day***
Cohort 1, Period 1	voriconazole or placebo	6mg/kg iv bid SBECD 96mg/kg iv bid	3mg/kg bid SBECD 48mg/kg iv bid	200mg po bid placebo po bid
WASHOUT PERIOD 7 DAYS				
Cohort 1, Period 2	voriconazole or placebo	6mg/kg iv bid SBECD 96mg/kg iv bid	5mg/kg iv bid SBECD 80mg/kg iv bid	400mg po bid placebo po bid
Cohort 2	voriconazole or placebo	6mg/kg iv bid SBECD 96mg/kg iv bid	4mg/kg iv bid SBECD 64mg/kg iv bid	300mg po bid placebo po bid

* doses were given bid from 8th - 13th day and qd on 14th day.
Note: there were 14 subjects per group (vori, placebo) in Cohort 1 and 7 subjects per group in Cohort 2.
Source: NDA 21,266: Study Report for Protocol 150-230; p. 8

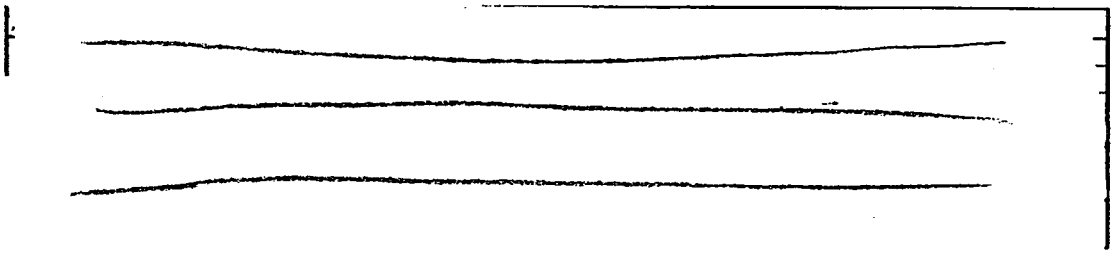
The pharmacokinetic results from the study are summarized in Table 6.

Table 6. Pharmacokinetic Results from Study 150-230						
	Low dose		**Medium dose**		**High dose**	
	3mg/kg	**200mg**	**4mg/kg**	**300mg**	**5mg/kg**	**400mg**
Plasma						
C_{max} ng/mL	3006	1885	5402	4839	7184	5272
AUCτ ng·h/mL	13919	9765	29467	30940	43374	37549
T_{max} h	1.07	1.50	1.04	1.43	1.02	1.81
Saliva						
C_{max} ng/mL	2081	1309	3353	2796	4308	3287
AUCτ ng·h/mL	8591	5970	19249	18634	24981	22047
T_{max} h	1.00	1.21	1.04	1.29	1.09	1.54

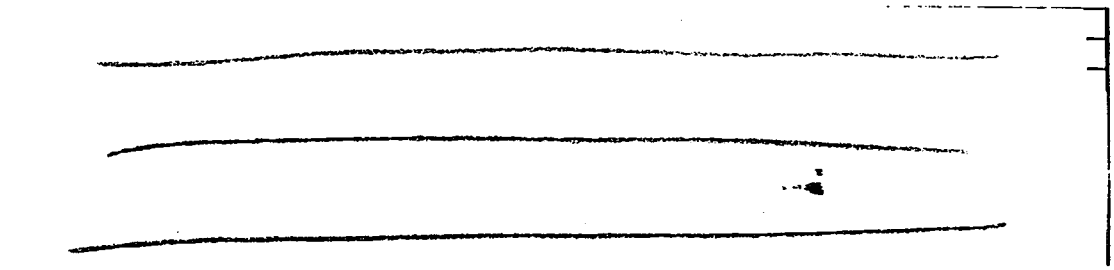
Source: NDA 21,266: Study Report for Protocol 150-230; p. 8

In Study 150-230 liver function abnormalities meeting the criteria for "clinically significant abnormal values"[5] were noted in 2 of the subjects in the highest dose group, one of whom was withdrawn on the 12th day of dosing during the second period (while receiving the 400 mg PO bid dose). In the 4 mg/kg IV followed by 300 mg PO bid group, one patient had clinically significant liver function abnormalities. There were no patients in the lowest dose voriconazole group with clinically significant abnormal LFTs.

The subject who was withdrawn from the highest dose group was subject 00110004. He had a clinically significant abnormal ALT and GGT. His ALT, AST, and GGT values are provided in Table 7. His alkaline phosphatase and T. Bilirubin remained normal throughout the duration of the study. The patient also had a negative serum HBsAg at Screening (Day –6).



The other subject in the high dose group with clinically significant abnormal liver function tests was subject 00110002 who had a clinically significant abnormal GGT. His ALT, AST, and GGT are provided in Table 8. His alkaline phosphatase and T. Bilirubin remained normal throughout the duration of the study except for a single reading of 1.6 mg/dL for T. Bili. (NR 0.2-1.3). The patient also had a negative serum HBsAg at Screening (Day –6).



The subject in the middle dose group with clinically significant liver function test abnormalities was subject 00110039, who had clinically significant abnormal values for ALT, AST, and GGT (Table 9). His T. Bilirubin and alkaline phosphatase remained normal for the duration of the study. He also had a negative HBsAg at Screening (Day -18).

[5] The Applicant defined the following levels of abnormality for the liver related analytes as "clinically significant abnormal laboratory values": T. Bilirubin >1.5xULN (where ULN = upper limit of normal); SGOT > 3xULN; SGPT > 3x ULN; GGT > 3xULN; Alkaline phosphatase > 3xULN.

[redacted]

MO Comment: With the pattern of clinically significant laboratory abnormalities occurring in the mid and higher dose groups and not in the low dose or placebo groups, a dose-response for abnormalities in ALT, AST, and GGT is suggested.

Other Analyses of Phase I data and Liver-related Laboratory Analytes

The Applicant fitted models to investigate the relationship between liver-related laboratory analytes and either AUC or C_{max}. The models examined either all observations for the liver analyte being evaluated or the last observation for the analyte being evaluated. The sponsor's models showed that AUC and C_{max} were strongly associated with ALT and in separate models a similarly strong association with AST. Models were also fitted for alkaline phosphatase that showed a positive association between AUC and C_{max} with alkaline phosphatase, but this association was not as strong as what was seen for AST or ALT. The results from these analyses were largely driven by results from patients from the previously discussed study 150-230. Models fitted to investigate a relationship between either AUC or C_{max} and T. bilirubin did not show a significant increase in percentage change in bilirubin with increasing C_{max} or AUC. Example curves for ALT, AST, and alkaline phosphatase are provided in the following sections (Figs. 1-3).

