PROPOSED US PACKAGE INSERT

PRODUCT NAME

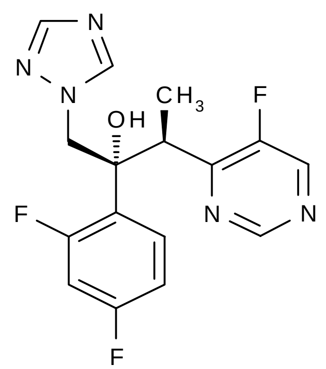
VFEND® (voriconazole) Tablets
VFEND® I.V. (voriconazole) for Injection

Version 22 May 02

DESCRIPTION

VFEND® (voriconazole), a triazole antifungal agent, is available as film-coated tablets for oral administration, and as a lyophilized powder for solution for intravenous infusion.

The structural formula is:



VFEND is designated chemically as (2R, 3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1*H* -1,2,4-triazol-1-yl)-2-butanol with an empirical formula of $C_{16}H_{14}F_3N_5O$ and a molecular weight of 349.3.

VFEND drug substance is a white to light-colored powder.

VFEND Tablets contain 50 mg or 200 mg of voriconazole. The inactive ingredients include lactose monohydrate, pregelatinized starch, croscarmellose sodium, povidone, magnesium stearate and a coating containing hydroxypropyl methylcellulose, titanium dioxide, lactose monohydrate and triacetin.

VFEND I.V. is a white lyophilized powder containing nominally 200 mg voriconazole and 3200 mg sulfobutyl ether beta-cyclodextrin sodium in a 30 mL Type I clear glass vial.

VFEND I.V. is intended for administration by intravenous infusion. It is a single dose, unpreserved product. Vials containing 200 mg lyophilized VFEND are intended for reconstitution with Water for Injection to produce a solution containing 10 mg/mL VFEND and 160 mg/mL of sulfobutyl ether beta-cyclodextrin sodium. The resultant solution is further diluted prior to administration as an intravenous infusion (see DOSAGE AND ADMINISTRATION).

CLINICAL PHARMACOLOGY

Pharmacokinetics

General Pharmacokinetic Characteristics

The pharmacokinetics of voriconazole have been characterized in healthy subjects, special populations and patients.

The pharmacokinetics of voriconazole are non-linear due to saturation of its metabolism. The interindividual variability of voriconazole pharmacokinetics is high. Greater than proportional increase in exposure is observed with increasing dose. It is estimated that, on average, increasing the oral dose in healthy subjects from 200 mg Q12h to 300 mg Q12h leads to a 2.5-fold increase in exposure (AUC_τ) while increasing the intravenous dose from 3 mg/kg Q12h to 4 mg/kg Q12h produces a 2.3- fold increase in exposure (Table 1).

Table 1
Population Pharmacokinetic Parameters of Voriconazole in Volunteers

	200 mg Oral Q12h	300 mg Oral Q12h	3 mg/kg IV Q12h	4 mg/kg IV Q12h
AUC_τ* (µg•h/mL) (CV%)	19.86 (94%)	50.32 (74%)	21.81 (100%)	50.40 (83%)

*Mean AUCτ are predicted values from population pharmacokinetic analysis of data from 236 volunteers

During oral administration of 200 mg or 300 mg twice daily for 14 days in patients at risk of aspergillosis (mainly patients with malignant neoplasms of lymphatic or hematopoietic tissue), the observed pharmacokinetic characteristics were similar to those observed in healthy subjects (Table 2).

Table 2
Pharmacokinetic Parameters of Voriconazole in Patients at Risk for Aspergillosis

	200 mg Oral Q12h (n=9)	300 mg Oral Q12h (n=9)
AUC_{τ}* (µg•h/mL) (CV%)	20.31 (69%)	36.51 (45%)
C_{max}* (µg/mL) (CV%)	3.00 (51%)	4.66 (35%)

*Geometric mean values on Day 14 of multiple dosing in 2 cohorts of patients

Sparse plasma sampling for pharmacokinetics was conducted in the therapeutic studies in patients aged 12-18 years. In 11 adolescent patients who received a mean voriconazole maintenance dose of 4 mg/kg IV, the median of the calculated mean plasma concentrations was 1.60 µg/mL (inter-quartile range 0.28 to 2.73 µg/mL). In 17 adolescent patients for whom mean plasma concentrations were calculated following a mean oral maintenance dose of 200 mg Q12h, the median of the calculated mean plasma concentrations was 1.16 µg/mL (inter-quartile range 0.85 to 2.14 µg/mL).

When the recommended intravenous or oral loading dose regimens are administered to healthy subjects, peak plasma concentrations close to steady state are achieved within the first 24 hours of dosing. Without the loading dose, accumulation occurs during twice-daily multiple dosing with steady-state peak plasma voriconazole concentrations being achieved by day 6 in the majority of subjects (Table 3).

Table 3
Pharmacokinetic Parameters of Voriconazole from Loading Dose and Maintenance Dose Regimens (Individual Studies in Volunteers)

	400 mg Q12h on Day 1, 200 mg Q12h on Days 2 to 10 (n=17)		6 mg/kg IV** Q12h on Day 1, 3 mg/kg IV Q12h on Days 2 to 10 (n=9)	
	Day 1, 1st dose	Day 10	Day 1, 1st dose	Day 10
AUC_τ* (μg•h/mL) (CV%)	9.31 (38%)	11.13 (103%)	13.22 (22%)	13.25 (58%)
C_{max} (μg/mL) (CV%)	2.30 (19%)	2.08 (62%)	4.70 (22%)	3.06 (31%)

*AUC_τ values are calculated over dosing interval of 12 hours
Pharmacokinetic parameters for loading and maintenance doses summarized for same cohort of volunteers
**IV infusion over 60 minutes

Steady state trough plasma concentrations with voriconazole are achieved after approximately 5 days of oral or intravenous dosing without a loading dose regimen. However, when an intravenous loading dose regimen is used, steady state trough plasma concentrations are achieved within one day.

Absorption

The pharmacokinetic properties of voriconazole are similar following administration by the intravenous and oral routes. Based on a population pharmacokinetic analysis of pooled data in healthy subjects (N=207), the oral bioavailability of voriconazole is estimated to be 96% (CV 13%).

Maximum plasma concentrations (C_{max}) are achieved 1-2 hours after dosing. When multiple doses of voriconazole are administered with high fat meals, the mean C_{max} and AUC_τ are reduced by 34% and 24%, respectively (see DOSAGE AND ADMINISTRATION).

In healthy subjects, the absorption of voriconazole is not affected by coadministration of oral ranitidine, cimetidine, or omeprazole, drugs that are known to increase gastric pH.

Distribution

The volume of distribution at steady state for voriconazole is estimated to be 4.6 L/kg, suggesting extensive distribution into tissues. Plasma protein binding is estimated to be 58% and was shown to be independent of plasma concentrations achieved following single and multiple oral doses of 200 mg or 300 mg (approximate range: 0.9-15 μg/ml). Varying degrees of hepatic and renal insufficiency do not affect the protein binding of voriconazole.

Metabolism

In vitro studies showed that voriconazole is metabolized by the human hepatic cytochrome P450 enzymes, CYP2C19, CYP2C9 and CYP3A4 (see CLINICAL PHARMACOLOGY - Drug Interactions).

In vivo studies indicated that CYP2C19 is significantly involved in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism. For example, 15-20% of Asian populations may be expected to be poor metabolizers. For Caucasians and Blacks, the prevalence of poor metabolizers is 3-5%. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolizers have, on average, 4-fold higher voriconazole exposure (AUC_τ) than their homozygous extensive metabolizer counterparts. Subjects who are heterozygous extensive metabolizers have, on average, 2-fold higher voriconazole exposure than their homozygous extensive metabolizer counterparts.

