Safety Data from the Pediatric Population

The experience with voriconazole therapy in the pediatric population is derived predominantly from two pharmacokinetic studies and the Compassionate Use program.

> **MO Comment:** The reader is also referred to Dr. Johann-Liang's Pediatric Safety Review.

There were 52 patients under twelve years of age in the November 2000 NDA submission. One of these patients was in the voriconazole Therapeutic Studies Population. The other 51 patients were in the Compassionate Use Population. The one patient in the NDA Therapeutic Studies population had three adverse events (rash, osteomalacia, and vomiting) but completed the study. The hepatic-related safety results for the remaining 51 patients are discussed in the following sections.

The duration of therapy for the 51 pediatric patients in the Compassionate Use Population is summarized in table 42.

Table 42. Pooled Safety Database - Duration of Therapy - NDA All Voriconazole Population – Patients Less than 12 Years

Duration of Treatment (days)	Patients <12 years (N=51) n (%)
Median duration	82
Number of patients receiving voriconazole for	
<14 days therapy	11 (21.6)
>14 days therapy	40 (78.4)
>28 days therapy	36 (70.6)
>84 days therapy	24 (47.1)
>180 days therapy	20 (39.2)
>365 days therapy	6 (11.8)

Source: adapted from the Applicant's Table 8-42 from p.133 of the Applicant's Advisory Committee Briefing Document

Of the 51 pediatric patients in the Compassionate Use Population, there was one discontinuation due to the adverse event of AST increased and one discontinuation due to the adverse event of ALT increased.

The liver-related safety results from the pediatric pharmacokinetic studies are as follows. In the Single Dose Pediatric Study (249) and the Multiple Dose Pediatric Study (1007) none of the serious adverse events were hepatic adverse events. The hepatic adverse events reported for the pediatric subjects in these studies are summarized in table 43.

Table 43. Multiple Dose Pediatric Study (1007) and Single Dose Pediatric Study (249) – Hepatic Adverse Events

Adverse Event	Multiple Dose Pediatric Study (1007) (N = 28) n (%)	Single Dose Pediatric Study (249)	
		3 mg/kg IV (N = 6) n (%)	4 mg/kg IV (N = 5) n (%)
Bilirubinemia	4	0	0
SGOT increased	0	1	0

Source: Adapted from the Applicant's Table 8-45, p. 136. from the Applicant's Advisory Committee Briefing Document

The laboratory abnormalities from the multiple-dose pediatric study are summarized in Table 44.

MO Comment: Data from additional pediatric patients would help to further determine the safety profile of voriconazole.

Table 44. Multiple Dose Pediatric Study (1007) - Liver Related Laboratory Abnormalities

Parameter	Criteria	Multiple Dose Pediatric Study (1007)	
		6 +3 mg/kg n (%)	4 mg/kg n (%)
Total bilirubin (mg/dl)	> 1.5 ULN	1/27 (3.7)	5/27 (18.5)
AST (IU/L)	> 3 ULN	1/27 (3.7)	1/27 (3.7)
ALT (IU/L)	> 3 ULN	2/27 (7.4)	3/27 (11.1)
Alkaline phosphatase (IU/L)	> 3 ULN	0/25 (0)	0/26 (0)

ALT = alanine transaminase; AST = aspartate transaminase; ULN = upper limit of normal

Conclusions Pediatric Population Data

The limited data available from the pediatric experience reveal some liver-related adverse events and laboratory abnormalities. It would be reasonable to obtain additional data to further evaluate the hepatic safety profile in future pediatric studies in populations of pediatric patients likely to be candidates for voriconazole therapy.

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Safety Data from the Non-therapeutic Studies Population

The Non-therapeutic Studies Population consisted of patients from the Dose Ranging Oropharyngeal Candidiasis Study (302) and the Multiple-Dose Adult Patient Pharmacokinetic Study (673).

Study 302 enrolled 167 patients divided among the following doses of voriconazole: 50 mg once daily (n=53), 200 mg once daily (n=58), or 200 mg bid (n=56). [Note: the results for the liver-related laboratory abnormalities are discussed in the portion of this review addressing data from phase I studies.] In study 302 there was a 30 year-old male with AIDS who received voriconazole for oropharyngeal candidiasis and developed worsening elevation of his alkaline phosphatase. His baseline alkaline phosphatase was 361 U/L (NR 73-207) and increased to 2754 U/L on Day 3. Voriconazole was discontinued on Day 4 due to his elevated alkaline phosphatase. His lab values for alkaline phosphatase were 3500 U/L on Day 9 and 1207 U/L on Day 44. The study investigator ascribed the patient's elevated alkaline phosphatase to sclerosing cholangitis.

> **MO Comment**: That voriconazole may have been a contributing factor to the observed alkaline phosphatase elevation cannot be excluded.

There was also a 37-year-old male with AIDS and oropharyngeal candidiasis. He received voriconazole 200 mg PO bid from Day 1 to Day 8. At baseline and during study he had a mildly elevated AST and ALT that ranged from 1.2 to 2.2 x the ULN. From Day 16 to 22 he received ceftazidime and also ciprofloxacin from Day 20 to 22. Then from Day 22 onward, he received erythromycin. He was also receiving other concomitant medications. On Day 45 the serious adverse event of hepatitis C and jaundice are reported. The patient was hospitalized and expired. His serious adverse event was ascribed to hepatitis C.

> **MO Comment:** Given the patient's abnormal AST and ALT at baseline pre-existing liver disease (such as hepatitis C) is plausible. The possibility that voriconazole or one of the other medications that the patient received contributed to the patient's hepatic disorder cannot be excluded.

Study 673 enrolled 9 patients who received voriconazole doses of 200 mg PO bid and 9 patients who received 300 mg PO bid. From study 673, there was one case of a "clinically meaningful" elevated SGOT in the group of patients receiving voriconazole 300 mg PO bid. This 60 year-old female patient's SGOT was normal at baseline and increased to 146 U/L (NR 9-34 U/L) on Day 14 of study treatment (SGPT on Day 14 was 94 U/L (NR 6-34). Her T. bilirubin and alkaline phosphatase were normal throughout the duration of the study). This event was considered of moderate severity and considered treatment-related by the study investigator. The patient's SGOT returned to within the normal range 13 days post-treatment (Day 27) and SGPT returned to within the normal range 24 days post-treatment (Day 38).

Reports of Hepatic Failure Cases

There were 26 reports of hepatic failure in the voriconazole development program. These cases were identified by the Applicant by a review of the serious adverse event reports. Among the voriconazole-treated patients, hepatic failure was reported in 19 of 2090 (0.9%), while in comparator-treated patients there were 7/856 (0.8%) patients with hepatic failure reported. All cases of patients with hepatic failure were in patients that expired. The number of hepatic failure events stratified by study are presented in Table 45. In the comparative studies there were no marked differences in the rates at which cases of hepatic failure were reported by treatment arm.

Table 45. Hepatic Failure Events stratified by Study* for Voriconazole and Comparators – Overall Pooled Population

Study	Voriconazole n/N (%)		Comparators n/N (%)	
Comparative Studies				
305	0/200	(0.0)	0/191	(0.0)
307/602	0/196	(0.0)	1/185	(0.5)
603	5/421	(1.2)	5/428	(1.2)
608	1/110	(0.9)	1/52	(1.9)
Non-Comparative Studies	13/1163	(1.1)	-	-
Total (Overall Pooled Population)	19/2090	(0.9)	7/856	(0.8)

*Only Studies with Events are included in the table.
Source: Adapted from data in the Applicant's Table 6. from p. 260 of Vol. 1 of the NDA ISS from the Nov 2000 submission and Table 8-55 pp. 145-147 of the Applicant's Advisory Committee Briefing Document.

A brief summary of the hepatic failure events is provided in Table 46. The table also includes the causality assessment of the Expert Hepatologist Panel. The distribution of causality scores are shown graphically in Figure 4.

Table 46. (cont'd). Summary of Patients with Hepatic Failure in the Overall Pooled Population

PID	Gender	Age (yr)	Duration Rx (day)	Day of Death	Clinical Event	Causality (Investigator Assessed)	Causality (Expert Panel)
Voriconazole (N=2090) continued							
604/6035	M	23	5	25	Respiratory distress, intermittent, Supraventricular tachycardia, acute renal dysfunction, sepsis, progression of acute myelocytic leukemia, hepatic failure	Other (Aspergillosis, acute myelocytic leukemia)	PN – 3 DN – 1 (3)
606/0131	M	17	34	42	Worsening hyperbilirubinemia, hepatic failure, pulmonary failure, Cytomegalovirus pneumonitis	Graft vs. host disease, association with study drug possible	Po – 2 PN – 2 (6)
606/0330	F	16	54	54	ARDS, progression of hepatic failure, progression of renal failure, graft vs. host disease	Other illness (hepatic failure due to graft vs. host disease)	Po – 1 PN – 3 (5)
606/0318	M	60	6	7	Progression of hepatic failure, brain abscess, respiratory failure, hepatitis C, subdural hematoma, renal failure, coagulopathy	Disease under study (invasive mycoses)	PN – 4 (4)
606/0209	M	37	21	28	Elevated bilirubin, elevated creatinine, pericarditis, pulmonary effusion, respiratory distress, hepatic failure	Other illness (venous occlusive disease, volume overload)	Po – 1 PN – 3 (5)
607/6066	F	37	257	323	Femoral vein thrombosis, exacerbation of hyper-bilirubinemia and systemic lupus erythematosus, elevated transaminases, hepatic failure	Study drug may have contributed	Pr – 1 Po – 3 (9)
608/0031	F	76	18	18	Sepsis, hepatic failure, worsening renal insufficiency, adult respiratory distress syndrome, pulmonary failure, multiple organ system failure	Other (perforated colon, pneumonia, sepsis)	Po – 1 PN – 3 (5)
1025297-1	M	35	75	75	Acute hepatic and renal failure	Other illness (AIDS, hepatitis, alcohol abuse)	Not Done

*DOD = day of death

** Causality as determined by the Expert Hepatologist Review Panel. Cases were rated by each of the four experts as Definitely related = D, Probably Related = Pr, Possibly Related = Po, Probably Not Related = PN, Definitely Not Related = DN. The composite score is the sum of the ratings of the four expert hepatologists where D = 4 points, Pr = 3 points, Po = 2 points, PN = 1 point, and DN = 0 points.

Source: Adapted from the Applicant's Table 6. from p. 260 of Vol. 1 of the NDA ISS from the Nov 2000 submission and Table 8-55 pp. 145-147 of the Applicant's Advisory Committee Briefing Document.