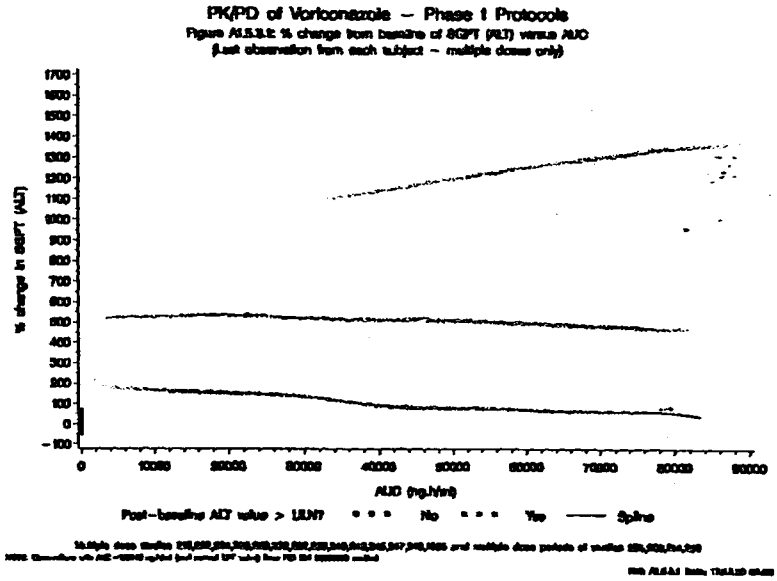


Figure 1. Percent change from baseline of SGPT (ALT) versus AUC

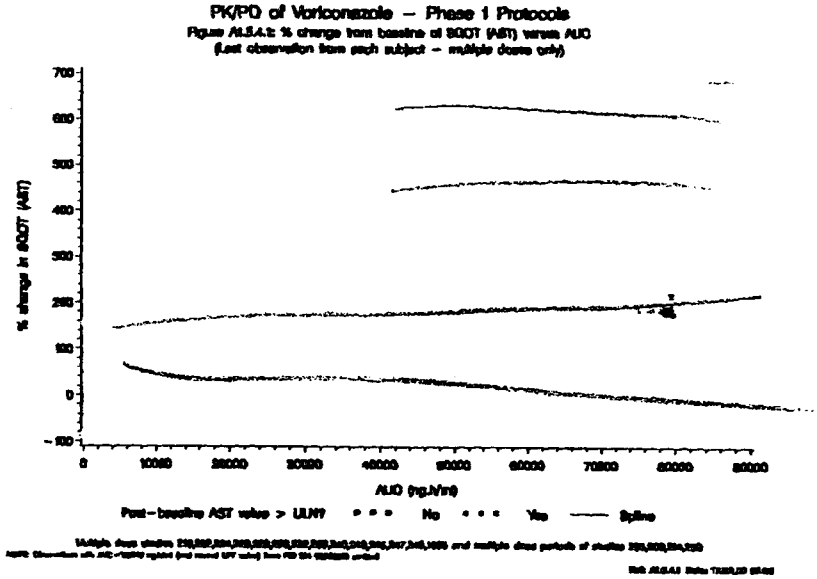


Figure 2. Percent change from baseline of SGOT (AST) versus AUC

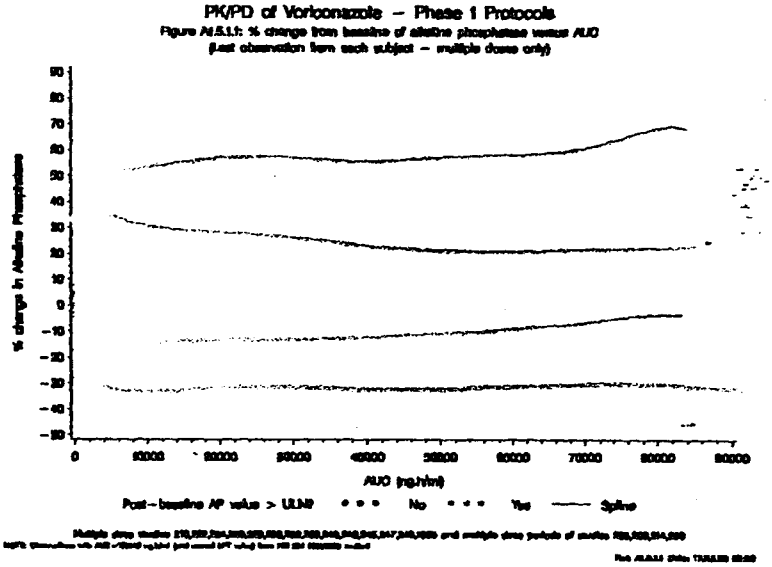


Figure 3. Percent change from baseline of Alkaline Phosphatase versus AUC

MO Comment: The results from the model fitting support an association between voriconazole and changes in ALT and AST. The model fitting for alkaline phosphatase also suggests an association between exposure and alkaline phosphatase level in the phase I multiple dose studies.

While not a phase I study, Study 302 provided some data that address dose-response and abnormalities of liver-related laboratory abnormalities. Therefore the results will be described within this section of this review. Study 302 was a double-blind dose ranging study of voriconazole for the treatment of oropharyngeal candidiasis. Patients were randomized to receive doses of oral voriconazole at 50 mg qd, 200 mg qd, or 200 mg po bid for a duration of 7 days. The results for abnormalities of liver-related laboratory analytes for this phase II study are provided in Table 10.

Table 10. Summary of LFT Abnormalities Study 302 – Phase II Dose Ranging Study of Voriconazole in Oropharyngeal Candidiasis

	Voriconazole 50mg qd		Voriconazole 200 mg qd		Voriconazole 200 mg bid	
AST and ALT ≤ ULN	16/21	76.2	26/33	78.8	13/29	44.8
AST or ALT ≥ ULN & < 2x ULN	4/21	19.0	5/33	15.2	11/29	37.9
AST or ALT ≥ 2x ULN & < 3x ULN	0/21	0.0	1/33	3.0	3/29	10.3
AST or ALT ≥ 3x ULN & < 5x ULN	1/21	4.8	1/33	3.0	2/29	6.9
AST or ALT ≥ 5x ULN & < 10x ULN	0/21	0.0	0/33	0.0	0/29	0.0
AST or ALT ≥ 10 x ULN	0/21	0.0	0/33	0.0	0/29	0.0
No AST or ALT data available	2		1		1	
T. Bili. ≤ ULN	18/21	85.7	31/32	96.9	28/29	96.6
T. Bili. ≥ ULN & < 2x ULN	2/21	9.5	1/32	3.1	1/29	3.4
T. Bili. ≥ 2x ULN & < 3x ULN	1/21	4.8	0/32	0.0	0/29	0.0
T. Bili. ≥ 3x ULN & < 5x ULN	0/21	0.0	0/32	0.0	0/29	0.0
T. Bili. ≥ 5x ULN & < 10x ULN	0/21	0.0	0/32	0.0	0/29	0.0
T. Bili. ≥ 10 x ULN	0/21	0.0	0/32	0.0	0/29	0.0
No T. Bili. Data available	2		2		1	
Concomitant (AST and ALT)≤ULN or T.Bili≤ULN	20/21	95.2	32/32	100.0	28/29	96.6
Concomitant (AST or ALT)>ULN and T.Bili>ULN	1/21	4.8	0/32	0.0	1/29	3.4
Concomitant (AST or ALT)>2xULN and T.Bili>2xULN	0/21	0.0	0/32	0.0	0/29	0.0
Concomitant (AST or ALT)>3xULN and T.Bili>3xULN	0/21	0.0	0/32	0.0	0/29	0.0
Concomitant (AST or ALT)>5xULN and T.Bili>5xULN	0/21	0.0	0/32	0.0	0/29	0.0
Concomitant (AST or ALT)>10xULN and T.Bili>10xULN	0/21	0.0	0/32	0.0	0/29	0.0
No Concomitant (AST or ALT) or T. Bili.	2		2		1	
Alk. Phos. ≤ ULN	35/38	92.1	41/44	93.2	38/44	86.4
Alk. Phos. ≥ ULN & < 2x ULN	3/38	7.9	3/44	6.8	6/44	13.6
Alk. Phos. ≥ 2x ULN & < 3x ULN	0/38	0.0	0/44	0.0	0/44	0.0
Alk. Phos. ≥ 3x ULN & < 5x ULN	0/38	0.0	0/44	0.0	0/44	0.0
Alk. Phos. ≥ 5x ULN & < 10x ULN	0/38	0.0	0/44	0.0	0/44	0.0
Alk. Phos. ≥ 10 x ULN	0/38	0.0	0/44	0.0	0/44	0.0
No Alk. Phos. Data available	3		1		1	

Source: Applicant's Tables from Response to FDA Query 086/10Aug01

MO Comment: The analysis of abnormalities of liver-related laboratory analytes from Study 302 supports an association between voriconazole dose and transaminase abnormalities. Within the limited number of patients with alkaline phosphatase abnormalities, the percentage of patients experiencing alkaline phosphatase abnormalities is greatest in the highest dose group.

Summary of Phase I Hepatic Findings

Data from the phase I studies and the dose-ranging phase II study (study 302) support a dose or exposure response relationship with voriconazole and transaminase increases and to a lesser extent alkaline phosphatase increases. There were two patients from the high dose group from study 230 that developed clinically significant abnormalities of at least one liver-related analyte (ALT or GGT). Hence these studies support an association between voriconazole exposure in humans and increases in transaminases and to a lesser degree alkaline phosphatase.

Phase II and III Clinical Studies

The phase II and III clinical studies in the voriconazole NDA database included both comparative and non-comparative studies. Most of the patients enrolled in these studies had other significant medical conditions. Almost all patients were receiving concomitant medications and typically received 20 or more concomitant medications while on study. Because of the complexities of the patient populations being evaluated, the liver-related safety results for the three large comparative phase III studies are described first (Study 307/602, Study 603, Study 305). Then the liver-related safety results for the other pooled safety populations are reviewed including the hepatic failure cases and the liver biopsy cases where study drug is noted as a possible contributing factor in the histopathologic report.

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Safety Data from Study 307/602

In the Global Comparative Aspergillosis Study 307/602, immunosuppressed patients with acute invasive aspergillosis were randomized to receive either voriconazole or amphotericin B deoxycholate. Patients receiving voriconazole were to receive at least 7 days of intravenous therapy and then could receive oral therapy for a total of 12 weeks with an option to extend to 16 weeks. Patients randomized to amphotericin B were to receive initial randomized therapy for a maximum duration of 12 weeks. Patients were allowed to switch to Other Licensed Antifungal Therapy (OLAT) if they failed to respond, experienced toxicity, or were unable to tolerate initial randomized therapy. OLAT was defined as any commercially available therapy approved for the treatment of aspergillosis or any unapproved therapy agent available by compassionate use. Patients could be treated with amphotericin B as OLAT but not voriconazole. Most patients in both treatment groups who were switched to OLAT received itraconazole. More voriconazole patients completed study on initial randomized therapy than amphotericin B patients. Patients were monitored for 16 weeks. Patients were to have newly diagnosed acute invasive aspergillosis. They were also allowed to receive up to 96 hours of prior antifungal therapy.

The majority of patients in each treatment group had malignant neoplasms of the lymphatic/hematopoietic tissues at baseline [voriconazole 114/196 (58.2%) and amphotericin B 108/185 (58.4%)].

The duration of treatment with initial randomized therapy for the safety population for Study 307/602 is shown in Table 11.

Table 11. Global Aspergillosis Study (307/602) - Duration of Initial Randomized Therapy (Elapsed) – Safety Population

Route of administration	Duration of therapy (days)* Median (range)	
	Voriconazole Initial Randomized Therapy (N = 196)	Amphotericin B Initial Randomized Therapy (N = 185)
Oral therapy	76 (2 – 232)	N/A
Intravenous	10 (2 – 85)	12 (1 – 84)
Total	73 (2 – 288)	12 (1 – 84)

N/A = not applicable
*Elapsed time
Source: Adapted from the Applicant's Table 8-8 from p.108 of the Applicant's Advisory Committee Briefing Document

The number of subject-days of drug exposure is shown in Table 12. The number of subject-days of voriconazole exposure (12,813 subject-days) is similar to the number of subject-days of exposure for amphotericin B plus OLAT following amphotericin B (11,243 subject-days). Therefore in some of the tables that follow, adverse events are presented for voriconazole treated patients and amphotericin B plus OLAT, where appropriate. For those patients who received OLAT in Study 307/602, over 60% received itraconazole.

> **MO Comment:** Because a considerable proportion of the amphotericin B population was receiving itraconazole as their OLAT, the rates for the comparator data for Ampho B + OLAT may be influenced by the predominant use of itraconazole as OLAT.