The major metabolite of voriconazole is the N-oxide, which accounts for 72% of the circulating radiolabelled metabolites in plasma. Since this metabolite has minimal antifungal activity, it does not contribute to the overall efficacy of voriconazole.

Excretion

Voriconazole is eliminated via hepatic metabolism with less than 2% of the dose excreted unchanged in the urine. After administration of a single radiolabelled dose of either oral or IV voriconazole, preceded by multiple oral or IV dosing, approximately 80% to 83% of the radioactivity is recovered in the urine. The majority (>94%) of the total radioactivity is excreted in the first 96 hours after both oral and intravenous dosing.

As a result of non-linear pharmacokinetics, the terminal half-life of voriconazole is dose dependent and therefore not useful in predicting the accumulation or elimination of voriconazole.

Pharmacokinetic-pharmacodynamic Relationships

In ten clinical trials, the median values for the average and maximum voriconazole plasma concentrations in individual patients across these studies (N=1121) was 2.51 μg/mL (inter-quartile range 1.21 to 4.44 μg/mL) and 3.79 μg/mL (inter-quartile range 2.06 to 6.31 μg/mL), respectively. A pharmacokinetic-pharmacodynamic analysis of patient data from 6 of these 10 clinical trials (N=280) could not detect a positive association between mean, maximum or minimum plasma voriconazole concentration and efficacy. However, PK/PD analyses of the data from all 10 clinical trials identified positive associations between plasma voriconazole concentrations and rate of both liver function test abnormalities and visual disturbances (see ADVERSE REACTIONS).

Pharmacokinetics in Special Populations

Gender

In a multiple oral dose study, the mean C_{max} and AUC_{τ} for healthy young females were 83% and 113% higher, respectively, than in healthy young males (18-45 years). In the same study, no significant differences in the mean C_{max} and AUC_{τ} were observed between healthy elderly males and healthy elderly females (≥65 years).

In the clinical program, no dosage adjustment was made on the basis of gender. The safety profile and plasma concentrations observed in male and female subjects were similar. Therefore, no dosage adjustment based on gender is necessary.

Geriatric

In an oral multiple dose study the mean C_{max} and AUC_{τ} in healthy elderly males (≥ 65 years) were 61% and 86% higher, respectively, than in young males (18-45 years). No significant differences in the mean C_{max} and AUC_{τ} were observed between healthy elderly females (≥ 65 years) and healthy young females (18-45 years).

In the clinical program, no dosage adjustment was made on the basis of age. An analysis of pharmacokinetic data obtained from 552 patients from 10 voriconazole clinical trials showed that the median voriconazole plasma concentrations in the elderly patients (>65 years) were approximately 80% to 90% higher than those in the younger patients (≤65 years) after either IV or oral administration. However, the safety profile of voriconazole in young and elderly subjects was similar and, therefore, no dosage adjustment is necessary for the elderly.

Pediatric

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

Hepatic Insufficiency

After a single oral dose (200 mg) of voriconazole in 8 patients with mild (Child-Pugh Class A) and 4 patients with moderate (Child-Pugh Class B) hepatic insufficiency, the mean systemic exposure (AUC) was 3.2-fold higher than in age and weight matched controls with normal hepatic function. There was no difference in mean peak plasma concentrations (C_{max}) between the groups. When only the patients with mild (Child-Pugh Class A) hepatic insufficiency were compared to controls, there was still a 2.3-fold increase in the mean AUC in the group with hepatic insufficiency compared to controls.

In an oral multiple dose study, AUC_{τ} was similar in six subjects with moderate hepatic impairment (Child-Pugh Class B) given a lower maintenance dose of 100 mg twice daily compared to six subjects with normal hepatic function given the standard 200 mg twice daily maintenance dose. The mean peak plasma concentrations (C_{max}) were 20% lower in the hepatically impaired group.

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 Class A and B) receiving voriconazole. No pharmacokinetic data are available for patients with severe hepatic cirrhosis (Child-Pugh Class C) (see DOSAGE AND ADMINISTRATION).

Renal Insufficiency

In a single oral dose (200 mg) study in 24 subjects with normal renal function and mild to severe renal impairment, systemic exposure (AUC) and peak plasma concentration (C_{max}) of voriconazole were not significantly affected by renal impairment. Therefore, no adjustment is necessary for oral dosing in patients with mild to severe renal impairment.

In a multiple dose study of IV voriconazole (6 mg/kg IV loading dose x 2, then 3 mg/kg IV x 5.5 days) in 7 patients with moderate renal dysfunction (creatinine clearance 30-50 mL/min), the systemic exposure (AUC) and peak plasma concentrations (C_{max}) were not significantly different from those in 6 volunteers with normal renal function.

However, in patients with moderate renal dysfunction (creatinine clearance 30 - 50 mL/min), accumulation of the intravenous vehicle, SBECD, occurs. The mean systemic exposure (AUC) and peak plasma concentrations (C_{max}) of SBECD were increased by 4-fold and almost 50%, respectively, in the moderately impaired group compared to the normal control group.

Intravenous voriconazole should be avoided in patients with moderate or severe renal impairment (creatinine clearance <50 mL/min), unless an assessment of the benefit/risk to the patient justifies the use of intravenous voriconazole (see DOSAGE AND ADMINISTRATION-Dosage Adjustment).

A pharmacokinetic study in subjects with renal failure undergoing hemodialysis showed that voriconazole is dialyzed with clearance of 121mL/min. The intravenous vehicle, SBECD, is hemodialyzed with clearance of 55 mL/min. A 4-hour hemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment.

Drug Interactions

Effects Of Other Drugs On Voriconazole

Voriconazole is metabolized by the human hepatic cytochrome P450 enzymes CYP2C19, CYP2C9, and CYP3A4. Results of *in vitro* metabolism studies indicate that the affinity of voriconazole is highest for CYP2C19, followed by CYP2C9, and is appreciably lower for CYP3A4. Inhibitors or inducers of these three enzymes may increase or decrease voriconazole systemic exposure (plasma concentrations), respectively.

The systemic exposure to voriconazole is significantly reduced or is expected to be reduced by the concomitant administration of the following agents and their use is contraindicated:

Rifampin **(potent CYP450 inducer):** Rifampin (600 mg once daily) decreased the steady state C_{max} and AUC_{τ} of voriconazole (200 mg Q12h x 7 days) by an average of 93% and 96%, respectively, in healthy subjects. Doubling the dose of voriconazole to 400 mg Q12h does not restore adequate exposure to voriconazole during coadministration with rifampin. **Coadministration of voriconazole and rifampin is contraindicated** (see CONTRAINDICATIONS, PRECAUTIONS - Drug Interactions).

Carbamazepine and long acting barbiturates **(potent CYP450 inducers):** Although not studied *in vitro* or *in vivo*, carbamazepine and long acting barbiturates (e.g. phenobarbital, mephobarbital) are likely to significantly decrease plasma voriconazole plasma concentrations. **Coadministration of voriconazole with carbamazepine or long acting barbiturates is contraindicated** (see CONTRAINDICATIONS, PRECAUTIONS - Drug Interactions).

Minor or no significant pharmacokinetic interactions that do not require dosage adjustment:

***Cimetidine* (non-specific CYP450 inhibitor and increases gastric pH):** Cimetidine (400 mg Q12h x 8 days) increased voriconazole steady state C_{max} and AUC_{τ} by an average of 18% (90% CI: 6%, 32%) and 23% (90% CI: 13%, 33%), respectively, following oral doses of 200 mg Q12h x 7 days to healthy subjects.