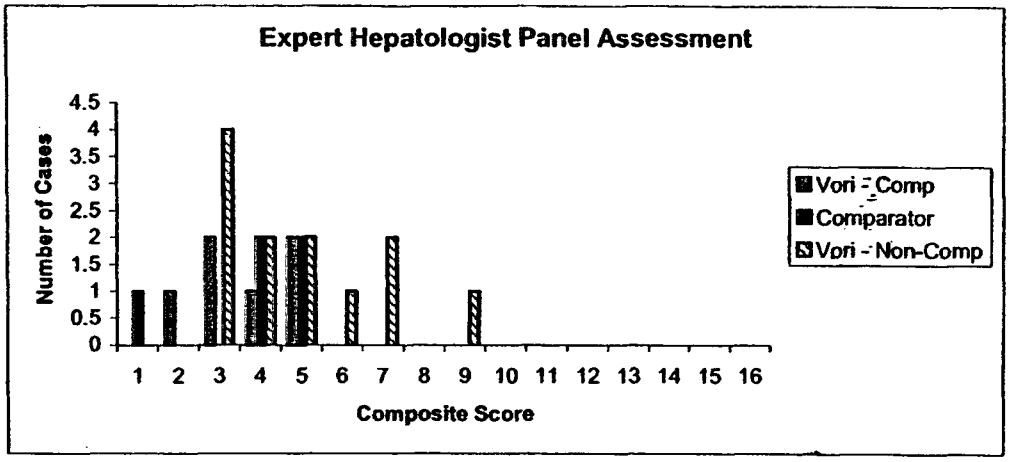


Figure 4. Composite scores for the expert hepatologists' assessment of causality for cases of hepatic failure. Data are shown for voriconazole-treated patients from the comparative studies (Vori-Comp) and their comparator-treated counterparts (Comparator). Data are also shown for the voriconazole-treated patients from the non-comparative studies (Vori-Non-Comp). Each case was scored by each of the four expert hepatologists as Definitely related = D, Probably Related = Pr, Possibly Related = Po, Probably Not Related = PN, Definitely Not Related = DN. The composite score is the sum of the ratings of the four expert hepatologists where D = 4 points, Pr = 3 points, Po = 2 points, PN = 1 point, and DN = 0 points. The maximum achievable score is 16 points for a patient that receives 4 scores of Definitely Related whereas a patient with four scores of Definitely Not Related would have a score of zero.

Patient Narratives for Selected Hepatic Failure Cases

Patient 150-607-8032-6066; (Pr – 1; Po – 3)

Patient 607/6066 was a 37-year-old female with autoimmune hemolytic anemia associated with underlying systemic lupus erythematosis, who received voriconazole for the extended treatment of central nervous system aspergillosis. The patient entered Study 607 as a continuation of treatment received in Study 604. On Day 210, the patient was admitted to the hospital with a one-week history of left lower extremity edema and was diagnosed with common femoral vein thrombosis. An arteriogram showed a left femoral clot around the area of her arteriovenous fistula which was used for hemodialysis. The patient was treated with enoxaparine. On Day 212, the patient developed an exacerbation of her lupus and was treated with intravenous methylprednisolone. On Day 257, voriconazole was temporarily discontinued due to a sustained elevation in aspartate transaminase (AST) and alanine transaminase (ALT). On Day 305 (49 days after the discontinuation of voriconazole) the patient was hospitalized for symptoms of worsening fatigue, chills without fever, right sided pleuritic chest pain, and increasing abdominal girth and was diagnosed with liver failure. She requested that no further invasive or resuscitative procedures be performed and died 67 days after the last dose of voriconazole. The investigator attributed the hypertransaminasemia and progressive liver failure (cause of death) to voriconazole. Review by the Sponsor attributed the hypertransaminasemia and progressive liver failure to the patient's chronic active autoimmune hepatitis and SLE; however, a causal relation to voriconazole could not be excluded.

(Source: Applicant's Advisory Committee Briefing Document, p. 148)

The summary of the expert hepatologists' deliberations on this case is provided below:
Patient 150-607-8032-6066
This was a difficult case to review with many confounding factors. The study drug may have triggered an exacerbation of elevated liver enzymes and possibly may have precipitated an autoimmune reaction. This patient had many reasons for developing abnormal liver enzymes. The patient was temporarily discontinued. Although described by the investigator as hepatic failure, the panel discussed that with such low transaminases this may be hepatic dysfunction as opposed to liver failure. The patient had renal disease making the elevated bilirubin difficult to assess. It is possible that there was a significant cholestatic component. Discussion of an underlying immune disease contributing to the liver failure was described as "speculative" as immune markers are uninformative and no liver scan or CT scan were done. The panel was in agreement that this case merited careful consideration - (1 X probably related; 3 X possibly related).
(Source: Hepatic Expert Panel Meeting Minutes, August 22, 2001)

Patient 150-309-2051-1487; (Po – 3; PN – 1)

Patient 309/1487 was a 64-year-old male with underlying non-Hodgkin's lymphoma. He had had an allogeneic bone marrow transplant, complicated by Graft vs. Host Disease and received voriconazole for refractory hepatic aspergillosis. Liver function test values were elevated at baseline. He had previously been treated with other antifungal agents: fluconazole (400mg daily), conventional amphotericin B (90mg daily) and liposomal amphotericin B (180mg daily). He received voriconazole for 19 days but was discontinued due to the onset of renal and hepatic failure. On day 27 a liver biopsy showed massive cholestasis, necrosis, Graft vs. Host Disease, no inflammation, vasculitis or evidence of fungal infection. On Day 40, the patient died from E. faecalis sepsis and hepatic and cardiac failure. In the opinion of the investigator, the cause of death was hepatic failure secondary to Graft vs. Host Disease, although a possible contribution of hepatic fungal infection or study drug could not be ruled out.
(Source: Applicant's Advisory Committee Briefing Document, p. 148)

The summary of the expert hepatologists' deliberations on this case is provided below:
Patient 150-309-2051-1487
This was described as a complicated case with many factors to consider: GVHD, previous antifungals and other drugs. Causality was broadly agreed by the panel - (3 X possibly related; 1 X probably not related). The experts ascribing causality as "possibly related" stressed that this relationship was to the cholestatic reaction and not the liver failure.
(Source: Hepatic Expert Panel Meeting Minutes, August 22, 2001)

Patient 150-604-1036-6168; (Po – 3; PN – 1)

Patient 604/6168 was a 13-year-old male with B cell ALL diagnosed in 1987 with subsequent recurrences in 1991 and December of 1998. He had cultures from a BAL done on January 26, 2001 positive for *Candida albicans*, an esophageal biopsy culture positive for *Candida albicans*, and CT of the chest and abdomen consistent with invasive fungal disease involving multiple organs. He was diagnosed with disseminated candidiasis (involving liver, spleen, kidneys, sinuses, esophagus, and lungs) based upon radiologic findings and cultures positive for *Candida albicans* from multiple sites. He had received prior therapy with Abelcet from February 7, 1999 to March 9, 1999. He entered study on March 11, 1999 as a failure of prior antifungal therapy. Liver function test values were normal at baseline except for an alkaline phosphatase slightly below the lower limit of normal at baseline. He received doses of voriconazole ranging from 100 to 200 mg daily from March 11, 1999 to July 9, 1999 and then was transferred over to protocol

150-607 for further therapy. On July 13, 1999 his study medication was permanently discontinued for the serious adverse event of liver failure. During the course of the study he also received multiple other medications including total parenteral nutrition during the study period. His AST, ALT, Alk. Phos., and T. bilirubin remained below the upper limits of the normal range at his week 1, 2, and 4 visits. At his week 8 visit his ALT was approximately 2.5 times the upper limit of normal with an unremarkable AST, Alk. Phos., and T. Bili. At his week 16 visit on July 9, 1999, his AST and ALT were within the normal range, but his T. Bili. was 2.9 (NR 0.2-1.2 mg/dL). The patient expired 4-days after discontinuation of study drug.
(Source: Narrative generated from information in the Patient's Case Report Forms)

The summary of the expert hepatologists' deliberations on this case is provided below:
Patient 150-604-1036-6168
The review of this case caused much discussion. It was noted that assessment of "dechallenge" was not possible as the patient died 3-4 days post stopping drug. It was agreed that the most likely cause of hepatic failure was GVHD, as this explained most of the changes, but with probable hepatic issues from fungemia and adenovirus. One expert commented that this patient was dying already. Individual assessments by experts prior to the meeting had been: 1 X probably related, 1 X possibly related and 2 X probably not related. However, following the discussion two experts asked to adjust their assessment. The final assessment was 3 X possibly related; 1 X probably not related. The panel felt that this was representative of their discussion and all agreed with final outcome.
(Source: Hepatic Expert Panel Meeting, Minutes August 22, 2001)

Patient 150-606-5020-0131; (Po – 2; PN – 2)
Patient 606/0131 was a 17-year-old male with a history of acute myelocytic leukemia status-post allogeneic bone marrow transplant complicated by graft vs. host disease of skin, gastrointestinal tract, and liver who developed pulmonary cryptococcosis which failed to respond to therapy with amphotericin B. The patient was started on compassionate use voriconazole and treated for 35 days and died seven days after the end of therapy. The investigator attributed death to Cytomegalovirus pneumonitis, hepatic failure and pulmonary failure. The final autopsy report attributed the cause of death to progressive hepatic and pulmonary failure. Autopsy findings included moderate hepatic graft vs. host disease of the liver, with severe cholestasis and periportal fibrosis, extensive fibrosis of the liver consistent with a history of chemotherapy, severe diffuse alveolar damage, bilateral focal Cytomegalovirus pneumonitis, and umbilical cord blood transplant.
(Source: Applicant's Advisory Committee Briefing Document, p. 148)

The summary of the expert hepatologists' deliberations on this case is provided below:
Patient 150-606-5020-0131
This case was discussed briefly only, as causality was broadly agreed – (2 X possibly related; 2 X probably not related).
(Source: Hepatic Expert Panel Meeting Minutes, August 22, 2001)

Histopathologic Results of Liver Biopsies

The Applicant provided a listing of all of the available histopathologic results for patients who underwent a liver biopsy or an autopsy with reported histopathologic examination of the liver. The results for the liver biopsies for selected patients in whom study drug was noted as a possible factor in the noted histopathologic findings are discussed below. The biopsy results (verbatim biopsy results as reported by the Applicant) are presented

for these cases and additional clinical history available from the patient's case report forms and or patient profile forms are provided in the following sections.

Patient 150 309 0137 1401 was a 16-year-old female subject in Germany who received voriconazole for the treatment of a fungal corneal infection of her left eye with a filamentous fungi noted on histopathology from a corneal excision. During the course of her voriconazole therapy she received oral, intravenous, eye drops, and intracanalicular injections of voriconazole (Table 47). She received voriconazole from Day 1 to Day 60.

Table 47. Voriconazole Therapy Received by Patient 309 0137 1401

Total Daily Dose (mg/day)	No. of Doses Per day	Route	Start Date	Stop Date	Start Day*	Stop Day*
300	1	IV infusion	04DEC1998	05DEC1998	1	2
200	1	IV infusion	05DEC1998	05DEC1998	2	2
400	2	IV infusion	06DEC1998	13DEC1998	3	10
300	1	Oral	14DEC1998	14DEC1998	11	11
200	1	IV infusion	14DEC1998	14DEC1998	11	11
0.032	32	Eye drops	14DEC1998	11JAN1999	11	39
0.0015	1	Intracanalicular injection	15DEC1998	15DEC1998	12	12
600	2	Oral	15DEC1998	11JAN1999	12	39
0.0015	1	Intracanalicular injection	17DEC1998	17DEC1998	14	14
400	2	Oral	12JAN1999	01FEB1999	40	60

*Day relative to start of study therapy (day 1)

MO Comment: The administration of voriconazole by eye drop and intracanalicular injection was a protocol violation.