Table 12. Number of Subjects Treated and Subject-Days of Drug Exposure				
	VORICONAZOLE	OLAT (FOLLOWING VORICONAZOLE)	AMPHOTERICIN B	OLAT (FOLLOWING AMPHOTERICIN B)
Number of:	n	n	n	n
Subjects Treated	196	75	185	144
Subjects-Days of Drug Exposure	12813	2834	2896	8347
Note : There were 3 voriconazole and 6 Amphotericin B subjects who received OLAT with their IRT treatment, and have been summarized under their IRT period. Source Study Report 307/602 Table 6.1.1.1				

In Study 307/602 approximately one-quarter of the patients received either an autologous or allogeneic bone marrow or stem cell transplant. All patients received concomitant medications. The mean number of concomitant medications was 26 in the voriconazole arm and 21 in the amphotericin B arm.

Treatment Emergent Adverse Events – 307/602

Liver-related treatment emergent adverse events (TEAEs) of all causality are summarized in Table 13. For the voriconazole versus amphotericin B plus OLAT comparison there were slightly more adverse events of liver function tests abnormal, hepatic enzymes increased, and SGPT (ALT) increased reported in the voriconazole-treated patients while there were more adverse events in the categories of liver damage and bilirubinemia reported for patients in the amphotericin B plus OLAT group.

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Table 13. Global Comparative Aspergillosis Study (307/602) – Hepatic-Related Treatment Emergent Adverse Events by Treatment Regimen – Safety Population

COSTART Preferred Term	All Causality				All Causality			
	Voriconazole -> OLAT (N = 196)		Amphotericin B -> OLAT (N = 185)		Voriconazole (N = 196)		Amphotericin B -> OLAT (N = 185)	
	n	(%)	n	(%)	n	(%)	n	(%)
Liver Function Tests Abnormal	16	(8.2)	12	(6.5)	16	(8.2)	12	(6.5)
Hepatic Enzymes Increased	16	(8.2)	9	(4.9)	14	(7.1)	9	(4.9)
Liver Damage	8	(4.1)	8	(4.3)	5	(2.6)	8	(4.3)
Alkaline Phosphatase Increased	8	(4.1)	5	(2.7)	7	(3.6)	5	(2.7)
SGPT (ALT) Increased	7	(3.6)	2	(1.1)	6	(3.1)	2	(1.1)
Cholestatic Jaundice	6	(3.1)	4	(2.2)	4	(2.0)	4	(2.2)
Bilirubinemia	5	(2.6)	6	(3.2)	4	(2.0)	6	(3.2)
SGOT (AST) Increased	4	(2.0)	0	(0.0)	3	(1.5)	0	(0.0)
Jaundice	3	(1.5)	4	(2.2)	1	(0.5)	4	(2.2)
Cholecystitis	2	(1.0)	1	(0.5)	1	(0.5)	1	(0.5)
Hepatic Failure	2	(1.0)	1	(0.5)	1	(0.5)	1	(0.5)
GGT increased	2	(1.0)	0	(0.0)	2	(1.0)	0	(0.0)
LDH Increased	2	(1.0)	0	(0.0)	2	(1.0)	0	(0.0)
Hepatitis	2	(1.0)	0	(0.0)	2	(1.0)	0	(0.0)
Liver Tenderness	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)
Hepatomegaly	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.5)
Total # of Hepatic-Related Adverse Events	84	-	53	-	69	-	53	-

Source: Study Report 307/602, Table 6.1.3.2 & 6.1.3.1

Liver-related treatment emergent adverse events (TEAEs) judged by the investigator to be treatment-related are summarized in Table 14. In general, more liver-related hepatic AEs were judged as treatment-related among the voriconazole-treated patients than among the amphotericin B plus OLAT group. For the voriconazole versus amphotericin B plus OLAT comparison there were slightly more adverse events of liver function tests abnormal, hepatic enzymes increased, and alkaline phosphatase abnormal reported as treatment-related adverse events in the voriconazole-treated patients.

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Table 14. Global Comparative Aspergillosis Study (307/602) – Hepatic-Related Treatment Emergent Adverse Events by Treatment Regimen – Safety Population

COSTART Preferred Term	Treatment-Related				Treatment-Related			
	Voriconazole (N = 196)		Amphotericin B (N = 185)		Voriconazole (N = 196)		Amphotericin B -> OLAT (N = 185)	
	n	(%)	n	(%)	n	(%)	n	(%)
Liver Function Tests Abnormal	9	(4.6)	4	(2.2)	9	(4.6)	4	(2.2)
Hepatic Enzymes Increased	7	(3.6)	3	(1.6)	7	(3.6)	5	(2.7)
Liver Damage	2	(1.0)	2	(1.1)	2	(1.0)	2	(1.1)
Alkaline Phosphatase Increased	6	(3.1)	3	(1.6)	6	(3.1)	4	(2.2)
SGPT (ALT) Increased	3	(1.5)	1	(0.5)	3	(1.5)	1	(0.5)
Cholestatic Jaundice	4	(2.0)	0	(0.0)	4	(2.0)	0	(0.0)
Bilirubinemia	1	(0.5)	3	(1.6)	1	(0.5)	3	(1.6)
SGOT (AST) Increased	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)
Jaundice	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
GGT increased	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)
LDH Increased	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)
Hepatitis	1	(0.5)	0	(0.0)	1	(0.5)	0	(0.0)
Total # of Hepatic-Related Adverse Events	36	-	16	-	36	-	19	-

Source: Study Report 307/602, Table 6.1.3.2 & 6.1.3.1

Laboratory Abnormalities – 307/602

Laboratory abnormalities by study group are tabulated (Table 15). The proportion of patients with abnormalities of total bilirubin or alkaline phosphatase is slightly greater in the group of patients receiving amphotericin B and OLAT than in the voriconazole group.

Table 15. Global Comparative Aspergillosis Study (307/602) - Occurrence of Clinically Significant Hepatic Function Test Abnormalities – Safety Population

Clinically Significant Hepatic Function Test Abnormalities	Hepatic Laboratory Parameter	Voriconazole (N = 196) n (%)	Amphotericin B/OLAT (N = 185) n (%)
Without regard to baseline*	Total bilirubin	35/180 (19.4)	46/173 (26.6)
	AST	21/180 (11.7)	18/174 (10.3)
	ALT	34/180 (18.9)	40/173 (23.1)
	Alkaline Phosphatase	29/181 (16.0)	38/173 (22.0)
With normal baseline*	Total bilirubin	13/135 (9.6)	29/148 (19.6)
	AST	15/147 (10.2)	9/136 (6.6)
	ALT	18/120 (15.0)	20/115 (17.4)
	Alkaline Phosphatase	8/114 (7.0)	17/118 (14.4)
With abnormal baseline**	Total bilirubin	7/45 (15.6)	11/25 (44.0)
	AST	4/33 (12.1)	8/38 (21.1)
	ALT	11/60 (18.3)	13/58 (22.4)
	Alkaline Phosphatase	17/67 (25.4)	19/55 (34.5)

ALT = alanine transaminase; AST = aspartate transaminase; OLAT = Other Licensed Antifungal Therapy
*Clinically significant defined as: total bilirubin mg/dL > 1.5 x ULN; AST, ALT, alkaline phosphatase IU/ L > 3x ULN
**Clinically significant defined as: total bilirubin, AST, ALT, alkaline phosphatase > 1.5 x baseline
Source: Adapted from the Applicant's Table 8-52, p. 143 from the Applicant's Advisory Committee Briefing Document

LFT Abnormalities by Degree of Abnormality – 307/602

In the population of patients with normal transaminases and bilirubin at baseline, the proportion of patients with an abnormal AST or ALT is slightly greater in the amphotericin B/OLAT arm, but the proportion of patients with higher level changes is slightly greater for the voriconazole-treated patients (Table 16). Total bilirubin changes appear more frequently and the degree of elevation is greater in the amphotericin B/OLAT arm. The proportion of patients with abnormal concomitant changes in AST or ALT and T. Bilirubin is greater for the amphotericin B/OLAT arm. While a smaller proportion of voriconazole-treated patients had a normal value for alkaline phosphatase, a slightly greater proportion of Ampho B / OLAT patients have alkaline phosphatase abnormalities in the higher level categories.

Table 16. Summary of LFT Abnormalities by Degree of Abnormality - Study 307/602

	Voriconazole		Ampho B / OLAT	
	n/N	%	n/N	%
AST and ALT ≤ ULN	35/84	41.7	29/69	37.7
AST or ALT > ULN & < 2x ULN	25/84	29.8	27/69	39.1
AST or ALT ≥ 2x ULN & < 3x ULN	9/84	10.7	4/69	5.8
AST or ALT ≥ 3x ULN & < 5x ULN	9/84	10.7	6/69	8.7
AST or ALT ≥ 5x ULN & < 10x ULN	4/84	4.8	2/69	2.9
AST or ALT ≥ 10 x ULN	2/84	2.4	1/69	1.4
No AST or ALT data available	0		4	
T. Bili. ≤ ULN	69/83	83.1	46/68	67.6
T. Bili. > ULN & < 2x ULN	12/83	14.5	14/68	20.6
T. Bili. ≥ 2x ULN & < 3x ULN	1/83	1.2	3/68	4.4
T. Bili. ≥ 3x ULN & < 5x ULN	0/83	0.0	4/68	5.9
T. Bili. ≥ 5x ULN & < 10x ULN	1/83	1.2	1/68	1.5
T. Bili. ≥ 10 x ULN	0/83	0.0	0/68	0.0
No T. Bili. Data available	1		5	
Concomitant (AST and ALT)≤ULN or T.Bili≤ULN	73/83	88.0	54/68	79.4
Concomitant (AST or ALT)>ULN and T.Bili>ULN	8/83	9.6	10/68	14.7
Concomitant (AST or ALT)>2xULN and T.Bili>2xULN	1/83	1.2	3/68	4.4
Concomitant (AST or ALT)>3xULN and T.Bili>3xULN	0/83	0.0	1/68	1.5
Concomitant (AST or ALT)>5xULN and T.Bili>5xULN	1/83	1.2	0/68	0.0
Concomitant (AST or ALT)>10xULN and T.Bili>10xULN	0/83	0.0	0/68	0.0
No Concomitant (AST or ALT) or T. Bili.	1		5	
Alk. Phos. ≤ ULN	33/103	32.0	35/87	40.2
Alk. Phos. ≥ ULN & < 2x ULN	53/103	51.5	30/87	34.5
Alk. Phos. ≥ 2x ULN & < 3x ULN	10/103	9.7	11/87	12.6
Alk. Phos. ≥ 3x ULN & < 5x ULN	6/103	5.8	7/87	8.0
Alk. Phos. ≥ 5x ULN & < 10x ULN	1/103	1.0	3/87	3.4
Alk. Phos. ≥ 10 x ULN	0/103	0.0	1/87	1.1
No Alk. Phos. Data available	1		6	