***Ranitidine* (increases gastric pH):** Ranitidine (150 mg Q12h) had no significant effect on voriconazole C_{max} and AUC_{τ} following oral doses of 200 mg Q12h x 7 days to healthy subjects.

***Macrolide antibiotics*:** Co-administration of **erythromycin** (CYP3A4 inhibitor;1g Q12h for 7 days) or **azithromycin** (500 mg qd for 3 days) with voriconazole 200 mg Q12h for 14 days had no significant effect on voriconazole steady state C_{max} and AUC_{τ} in healthy subjects. The effects of voriconazole on the pharmacokinetics of either erythromycin or azithromycin are not known.

Effects Of Voriconazole On Other Drugs

In vitro studies with human hepatic microsomes show that voriconazole inhibits the metabolic activity of the cytochrome P450 enzymes CYP2C19, CYP2C9, and CYP3A4. In these studies, the inhibition potency of voriconazole for CYP3A4 metabolic activity was significantly less than that of two other azoles, ketoconazole and itraconazole. *In vitro* studies also show that the major metabolite of voriconazole, voriconazole N-oxide, inhibits the metabolic activity of CYP2C9 and CYP3A4 to a greater extent than that of CYP2C19. Therefore, there is potential for voriconazole and its major metabolite to increase the sytemic exposure (plasma concentrations) of other drugs metabolized by these CYP450 enzymes.

The systemic exposure of the following drugs is significantly increased or is expected to be significantly increased by coadministration of voriconazole and their

use is contraindicated:

***Sirolimus* (CYP3A4 substrate):** Repeat dose administration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 8 days) increased the C_{max} and AUC of sirolimus (2 mg single dose) an average of 7-fold (90% CI: 5.7, 7.5) and 11-fold (90% CI: 9.9, 12.6), respectively, in healthy subjects. **Coadministration of voriconazole and sirolimus is contraindicated** (see CONTRAINDICATIONS, PRECAUTIONS - Drug Interactions).

***Terfenadine, astemizole, cisapride, pimozide and quinidine* (CYP3A4 substrates):** Although not studied *in vitro* or *in vivo*, concomitant administration of voriconazole with terfenadine, astemizole, cisapride, pimozide or quinidine may result in inhibition of the metabolism of these drugs. Increased plasma concentrations of these drugs can lead to QT prolongation and rare occurrences of *torsade de pointes*. **Coadministration of voriconazole and terfenidine, astemizole, cisapride, pimozide and quinidine is contraindicated** (see CONTRAINDICATIONS, PRECAUTIONS - Drug Interactions).

***Ergot alkaloids*:** Although not studied *in vitro* or *in vivo*, voriconazole may increase the plasma concentration of ergot alkaloids (ergotamine and dihydroergotamine) and lead to ergotism. **Coadministration of voriconazole with ergot alkaloids is contraindicated** (see CONTRAINDICATIONS, PRECAUTIONS - Drug Interactions).

Coadministration of voriconazole with the following agents results in increased exposure or is expected to result in increased exposure to these drugs. Therefore, careful monitoring and/or dosage adjustment of these drugs is needed:

***Cyclosporine* (CYP3A4 substrate):** In stable renal transplant recipients receiving chronic cyclosporine therapy, concomitant administration of oral voriconazole (200 mg Q12h for 8 days) increased cyclosporine C_{max} and AUC_{τ} an average of 1.1 times (90% CI: 0.9, 1.41) and 1.7 times (90% CI: 1.5, 2.0), respectively, as compared to when cyclosporine was administered without voriconazole. When initiating therapy with voriconazole in patients already receiving cyclosporine, it is recommended that the cyclosporine dose be reduced to one-half of the original dose and followed with frequent monitoring of the cyclosporine blood levels. Increased cyclosporine levels have been associated with nephrotoxicity. When voriconazole is discontinued, cyclosporine levels should be frequently monitored and the dose increased as necessary (see PRECAUTIONS-Drug Interactions).

***Tacrolimus* (CYP3A4 substrate):** Repeat oral dose administration of voriconazole (400 mg Q12h x 1 day then 200 mg Q12h x 6 days) increased tacrolimus (0.1 mg/kg single dose) C_{max} and AUC_t (in healthy subjects by an average of 2-fold (90% CI: 1.9, 2.5) and 3-fold (90% CI: 2.7, 3.8), respectively. When initiating therapy with voriconazole in patients already receiving tacrolimus, it is recommended that the tacrolimus dose be reduced to one-third of the original dose and followed with frequent monitoring of the tacrolimus blood levels. Increased tacrolimus levels have been associated with nephrotoxicity. When voriconazole is discontinued, tacrolimus levels should be carefully monitored and the dose increased as necessary (see PRECAUTIONS - Drug Interactions).

***Warfarin* (CYP2C9 substrate):** Coadministration of voriconazole (300 mg Q12h x 12 days) with warfarin (30 mg single dose) significantly increased maximum prothrombin time by approximately 2-times that of placebo in healthy subjects. Close monitoring of prothrombin time or other suitable anti-coagulation tests is recommended if warfarin and voriconazole are coadministered and the warfarin dose adjusted accordingly (see PRECAUTIONS-Drug Interactions).

Oral Coumarin Anticoagulants **(CYP2C9, CYP3A4 substrates):** Although not studied *in vitro* or *in vivo*, voriconazole may increase the plasma concentrations of coumarin anticoagulants and therefore may cause an increase in prothrombin time. If patients receiving coumarin preparations are treated simultaneously with voriconazole, the prothrombin time or other suitable anti-coagulation tests should be monitored at close intervals and the dosage of anticoagulants adjusted accordingly (see PRECAUTIONS-Drug Interactions).

Statins **(CYP3A4 substrates):** Although not studied clinically, voriconazole has been shown to inhibit lovastatin metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase the plasma concentrations of statins that are metabolized by CYP3A4. It is recommended that dose adjustment of the statin be considered during coadministration. Increased statin concentrations in plasma have been associated with rhabdomyolysis (see PRECAUTIONS-Drug Interactions).

Benzodiazepines **(CYP3A4 substrates):** Although not studied clinically, voriconazole has been shown to inhibit midazolam metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase the plasma concentrations of benzodiazepines that are metabolized by CYP3A4 (e.g., midazolam, triazolam, and alprazolam) and lead to a prolonged sedative effect. It is recommended that dose adjustment of the benzodiazepine be considered during coadministration (see PRECAUTIONS-Drug Interactions).

Calcium Channel Blockers **(CYP3A4 substrates):** Although not studied clinically, voriconazole has been shown to inhibit felodipine metabolism *in vitro* (human liver microsomes). Therefore, voriconazole may increase the plasma concentrations of calcium channel blockers that are metabolized by CYP3A4. Frequent monitoring for adverse events and toxicity related to calcium channel blockers is recommended during coadministration. Dose adjustment of the calcium channel blocker may be needed (see PRECAUTIONS-Drug Interactions).

Sulfonylureas **(CYP2C9 substrates):** Although not studied *in vitro* or *in vivo*, voriconazole may increase plasma concentrations of sulfonylureas (e.g., tolbutamide, glipizide, and glyburide) and therefore cause hypoglycemia. Frequent monitoring of blood glucose and appropriate adjustment (i.e., reduction) of the sulfonylurea dosage is recommended during coadministration (see PRECAUTIONS-Drug Interactions).