The concomitant medications received by this patient are listed in Table 48. Around the time that her elevated liver function tests were first noted the only medication that she was reported to be receiving was voriconazole.

Table 48. Concomitant Medications Received by Patient 309 0137 1401

Drug Name	Start Date	Stop Date	Start Day	Stop Day	Elapsed Time (Days)*
Tobramycin	18NOV1998	30NOV1998	-15	-3	13
Acetaminophen	17DEC1998	17DEC1998	14	14	1
Tramadol	26NOV1998	18DEC1998	-7	15	23
Atropine	10NOV1998	24DEC1998	-23	21	45
Amphotericin	26NOV1998	14DEC1998	-7	11	19
Fluconazole	26NOV1998	30NOV1998	-7	-3	5
Itraconazole	01DEC1998	04DEC1998	-2	1	4
Ceftazidime	18NOV1998	30NOV1998	-15	-3	13
Clindamycin	18NOV1998	20DEC1998	-15	17	33
Azidamfenicol	UNK	22DEC1998	UNK	19	N/A
Chloramphenicol	20NOV1998	24DEC1998	-13	21	35
Fluocortolone	12NOV1998	03DEC1998	-21	0	22
Famotidine	12NOV1998	12DEC1998	-21	9	31

+ Drug information is collapsed by preferred term so may include periods of differing dose or formulation
* Elapsed time = last stop date – first start date plus one so may include periods of no treatment
If concomitant drug treatment is ongoing the end of study date is used for the last stop date and to calculate elapsed time

The specialist's report from the clinical site provides the following assessment of the case:

> *Taking the medical history and all clinical, laboratory as well as the histological, findings into consideration, [the patient] most probably suffers from drug-induced hepatosis caused by the triazole derivative voriconazole (study drug of Pfizer Ltd.). This is especially supported by the fact that transaminases started to increase during drug intake, taking into account that the rise in transaminases continued for an unusually long period of time following withdrawal of the drug.*
>
> ...
>
> *The histological findings also favor the diagnosis of toxic hepatosis, and there are no hints to any other hepatotoxic substances in the medical history of [the patient]. The above mentioned diagnosis is also supported by the clinical course with a decrease of transaminases at present to the upper normal range [07June1999, AST 19 U/L, ALT 22 U/L]. Other causes of liver disease were practically completely excluded by very extended examinations.*
>
> *In view of the next operation planned, [the patient] was advised to await complete normalization of transaminases, if possible. At present there is no reason for any specific medication. However, it is mandatory to avoid any use of triazole derivatives in the future.*

The final diagnosis of her liver event was "toxic hepatosis." In the opinion of the investigator, the patient's "toxic hepatosis" was due to voriconazole.

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.

> **MO Comment:** This woman's event of "toxic hepatosis" may represent a drug-related hepatic event. The case provides information about the possible hepatotoxic potential of voriconazole in a patient who is not suffering from other serious systemic illnesses and who is only on limited other medications around the time of the study. (This is in contrast to the most of the patients in the phase III studies who often are taking multiple medications and have other confounding factors that complicate the assessment of causality for hepatic adverse events.)

Patient 150 607 8010 6128 had a biopsy of the liver on Day 226 (voriconazole was discontinued on Day 221) with the following reading:

> *Mild acute portal tract inflammation. Neutrophil infiltrates within portal tract. There is also a minor degree of lobular involvement by neutrophils. The bile ducts do not show cytoplasmic vacuolation, nuclear or apoptotic bodies. No canalicular cholestasis or bile duct plugging is seen. No findings of GVHD. These changes may be due to drug effect. The neutrophils within portal tracts, as well as in*

occasional clusters within lobules, suggest the possibility of CMV. Immunochemical staining for CMV negative.

The patient was a 55-year-old female with CML and chronic GvHD of the liver who entered study 607 on 18 Jan 2000 (Study 607 was an open-label, non-comparative protocol to evaluate the safety and tolerance of extended voriconazole treatment of invasive fungal infections). Only limited information is available from the patient's case report forms. Her medication case report form notes that she received voriconazole 300 mg PO BID from 18 January 2000 (Day 1) to 28 August 2000 (Day 223). [Note: there is a 3-day difference in the date of discontinuation of medication comparing the adverse event CRF to the medication CRF.] On her "week 4" visit on 04 February 2000 (Day 17), she is noted to have an elevated alkaline phosphatase that is resolving (no lab value noted). On 18 August 2000 (day 213) she is noted to have an elevated alkaline phosphatase, SGPT, SGOT, and urea nitrogen levels (no lab values noted). On 25 August 2000, the investigator records the adverse event of "hepatic inflammation." The event was classified as severe and serious. The adverse event report notes that voriconazole therapy was discontinued because of the event of hepatic inflammation. The event resolved on 27 September 2000.

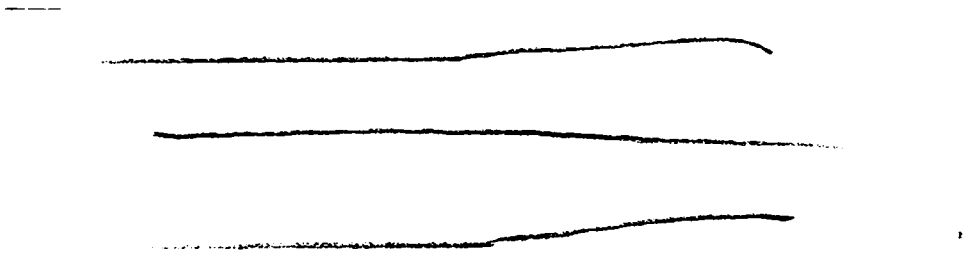
Patient 150 607 8010 6128 received multiple concomitant medications during the course of the study. The medications that she was receiving or had been receiving during the two weeks prior to 25 August 2000 included the following: Neurontin (gabapentin) (D/C'd 18 August 2000 & resumed 28 August 2000), Prempro, Aspirin, fiber supplement, famotidine (D/C'd 11 August 2000), erythropoietin, multivitamin, prednisone (D/C'd 25 August 2000 & resumed 31 August 2000), solumedrol (25 August 2000 through 30 August 00), Bactrim (D/C'd 27 August 2000), acyclovir (D/C'd 11 August 2000) cozaar, hydrochlorothiazide (D/C'd 25 August 2000), ketoconazole cream, cyclosporine (D/C'd 25 August 2000), nizoral (route not described, e.g., oral or topical, shampoo, etc.), minoxidil 5%, Ambien (begun 13 August 2000), Celexa (begun 25 August 2000), packed red blood cells (25-26 August 2000), FK506 (25-31 August 2000), KCl (25-28 August 2000), megace (begun 26 August 2000). She underwent liver biopsy on 29 August 2000 (the findings of the biopsy are noted above). The only LFTs available in the patient's CRFs are from 04 September 2000. They include a T. Bili. of 1.8 mg/dL (NR 0.3-1.3), Alk. Phos. 313 IU/L (NR 30-115), AST 85 IU/L (NR 16-41), ALT 321 IU/L (NR11-35).

MO Comment: This patient was on multiple medications and we lack information on laboratory values at times other than 04 September 2000. She had also recently received a blood transfusion. The investigator attributed the adverse event of "hepatic inflammation" to study drug and the pathological report notes that the observed changes may be due to drug effect (she was on multiple medications). It is reasonable to consider the possibility that the adverse event of hepatic inflammation was possibly associated with voriconazole.

Patient 150 309 2051 1487 had a liver biopsy and also is one of the patients that is discussed under the hepatic failure cases. The reader is referred to the discussion under that section for further details of this patient's clinical course. Her liver biopsy was performed on Day 129 with the report as follows:

Liver cirrhosis as well as inflammatory infiltrate which is more lobular than portal. No evidence of AML. Rare fungal structure, may be hyphae. Histological features may represent acute drug-induced hepatitis. Granulomas may be either drug-induced or may represent reaction to fungal organisms or unknown mycobacterial organisms.

Patient 150 602 8050 2164 was a 58-year-old female with acute myeloid leukemia (diagnosed August 1999) with pre-existing myelodysplastic syndrome and s/p previous "gallbladder surgery." She entered study 602 on September 11, 1999 (Day 1) with sinus aspergillosis and aspergillosis of the liver. She received voriconazole therapy either intravenously or orally from study entry to December 30, 1999 (Day 111). On 11 September 1999 (Day 1) her baseline ALT, AST, alkaline phosphatase, and T. bilirubin were all below the maximum of the normal ranges. Her LFTs after baseline are provided in Table 50. Not included in the table of LFTs below (because the labs were analyzed at a different laboratory with different normal ranges) are LFTs from Day 111 which show an AST, ALT, and T. Bili. within normal range and an alkaline phosphatase slightly elevated at less than 1.5x ULN.



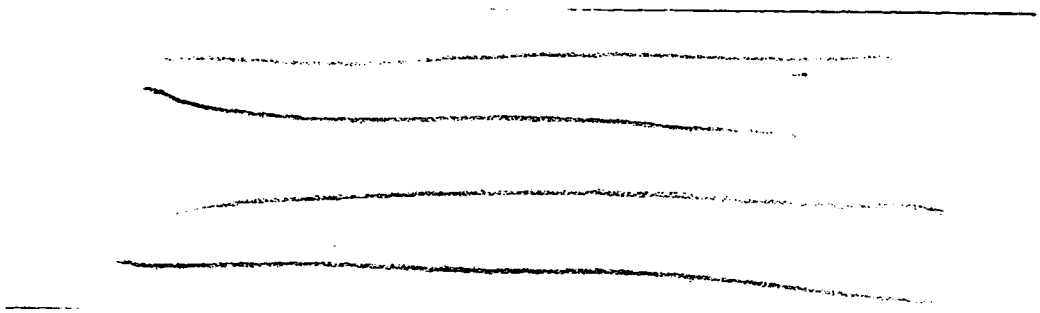
The investigator notes at the November 9, 1999 visit that the elevations in LFTs noted on November 6, 1999 are clinically consistent with liver infection. Voriconazole was administered until 30 December 1999 (Day 111). On 17 January 2000 (Day 129) she underwent liver biopsy with the histopathology reported as follows:

Liver cirrhosis as well as inflammatory infiltrate which is more lobular than portal. No evidence of AML. Rare fungal structures, may be hyphae. Histological features may represent acute drug-induced hepatitis. Granulomas may be either drug-induced or may represent reaction to fungal organisms or unknown mycobacterial organisms.

The concomitant medication CRFs and datasets note only the following concomitant medications continuing beyond December 3, 1999: vancomycin completed December 10, 1999 and oral potassium supplements.

MO Comment: There are several factors that make it difficult to assess likely causal factors for the features noted on liver biopsy. These factors include 1.) the limited details on medication intake after 30 December 1999 (i.e., other drugs that may have been received after completing voriconazole therapy but prior to the liver biopsy); the chronology of her LFTs in relation to the biopsy findings; and *Aspergillus* infection involving the liver. Given the information available, voriconazole cannot be excluded as a potential cause of the possible drug-induced hepatitis noted on biopsy. However, the available information does not exclude the possibility that other causal factors could be involved.