Source: Applicant's Tables from Response to FDA Query 086/10Aug01

Discontinuations due to Adverse Events or Laboratory Abnormalities – 307/602

A greater proportion of patients receiving amphotericin B discontinued because of adverse events or laboratory abnormalities [voriconazole 40/196 (20.4%) vs.

amphotericin B 103/185 (55.7%)]. The liver-related reasons for discontinuation from initial randomized therapy are summarized in Table 17. The differences between treatment arms in the liver-related adverse events and number of patients discontinued from initial randomized therapy are small.

Table 17. Global Comparative Aspergillosis Study (307/602) – Reasons for Discontinuation from Initial Randomized Therapy Due to Liver-Related Adverse Events or Liver-Related Laboratory Abnormalities – Safety Population

	Voriconazole Initial Randomized Therapy (N = 196)		Amphotericin B Initial Randomized Therapy (N = 185)	
	n	(%)	n	(%)
Discontinuations due to adverse events				
Liver Damage	1	(0.5)	1	(0.5)
Discontinuations due to laboratory abnormalities				
Liver Function Test Abnormal	2	(1.0)	1	(0.5)
Hepatic enzymes Increased	1	(0.5)	0	(0.0)
Alkaline phosphatase Increased	1	(0.5)	0	(0.0)
SGPT (ALT) Increased	1	(0.5)	1	(0.5)
SGOT (AST) Increased	1	(0.5)	0	(0.0)
Bilirubinemia	1	(0.5)	2	(1.0)
Total # of hepatic-related adverse events or laboratory abnormalities leading to discontinuation	8	-	5	-
Total # of Patients with hepatic-related adverse events leading to discontinuation	7	(3.6)	5	(2.7)

ALT = alanine transaminase; AST = aspartate transaminase;
Source: Study Report 307/602: Tables 4.2.3 and 4.2.5 and from the Applicant's Table 8-10 from p. 109 of the Applicant's Advisory Committee Briefing Document.

MO Comment: The treatment discontinuation table examines discontinuation from initial randomized therapy. Two factors deserve mention when considering these data (1) that patients could be switched from amphotericin B deoxycholate IV to OLAT (2) the number of subject-days of exposure for amphotericin B was less than for voriconazole.

Serious Adverse Events – 307/602

The serious adverse events reported by treatment group are summarized in Table 18. There were more serious adverse events reported that involved hepatic-related adverse events in the voriconazole arm of the study.

Table 18. Global Comparative Aspergillosis Study (307/602) – Serious Adverse Events by Treatment Regimen – Safety Population

Preferred Event Term	Voriconazole (N = 196)		Amphotericin B (N = 185)	
	n	(%)	n	(%)
SGPT (ALT) Increased	2	(1.0)	1	(0.5)
SGOT (AST) Increased	2	(1.0)	0	(0.0)
Hepatocellular Damage	1	(0.5)	1	(0.5)
Cholecystitis	1	(0.5)	0	(0.0)
GGT increased	1	(0.5)	0	(0.0)
Hepatitis	1	(0.5)	0	(0.0)
Bilirubinemia	1	(0.5)	0	(0.0)
Alkaline Phosphatase Increased	0	(0.0)	1	(0.5)
Hepatic Failure	0	(0.0)	1	(0.5)
Total Number of Serious Hepatic-Related Adverse Events	9	-	4	-
Total Number of Patients Experiencing Serious Hepatic-Related Adverse Events	6	(3.1)	3	(1.6)

Source: Study Report 307/602, Table 6.4.1 and Table 6.4.2
Note: A Case is a single event or a series of related events not separated in time occurring in a single subject. A Case coded to several body systems may be counted as separate events and may include both serious and non-serious events.

The individual listings of cause of death within 30-days of the end-of-therapy for patients in Study 307/602 were reviewed. There was one patient in the study with a cause of death that specifically included liver failure. This patient received amphotericin B deoxycholate and had a cause of death of "progression of non-Hodgkin's lymphoma; liver failure." Review of the listings of cause of death for deaths occurring greater than 30-days after end-of-therapy did not reveal any causes of death citing primarily a liver disorder as the cause of death. Hepatic failure cases are reviewed in the section of this review titled Reports of Hepatic Failure Cases.

Conclusions – 307/602

In the voriconazole arm there were no marked differences in the reporting rates for hepatic-related adverse events of all causality. However, investigators more frequently consider these hepatic adverse events to be treatment-related among voriconazole-treated patients. Analysis of liver-related laboratory test found that elevations in transaminases were similar between treatment groups. Elevations of T. bilirubin were more frequent among patients in the amphotericin B arm of the study. Similarly, combined elevations of transaminases and bilirubin were infrequent, but slightly more common in the amphotericin B arm of the study. The occurrence of clinically significant abnormal alkaline phosphatase laboratory values was more frequent among patients in the amphotericin B arm of the study. Patients experiencing a serious adverse event involving a hepatic-related adverse event were more frequently reported in the voriconazole arm of the study.

Safety Data from Study 603

In the Empirical Therapy Study (603), patients with persistent fever and neutropenia were randomized to either voriconazole or liposomal amphotericin B (AmBisome®). Patients were treated until three days after recovery from neutropenia or for up to 12 weeks, in the event of a confirmed fungal infection. The median duration of intravenous treatment with study drug was similar for voriconazole and liposomal amphotericin B treated patients (6 and 7 days, respectively) (Table 19). Ninety-two of the voriconazole-treated patients received oral treatment, with a median duration of 6 days. Approximately half of the patients enrolled underwent autologous or allogeneic stem cell or bone marrow transplantation. All patients received concomitant medications with the mean number of concomitant medications of 23 for the voriconazole group and 24 for the liposomal amphotericin B group.

Table 19. Empirical Study (603) - Duration of Initial Randomized Therapy (Elapsed) – Safety Population

Route of administration	Duration of therapy (days)* Median (range)	
	Voriconazole Initial Randomized Therapy (N = 421)	AmBisome Initial Randomized Therapy (N = 428)
Intravenous	6 (1 – 46)	7 (1 – 84)
Oral therapy	6 (1 – 95)	N/A
Total	7 (1 – 133)	7 (1 – 84)

N/A = not applicable
*Elapsed time
Source: adapted from the Applicant's Table 3.1.2 from the Study Report for Study 603

Treatment Emergent Adverse Events – 603

Liver-related treatment emergent adverse events (TEAEs) of all causality are summarized in table 20. For the voriconazole versus AmBisome® comparison there were more adverse events of bilirubinemia and jaundice reported among the patients in the AmBisome arm of the study. The adverse event of liver function tests abnormal was reported at a similar frequency between treatment groups. The adverse events of alkaline phosphatase increased, SGPT (ALT) increased, hepatic enzymes increased, and SGOT (AST) increased were reported more frequently in voriconazole-treated patients. The total number of hepatic-related adverse events of all causalities were similar between treatment groups.

Table 20. Empirical Study (603) – Treatment Emergent Adverse Events of All Causalities by Treatment Regimen – Safety Population				
COSTART Preferred Term	**Voriconazole (N = 421)**		**AmBisome (N = 428)**	
	n	**(%)**	**n**	**(%)**
Bilirubinemia	23	(5.5)	32	(7.5)
Jaundice	22	(5.2)	37	(8.6)
Liver Function Tests Abnormal	15	(3.6)	14	(3.3)
Alkaline Phosphatase Increased	10	(2.4)	4	(0.9)
SGPT (ALT) Increased	8	(1.9)	5	(1.2)
Hepatic Enzymes Increased	8	(1.9)	2	(0.5)
SGOT (AST) Increased	7	(1.7)	4	(0.9)
Hepatomegaly	4	(1.0)	7	(1.6)
Cholestatic Jaundice	3	(0.7)	2	(0.5)
LDH Increased	3	(0.7)	1	(0.2)
Liver Damage	3	(0.7)	1	(0.2)
Hepatic Failure	2	(0.5)	4	(0.9)
Cholecystitis	2	(0.5)	2	(0.5)
Cholelithiasis	2	(0.5)	2	(0.5)
Hepatosplenomegaly	2	(0.5)	1	(0.2)
Liver Tenderness	2	(0.5)	0	(0.0)
Bilirubinuria	0	(0.0)	1	(0.2)
Hepatitis	0	(0.0)	1	(0.2)
Total # of Hepatic-Related Adverse Events	116		120	
Source: Study Report 603, Table 6.1.3				

Liver-related treatment emergent adverse events (TEAEs) judged by the investigator to be treatment-related are summarized in Table 21. More adverse events in the categories of liver function tests abnormal, alkaline phosphatase increased, SGPT (ALT) increased, hepatic enzymes increased, and SGOT (AST) increased were reported as being treatment-related among voriconazole-treated patients. More of the hepatic-related adverse events were reported as treatment-related for voriconazole treated patients than for comparator-treated patients.