Vinca Alkaloids **(CYP3A4 substrates):** Although not studied *in vitro* or *in vivo*, voriconazole may increase the plasma concentrations of the vinca alkaloids (e.g., vincristine and vinblastine) and lead to neurotoxicity. Therefore, it is recommended that dose adjustment of the vinca alkaloid be considered.

No significant pharmacokinetic interactions were observed when voriconazole was coadministered with the following agents. Therefore, no dosage adjustment for these agents is recommended.

Prednisolone **(CYP3A4 substrate):** Voriconazole (200 mg Q12h x 30 days) increased C_{max} and AUC of prednisolone (60 mg single dose) by an average of 11% and 34%, respectively in healthy subjects.

Digoxin **(P-glycoprotein mediated transport):** Voriconazole (200 mg Q12h x 12 days) had no significant effect on steady state C_{max} and AUC_{τ} of digoxin (0.25 mg once daily for 10 days) in healthy subjects.

Mycophenolic acid **(UDP-glucuronyl transferase substrate):** Voriconazole (200 mg Q12h x 5 days) had no significant effect on the C_{max} and AUC_t of mycophenolic acid and its major metabolite, mycophenolic acid glucuronide after administration of a 1 g single oral dose of mycophenolate mofetil.

Two-way Interactions

Concomitant use of the following agent with voriconazole is contraindicated:

***Rifabutin* (potent CYP450 inducer):** Rifabutin (300 mg once daily) decreased the C_{max} and AUC_τ of voriconazole at 200 mg twice daily by an average of 67% (90% CI: 58%, 73%) and 79% (90% CI: 71%, 84%), respectively, in healthy subjects. During coadministration with rifabutin (300 mg once daily), the steady state C_{max} and AUC_τ of voriconazole following an increased dose of 400 mg twice daily were on average approximately 2-times higher, compared with voriconazole alone at 200 mg twice daily. Coadministration of voriconazole at 400 mg twice daily with rifabutin 300 mg twice daily increased the C_{max} and AUC_τ of rifabutin by an average of 3-times (90% CI: 2.2, 4.0) and 4-times (90% CI: 3.5, 5.4), respectively, compared to rifabutin given alone. **Coadministration of voriconazole and rifabutin is contraindicated.**

Significant drug interactions that may require dosage adjustment, frequent monitoring of drug levels and/or frequent monitoring of drug-related adverse events/toxicity:

***Phenytoin* (CYP2C9 substrate and potent CYP450 inducer):** Repeat dose administration of phenytoin (300 mg once daily) decreased the steady state C_{max} and AUC_τ of orally administered voriconazole (200 mg Q12h x 14 days) by an average of 50% and 70%, respectively, in healthy subjects. Administration of a higher voriconazole dose (400 mg Q12h x 7 days) with phenytoin (300 mg once daily) resulted in comparable steady state voriconazole C_{max} and AUC_τ estimates as compared to when voriconazole was given at 200 mg Q12h without phenytoin.

Phenytoin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased from 4 mg/kg to 5 mg/kg intravenously every 12 hours or from 200 mg to 400 mg orally, every 12 hours (100 mg to 200 mg orally, every 12 hours in patients less than 40 kg) (see DOSAGE AND ADMINISTRATION).

Repeat dose administration of voriconazole (400 mg Q12h x 10 days) increased the steady state C_{max} and AUC_{τ} of phenytoin (300 mg once daily) by an average of 70% and 80%, respectively, in healthy subjects. The increase in phenytoin C_{max} and AUC when coadministered with voriconazole may be expected to be as high as 2-times the C_{max} and AUC estimates when phenytoin is given without voriconazole. Therefore, frequent monitoring of plasma phenytoin concentrations and phenytoin-related adverse effects is recommended when phenytoin is coadministered with voriconazole (see PRECAUTIONS-Drug Interactions).

Omeprazole **(CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate)**: Coadminstration of omeprazole (40 mg once daily x 10 days) with oral voriconazole (400 mg Q12h x 1 day, then 200 mg Q12h x 9 days) increased the steady state C_{max} and AUC_{τ} of voriconazole by an average of 15% (90% CI: 5%, 25%) and 40% (90% CI: 29%, 55%), respectively in healthy subjects. No dosage adjustment of voriconazole is recommended.

Coadministration of voriconazole (400 mg Q12h x 1 day, then 200 mg x 6 days) with omeprazole (40 mg once daily x 7 days) to healthy subjects significantly increased the steady state C_{max} and AUC_{τ} of omeprazole an average of 2-times (90% CI: 1.8, 2.6) and 4-times (90% CI: 3.3, 4.4), respectively, as compared to when omeprazole is given without voriconazole. When initiating voriconazole in patients already receiving omeprazole doses of 40 mg or greater, it is recommended that the omeprazole dose be reduced by one-half (see PRECAUTIONS-Drug Interactions).

The metabolism of other proton pump inhibitors that are CYP2C19 substrates may also be inhibited by voriconazole and may result in increased plasma concentrations of these drugs.

No significant pharmacokinetic interaction was seen and

no dosage adjustment of these drugs is recommended:

***Indinavir* (CYP3A4 inhibitor and substrate):** Repeat dose administration of indinavir (800 mg tid for 10 days) had no significant effect on voriconazole C_{max} and AUC following repeat dose administration (200 mg Q12h for 17 days) in healthy subjects.

Repeat dose administration of voriconazole (200 mg Q12h for 7 days) did not have a significant effect on steady state C_{max} and AUC_{τ} of indinavir following repeat dose administration (800 mg TID for 7 days) in healthy subjects.

Other Two-Way Interactions Expected to be Significant Based on *In Vitro* Findings:

***Other HIV Protease Inhibitors (CYP3A4 substrates and inhibitors*):** *In vitro* studies (human liver microsomes) suggest that voriconazole may inhibit the metabolism of HIV protease inhibitors (e.g. saquinavir, amprenavir and nelfenavir). *In vitro* studies (human liver microsomes) also show that the metabolism of voriconazole may be inhibited by HIV protease inhibitors (e.g., ritonavir, saquinavir, and amprenavir). Patients should be frequently monitored for drug toxicity during the coadministration of voriconazole and HIV protease inhibitors (see PRECAUTIONS-Drug Interactions).

***Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)* (CYP3A4 substrates, inhibitors or CYP450 inducers)**: *In vitro* studies (human liver microsomes) show that the metabolism of voriconazole may be inhibited by an NNRTI (e.g., delavirdine and efavirenz). Although not studied *in vitro* or *in vivo*, the metabolism of voriconazole may be induced by an NNRTI, such as efavirenz or nevirapine. *In vitro* studies (human liver microsomes) show that voriconazole may also inhibit the metabolism of an NNRTI (e.g., delavirdine). Patients should be frequently monitored for drug toxicity during the co-administration of voriconazole and an NNRTI (see PRECAUTIONS-Drug Interactions).

MICROBIOLOGY

Mechanism Of Action

Voriconazole is a triazole antifungal agent. The primary mode of action of voriconazole is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell wall and may be responsible for the antifungal activity of voriconazole. Voriconazole has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.

Activity *In Vitro* And *In Vivo*

Voriconazole has demonstrated *in vitro* activity against *Aspergillus fumigatus* isolates as well as *A. flavus*, *A. niger* and *A. terreus*. Variable *in vitro* activity against *Scedosporium apiospermum* and *Fusarium* spp., including *Fusarium solani*, has been seen. Most of the speciated isolates from clinical studies were *Aspergillus fumigatus* but clinical efficacy was also seen in a small number of species other than *A. fumigatus* (see INDICATIONS AND USAGE and CLINICAL STUDIES - Invasive Aspergillosis).