Patient 150 301 2138 0001 was a 14-year-old female with cystic fibrosis (CF), asthma, CF-related arthropathy, s/p liver transplant, w/chronic renal insufficiency, and diabetes mellitus. She was admitted to Study 301 on 01 March 2000 (Day 1) with the diagnosis of pulmonary aspergillosis. Her AST and T. Bili. were within normal limits at study entry and her alkaline phosphatase was 194 IU/L (NR 30-130). She received voriconazole (either IV or PO) from 01 March 2000 through 30 November 2000 (Day 275). The patient's CRFs note an ultrasound of the liver during her 4 November 2000 (Day 249) admission to the hospital that showed "cavities ?abscesses – aspiration = blood only, no growth." (She was admitted for fever.) Information on concomitant medications is not available from the CRFs. Her LFTs are provided in Table 51.



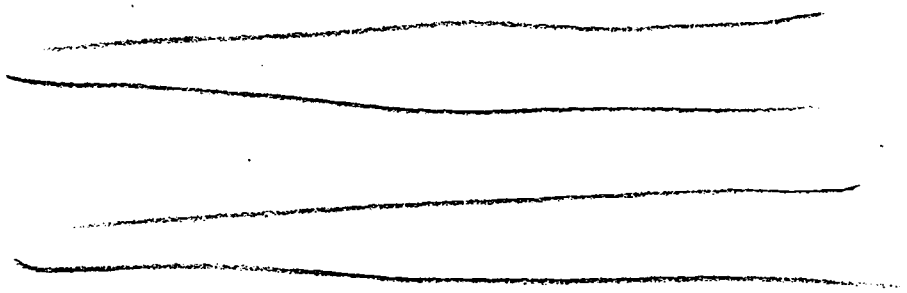
The investigator recorded the adverse event of "jaundice chronic liver graft rejection" on 6 November 2000 and "raised serum AST" on 4 November 2000. Both of these AEs were considered severe and serious by the investigator and neither was classified by the investigator as most likely secondary to study drug. The investigator ascribed the events to chronic liver graft rejection. The patient underwent liver biopsy on Day 262 with the pathologic report as follows.

> *A mild, focally cholangiolitic portal inflammation which includes a few eosinophils. The lobular parenchyma show a fair number of single eosinophilic necrotic cells and apoptotic bodies which are present in the periportal areas too. There are frequent mitosis and discreet foci of inflammation, occasionally enlarged Kupffer cells contain iron. There is a periventricular hepatocyte pigmentation (?bile pigment). Diagnosis Liver biopsy: portal and lobular hepatitis (viral or drug related).*

Voriconazole therapy was discontinued because of treatment failure noted on 30 November 2000 (Day 275).

> **MO Comment:** The limited information regarding this patient's adverse event limits what can be concluded about causality. The patient's concomitant medications are not available. However, for a patient with a liver transplant and a recent febrile episode, it is likely that she was on multiple other medications. Study drug (voriconazole) as a causal or contributing factor cannot be excluded and remains a possible causal or contributory factor for the findings noted on liver biopsy.

Patient 150 309 0014 1010 was a 32-year-old male with HIV infection and AIDS, with a CD4 cell count of 4/mm^3 in November 1998 with a history of CNS toxoplasmosis, CMV esophagitis, prior oral thrush and candida esophagitis, atypical mycobacterial infection involving the lung and the gastrointestinal tract and thrombotic microangiopahty (thrombotic thrombocytopenic purpura) who was admitted to Study 309 on 30 December 1998 with refractory esophageal candidiasis. He received voriconazole orally at a total daily dose of 400mg on 30 December 1998 (Day 1), 800mg from 31 December 1998 to 22 April 1999 and 400mg on 23 April 1999, a total of 115 days. The patient was hospitalized from 24 March 1999 (Day 85) to 29 March 1999 (Day 90) due to myelitis and encephalitis that began during January 1999. On 14 April 1999 (Day 106) the patient was noted to have thrombotic microangiopathy (TTP) and elevated liver function tests (Table 52). Voriconazole was stopped on 23 April 1999 (Day 115) due to TTP and elevated LFTs. Following the discontinuation of voriconazole the patient's LFTs improved, so voriconazole was not re-started. The reason given for the permanent discontinuation of voriconazole was the serious adverse event of cholestatic jaundice (investigator term "cholestatic hepatitis").

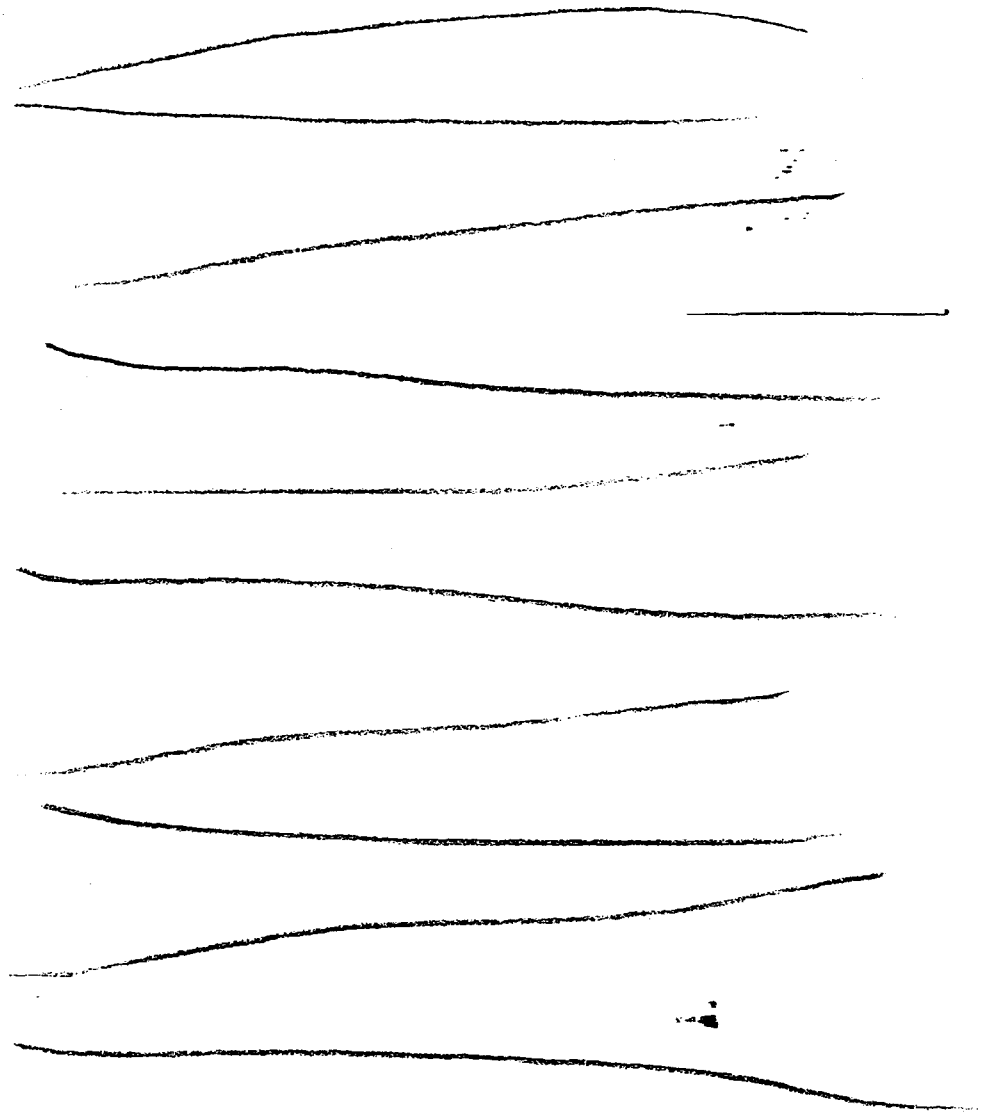


The report from the patient's liver biopsy performed on 16 April 1999 (Day 108) is as follows:

> *Severe cholestasis most of all located around centrilobular veins. Can be associated with drug toxicity.*

The subject was re-hospitalized from 17 to 22 May 1999 (Day 139 – 144) to assess his thrombotic microangiopathy, elevated liver function tests and AIDS. The events were considered resolved on 15 June 1999 (Day 168).

A list of the patient's concomitant medications is provided below (Table 53).



In the opinion of the investigator the thrombotic microangiopathy was due to other illness and elevated liver function tests were due to voriconazole. Review by the study sponsor concluded that an association with voriconazole could not be excluded for the elevated liver function tests.

MO Comment: In this patient with advanced HIV disease with TTP and on multiple other medications who develops elevated liver function tests and has the noted histopathologic findings on liver biopsy, voriconazole cannot be excluded as a causal or contributory factor in the patient's hepatic abnormalities.

Patient 150 301 0205 0003 was a 17-year-old female patient in Spain status-post liver transplantation (for secondary biliary cirrhosis) in February 1999, with diabetes mellitus, who received voriconazole for the treatment of an invasive *Scedosporium prolificans* pulmonary infection. Voriconazole was administered intravenously at total daily doses of

- 540mg IV on 06 August 1999 (Day 1)
- 270mg IV from 07 August 1999 until 02 September 1999
- 330mg IV from 03 September 1999 until 28 September 1999
- 400mg IV from 29 September 1999 until 15 December 1999

This represents a total of 132 days of voriconazole therapy.

On 16 August 1999 (Day 11) the adverse event of thrombocytopenia of moderate severity was reported. A platelet count of "41,000" is noted on one of her CRFs dated 16 August 1999. Her thrombocytopenia led to prolongation of her hospitalization making this a serious adverse event. On 12 September 1999 she is noted to have petechiae. On 15 October 1999 (Day 71) the adverse event of eosinophilia, graded as severe, was reported. Her CRFs note that the action taken in response to the event was to "stop GSF".

> **MO Comment:** The patient's list of concomitant medications notes that she was receiving Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF), not G-CSF. It is possible that the patient's prior adverse event of thrombocytopenia may have been a factor in the clinician's choice to administer or continue GM-CSF. It is also quite possible that the observed eosinophilia may be a response to the GM-CSF the patient was receiving. From the limited information available on concomitant medications it is not clear that the patient's GM-CSF was discontinued.

Within the patient's CRFs there is a notation that the patient's absolute eosinophil count on 23 August 1999 was "9300". The patient's death narrative notes that eosinophilia, eosinophilic liver infiltrates, and deterioration of liver function were events that led to prolongation of the patient's hospitalization.

On 18 October 1999 (Day 74) she had a liver biopsy performed. The histopathological reading on the liver biopsy follow:

> *Important eosinophilia probably related to voriconazole, but this is not sure because could be rejection of transplant although no evidence.*

The patient's CRFs include laboratory values for liver-related laboratory analytes. Although the normal ranges are not provided for the data for this patient, the normal ranges are available in the SAS.txp datasets for other patients from the same center. Patient 150 301 0205 0003's AST, ALT and T. Bili appear to be within normal range when tested on 05 August 1999, 16 August 1999, 03 September 1999, 07 October 1999, 10 November 1999, and 7 December 1999. Her alkaline phosphatase appears to be increased on laboratories from 03 September 1999 through 10 November 1999, but the elevated values are less than what is expected

to be 2x the ULN for the center (laboratory normal ranges for this patient's laboratory values were not available).