Table 21. Empirical Study (603) – Treatment-Related* Treatment Emergent Adverse Events by Treatment Regimen – Safety Population				
COSTART Preferred Term	**Voriconazole (N = 421)**		**AmBisome (N = 428)**	
	n	**(%)**	**n**	**(%)**
Bilirubinemia	5	(1.2)	5	(1.2)
Jaundice	1	(0.2)	2	(0.5)
Liver Function Tests Abnormal	8	(1.9)	4	(0.9)
Alkaline Phosphatase Increased	4	(1.0)	0	(0.0)
SGPT (ALT) Increased	6	(1.4)	1	(0.2)
Hepatic Enzymes Increased	3	(0.7)	0	(0.0)
SGOT (AST) Increased	6	(1.4)	0	(0.0)
Cholestatic Jaundice	1	(0.2)	0	(0.0)
LDH Increased	1	(0.2)	0	(0.0)
Liver Damage	1	(0.2)	1	(0.2)
Cholelithiasis	1	(0.2)	0	(0.0)
Hepatosplenomegaly	1	(0.2)	0	(0.0)
Total # of Hepatic-Related Adverse Events	38	-	13	-
Source: Study Report 603, Table 6.2.3 *As determined by the study investigators				

Laboratory Abnormalities– 603

Laboratory abnormalities by study group are tabulated (Table 22). Across the groups of patients analyzed, the proportion of patients with abnormalities of total bilirubin is greater in the group of patients receiving AmBisome than in the voriconazole group. There were no marked differences in changes for the other liver-related values by treatment group in this analysis.

Table 22. Empirical Therapy Study (603/MSG42) - Occurrence of Clinically Significant Hepatic Function Test Abnormalities – Intention to Treat Population			
Clinically Significant Hepatic Function Test Abnormalities	**Hepatic Laboratory Parameter**	**Voriconazole (N = 421) n (%)**	**AmBisome (N = 428) n (%)**
Without regard to baseline*	Bilirubin	106/400 (26.5)	128/393 (32.6)
	AST	22/396 (5.6)	17/393 (4.3)
	ALT	30/385 (7.8)	25/374 (6.7)
	Alkaline phosphatase	27/399 (6.8)	26/394 (6.6)
With normal baseline*	Bilirubin	33/282 (11.7)	48/276 (17.4)
	AST	15/364 (4.1)	14/363 (3.9)
	ALT	18/330 (5.5)	18/318 (5.7)
	Alkaline phosphatase	10/317 (3.2)	14/326 (4.3)
With abnormal baseline**	Bilirubin	36/118 (30.5)	42/117 (35.9)
	AST	5/32 (15.6)	3/30 (10.0)
	ALT	7/55 (12.7)	7/56 (12.5)
	Alkaline Phosphatase	12/82 (14.6)	9/68 (13.2)
ALT = alanine transaminase; AST = aspartate transaminase *Clinically significant defined as: total bilirubin mg/dL > 1.5 x ULN; AST, ALT, alkaline phosphatase IU/ L > 3 x ULN **Clinically significant defined as: total bilirubin, AST, ALT, alkaline phosphatase > 1.5 x baseline Source: adapted from the Applicant's Table 8-53 from p.143 of the Applicant's Advisory Committee Briefing Document			

LFT Abnormalities by Degree of Abnormality – 603

In the population of patients with normal transaminases and bilirubin at baseline, a slightly greater proportion of voriconazole-treated patients had an abnormal AST or ALT (Table 23.). More AmBisome-treated patients had abnormal T. bilirubin levels (mostly lower level elevations). Concomitant elevations in T. Bilirubin and ALT or AST above the upper limits of normal occurred in a similar proportion of patients by treatment arm. However, there is a slightly greater proportion of patients with higher level elevations of T. Bilirubin and ALT or AST in the voriconazole treatment arm. Alkaline phosphatase elevations occurred slightly more frequently in the AmBisome treatment arm – a trend that in general is found throughout the ranges evaluated.

Table 23. Summary of LFT Abnormalities by Treatment Regimen - Study 603

	Voriconazole		AmBisome	
	n/N	%	n/N	%
AST and ALT ≤ ULN	154/233	66.1	160/226	70.8
AST or ALT ≥ ULN & < 2x ULN	52/233	22.3	45/226	19.9
AST or ALT ≥ 2x ULN & < 3x ULN	11/233	4.7	11/226	4.9
AST or ALT ≥ 3x ULN & < 5x ULN	11/233	4.7	7/226	3.1
AST or ALT ≥ 5x ULN & < 10x ULN	4/233	1.7	3/226	1.3
AST or ALT ≥ 10 x ULN	1/233	0.4	0/226	0.0
No AST or ALT data available	10		17	
T. Bili. ≤ ULN	186/226	82.3	161/218	73.9
T. Bili. ≥ ULN & < 2x ULN	23/226	10.2	37/218	17.0
T. Bili. ≥ 2x ULN & < 3x ULN	5/226	2.2	12/218	5.5
T. Bili. ≥ 3x ULN & < 5x ULN	8/226	3.5	3/218	1.4
T. Bili. ≥ 5x ULN & < 10x ULN	4/226	1.8	3/218	1.4
T. Bili. ≥ 10 x ULN	0/226	0.0	2/218	0.9
No T. Bili. Data available	17		25	
Concomitant (AST and ALT)≤ULN or T.Bili≤ULN	200/225	88.9	192/218	88.1
Concomitant (AST or ALT)>ULN and T.Bili>ULN	17/225	7.6	23/218	10.6
Concomitant (AST or ALT)>2xULN and T.Bili>2xULN	4/225	1.8	1/218	0.5
Concomitant (AST or ALT)>3xULN and T.Bili>3xULN	4/225	1.8	1/218	0.5
Concomitant (AST or ALT)>5xULN and T.Bili>5xULN	0/225	0.0	1/218	0.5
Concomitant (AST or ALT)>10xULN and T.Bili>10xULN	0/225	0.0	0/218	0.0
No Concomitant (AST or ALT) or T. Bili.	18		25	
Alk. Phos. ≤ ULN	208/298	69.8	197/308	64.0
Alk. Phos. > ULN & < 2x ULN	73/298	24.5	84/308	27.3
Alk. Phos. ≥ 2x ULN & < 3x ULN	7/298	2.3	14/308	4.5
Alk. Phos. ≥ 3x ULN & < 5x ULN	6/298	2.0	10/308	3.2
Alk. Phos. ≥ 5x ULN & < 10x ULN	4/298	1.3	3/308	1.0
Alk. Phos. ≥ 10 x ULN	0/298	0.0	0/308	0.0
No Alk. Phos. Data available	12		24	

Source: Applicant's Tables from Response to FDA Query 086/10Aug01

Discontinuations due to AEs or Laboratory Abnormalities – 603

The liver-related reasons for discontinuation from study therapy are summarized in Table 24. More liver-related adverse events were reported for patients discontinued from voriconazole therapy than for comparator.

Table 24. Empirical Study 603 – Reasons for Discontinuation from Study Therapy due to Liver-Related Adverse Events – Safety Population				
COSTART Preferred Term	Voriconazole (N = 421)		AmBisome (N = 428)	
	n	(%)	n	(%)
Discontinuations due to adverse events				
SGPT (ALT) Increased	1	(0.2)	1	(0.2)
Cholestatic Jaundice	1	(0.2)	0	(0.0)
Hepatic Failure	1	(0.2)	0	(0.0)
Jaundice	1	(0.2)	0	(0.0)
Bilirubinemia	1	(0.2)	0	(0.0)
Liver Function Tests Abnormal	1	(0.2)	0	(0.0)
Discontinuations due to laboratory abnormalities				
Liver Damage	1	(0.2)	0	(0.0)
Liver Function Test Abnormal	2	(0.5)	4	(0.9)
Hepatic enzymes Increased	1	(0.2)	1	(0.2)
SGOT (AST) Increased	1	(0.2)	0	(0.0)
Bilirubinemia	2	(0.5)	1	(0.2)
Total Number of Hepatic-Related Adverse Events or Laboratory Abnormalities	13	-	7	-
Total Number of Patients with Hepatic-Related Adverse Events or Laboratory Abnormalities	11	(2.6)	7	(1.6)

ALT = alanine transaminase; AST = aspartate transaminase
Source: Study Report 603: Table 4.2.1, 4.2.3
Note: A patient may have had more than one AE leading to discontinuation.

Serious Adverse Events – 603

The serious adverse events reported by treatment group are summarized in Table 25. There were more serious adverse events reported that involved hepatic-related adverse events in the voriconazole arm of the study.

Table 25. Empirical Study (603) – Serious Adverse Events by Treatment Regimen – Safety Population

Preferred Event Term	Voriconazole (N = 421)		AmBisome (N = 428)	
	n	(%)	n	(%)
Bilirubinemia	7	(1.7)	0	(0.0)
Hepatic Failure	5	(1.2)	5	(1.2)
SGOT (AST) Increased	2	(0.5)	2	(0.5)
SGPT (ALT) Increased	2	(0.5)	0	(0.0)
Hepatitis	1	(0.2)	2	(0.5)
Alkaline Phosphatase Increased	1	(0.2)	1	(0.2)
Cholecystitis	1	(0.2)	1	(0.2)
Cholelithiasis	1	(0.2)	0	(0.0)
Hepatic Necrosis	1	(0.2)	0	(0.0)
Hepatitis Cholestatic	1	(0.2)	0	(0.0)
Hepatitis Infectious	1	(0.2)	0	(0.0)
Hepatocellular Damage	1	(0.2)	0	(0.0)
GGT increased	0	(0.0)	1	(0.2)
Total Number of Hepatic-Related Serious Adverse Events	24	-	12	-
Total Number of Patients with Hepatic-Related Serious Adverse Events	19	(4.5)	10	(2.3)

Source: Study Report 603, Table 6.4.1
Note: A Case is a Single Event or a Series of Related Events not Separated in Time Occurring in a Single Subject. A Case Coded to Several Body Systems May be Counted as Separate Events and May Include Both Serious and Non-Serious Events.