In vitro susceptibility testing was performed according to the National Committee for Clinical Laboratory Standards (NCCLS) proposed method (M38-P). Voriconazole breakpoints have not been established for any fungi. The relationship between clinical outcome and *in vitro* susceptibility results remains to be elucidated.

Voriconazole has demonstrated *in vivo* activity in normal and immunocompromised guinea pigs with established systemic *A. fumigatus* infections in which the endpoints were prolonged survival of infected animals and reduction of mycological burden from target organs. Activity has also been shown in immunocompromised guinea pigs with pulmonary *A. fumigatus* infections. Voriconazole demonstrated activity in immunocompromised guinea pigs with systemic infections produced by an *A. fumigatus* isolate with reduced susceptibility to itraconazole

(itraconazole MIC 3.1 μg/mL). The exact mechanism of resistance was not identified for that particular isolate. In one experiment, voriconazole exhibited activity against *Scedosporium apiospermum* infections in immune competent guinea pigs.

Drug Resistance

Voriconazole drug resistance development has not been adequately studied *in vitro* against the filamentous fungi, including *Aspergillus*, *Scedosporium* and *Fusarium* species. The frequency of drug resistance development for the various fungi for which this drug is indicated is not known.

Fungal isolates exhibiting reduced susceptibility to fluconazole or itraconazole may also show reduced susceptibility to voriconazole, suggesting cross-resistance can occur among these azoles. The relevance of cross-resistance and clinical outcome has not been fully characterized. Clinical cases where azole cross-resistance is demonstrated may require alternative antifungal therapy.

INDICATIONS AND USAGE

VFEND is indicated for use in the treatment of the following fungal infections:

> Treatment of invasive aspergillosis.
> In clinical trials, the majority of isolates recovered were *Aspergillus fumigatus*. There was a small number of cases of culture-proven disease due to species of *Aspergillus* other than *A. fumigatus* (see CLINICAL STUDIES and MICROBIOLOGY sections).
>
> Treatment of serious fungal infections caused by *Scedosporium apiospermum* (asexual form of *Pseudallescheria boydii*) and *Fusarium* spp. including *Fusarium solani*, in patients intolerant of, or refractory to, other therapy.

Specimens for fungal culture and other relevant laboratory studies (including histopathology) should be obtained prior to therapy to isolate and identify causative organism(s). Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

CLINICAL STUDIES

Voriconazole, administered orally or parenterally, has been evaluated as primary or salvage therapy in 520 patients aged 12 years and older with infections caused by *Aspergillus* spp., *Fusarium* spp., and *Scedosporium* spp.

Invasive Aspergillosis

Voriconazole was studied in patients for primary therapy of invasive aspergillosis (randomized, controlled study 307/602), for primary and salvage therapy of aspergillosis (non-comparative study 304) and for treatment of patients with invasive aspergillosis who were refractory to, or intolerant of, other antifungal therapy (non-comparative study 309/604).

Study 307/602

The efficacy of voriconazole compared to amphotericin B in the primary treatment of acute invasive aspergillosis was demonstrated in 277 patients treated for 12 weeks in Study 307/602. The majority of study patients had underlying hematologic malignancies, including bone marrow transplantation. The study also included patients with solid organ transplantation, solid tumors, and AIDS. The patients were mainly treated for definite or probable invasive aspergillosis of the lungs. Other aspergillosis infections included disseminated disease, CNS infections and sinus infections. Diagnosis of definite or probable invasive aspergillosis was made according to criteria modified from those established by the National Institute of Allergy and Infectious Diseases Mycoses Study Group/ European Organisation for Research and Treatment of Cancer (NIAID MSG/EORTC).

Voriconazole was administered intravenously with a loading dose of 6mg/kg every 12 hours for the first 24 hours followed by a maintenance dose of 4 mg/kg every 12 hours for a minimum of seven days. Therapy could then be switched to the oral formulation at a dose of 200 mg Q12h. Median duration of IV voriconazole therapy was 10 days (range 2-90 days). After IV voriconazole therapy, the median duration of PO voriconazole therapy was 76 days (range 2-232 days).

Patients in the comparator group received conventional amphotericin B as a slow infusion at a daily dose of 1.0-1.5 mg/kg/day. Median duration of IV amphotericin therapy was 12 days (range 1-85 days). Treatment was then continued with other licensed antifungal therapy (OLAT), including itraconazole and lipid amphotericin B formulations. Although initial therapy with conventional amphotericin B was to be continued for at least two weeks, actual duration of therapy was at the discretion of the investigator. Patients who discontinued initial randomized therapy due to toxicity or lack of efficacy were eligible to continue in the study with OLAT treatment.

A satisfactory global response at 12 weeks (complete or partial resolution of all attributable symptoms, signs, radiographic/bronchoscopic abnormalities present at baseline) was seen in 53% of voriconazole treated patients compared to 32% of amphotericin B treated patients (Table 4). A benefit of voriconazole compared to amphotericin B on patient survival at Day 84 was seen with a 71% survival rate on voriconazole compared to 58% on amphotericin B (Table 4).

Table 4 also summarizes the response (success) based on mycological confirmation and species.

Table 4
Overall Efficacy and Success by Species in the PrimaryTreatment of Acute Invasive Aspergillosis Study 307/602

	Voriconazole	**Ampho B** [c]	Stratified Difference (95% CI) [d]
	n/N (%)	n/N (%)	
Efficacy as Primary Therapy			
Satisfactory Global Response [a]	76/144 (53)	42/133 (32)	21.8% (10.5%, 33.0%) p<0.0001
Survival at Day 84 [b]	102/144 (71)	77/133 (58)	13.1% (2.1%, 24.2%)
Success by Species			
	Success n/N (%)		
Overall success	76/144 (53)	42/133 (32)	
Mycologically confirmed [e]	37/84 (44)	16/67 (24)	
Aspergillus spp.[f]			
A. fumigatus	28/63 (44)	12/47 (26)	
A. flavus	3/6	4/9	
A. terreus	2/3	0/3	
A. niger	1/4	0/9	
A. nidulans	1/1	0/0	

a Assessed by independent Data Review Committee (DRC)
b Proportion of subjects alive
c Amphotericin B followed by other licensed antifungal therapy
d Difference and corresponding 95% confidence interval are stratified by protocol
e Not all mycologically confirmed specimens were speciated
f Some patients had more than one species isolated at baseline

Study 304

The results of this comparative trial (Study 307/602) confirmed the results of an earlier trial in the primary and salvage treatment of patients with acute invasive aspergillosis (Study 304). In this earlier study, an overall success rate of 52 % (26/50) was seen in patients treated with voriconazole for primary therapy. Success was seen in 17/29 (59%) with *Aspergillus fumigatus* infections and 3/6 (50%) patients with infections due to non-*fumigatus* species [*A. flavus* (1/1); *A. nidulans* (0/2); *A. niger* (2/2); *A. terreus* (0/1)]. Success in patients who received voriconazole as salvage therapy is presented in Table 5.

Study 309/604

Additional data regarding response rates in patients who were refractory to, or intolerant of, other antifungal agents are also provided in Table 5. Overall mycological eradication for culture-documented infections due to fumigatus and non-fumigatus species of Aspergillus was 36/82 (44%) and 12/30 (40%), respectively, in voriconazole treated patients. Patients had various underlying diseases and species other than A. fumigatus contributed to mixed infections in some cases.