On 14 December 1999 (Day 131) the subject's clinical status deteriorated with the emergence of fever, vomiting, headache and neurological deterioration. A diagnosis of meningitis was made and a CT scan of the chest and head were performed. A lumbar puncture was carried out as part of the evaluation of her neurologic deterioration. Both CT scans were "normal" compared to previous scans but the lumbar puncture showed an increased intracranial pressure of 50cm of H_2O. The subject deteriorated further over the following hours and her consciousness level decreased. On 15 December 1999 (Day 132) and 16 December 1999 (Day 133) all treatment was stopped and only sedative medications were administered. Her concomitant medications are listed in Table 54. On 16 December 1999 (Day 133) she experienced difficulty breathing and cyanosis and died the same day with the cause of death reported as meningitis. At the time of death the patient's death narrative notes that the patient was still experiencing thrombocytopenia, eosinophilia, eosinophilic liver infiltrates, and deteriorated liver function. An autopsy result was not available.

In the opinion of the investigator, the cause of death was due to meningitis. Review by the study sponsor concluded that the death was not causally related to voriconazole.

Table 54. Concurrent Medications at the Time of the Serious Adverse Event (14 December 1999)

Preferred Term	Investigator entry	Current at Onset of SAE (Y/N) (14 December 1999)
Acetaminophen	Paracetamol	Y
Acetylcysteine	Fluimucil	Y
Albuterol	Ventolin	Y
Amylase/Lipase/Protease	Pancrease	Y
Bromazepam	Lexatin	Y
Budesonide	Pulmicort	Y
Chlorpheniramine	Polaramine	Y
Cisapride	Propulsid	Y
Clebopride/ Simethicone	Flatoril	Y
Colistin	Colimicine	Y
Dipyrone	Nolotil	Y
Dornase Alfa	Pulmozyme	Y
Granulocyte-Macrophage Colony Stimulating Factor	Leucomax	Y
Hexetidine	Oraldine	Y
Ipratropium	Atrovent	Y
Isophane Insulin	Insuline NPH	Y
Lorazepam	Orfidal	Y
Metoclopramide	Primperam	Y
Midazolam	Midazolam	Y
Morphine	Morphine Sulfate	Y
Morphine	Sevredol	Y
Omeprazole	Omeprazole	Y
Parenteral Feeding	Parenteral Nutrition	Y
Prednisone	Prednisone	Y
Regular Insulin	Actrapid Insulin	Y
Sodium Chloride	NaCl	Y
Tacrolimus	FK-506	Y

MO Comment: This patient's eosinophilia and eosinophilic infiltrates noted on biopsy present some interesting questions. First, what the role of GM-CSF was in the patient's eosinophilia. It is not clear that her GM-CSF was discontinued. Second, given her marked peripheral eosinophilia and the lack of a remarkable changes or abnormalities in her AST, ALT, and T. Bili., and only a minor increase in her alkaline phosphatase what is the effect of the eosinophils on liver tissue noted on biopsy. The patient's death narrative notes "deterioration of liver function" but it isn't clear what laboratory data support that a deterioration of liver function has occurred. The laboratory values available do not include a prothrombin time, or albumin. While she is reported to have experienced a decline in her neurologic status, this event is attributed to "meningitis". Encephalitis (not further specified) is also mentioned in the patient's CRFs. In addition, this patient is status post a liver transplant and is on multiple concomitant medications. All of these factors interfere with the ability to clearly assess the role of voriconazole in the patient's adverse event of eosinophilia and in the findings noted on liver biopsy.

Patient 606-8032-0165 was a 52-year-old female s/p liver transplant (12/98) for autoimmune hepatitis. She entered protocol 606 on 03 May 2000. The condition leading to her admission into the study was *Torulopsis glabrata* peritonitis. Her case report forms note a history of a number of other medical conditions including prior bacterial peritonitis, a history of deep venous thrombosis, s/p IVC filter placement, hypertension, glucose intolerance, chronic renal failure, splenomegaly, thrombocytopenia. Also included among the patient's history of past medical problems are esophageal candidiasis, herpes esophagitis, acute liver rejection, esophageal varices, atypical mycobacterial infection, and a central nervous system aspergillus infection. Also of note is her admission weight of 42 kg.

She was started on voriconazole on 04 May 2000 (Day 1). Her voriconazole dose ranged from 150 mg bid to 400 mg bid during the study. She received voriconazole through 09 June 2000. On 09 June 2000 her voriconazole therapy was discontinued and the patient was switched to AmBisome. On 06 June 2000 she is noted to have an ascites fluid culture positive for "fungus". At her 12 June 2000 visit she is noted to have a response of failure. Hence, her switch to AmBisome appears to be as a result of her failure to respond. The records do not provide the duration of her AmBisome therapy. She underwent liver biopsy on 11 July 2000 and then a second liver biopsy on 20 July 2000. Her liver biopsy results are as noted below:

11 July 00-biopsy - mixed cellular infiltrate, possibly liver vasculitis. Diagnosis of acute cellular rejection.

20 July 00-biopsy -marked centrilobular cholestasis and hepatocellular ballooning with hepatocellular necrosis and mild portal inflammation: the portal areas contain sparse to mild infiltrate of lymphoid cells, the bile ducts are intact and there is no endothelialiatis. Marked hepatocellular and canalicular cholestasis with hepatocellular ballooning is present in centrilobular region. Focally, there is loss of hepatocytes in the centrilobular region and some scattered acidophilic bodies are present in the lobules. There are some scattered inflammatory cells in the lobules. Viral inclusion bodies are not recognized. Many Kupffer cells stain for iron. Faint staining of some hepatocytes for iron is also

present. The intensity of inflammatory cell infiltrate is less than in previous biopsy. The marked cholestasis and hepatocellular changes in the present biopsy suggest drug-induced liver injury. A possibility of ischemic injury cannot be excluded.

Concomitant medication data was not recorded. (Given her liver transplant, she is likely to be maintained on at least several medications.) Other adverse events that she experienced included severe cholestasis and moderate aminotransferase elevations on 08 May 2000 leading to a reduction in her voriconazole dose (lab values for 08 May 2000 are not available). The adverse event of elevated liver function tests (graded as severe and serious) was reported on 10 July 2000 and was considered by the investigator to be secondary to organ rejection.

Normal ranges and units were not provided for her laboratory data. However, it is notable that her alkaline phosphatase which appears to be slightly elevated at baseline triples by the Day 10 visit (11 May 2000). The case report forms also note elevations of transaminases on 15 and 16 May 2000 which are attributed by the investigator on 16 May 2000 to septic shock.

MO Comment: This patient's first liver biopsy, which occurs 32 days after voriconazole therapy was discontinued, shows acute cellular rejection. Her second biopsy, 42 days after voriconazole therapy has been discontinued (and following her episode of acute cellular rejection) is read as showing "marked cholestasis and hepatocellular changes in the present biopsy suggest drug-induced liver injury." Unfortunately concomitant medications were not recorded. Presumably she would have received therapy for her episode of acute cellular rejection. Given the chronology, and sequence of events noted with regards to the liver biopsy findings, the role of voriconazole in these events is unclear. The reported adverse events that occurred while the patient was on voriconazole of "cholestasis" and "elevation of alanine aminotransferase" were considered most likely related to voriconazole therapy.

Analysis of Demographic Factors

Analyses of Clinically Significant Abnormalities of Transaminases (CSAT) between different strata of gender, race, age, and weight were performed in selected populations (Table 55). When considering the data across the three voriconazole populations analyzed, there are no consistent differences in the proportion of patients experiencing CSAT by gender. The analyses stratifying by race are somewhat limited by the small numbers of patients in some racial groups in the populations analyzed. With this limitation in mind, there may be a trend toward less frequent CSAT in the race group of Black. Regarding differences by age, within the limited number of patients in the younger age groups, CSAT appear to be more common among the younger age groups (<12 and 12-15). Also noteworthy is that a large proportion of the patients in the younger age groups are from the Compassionate Use studies. In the strata of patients with weight less than 40kg (a limited number of patients) CSAT are more frequent than in the patients of 40kg or more.

> **MO Comment:** The results from the stratified analysis should be interpreted with some degree of caution because the limited numbers of patients in some patient groups and the potential that other factors beyond the single stratification variable examined in each of these analyses may also play a role in the abnormal transaminases laboratory values.

> **MO Comment:** As noted in the section of this review addressing the experience with voriconazole in pediatric patients, additional information on liver-related adverse events and laboratory abnormalities should be collected in future studies in pediatric patients.

Table 55. Incidence of Subjects with Clinically Significant Abnormalities* of Transaminases (CSAT) by Demographic Characteristics

		Voriconazole Therapeutic Studies			Amphotericin B Formulations Therapeutic Studies			Voriconazole All Subjects			Voriconazole Compassionate Use		
		n	N	(%)	n	N	(%)	n	N	(%)	n	N	(%)
Incidence of CSAT n of N Subjects		200	1493	(13.4)	71	665	(10.7)	293	2090	(14.0)	93	597	(15.6)
Stratification Variables													
Gender	Male	118	931	(12.7)	38	358	(10.6)	188	1333	(14.1)	70	402	(17.4)
	Female	82	562	(14.6)	33	307	(10.7)	105	756	(13.9)	23	194	(11.9)
	Unknown	0	0	-	0	0	-	0	1	(0.0)	0	1	(0.0)
Race	White	162	1207	(13.4)	60	537	(11.2)	240	1663	(14.4)	78	456	(17.1)
	Black	15	141	(10.6)	1	50	(2.0)	17	158	(10.8)	2	17	(11.8)
	Asian	12	80	(15.0)	3	34	(8.8)	14	97	(14.4)	2	17	(11.8)
	Hispanic	11	65	(16.9)	7	44	(15.9)	12	79	(15.2)	1	14	(7.1)
	Other	0	0	-	0	0	-	0	0	-	0	0	-
	Unknown	0	0	-	0	0	-	10	93	(10.8)	10	93	(10.8)
Age (years)	<12	0	1	-	0	0	-	12	56	(21.4)	12	55	(21.8)
	12-15	10	25	(40.0)	2	20	(10.0)	20	61	(32.8)	10	36	(27.8)
	16-44	86	704	(12.2)	24	260	(9.2)	132	974	(13.6)	46	270	(17.0)
	45-64	79	573	(13.8)	31	289	(10.7)	100	755	(13.2)	21	182	(11.5)
	65-74	20	149	(13.4)	10	71	(14.1)	23	185	(12.4)	3	36	(8.3)
	>=75	5	41	(12.2)	4	25	(16.0)	6	57	(10.5)	1	16	(6.3)
	Unknown	0	0	-	0	0	-	0	2	(0.0)	0	2	(0.0)
Weight (kg)	<40 kg	7	36	(19.4)	0	11	(0.0)	30	138	(21.7)	23	102	(22.5)
	>=40 kg	193	1457	(13.2)	71	654	(10.9)	254	1860	(13.7)	61	403	(15.1)
	Unknown	0	0	-	0	0	-	9	92	(9.8)	9	92	(9.8)

Note:
1. Protocols included are 301, 303, 303A, 304, 304A, 305, 307, 309, 311, 312, 602, 603, 604, 606, 607, 608
2. * BL<2xULN and value>=5xBL, or 2xULN<=BL<5xULN and value>=3xBL, or 5xULN<=BL<=10xULN and value>=2xBL, or BL>=10xULN and value>=1.5xBL
3. BL = Baseline result in standard units, ULN = Upper Limit of Normal in standard units
4. n = Number of subjects with a clinically significant abnormality of transaminases
5. N = Number of subjects tested

Source: Applicant's table 4-3 from the June 2001 ISS safety Update

patients taking voriconazole than fluconazole (the comparator agent for the esophageal candidiasis study). While the numbers are small, serious adverse events were reported more frequently among patients receiving voriconazole in the phase III comparative studies than among patients receiving comparators. Discontinuations from initial randomized therapy for liver-related adverse events occurred more frequently among patients receiving voriconazole than comparators. Note that for amphotericin B deoxycholate, discontinuations for renal-related adverse events were more frequent than for voriconazole.