The individual listings of cause of death within 30-days of the end-of-therapy for patients in Study 603 were reviewed. There was one patient in the study with a cause of death that specifically included liver failure. This patient received AmBisome and had a cause of death of "liver failure; progression of graft vs. host disease." Review of the listings of cause of death for deaths occurring greater than 30-days after end-of-therapy did not reveal any causes of death citing a primary liver disorder as the cause of death. Hepatic failure cases are reviewed in the section of this review titled Reports of Hepatic Failure Cases.

Conclusions – 603

For hepatic-related adverse events of all causality, bilirubinemia and jaundice were reported more frequently in patients randomized to AmBisome. Alkaline phosphatase increased, SGPT (ALT) increased, hepatic enzymes increased, and SGOT (AST) increased were reported more frequently among patients randomized to voriconazole. When examining the treatment-related (as determined by the study investigator) adverse events, liver function tests abnormal, alkaline phosphatase increased, SGPT (ALT) increased, hepatic enzymes increased, and SGOT (AST) increased, were reported more frequently in the voriconazole arm than in comparator-treated patients. Analysis of liver-related laboratory test found no marked differences in elevations in transaminases between treatment groups. Elevations of T. bilirubin were more frequent among patients in the AmBisome arm of the study. Combined elevations of transaminases and bilirubin greater than the upper limit of normal occurred in a similar proportion of patients.

However, there was a slightly greater proportion of patients with higher level elevations of T. Bilirubin and ALT or AST in the voriconazole treatment arm. More liver-related adverse events led to a greater number of discontinuations of treatment for voriconazole than comparator-treated patients. Patients experiencing a serious adverse event involving a hepatic-related adverse event were more frequently reported in the voriconazole arm of the study.

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Table 27. Esophageal Candidiasis (305) – Treatment-Related* Treatment Emergent Adverse Events – by Treatment Regimen – Safety Population				
COSTART Preferred Term	Voriconazole 200 mg po bid (N = 200)		Fluconazole 200 mg po qd (N = 191)	
	n	(%)	n	(%)
Alkaline Phosphatase Increased	10	(5.0)	3	(1.6)
SGOT (AST) Increased	8	(4.0)	2	(1.0)
Liver Function Tests Abnormal	6	(3.0)	2	(1.0)
SGPT (ALT) Increased	6	(3.0)	2	(1.0)
Cholestatic Jaundice	3	(1.5)	0	(0.0)
Hepatic Enzymes Increased	3	(1.5)	0	(0.0)
Hepatitis	2	(1.0)	0	(0.0)
Bilirubinemia	1	(0.5)	0	(0.0)
GGT Increased	1	(0.5)	0	(0.0)
Jaundice	1	(0.5)	0	(0.0)
Total # of Hepatic-Related Adverse Events	41		9	
Source: Study Report 305, Table 6.1.3 *As determined by the study investigators				

Laboratory Abnormalities – 305

More voriconazole-treated patients had clinically significant abnormal AST and ALT laboratory values (Table 28). To a lesser degree more voriconazole-treated patients had elevations in alkaline phosphatase (Table 28).

Table 28. Esophageal Candidiasis Study (305) - Occurrence of Clinically Significant Hepatic Function Test Abnormalities – Intention to Treat Population			
Clinically Significant Hepatic Function Test Abnormalities	Hepatic Laboratory Parameter	Voriconazole (N = 200) n (%)	Fluconazole (N = 191) n (%)
Without regard to baseline*	Bilirubin	8/185 (4.3)	7/186 (3.8)
	AST	38/187 (20.3)	15/186 (8.1)
	ALT	20/187 (10.7)	12/186 (6.5)
	Alkaline Phosphatase	19/187 (10.2)	14/186 (7.5)
With normal baseline*	Bilirubin	4/174 (2.3)	5/179 (2.8)
	AST	7/93 (7.5)	3/102 (2.9)
	ALT	8/119 (6.7)	4/139 (2.9)
	Alkaline Phosphatase	7/128 (5.5)	3/140 (2.1)
With abnormal baseline**	Bilirubin	0/11	0/7
	AST	24/94 (25.5)	9/84 (10.7)
	ALT	7/68 (10.3)	6/47 (12.8)
	Alkaline Phosphatase	9/59 (15.3)	4/46 (8.7)
ALT = alanine transaminase; AST = aspartate transaminase *Clinically significant defined as: total bilirubin mg/dL > 1.5 x ULN; AST, ALT, alkaline phosphatase IU/ L > 3 x ULN **Clinically significant defined as: total bilirubin, AST, ALT, alkaline phosphatase > 1.5 x baseline Source: Adapted from the Applicant's Table 8-54, p. 144 from the Applicant's Advisory Committee Briefing Document			

LFT Abnormalities by Degree of Abnormality – 305

In the population of patients with normal transaminases and bilirubin at baseline, a greater proportion of voriconazole-treated patients had an abnormal AST or ALT (Table 29). This trend extends as one examines higher levels of elevations of AST or

ALT. Elevations in T. Bilirubin were similar across both treatment groups. Concomitant elevations in AST or ALT and T. Bilirubin were infrequent in both treatment groups. The greater proportion of voriconazole-treated patients with elevations in alkaline phosphatase was in general, found through the range of elevations evaluated.

Table 29. Study 305 Summary of LFT Abnormalities

	Voriconazole		Fluconazole	
	n/N	%	n/N	%
AST and ALT ≤ ULN	35/76	46.1	57/92	62.0
AST or ALT ≥ ULN & < 2x ULN	28/76	36.8	31/92	33.7
AST or ALT ≥ 2x ULN & < 3x ULN	7/76	9.2	2/92	2.2
AST or ALT ≥ 3x ULN & < 5x ULN	4/76	5.3	2/92	2.2
AST or ALT ≥ 5x ULN & < 10x ULN	1/76	1.3	0/92	0.0
AST or ALT ≥ 10 x ULN	1/76	1.3	0/92	0.0
No AST or ALT data available	7		4	
T. Bili. ≤ ULN	72/74	97.3	90/92	97.8
T. Bili. ≥ ULN & < 2x ULN	1/74	1.4	1/92	1.1
T. Bili. ≥ 2x ULN & < 3x ULN	0/74	0.0	1/92	1.1
T. Bili. ≥ 3x ULN & < 5x ULN	0/74	0.0	0/92	0.0
T. Bili. ≥ 5x ULN & < 10x ULN	1/74	1.4	0/92	0.0
T. Bili. ≥ 10 x ULN	0/74	0.0	0/92	0.0
No T. Bili. Data available	9		4	
Concomitant (AST and ALT)≤ULN or T.Bili≤ULN	72/74	97.3	91/92	98.9
Concomitant (AST or ALT)>ULN and T.Bili>ULN	2/74	2.7	1/92	1.1
Concomitant (AST or ALT)>2xULN and T.Bili>2xULN	0/74	0.0	0/92	0.0
Concomitant (AST or ALT)>3xULN and T.Bili>3xULN	0/74	0.0	0/92	0.0
Concomitant (AST or ALT)>5xULN and T.Bili>5xULN	0/74	0.0	0/92	0.0
Concomitant (AST or ALT)>10xULN and T.Bili>10xULN	0/74	0.0	0/92	0.0
No Concomitant (AST or ALT) or T. Bili.	9		4	
Alk. Phos. ≤ ULN	79/128	61.7	106/141	75.2
Alk. Phos. ≥ ULN & < 2x ULN	36/128	28.1	32/141	22.7
Alk. Phos. ≥ 2x ULN & < 3x ULN	7/128	5.5	0/141	0.0
Alk. Phos. ≥ 3x ULN & < 5x ULN	4/128	3.1	1/141	0.7
Alk. Phos. ≥ 5x ULN & < 10x ULN	2/128	1.6	1/141	0.7
Alk. Phos. ≥ 10 x ULN	0/128	0.0	1/141	0.7
No Alk. Phos. Data available	9		4	
Source: Applicant's Tables from Response to FDA Query 086/10Aug01				

Discontinuations due to AEs or Laboratory Abnormalities

The liver-related adverse events or laboratory abnormalities leading to discontinuations in study therapy are summarized in Table 30. Hepatic-related adverse events leading to discontinuation of study therapy were reported more frequently among voriconazole-treated patients. A greater proportion of voriconazole-treated patients were discontinued from study therapy for hepatic-related adverse events or laboratory abnormalities.

Table 30. Esophageal Candidiasis Study (305) – Treatment-Emergent Hepatic Adverse Events or Laboratory Abnormalities Leading to Discontinuation– Intention to Treat Population				
Hepatic Adverse Events or Laboratory Abnormalities Leading to Discontinuation	**Voriconazole N = 200 n (%)**		**Fluconazole N = 191 n (%)**	
Alkaline phosphatase increased	4	(2.0)	3	(1.6)
Cholestatic jaundice	2	(1.0)	0	(0.0)
Hepatitis	1	(0.5)	0	(0.0)
Jaundice	1	(0.5)	0	(0.0)
Liver Function Tests Abnormal	1	(0.5)	0	(0.0)
Hepatic Enzymes Increased	1	(0.5)	0	(0.0)
Total Number of Hepatic-Related Adverse Events of Laboratory Abnormalities	10	-	3	-
Total Number of Patients with Hepatic-Related Adverse Events of Laboratory Abnormalities	7	(3.5)	3	(1.6)
Source: Study 305 Study Report, Table 4.2.3				

Serious Adverse Events – 305

The serious adverse events reported by treatment group are summarized in Table 31. Although the total number of events is small, there were more serious adverse events reported that involved hepatic related adverse events in the voriconazole arm of the study.