For patients who were infected with a single pathogen and were refractory to, or intolerant of, other antifungal agents, the satisfactory response rates for voriconazole in studies 304 and 309/604 are presented in Table 5.

Table 5 Combined Response Data in Salvage Patients with Single Aspergillus Species (Studies 304 and 309/604)

	Success n/N
A. fumigatus	43/97 (44%)
A. flavus	5/12
A. nidulans	1/3
A. niger	4/5
A. terreus	3/8
A. versicolor	0/1

Nineteen patients had more than one species of *Aspergillus* isolated. Success was seen in 4/17 (24%) of these patients.

Other Serious Fungal Pathogens

In pooled analyses of patients, voriconazole was shown to be effective against the following additional fungal pathogens:

Scedosporium apiospermum - Successful response to voriconazole therapy was seen in 15 of 24 patients (63%). Three of these patients relapsed within 4 weeks, including 1 patient with pulmonary, skin and eye infections, 1 patient with cerebral disease, and 1 patient with skin infection. Ten patients had evidence of cerebral disease and 6 of these had a successful outcome (1 relapse). In addition, a successful response was seen in one of three patients with mixed organism infections.

Fusarium spp.- Nine of 21 (43%) patients were successfully treated with voriconazole. Of these nine patients, three had eye infections, one had an eye and blood infection, one had a skin infection, one had a blood infection alone, two had sinus infections, and one had disseminated infection (pulmonary, skin, hepatosplenic). Three of these patients (one with disseminated disease, one with an eye infection and one with a blood infection) had *Fusarium solani* and were complete successes. Two of these patients relapsed, one with a sinus infection and profound neutropenia and one post surgical patient with blood and eye infections.

CONTRAINDICATIONS

VFEND is contraindicated in patients with known hypersensitivity to voriconazole or its excipients. There is no information regarding cross-sensitivity between VFEND (voriconazole) and other azole antifungal agents. Caution should be used when prescribing VFEND to patients with hypersensitivity to other azoles.

Coadministration of the CYP3A4 substrates, terfenadine, astemizole, cisapride, pimozide or quinidine with VFEND are contraindicated since increased plasma concentrations of these drugs can lead to QT prolongation and rare occurrences of *torsade de pointes* (see CLINICAL PHARMACOLOGY - Drug Interactions, PRECAUTIONS-Drug Interactions).

Coadministration of VFEND with sirolimus is contraindicated because VFEND significantly increases sirolimus concentrations in healthy subjects (see CLINICAL PHARMACOLOGY - Drug Interactions, PRECAUTIONS-Drug Interactions).

Coadministration of VFEND with rifampin, carbamazepine and long-acting barbiturates is contraindicated since these drugs are likely to decrease plasma voriconazole concentrations significantly (see CLINICAL PHARMACOLOGY - Drug Interactions, PRECAUTIONS - Drug Interactions).

Coadministration of VFEND with rifabutin is contraindicated since VFEND significantly increases rifabutin plasma concentrations and rifabutin also significantly decreases voriconazole plasma concentrations (see CLINICAL PHARMACOLOGY - Drug Interactions, PRECAUTIONS-Drug Interactions).

Coadministration of VFEND with ergot alkaloids (ergotamine and dihydroergotamine) is contraindicated because VFEND may increase the plasma concentration of ergot alkaloids, which may lead to ergotism.

WARNINGS

VISUAL DISTURBANCES: **The effect of VFEND on visual function is not known if treatment continues beyond 28 days.** If treatment continues beyond 28 days, visual function including visual acuity, visual field and color perception should be monitored **(see PRECAUTIONS – Information for Patients and ADVERSE EVENTS – Visual Disturbances).**

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 **(see PRECAUTIONS – Laboratory Tests and ADVERSE EVENTS – Clinical Laboratory Values.**

Monitoring of hepatic function: Liver function tests should be evaluated at the start of and during the course of VFEND therapy. 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-Laboratory Tests, DOSAGE AND ADMINISTRATION-Dosage Adjustment, ADVERSE EVENTS-Clinical Laboratory Tests).

Pregnancy Category D: Voriconazole can cause fetal harm when administered to a pregnant woman.

Voriconazole was teratogenic in rats (cleft palates, hydronephrosis/hydroureter) from 10 mg/kg (0.3 times the recommended maintenance dose (RMD) on a mg/m^2 basis) and embryotoxic in rabbits at 100 mg/kg (6 times the

RMD). Other effects in rats included reduced ossification of sacral and caudal vertebrae, skull, pubic and hyoid bone, super numerary ribs, anomalies of the sternebrae and dilatation of the ureter/renal pelvis. Plasma estradiol in pregnant rats was reduced at all dose levels. Voriconazole treatment in rats produced increased gestational length and dystocia, which were associated with increased perinatal pup mortality at the 10 mg/kg dose. The effects seen in rabbits were an increased embryomortality, reduced fetal weight and increased incidences of skeletal variations, cervical ribs and extra sternebral ossification sites.

If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Galactose intolerance: VFEND tablets contain lactose and should not be given to patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

PRECAUTIONS

General

(See WARNINGS, DOSAGE AND ADMINISTRATION)

Infusion Related Reactions

During infusion of the intravenous formulation of voriconazole in healthy subjects, anaphylactoid-type reactions, including flushing, fever, sweating, tachycardia, chest tightness, dyspnea, faintness, nausea, pruritus and rash, have occurred uncommonly. Symptoms appeared immediately upon initiating the infusion. Consideration should be given to stopping the infusion should these reactions occur.

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.

Laboratory Tests

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

Drug Interactions

Tables 6 and 7 provide a summary of significant drug interactions with voriconazole that either have been studied *in vivo* (clinically) or that may be expected to occur based on results of *in vitro* metabolism studies with human liver microsomes. For more details, see CLINICAL PHARMACOLOGY - Drug Interactions.

Table 6: Effect of Other Drugs on Voriconazole Pharmacokinetics

Drug/Drug Class (Mechanism of Interaction by the Drug)	Voriconazole Plasma Exposure (C_{max} and AUC_{τ} after 200 mg Q12h)	Recommendations for Voriconazole Dosage Adjustment/Comments
Rifampin* and Rifabutin* (CYP450 Induction)	Significantly Reduced	**Contraindicated**
Carbamazepine (CYP450 Induction)	Not Studied *In Vivo* or *In Vitro*, but Likely to Result in Significant Reduction	**Contraindicated**
Long Acting Barbiturates CYP450 Induction	Not Studied *In Vivo* or *In Vitro*, but Likely to Result in Significant Reduction	**Contraindicated**
Phenytoin* (CYP450 Induction)	Significantly Reduced	Increase voriconazole maintenance dose from 4 mg/kg to 5 mg/kg IV every 12 hrs or from 200 mg to 400 mg orally every 12 hrs (100 mg to 200 mg orally every 12 hrs in patients weighing less than 40 kg)
HIV Protease Inhibitors (CYP3A4 Inhibition)	*In Vivo* Studies Showed No Significant Effects of Indinavir on Voriconazole Exposure *In Vitro* Studies Demonstrate Potential for Inhibition of Voriconazole Metabolism (Increased Plasma Exposure)	No dosage adjustment in the voriconazole dosage needed when coadministered with indinavir Frequent monitoring for adverse events and toxicity related to voriconazole when coadministered with other HIV protease inhibitors
NNRTI** (CYP3A4 Inhibition or CYP450 Induction)	*In Vitro* Studies Demonstrate Potential for Inhibition of Voriconazole Metabolism (Increased Plasma Exposure) Not Studied *In Vitro* or *In Vivo*, but Metabolism of Voriconazole May also be Induced (Decreased Plasma Exposure)	Frequent monitoring for adverse events and toxicity related to voriconazole Careful assessment of voriconazole effectiveness