The cases of hepatic failure from the NDA database were reviewed. All of the patients with hepatic failure events expired. Review of these cases to evaluate the potential causal or contributory factors was challenging because of the number of confounding medical conditions and multiple concomitant medications that patients were receiving. These cases of hepatic failure all also underwent blinded review and assessment by a panel of expert hepatologists. Comparison of the liver-related deaths from the comparative studies revealed no marked differences between the deaths in the voriconazole-treated patients and the comparator-treated patients. The four cases that were scored the highest in terms of likelihood that study drug was related were all from the non-comparative studies. There were 4 hepatic failure cases from the non-comparative studies that at least two of the four expert hepatologists scored the case as at least possibly related to study drug.

The histopathologic readings for all patients for whom histopathologic evaluation of liver tissue was available (from either biopsy or autopsy) were reviewed. Similar to the hepatic failure cases, many of these cases involved patients with other serious medical conditions, receiving other medications, and in some cases recipients of liver transplants. There were three cases where eosinophilia was noted on the liver biopsy report. All three patients were liver transplant recipients. One of the three patients also had marked peripheral eosinophilia in the absence of hepatocellular damage noted on biopsy and with normal transaminases. Voriconazole as a possible contributing factor to the findings noted on liver biopsy in these three cases 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.

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.

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Medical Officer's Recommendations for Phase IV Studies

In order to facilitate monitoring of hepatic adverse events in the post-approval period, the Applicant should provide quarterly reports summarizing reported liver-related adverse events reported for the first year or two (depending on the volume of use) after marketing is initiated. Ideally vigilant reporting will help to detect an excess of liver-related events at the earliest opportunity should an excess number of events be occurring when the drugs is marketed. No other formal phase IV studies are recommended at present.

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Medical Officer's Labeling Recommendations

The portions of the label for which the MO has recommended changes are provided in the following sections. Note that only those sections or subsections where the MO has suggested revisions are provided below.

WARNINGS section

A revised version of the Hepatic toxicity subsection incorporating the MO's recommended changes with (the changes tracked) is provided below.

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:

patients who develop abnormal 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).

PRECAUTIONS section

The following subsections within the PRECAUTIONS section contains the following hepatic-related information.

Laboratory Tests

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

...

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.

MO Comments/Recommendations: The MO has no suggested changes to the above hepatic-related information from the PRECAUTIONS section.

ADVERSE REACTIONS section

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

Overview

The safety of voriconazole must be considered within the context of the patient populations in whom it has been studied and in whom it is intended to be used. The frequency and nature of adverse events reported during voriconazole therapy reflects both the effects of treatment as well as the severe underlying condition of the patients. The most frequent serious adverse events were related to infectious processes in these immunocompromised patients.

The most frequently reported adverse events (all causalities) in the therapeutic trials were visual disturbances, fever, rash, vomiting, nausea, diarrhea, headache, sepsis, peripheral

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

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

MO Comment/Recommendation: For purposes of fair balance and also to provide health care providers with important information, a similar table with data from Study 305 should be presented. The analogous table for Study 305 can replace the current table for Study

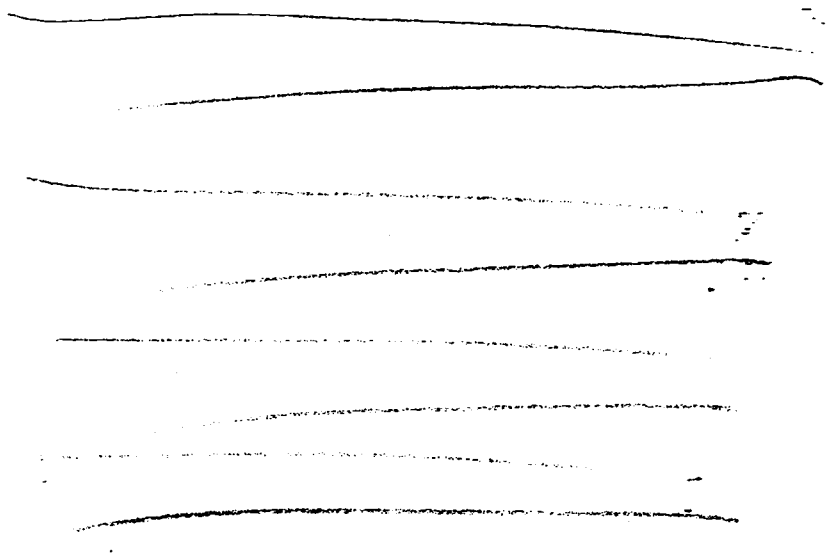
PROTOCOL 305
Clinically Significant Laboratory Test Abnormalities

	Criteria*	VORICONAZOLE	FLUCONAZOLE
		n/N (%)	n/N (%)
T. Bilirubin	>1.5x ULN	8/185 (4.3)	7/186 (3.8)
AST	>3.0x ULN	38/187 (20.3)	15/186 (8.1)
ALT	>3.0x ULN	20/187 (10.7)	12/186 (6.5)
Alk. phos.	>3.0x ULN	19/187 (10.2)	14/186 (7.5)

* Without regard to baseline value
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

DOSAGE AND ADMINISTRATION section

The DOSAGE AND ADMINISTRATION section includes a subsection entitled "Use in Patients With Hepatic Insufficiency", which includes information regarding dose adjustment.



The available data do not allow for any specific guidance to be provided regarding severe acute hepatic injury. Therefore the MO's suggests that the language advising the clinician that no dosage adjustment is necessary in acute hepatic injury be removed.

Use in 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).

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.

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/s/

Edward Cox
5/14/02 05:51:32 PM
MEDICAL OFFICER

Marc Cavaille Coll
6/7/02 04:24:08 PM
MEDICAL OFFICER

Renata Albrecht
6/12/02 08:53:05 AM
MEDICAL OFFICER

Medical Officer's Consultation Review of NDA 21-266
Ophthalmology

NDA #21-266	Submission date:	6/21/01
Ophthalmology	Received date:	6/21/01
	Review date:	11/21/01

Proposed name: VFEND™ (voriconazole) Film-Coated Tablets

Sponsor: Pfizer

Drug class: Anti-fungal

Table of Contents

Executive Summary

I. Recommendations

A. Recommendation on Approvability

From an ophthalmology prospective, there is no objection to the approval of this NDA provided appropriate Warning, Precaution and Adverse Experience information is included in the labeling as outlined in this review.

B. Recommendation on Phase 4 Studies and Risk Management Steps

Additional Phase 4 studies are recommended to investigate the long-term ocular consequences (i.e., greater than 28 days of treatment).

Additional Phase 4 studies are recommended to investigate the visual effects in children under 9 years of age.

II. Summary of Clinical Findings

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

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

These effects were noted in:

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

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

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

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

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

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

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

9) Effects on ocular function of the developing eye (children less than 9 years of age) is unknown.

10) Treatment of ocular infections with topical formulation of voriconazole have generally not been successful. No formal efforts to develop an ocular formulation appear to have occurred.

PHARMACOKINETIC-PHARMACODYNAMIC RELATIONSHIPS

Pharmacokinetic-pharmacodynamic analyses of clinical trial data identified positive associations between plasma voriconazole concentrations and both liver function test abnormalities and visual disturbances (see ADVERSE REACTIONS).

Reviewer Comments: *Acceptable.*

WARNINGS

The effect of VFEND of visual function is not known if treatment continues beyond 28 days. If treatment continues beyond 28 days, visual function including visual field and color perception should be monitored.

PRECAUTIONS

Information For Patients

Patients should be advised:

- that VFEND Tablets should be taken at least one hour before, or one hour following, a meal.
- that they should not drive at night while taking VFEND. VFEND may cause changes to vision, including blurring and/or photophobia.
- that they should avoid potentially hazardous tasks, such as driving or operating machinery if they perceive any change in vision.
- that strong, direct sunlight should be avoided during VFEND therapy.

patients (421 on voriconazole, 428 on AmBisome®) were treated to evaluate empirical therapy in febrile neutropenic patients. Voriconazole-treated patients had a higher rate of visual disturbances and hallucinations and a lower rate of infusion related adverse events (fever, chills, vasodilatation, tachycardia, and dyspnea), ~~and a higher rate of visual disturbances and hallucinations.~~ Laboratory test abnormalities are discussed under Clinical Laboratory Values below.

Table 4
TREATMENT- EMERGENT ADVERSE EVENTS
All Causalities
Rate ≥ 5% and Adverse Events of Concern with Rate 2 - < 5% in All Therapeutic Studies

	All Therapeutic Studies	**Empirical Therapy** Protocol 603		**Aspergillosis** Protocols 307/602	
	Voriconazole N=1493	Voriconazole N = 421	AmBisome® N = 428	Voriconazole N =196	Ampho B* N = 185
	N (%)	N (%)	N (%)	N (%)	N (%)
Special senses					
Abnormal vision	363 (24.3)	110 (26.1)	21 (4.9)	65 (33.2)	8 (4.3)
Photophobia	46 (3.1)	10 (2.4)	4 (0.9)	8 (4.1)	1 (0.5)
Eye hemorrhage	43 (2.9)	24 (5.7)	21 (4.9)	4 (2.0)	7 (3.8)

*Amphotericin B followed by other licensed antifungal therapy

Visual Disturbances: Voriconazole treatment-related visual disturbances are common. In clinical trials, approximately 30% of patients experienced altered/enhanced visual perception, blurred vision, color vision change and/or photophobia. The visual disturbances

generally mild ~~and rarely~~ resulted in discontinuation . Visual disturbances may be associated with higher plasma concentrations and/or doses.

The mechanism of action of the visual disturbances is unknown, although the site of action is most likely to be within the retina. In a study in healthy volunteers investigating the effect of 28 day treatment with voriconazole on retinal function, voriconazole caused a decrease in the electroretinogram (ERG) waveform amplitude, a decrease in the visual field and an alteration in color perception. The ERG measures electrical currents in the retina.