Table 31. Empirical Study (305) – Serious Adverse Events by Treatment Regimen – Safety Population				
Preferred Event Term	**Voriconazole (N = 200)**		**Fluconazole (N = 191)**	
	n	**(%)**	**n**	**(%)**
Cholecystitis	1	(0.5)	0	(0.0)
Hepatic Function Abnormal	1	(0.5)	0	(0.0)
Hepatitis	1	(0.5)	0	(0.0)
Total Number of Hepatic-Related Serious Adverse Events	3	-	0	-
Total Number of Patients with Hepatic-Related Serious Adverse Events	3	1.5	0	0.0
Source: Study Report 305, Table 6.4.1				

The individual listings of cause of death within 30-days of the end-of-therapy for patients in Study 305 were reviewed. There were no patients in the study with a cause of death that specifically included liver failure. Review of the listings of cause of death for deaths occurring greater than 30-days after end-of-therapy did not reveal any causes of death citing a primarily liver disorder as the cause of death. Hepatic failure cases are reviewed in the section of this review titled Reports of Hepatic Failure Cases.

Conclusions – Study 305

Hepatic-related adverse events of all causality and treatment-related hepatic adverse events were reported more frequently in patients in the voriconazole arm of the study. Analyses of laboratory data found more frequent and larger degree of abnormalities in transaminases and alkaline phosphatase among voriconazole-treated patients. Treatment discontinuations involving hepatic adverse events or laboratory abnormalities were more frequent among the voriconazole-treated group. Although the number of serious adverse events involving the liver was small, serious adverse events involving the liver were only reported in the voriconazole arm of the study.

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Safety Data from the Pooled Safety Database - Therapeutic Studies Population and the Overall Pooled Population

The Therapeutic Studies safety database included 1493 voriconazole-treated patients from the voriconazole clinical studies. The duration of treatment for the therapeutic Studies population is provided in Table 32. Similar data on duration of treatment are also presented for the Overall Pooled population (n=2090) which is composed of the Therapeutic studies population and the Compassionate Use Population.

Table 32. Pooled Safety Database – Duration of Treatment - Therapeutic Studies and Overall Pooled Populations

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

*Actual time
Source: adapted from the Applicant's Table 8-32 from p.126 of the Applicant's Advisory Committee Briefing Document

These pooled populations of patients are derived from both comparative and non-comparative studies. Most of the studies enrolled patients with significant medical conditions and receiving multiple concomitant medications. In this population one would expect a certain background rate for liver-related adverse events because of the often serious underlying medical conditions of the patients enrolled and the possibility of medications other than study drug contributing to observed events. Precise "hypothetical comparator group" rates are somewhat difficult to estimate for the composite group of patients being evaluated in these pooled populations because these studies included patients with other likely causes of liver disease such as graft versus host disease, veno-occlusive disease of the liver, and active viral hepatitis in addition to other pre-existing medical conditions and multiple concomitant medications.

Treatment Emergent Adverse Events – Therapeutic Studies and Overall Pooled Populations

Liver-related treatment emergent adverse events (TEAEs) of all causality are summarized in Table 33. The trends in the rates for adverse events are in general similar to what was noted in the previously reviewed comparative studies.

Table 33. Treatment Emergent Adverse Events (All Causalities)

Event	Voriconazole Therapeutic Studies Population N = 1493 N (%)	Voriconazole Overall Pooled Population N = 2090 N (%)	Amphotericin B† Formulations N = 665 N (%)	Comparators† (Amphotericin and Fluconazole combined) N = 856 N (%)
AP increased	90 (6.0)	133 (6.4)	12 (1.8)	22 (2.6)
Liver function tests abnormal	73 (4.9)	114 (5.5)	25 (3.8)	32 (3.7)
Hepatic enzymes increased	53 (3.5)	69 (3.3)	9 (1.4)	13 (1.5)
Bilirubinemia	49 (3.3)	69 (3.3)	38 (5.7)	40 (4.7)
SGOT (AST) increased	39 (2.6)	50 (2.4)	4 (0.6)	7 (0.8)
SGPT (ALT) increased	39 (2.6)	55 (2.6)	8 (1.2)	11 (1.3)
Jaundice	31 (2.1)	36 (1.7)	39 (5.9)	41 (4.8)
Cholestatic jaundice	28 (1.9)	43 (2.1)	6 (0.9)	N.D.
Hepatomegaly	11 (0.7)	12 (0.6)	9 (1.4)	11 (1.3)
Gamma glutamyl transpeptidase (GGT) increased	12 (0.8)	22 (1.1)	0	0
Hepatitis	11 (0.7)	17 (0.8)	1 (0.2)	1 (0.1)
Lactic dehydrogenase increased	8 (0.5)	9 (0.4)	1 (0.2)	2 (0.2)
Liver damage	17 (1.1)	30 (1.4)	6 (0.9)	11 (1.3)
Cholecystitis	6 (0.4)	8 (0.4)	3 (0.5)	3 (0.4)
Cholelithiasis	7 (0.5)	8 (0.4)	2 (0.3)	2 (0.2)
Hepatic failure	7 (0.5)	10 (0.5)	4 (0.6)	5 (0.6)
Liver tenderness	4 (0.3)	5 (0.2)	0	0
Gall/bladder/biliary tract disorder	2 (0.1)	4 (0.2)	3 (0.5)	3 (0.4)
Hepatic coma	1 (0.1)	1 (0.0)	0	0
Veno-occlusive Liver Disease*	2 (0.1) + ND	14 (0.7)	10 (1.5)	10 (1.2)
Graft versus Host Disease*	75 (0.5) + ND	216 (10.3)	55 (8.3)	55 (6.4)
Hepatitis B*	ND	35 (1.7)	4 (0.6)	12 (1.4)
Hepatitis C*	ND	52 (2.5)	11 (1.7)	38 (4.4)
Hepatitis Unspecified*	ND	32 (1.5)	2 (0.3)	4 (0.5)
Coagulation Related*	ND	19 (0.9)	12 (1.8)	12 (1.4)
Disseminated Intravascular Coagulopathy*	ND	1 (0.0)	3 (0.5)	0

Note * includes search of medical history terms with status 'present' for the populations of Overall Pooled, Amphotericin B Formulations, and Comparators (Amphotericin B and Fluconazole combined) but not for the Therapeutic Studies Population. The data for the Therapeutic Studies Population are derived from the Applicant's Table 3.1 in the June 2001 Safety Update. ND= not done

† Note: these populations do not represent true comparator populations

Source of data for Overall Pooled, Amphotericin B Formulations, and Comparators (Amphotericin B and Fluconazole combined) Populations data is the Applicant's Table R4, FDA Query 081 – BARRT 595.

Treatment Emergent Laboratory Abnormalities – Therapeutic Studies and Overall Pooled Populations

Liver-related clinically significant laboratory abnormalities from the Therapeutic Studies Population are summarized in Table 34. Although the data for amphotericin B formulations are not a true comparator, the trends and relative differences in rates noted are, in general, similar to what was noted for the comparative studies. The pattern of laboratory abnormalities from the compassionate use studies also display a similar pattern for to what was noted in the Therapeutic Studies Population and the comparative studies (Table 35).

Table 34. Clinically Significant Post-Baseline Laboratory Test Abnormalities Without Regard to Baseline – Therapeutic Studies Population

			Voriconazole		Amphotericin B Formulations	
	Units	Criterion	n/N	%	n/N	%
Total bilirubin	mg/dL	>1.5xULN	290/1402	21	168/607	28
SGOT	IU/L	>3.0xULN	179/1402	13	34/609	6
SGPT	IU/L	>3.0xULN	169/1390	12	62/587	11
Alkaline phosphatase	IU/L	>3.0xULN	238/1407	17	66/608	11

Source: Table 4.1, June 2001 Safety Update

Table 35. Clinically Significant Post-Baseline Laboratory Test Abnormalities Without Regard to Baseline – Compassionate/Extension Studies

			Voriconazole	
	Units	Criterion	n/N	%
Total bilirubin	mg/dL	>1.5xULN	124/458	27
SGOT	IU/L	>3.0xULN	64/436	15
SGPT	IU/L	>3.0xULN	69/446	15
Alkaline phosphatase	IU/L	>3.0xULN	103/455	23

Source: Table 4.2, June 2001 Safety Update

Discontinuations due to AEs or Laboratory Abnormalities – Therapeutic Studies and Overall Pooled Populations

The hepatic adverse events and laboratory abnormalities leading to treatment discontinuation are summarized in Table 36. The relative frequency of the reported events leading to treatment discontinuation are similar to what was noted in the comparative studies.

Table 36. Pooled Safety Database – Most Frequent Hepatic Adverse Events or Laboratory Abnormalities Leading to Discontinuation – Therapeutic Studies and Overall Pooled Populations

Adverse events* (Reasons for discontinuation**)	Voriconazole Therapeutic Studies (N = 1493) n (%)	Voriconazole Overall Pooled (N = 2090) n (%)
Elevated alkaline phosphatase	25 (1.7)	29 (1.4)
Increased hepatic enzymes	19 (1.3)	20 (1.0)
Liver function tests abnormal	13 (0.9)	23 (1.1)
Bilirubinemia	12 (0.8)	14 (0.7)
Cholestatic jaundice	10 (0.7)	10 (0.5)

*Most frequent = adverse events leading to discontinuation occurring in ≥8 patients in the Therapeutic Studies population
**Patients can discontinue for more than one reason.
Source: adapted from the Applicant's Table 8-33 from p.127 of the Applicant's Advisory Committee Briefing Document

Serious AEs – Therapeutic Studies and Overall Pooled Populations

The serious adverse events for the voriconazole Therapeutic Studies and Overall Pooled Populations are presented in Table 37. The three most frequently reported liver-related serious adverse events in the Therapeutic Studies and Overall Pooled Populations were bilirubinemia, hepatic failure, and alkaline phosphatase increased. The cases of hepatic

failure were all in patients who expired and are further discussed in the section of this review addressing cases of hepatic failure.