*Results based on *in vivo* clinical studies generally following repeat oral dosing with 200 mg Q12h voriconazole to healthy subjects
** Non-Nucleoside Reverse Transcriptase Inhibitors

Table 7 Effect of Voriconazole on Pharmacokinetics of Other Drugs

Drug/Drug Class (Mechanism of Interaction by Voriconazole)	**Drug Plasma Exposure (C_{max} and AUC_τ)**	**Recommendations for Drug Dosage Adjustment/Comments**
Sirolimus* (CYP3A4 Inhibition)	Significantly Increased	**Contraindicated**
Rifabutin* (CYP3A4 Inhibition)	Significantly Increased	**Contraindicated**
Terfenadine, Astemizole, Cisapride, Pimozide, Quinidine (CYP3A4 Inhibition)	Not Studied *In Vivo* or *In Vitro*, but Drug Plasma Exposure Likely to be Increased	**Contraindicated** because of potential for QT prolongation and rare occurrence of *torsade de pointes*
Ergot Alkaloids (CYP450 Inhibition)	Not Studied *In Vivo* or *In Vitro*, but Drug Plasma Exposure Likely to be Increased	**Contraindicated**
Cyclosporine* (CYP3A4 Inhibition)	$AUC\tau$ Significantly Increased; No Significant Effect on C_{max}	When initiating therapy with VFEND in patients already receiving cyclosporine, reduce the cyclosporine dose to one-half of the starting dose and follow with frequent monitoring of cyclosporine blood levels. Increased cyclosporine levels have been associated with nephrotoxicity. When VFEND is discontinued, cyclosporine concentrations must be frequently monitored and the dose increased as necessary.
Tacrolimus* (CYP3A4 Inhibition)	Significantly Increased	When initiating therapy with VFEND in patients already receiving tacrolimus, reduce the tacrolimus dose to one-third of the starting dose and follow with frequent monitoring of tacrolimus blood levels. Increased tacrolimus levels have been associated with nephrotoxicity. When VFEND is discontinued, tacrolimus concentrations must be frequently monitored and the dose increased as necessary.
Phenytoin* (CYP2C9 Inhibition)	Significantly Increased	Frequent monitoring of phenytoin plasma concentrations and frequent monitoring of adverse effects related to phenytoin
Warfarin* (CYP2C9 Inhibition)	Prothrombin Time Significantly Increased	Monitor PT or other suitable anti-coagulation tests. Adjustment of warfarin dosage may be needed.
Omeprazole* (CYP2C19/3A4 Inhibition)	Significantly Increased	When initiating therapy with VFEND in patients already receiving omeprazole doses of 40 mg or greater, reduce the omeprazole dose by one-half. The metabolism of other proton pump inhibitors that are CYP2C19 substrates may also be inhibited by voriconazole and may result in increased plasma concentrations of other proton pump inhibitors.

Drug/Drug Class (Mechanism of Interaction by Voriconazole)	Drug Plasma Exposure (C_{max} and AUC_{τ})	Recommendations for Drug Dosage Adjustment/Comments
HIV Protease Inhibitors (CYP3A4 Inhibition)	*In Vivo* Studies showed No Significant Effects on Indinavir Exposure *In Vitro* Studies Demonstrate Potential for Voriconazole to Inhibit Metabolism (Increased Plasma Exposure)	No dosage adjustment for indinavir when coadministered with VFEND Frequent monitoring for adverse events and toxicity related to other HIV protease inhibitors
NNRTI** (CYP3A4 Inhibition)	*In Vitro* Studies Demonstrate Potential for Voriconazole to Inhibit Metabolism (Increased Plasma Exposure)	Frequent monitoring for adverse events and toxicity related to NNRTI
Benzodiazepines (CYP3A4 Inhibition)	*In Vitro* Studies Demonstrate Potential for Voriconazole to Inhibit Metabolism (Increased Plasma Exposure)	Frequent monitoring for adverse events and toxicity (i.e., prolonged sedation) related to benzodiazepines metabolized by CYP3A4 (e.g., midazolam, triazolam, alprazolam). Adjustment of benzodiazepine dosage may be needed.
HMG-CoA Reductase Inhibitors (Statins) (CYP3A4 Inhibition)	*In Vitro* Studies Demonstrate Potential for Voriconazole to Inhibit Metabolism (Increased Plasma Exposure)	Frequent monitoring for adverse events and toxicity related to statins. Increased statin concentrations in plasma have been associated with rhabdomyolysis. Adjustment of the statin dosage may be needed.
Dihydropyridine Calcium Channel Blockers (CYP3A4 Inhibition)	*In Vitro* Studies Demonstrate Potential for Voriconazole to Inhibit Metabolism (Increased Plasma Exposure)	Frequent monitoring for adverse events and toxicity related to calcium channel blockers. Adjustment of calcium channel blocker dosage may be needed.
Sulfonylurea Oral Hypoglycemics (CYP2C9 Inhibition)	Not Studied *In Vivo* or *In Vitro*, but Drug Plasma Exposure Likely to be Increased	Frequent monitoring of blood glucose and for signs and symptoms of hypoglycemia. Adjustment of oral hypoglycemic drug dosage may be needed.
Vinca Alkaloids (CYP3A4 Inhibition)	Not Studied *In Vivo* or *In Vitro*, but Drug Plasma Exposure Likely to be Increased	Frequent monitoring for adverse events and toxicity (i.e., neurotoxicity) related to vinca alkaloids. Adjustment of vinca alkaloid dosage may be needed.

*Results based on *in vivo* clinical studies generally following repeat oral dosing with 200 mg BID voriconazole to healthy subjects
** Non-Nucleoside Reverse Transcriptase Inhibitors

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 Class A and B) receiving VFEND (see CLINICAL PHARMACOLOGY-Hepatic Insufficiency, DOSAGE and ADMINISTRATION - Hepatic Insufficiency).

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.

Patients With Renal Insufficiency

In patients with moderate to severe renal dysfunction (creatinine clearance <50 mL/min), accumulation of the intravenous vehicle, SBECD, occurs. Oral voriconazole should be administered to these patients, unless an assessment of the benefit/risk to the patient justifies the use of intravenous voriconazole. Serum creatinine levels should be closely monitored in these patients, and if increases occur, consideration should be given to changing to oral voriconazole therapy (see CLINICAL PHARMACOLOGY-Renal Insufficiency, DOSAGE AND ADMINISTRATION- Renal Insufficiency).

Renal adverse events

Acute renal failure has been observed in severely ill patients undergoing treatment with VFEND. Patients being treated with voriconazole are likely to be treated concomitantly with nephrotoxic medications and have concurrent conditions that my result in decreased renal function.

Monitoring of renal function

Patients should be monitored for the development of abnormal renal function. This should include laboratory evaluation, particularly serum creatinine.

Dermatological Reactions

Patients have rarely developed serious cutaneous reactions, such as Stevens-Johnson syndrome, during treatment with VFEND. If patients develop a rash, they should be monitored closely and consideration given to discontinuation of VFEND. VFEND has been infrequently associated with photosensitivity skin reaction, especially during long-term therapy. It is recommended that patients avoid strong, direct sunlight during VFEND therapy.