Less Common Adverse Events

The following adverse events occurred in < — of voriconazole-treated patients, including healthy volunteers and patients treated under compassionate use protocols (total N = 2090). This listing includes events where a causal relationship to voriconazole cannot be ruled out or those which may help the physician in managing the risks to the patients. The list does not include events included in Table —above and does not include every event reported in the voriconazole clinical program.

Special senses: abnormality of accommodation, blepharitis, color blindness, conjunctivitis, corneal opacity, deafness, ear pain, eye pain, dry eyes, keratitis, keratoconjunctivitis, mydriasis, night blindness, optic atrophy, optic neuritis, otitis externa, papilledema, retinal hemorrhage, retinitis, scleritis, taste loss, taste perversion, tinnitus, uveitis, visual field defect

Reviewer Comments: *Acceptable.*

Study 1501004

A DOUBLE BLIND, RANDOMISED, PLACEBO CONTROLLED, PARALLEL GROUP STUDY TO INVESTIGATE THE EFFECT OF MULTIPLE ORAL DOSES OF VORICONAZOLE ON VISUAL FUNCTION IN HEALTHY MALE SUBJECTS

2053 Investigator: Dr D Kleinermans
Biotrial Rue Jean-Louis Bertrand Technopole
Atalante Villejean 35000 – RENNES, FRANCE

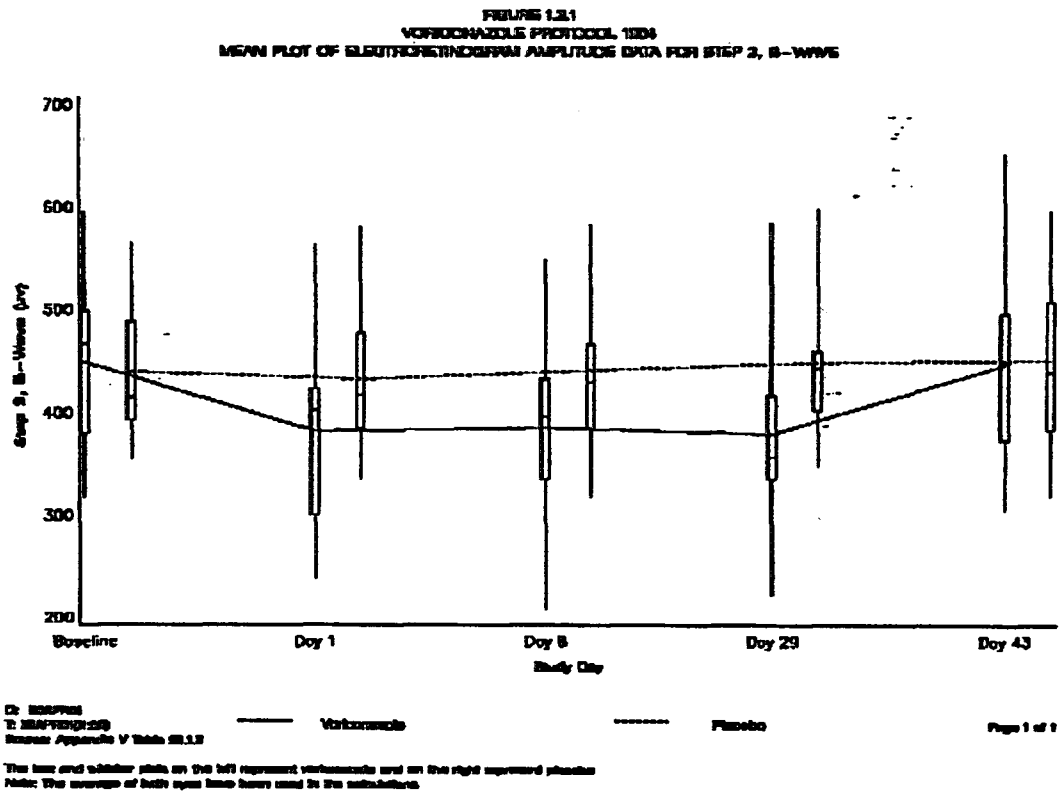
Co-investigator: [redacted]

Study Design: This was a double blind, randomized, placebo controlled, parallel group study. A sufficient number of subjects were to be screened to ensure that 36 subjects completed the study. Subjects were to be stratified according to age (Group A: 18 to 25 years, Group B: 26 to 35 years and Group C: 36 to 45 years). The study consisted of one study period of 43 days. Subjects received oral voriconazole (400mg every 12 hours (q12h) on Day 1 followed by 300mg q12h for 27.5 days) or matched placebo q12h for 28.5 days. ERGs were performed during screening and on Days 1, 8, 29 and 43. Farnsworth-Munsell 100 Hue test, Humphrey visual field test, slit lamp test, visual acuity test, external eye examinations and funduscopy were performed during screening and on Days 3, 7, 28 and 42.

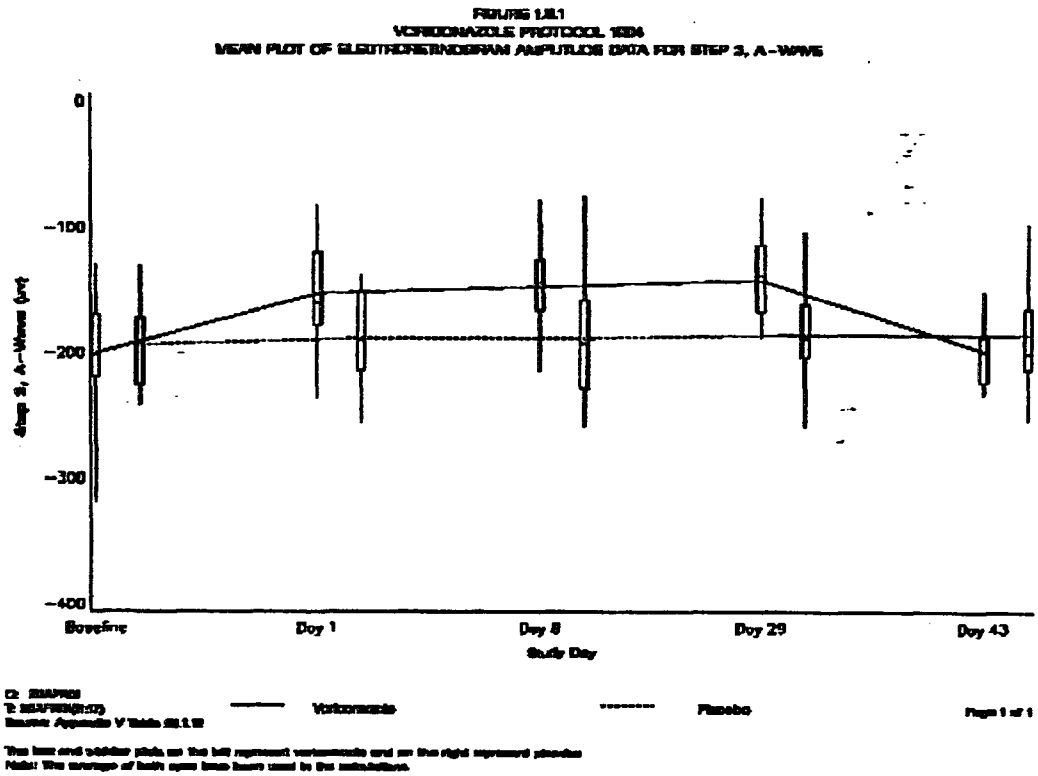
Drug Administration:

Dosage Form	Voriconazole was supplied as 200mg and 50mg tablets.
Dosing	Two x 200mg tablets were taken for the 400mg dose (Day 1 q12h) and one x 200mg tablet and two x 50mg tablets for the 300mg dose (Days 2 to 28 q12h and Day 29 morning dose only). Two x matched placebo tablets were taken on Day 1 q12h and three x matched placebo tablets were taken on Days 2 to 28 q12h and Day 29 morning dose only.
Duration	Total duration of dosing was 28.5 days.

ERG Summary – B Wave



Reviewer Comments: *Patients treated with voriconazole demonstrate a reduction in applitude from day 1 throughout the 28 day treatment period. The applitude returns to normal after a 14 day recovery period.*



Reviewer Comments: *A- waves of the ERG are also affected.*

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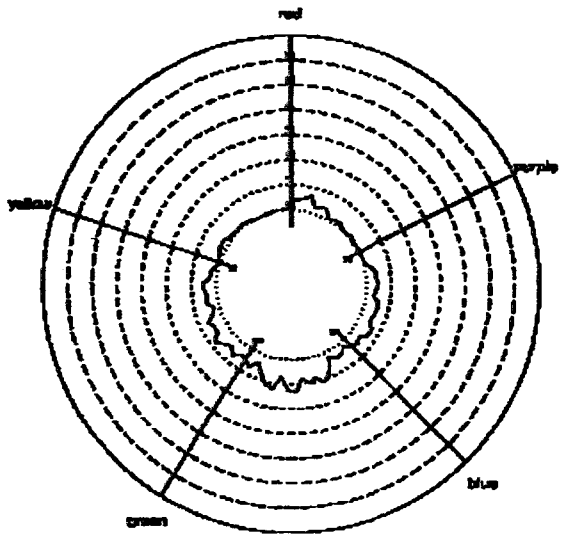
FIGURE 6.1.1
VORICONAZOLE PROTOCOL 1004
FARNSWORTH–MUNSELL 100 HUE TEST
MEAN ERROR SCORE FOR EACH DAP – VORICONAZOLE BASELINE

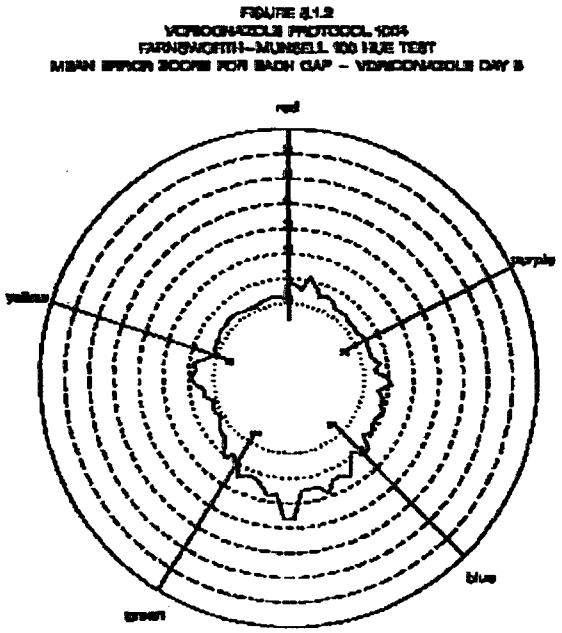


D : 19AFR01
T : 19AFR01[4.1E]
Source: Appendix V Tables 22.1 and 23.2

Page 1 of 1

Reviewer Comments: *The baseline Color vision is normal.*

Color Vision Day 3



D : 19APR01
T : 19APR01043B
Source: Appendix V Tables 23.1 and 23.2

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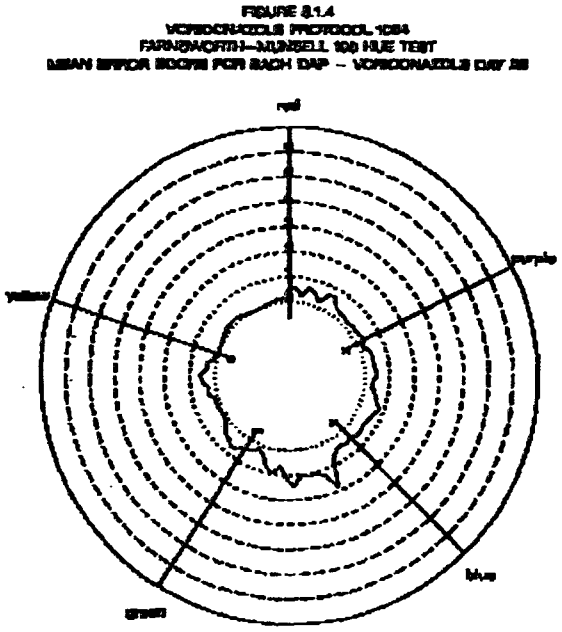
Reviewer Comments: *The color vision demonstrates confusion in the blue-green region.*