Table 37. Empirical Study – Serious Adverse Events by Treatment Regimen – Safety Population

Preferred Event Term	Voriconazole Therapeutic Studies Population (N = 1493)		Voriconazole Overall Pooled (N = 2090)	
	n	(%)	n	(%)
Bilirubinemia	10	(0.7)	14	(0.7)
Hepatic Failure	10	(0.7)	13	(0.6)
Alkaline Phosphatase Increased	6	(0.4)	13	(0.6)
Cholecystitis	6	(0.4)	8	(0.5)
SGOT Increased	5	(0.3)	12	(0.6)
SGPT Increased	5	(0.3)	10	(0.5)
Hepatic Function Abnormal	5	(0.3)	9	(0.4)
Cholelithiasis	5	(0.3)	6	(0.3)
Hepatitis	4	(0.3)	8	(0.4)
Gall Bladder Biliary Tract Disorder	3	(0.2)	3	(0.1)
GGT Increased	2	(0.1)	8	(0.4)
Hepatitis Cholestatic	2	(0.1)	6	(0.3)
Hepatocellular Damage	2	(0.1)	2	(0.1)
Hepatitis Infectious	1	(0.1)	3	(0.1)
Hepatic Necrosis	1	(0.1)	1	(<0.1)
Veno-Occlusive Liver Disease	1	(0.1)	1	(<0.1)
LDH Increased	1	(0.1)	1	(<0.1)
Jaundice	0	(0.0)	2	(0.1)
Coma Hepatic	0	(0.0)	1	(<0.1)
Hepatic Enzymes Increased	0	(0.0)	1	(<0.1)
Hepatomegaly	0	(0.0)	1	(<0.1)
Hepatorenal Syndrome	0	(0.0)	1	(<0.1)
Total Number of Hepatic-Related Serious Adverse Events	69	-	124	-

Source: Tables 2.5.3 & 2.5.4 from Volume 4 of 20 NDA ISS pp. 1177- 1214. Nov. 2000
Tables 5.5 & 5.6 from Volume 1 of 1 of NDA Safety Update pp. 121- 136, June 2001

Conclusions – Therapeutic Studies Population and Overall Pooled Populations

The reported adverse events, laboratory abnormalities, reasons for discontinuation of therapy, and serious adverse events were, in general, similar to what was reported in the three comparative studies. There was a wider spectrum of hepatic-related adverse events reported in the larger population of patients in the Therapeutic Studies and Overall Pooled Populations compared with the three previously reviewed comparative studies.

Hepatic failure cases (all of which were in patients that expired) are discussed in the section of this review addressing hepatic failure cases. Following the review of the hepatic failure cases, selected patients for whom liver histopathology results are available where there is a noted possible association with study drug are discussed.

Safety Data from the Long-term Study Subpopulation

The Applicant provided analyses of the subpopulation from the NDA database that received voriconazole therapy for more than 84 days, the Long-term Study Subpopulation. The median duration of voriconazole therapy in this group of patients was 163 days with the longest duration of therapy 1014 days. The data from the NDA Long-term Study Subpopulation were compared to the NDA All Voriconazole Population. The median duration of therapy in the NDA All Voriconazole Population was 14 days (Table 38).

Table 38. Pooled Safety Database - Duration of Therapy - NDA Long-Term Voriconazole Therapy Population and NDA All Voriconazole Population

Duration of Treatment (days)	NDA Long-term Voriconazole Therapy (N = 304)	NDA All Voriconazole (N= 1946)
Median	163	14
n (%) patients receiving randomized treatment for:		
<14 days therapy	N/A	1065 (54.7)
>14 days therapy	N/A	881 (45.3)
>28 days therapy	N/A	553 (28.4)
>84 days therapy	304 (100.0)	304 (15.6)
>180 days therapy	117 (38.5)	117 (6.0)
>365 days therapy	17 (5.6)	17 (0.9)

Source: Applicant's Table 8-38 from Page 131 of the Applicant's Briefing Document

The frequency of adverse events reported for the NDA Long-Term Voriconazole Therapy Population and the NDA All Voriconazole population are provided in Table 39. There were no marked differences in the reporting rates when comparing these two populations.

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Table 39. Treatment Emergent Hepatic-Related Adverse Events – NDA Long-Term Voriconazole Therapy Population and NDA All Voriconazole Population – All Causalities		
Serious Adverse Events	**NDA Long-Term Voriconazole Therapy (N=304) n (%)**	**NDA All Voriconazole (N=1946) n (%)**
Cholecystitis	2 (0.7)	5 (0.3)
Cholelithiasis	1 (0.3)	6 (0.3)
Cholestatic Jaundice	4 (1.3)	24 (1.2)
Gall Bladder / Biliary Tract Disorder	2 (0.7)	4 (0.2)
GGT Increased	0 (0.0)	11 (0.6)
Hepatic Coma	0 (0.0)	1 (0.1)
Hepatic Failure	1 (0.3)	4 (0.2)
Hepatitis	2 (0.7)	11 (0.6)
Hepatomegaly	1 (0.3)	9 (0.5)
Jaundice	1 (0.3)	32 (1.6)
Liver Damage	2 (0.7)	10 (0.5)
Liver Function Tests Abnormal	11 (3.6)	73 (3.8)
Liver Tenderness	0 (0.0)	3 (0.2)
Alkaline Phosphatase Increased	7 (2.3)	95 (4.9)
Bilirubinemia	1 (0.3)	52 (2.7)
Hepatic Enzymes Increased	4 (1.3)	55 (2.8)
LDH Increased	0 (0.0)	7 (0.4)
SGOT Increased	2 (0.7)	36 (1.8)
SGPT Increased	3 (1.0)	36 (1.8)
Source: Table 3.6.2 ISS Nov 2000 Submission & Table 2.6.3. ISS Nov 2000 Submission.		

The incidence of abnormalities of liver-related laboratory analytes was greater in the Long-Term therapy population compared to the NDA All Voriconazole Population (Table 40).

> **MO Comment:** Note that this analysis doesn't control for other factors that may be influencing the frequency of abnormal liver-related analytes (e.g., differences in the patient populations or other non-patient factors).

Table 40. Incidence of Clinically Significant Laboratory Test Abnormalities – Irrespective of Baseline Abnormality NDA Long-Term Voriconazole Therapy Population and NDA All Voriconazole Population			
Laboratory Parameter	**Criteria**	**NDA Long-Term Voriconazole Therapy n (%)**	**NDA All Voriconazole n (%)**
T. Bilirubin	> 1.5 x ULN	60/184 (33)	308/1504 (21)
SGOT (AST)	> 3 x ULN	59/183 (32)	182/1494 (12)
SGPT (ALT)	> 3 x ULN	72/184 (39)	174/1487 (12)
Alkaline Phosphatase	> 3 x ULN	54/184 (29)	227/1507 (15)
Source: Table 2.7.1 ISS Nov 2000 Submission & Table 3.7.1 ISS Nov 2000 Submission.			

The frequency and types of hepatic-related adverse events leading to discontinuation are similar between the NDA Long-Term and the NDA All Voriconazole Population (Table 41).

Table 41. Pooled Safety Database – Hepatic Adverse Events Leading to Discontinuation – NDA Long-Term Voriconazole Therapy Population and NDA All Voriconazole Population

	NDA Long-Term Voriconazole Therapy (N=304) n (%)	NDA All Voriconazole (N=1946) n (%)
Patients with adverse events	289 (95.1)	1694 (87.1)
Patients discontinued due to adverse events	27 (8.9)	259 (13.3)
Adverse event leading to discontinuation		
Abnormal liver function tests	3 (1.0)	13 (0.7)
Increased alkaline phosphatase	2 (0.7)	27 (1.4)
Increased hepatic enzymes	2 (0.7)	19 (1.0)
Cholestatic jaundice	1 (0.5)	8 (0.4)
Bilirubinemia	0 (0.0)	11 (0.6)
SGOT increased	0 (0.0)	7 (0.4)
SGPT increased	0 (0.0)	5 (0.3)
Hepatitis	0 (0.0)	4 (0.2)
GGT Increased	0 (0.0)	3 (0.2)
Jaundice	0 (0.0)	3 (0.2)
Liver Damage	0 (0.0)	2 (0.1)
Hepatic Failure	0 (0.0)	1 (0.1)

Source: Table 2.4.2 ISS Nov 2000 Submission, Table 3.4.2 ISS Nov 2000 Submission and the Applicant's Table 8-39 from p.131 of the Applicant's Advisory Committee Briefing Document

Review of the serious adverse events leading to treatment discontinuation in the NDA Long-Term Voriconazole Therapy Population did not reveal an excess of liver-related serious adverse events in the Long-Term Therapy Population when compared to the NDA All Voriconazole Population.

Conclusions – Long-term Study Population

Comparing the adverse events, treatment discontinuations, and serious adverse events between the Long-term Therapy Subpopulation with the NDA All Voriconazole Population did not reveal differences between these two groups. Abnormalities of T. bilirubin, AST, ALT, and alkaline phosphatase were more frequent in the NDA Long-Term Subpopulation than in the NDA All Voriconazole Population. However, these results should be interpreted cautiously because such comparisons do not control for the other possible differences in these two populations that may influence hepatic laboratory abnormalities.