Color Vision Day 28

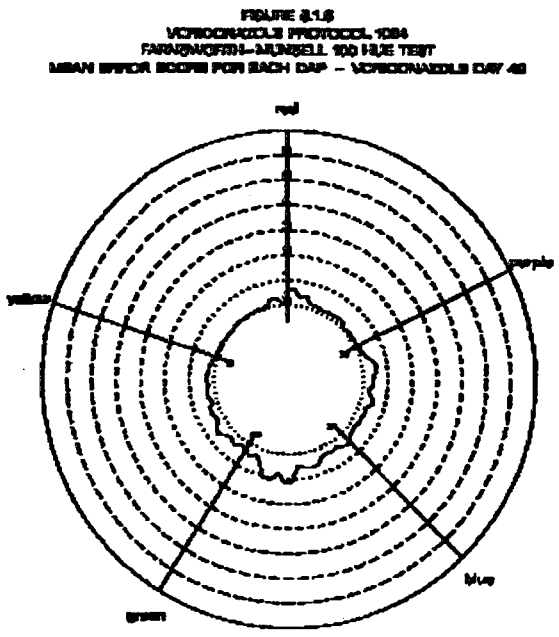


D : 19APR01
T : 19APR01[illegible]
Source: Appendix V Tables 23.1 and 23.2

Page 1 of 1

Reviewer Comments: *There are continued defects at day 28.*

Color Vision – 14 days after the end of treatment



D : 19APR01
T : 19APR01(9:47)
Source: Appendix V Tables 23.1 and 23.2

Page 1 of 1

Reviewer Comments: *The color vision changes return to normal, 14 days after treatment.*

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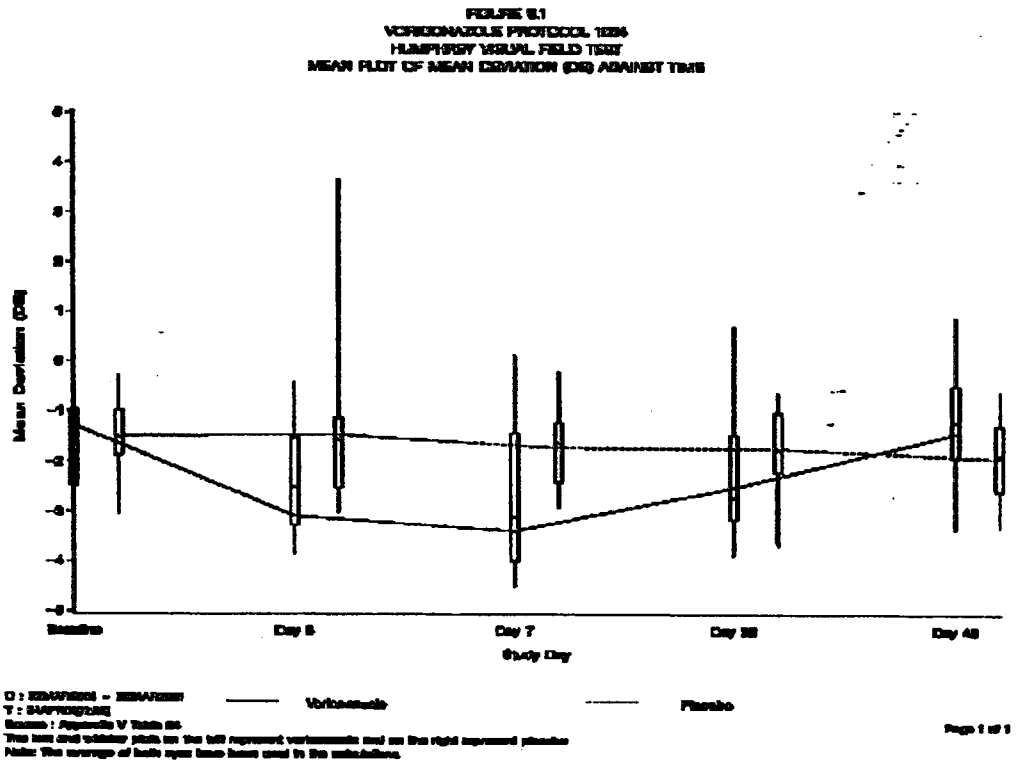
Visual field testing



Reviewer Comments: *Patients treated with voriconazole demonstrate a reduction in threshold visual field from day 1 throughout the 28 day treatment period. The visual field returns to normal after a 14 day recovery period.*

Reported Adverse Experiences

VORICONAZOLE PROTOCOL 1004
INCIDENCE OF VISUAL ADVERSE EVENTS (TREATMENT EMERGENT, TREATMENT RELATED)

	VORICONAZOLE	PLACEBO
NUMBER OF:	n	n
Evaluable Subjects	18	18
Subjects with Visual Adverse Events	15	5
ENHANCED/ALTERED VISUAL PERCEPTION	9	3
BLURRED VISION	5	1
CHANGES IN COLOUR VISION	4	0
PHOTOPHOBIA	12	3
OTHER	9	1

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Summary of Adverse Events – All studies

Adverse Events (All Causalities) Occurring in ≥ — of Voriconazole-Treated Subjects

	Voriconazole		Amphotericin B Formulations	
	N	%	N	%
Total Treated	1493		665	
No. with Adverse Events	1437	96.2	657	98.8
Adverse Events				
Abnormal vision	363	24.3	28	4.2

Reviewer Comments: *This percentage is lower than the larger individual studies. This is probably due to the differences in individual study duration. As listed below, larger individual studies reported abnormal vision in approximately one third of patients.*

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Ocular Adverse Events from Studies 307/602

	VORICONAZOLE				OLAT (FOLLOWING VORICONAZOLE)				AMPHOTERICIN B				OLAT (FOLLOWING AMPHOTERICIN B)			
NUMBER OF SUBJECTS BY	n=196					n=75				n=185				n=144		
		SEV.*				SEV.*				SEV.*				SEV.*		
BODY SYSTEM COSTART Preferred Term	n(%)	MILD	MOD.	SEV.	n(%)	MILD	MOD.	SEV.	n(%)	MILD	MOD.	SEV.	n(%)	MILD	MOD.	SEV.
SPECIAL SENSES	93(47.4)	73	25	5	21(28.0)	9	8	7	13 (7.0)	9	5	0	25(17.4)	16	11	0
Abnormal vision	65(33.2)	51	14	0	5 (6.7)	3	2	0	6 (3.2)	5	1	0	3 (2.1)	1	2	0
Blepharitis	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.7)	0	1	0
Cataract nos	1 (0.5)	1	0	0	0	0	0	0	1 (0.5)	1	0	0	0	0	0	0
Chromatopsia	2 (1.0)	1	0	1	1 (1.3)	0	0	1	0	0	0	0	0	0	0	0
Conjunctivitis	4 (2.0)	2	2	0	1 (1.3)	0	1	0	0	0	0	0	4 (2.8)	2	2	0
Dry eyes	1 (0.5)	1	0	0	0	0	0	0	0	0	0	0	2 (1.4)	1	1	0
Eye disorder	1 (0.5)	1	0	0	1 (1.3)	1	0	0	0	0	0	0	1 (0.7)	0	1	0
Eye hemorrhage	4 (2.0)	2	2	0	3 (4.0)	1	1	1	1 (0.5)	1	0	0	6 (4.2)	4	2	0
Eye pain	2 (1.0)	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Glaucoma	3 (1.5)	3	0	0	1 (1.3)	1	0	0	0	0	0	0	1 (0.7)	0	1	0
Keratitis	1 (0.5)	0	1	0	0	0	0	0	0	0	0	0	1 (0.7)	0	1	0
Keratoconjunctivitis	0	0	0	0	1 (1.3)	0	1	0	0	0	0	0	0	0	0	0
Lacrimation disorder	1 (0.5)	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Optic neuritis	1 (0.5)	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
Photophobia	8 (4.1)	7	1	0	0	0	0	0	0	0	0	0	1 (0.7)	1	0	0
Ptosis	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.7)	1	0	0
Retinal disorder	4 (2.0)	1	2	1	0	0	0	0	0	0	0	0	1 (0.7)	0	1	0
Retinal hemorrhage	5 (2.6)	2	2	1	4 (5.3)	1	1	2	0	0	0	0	1 (0.7)	1	0	0
Retinitis	1 (0.5)	0	1	0	1 (1.3)	0	1	0	0	0	0	0	1 (0.7)	0	1	0
Uveitis	1 (0.5)	0	0	1	1 (1.3)	0	0	1	0	0	0	0	0	0	0	0
Visual field defect	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.7)	1	0	0

Additional Findings during Review

Reviewer Comments:

1. *A number of patients with ocular disease were attempted to be treated with ophthalmic formulations of voriconazole. These attempts at treatment were generally outside the planned protocol and were generally unsuccessful in clearing the infection.*

2. *Most ocular events were followed until resolution, however some patients were lost to follow-up.*

3. *The abnormal retinal findings (thinning) in the carcinogencity studies have not been demonstrated in the human studies, however, the duration of treatment has not been equivalent.*

4. *No abnormalities have been noted in slit lamp examinations of the anterior segment.*

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Summary of Clinical Findings

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

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

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

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

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

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

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

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

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

9. Effects on ocular function of the developing eye (children less than 9 years of age) is unknown.

10. Treatment of ocular infections with topical formulations of voriconazole have generally not been successful. No formal efforts to develop an ocular formulation appear to have occurred

Recommendations:

1. From an ophthalmologic prospective, the application may be approved with the labeling revisions identified in this review.

2. Additional studies are recommended to evaluate the ocular effects of long term (i.e., greater than 28 days) of treatment. The testing should include visual acuity, visual field (automated threshold testing), color vision (Farnsworth-Munsell 100 hue) and dilated funduscopy.

3. Additional studies are recommended to evaluate the ocular effects in children under the age of 9 years. The testing should include visual acuity, visual field, color vision 100 hue) and dilated funduscopy.

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

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