Carcinogenesis, Mutagenesis, Impairment Of Fertility

Two-year carcinogenicity studies were conducted in rats and mice. Rats were given oral doses of 6, 18 or 50 mg/kg voriconazole, or 0.2, 0.6, or 1.6 times the recommended maintenance dose (RMD) on a mg/m^2 basis. Hepatocellular adenomas were detected in females at 50 mg/kg and hepatocellular carcinomas were found in males at 6 and 50 mg/kg. Mice were given oral doses of 10, 30 or 100 mg/kg voriconazole, or 0.1, 0.4, or 1.4 times the RMD on a mg/m^2 basis. In mice, hepatocellular adenomas were detected in males and females and hepatocellular carcinomas were detected in males at 1.4 times the RMD of voriconazole.

Voriconazole demonstrated clastogenic activity (mostly chromosome breaks) in human lymphocyte cultures *in vitro*. Voriconazole was not genotoxic in the Ames assay, CHO assay, the mouse micronucleus assay or the DNA repair test (Unscheduled DNA Synthesis assay).

Voriconazole produced a reduction in the pregnancy rates of rats dosed at 50 mg/kg, or 1.6 times the RMD. This was statistically significant only in the preliminary study and not in a larger fertility study.

Teratogenic Effects

Pregnancy category D. See WARNINGS

Women Of Child-bearing Potential

Women of childbearing potential should use effective contraception during treatment.

Nursing Mothers

The excretion of voriconazole in breast milk has not been investigated. VFEND should not be used by nursing mothers unless the benefit clearly outweighs the risk.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

A total of 22 patients aged 12-18 years with invasive aspergillosis were included in the therapeutic studies. Twelve out of 22 (55%) patients had successful response after treatment with a maintenance dose of voriconazole 4 mg/kg Q12h**.**

Sparse plasma sampling for pharmacokinetics in adolescents was conducted in the therapeutic studies (see CLINICAL PHARMACOLOGY - Pharmacokinetics, General Pharmacokinetic Characteristics).

Geriatric Use

In multiple dose therapeutic trials of voriconazole, 9.2% of patients were ≥ 65 years of age and 1.8% of patients were ≥ 75 years of age. In a study in healthy volunteers, the systemic exposure (AUC) and peak plasma concentrations (C_{max}) were increased in elderly males compared to young males. Pharmacokinetic data obtained from 552 patients from 10 voriconazole therapeutic trials showed that voriconazole plasma concentrations in the elderly patients were approximately 80% to 90% higher than those in younger patients after either IV or oral administration. However, the overall safety profile of the elderly patients was similar to that of the young so no dosage adjustment is recommended (see CLINICAL PHARMACOLOGY - Pharmacokinetics in Special Populations).

ADVERSE REACTIONS

Overview

The most frequently reported adverse events (all causalities) in the therapeutic trials were visual disturbances, fever, rash, vomiting, nausea, diarrhea, headache, sepsis, peripheral edema, abdominal pain, and respiratory disorder. 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).

Discussion Of Adverse Reactions

The data described in the table below reflect exposure to voriconazole in 1493 patients in the therapeutic studies. This represents a heterogeneous population, including immunocompromised patients, e.g., patients with hematological malignancy or HIV and non-neutropenic patients. This subgroup does not include healthy volunteers and patients treated in the compassionate use and non-therapeutic studies. This patient population was 62% male, had a mean age of 45.1 years (range 12-90, including 49 patients aged 12-18 years), and was 81% white and 9% black. Five hundred sixty-one patients had a duration of voriconazole therapy of greater than 12 weeks, with 136 patients receiving voriconazole for over six months. Table 8 includes all adverse events which were reported in therapeutic studies at an incidence of ≥1% as well as events of concern which occurred at an incidence of <1% during voriconazole therapy.

In study 307/602, 381 patients (196 on voriconazole, 185 on amphotericin B) were treated to compare voriconazole to amphotericin B followed by other licensed antifungal therapy in the primary treatment of patients with acute invasive aspergillosis. Study 305 evaluated the effects of oral voriconazole (200 patients) and oral fluconazole (191 patients) for another indication in immunocompromised (primarily HIV) patients. Laboratory test abnormalities for these studies are discussed under Clinical Laboratory Values below.

Table 8

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

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

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

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

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 were 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 disturbance 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. The effects were noted early in administration of voriconazole and continued through the course of study drug dosing.

Fourteen days after end of dosing, ERG, visual fields and color perception returned to normal (see WARNINGS, PRECAUTIONS – Information For Patients).

Dermatological Reactions: Dermatological reactions were common in the patients treated with voriconazole. The mechanism underlying these dermatologic adverse events remains unknown. In clinical trials, rashes considered related to therapy were reported by 6% (86/1493) of voriconazole-treated patients. The majority of rashes were of mild to moderate severity. Cases of photosensitivity reactions appear to be more likely to occur with long-term treatment. Patients have rarely developed serious cutaneous reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme during treatment with VFEND. If patients develop a rash, they should be monitored closely and consideration given to discontinuation of VFEND. It is recommended that patients avoid strong, direct sunlight during VFEND therapy.

Less Common Adverse Events

The following adverse events occurred in <1% of all 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 8 above and does not include every event reported in the voriconazole clinical program.

Body as a whole: abdomen enlarged, allergic reaction, anaphylactoid reaction (see PRECAUTIONS), ascites, asthenia, back pain, cellulitis, edema, face edema, flank pain, flu syndrome, graft versus host reaction, granuloma, infection, bacterial infection, fungal infection, injection site pain, injection site infection/inflammation, mucous membrane disorder, multi-organ failure, pain, pelvic pain, peritonitis, sepsis, substernal chest pain

Cardiovascular: atrial arrhythmia, atrial fibrillation, AV block complete, bigeminy, bradycardia, bundle branch block, cardiomegaly, cardiomyopathy, cerebral hemorrhage, cerebral ischemia, cerebrovascular accident, congestive heart failure, deep thrombophlebitis, endocarditis, extrasystoles, heart arrest, myocardial infarction, nodal arrhythmia, palpitation, phlebitis, postural hypotension, pulmonary embolus, QT interval prolonged, supraventricular tachycardia, syncope, thrombophlebitis, vasodilatation, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia (including possible *torsade de pointes)*

Digestive: anorexia, cheilitis, cholecystitis, cholelithiasis, constipation, duodenal ulcer perforation, duodenitis, dyspepsia, dysphagia, esophageal ulcer, esophagitis, flatulence, gastroenteritis, gastrointestinal hemorrhage, GGT/LDH elevated, gingivitis, glossitis, gum hemorrhage, gum hyperplasia, hematemesis, hepatic coma, hepatic failure, hepatitis, intestinal perforation, intestinal ulcer, enlarged liver, melena, mouth ulceration, pancreatitis, parotid gland enlargement, periodontitis, proctitis, pseudomembranous colitis, rectal disorder, rectal hemorrhage, stomach ulcer, stomatitis, tongue edema

*Endocrine****:*** adrenal cortex insufficiency, diabetes insipidus, hyperthyroidism, hypothyroidism

Hemic and lymphatic: agranulocytosis, anemia (macrocytic, megaloblastic, microcytic, normocytic), aplastic anemia, hemolytic anemia, bleeding time increased, cyanosis, DIC, ecchymosis, eosinophilia, hypervolemia, lymphadenopathy, lymphangitis, marrow depression, petechia, purpura, enlarged spleen, thrombotic thrombocytopenic purpura

*Metabolic and Nutritional***:** albuminuria, BUN increased, creatine phosphokinase increased, edema, glucose tolerance decreased, hypercalcemia, hypercholesteremia, hyperglycemia, hyperkalemia, hypermagnesemia, hypernatremia, hyperuricemia, hypocalcemia, hypoglycemia, hyponatremia, hypophosphatemia, uremia

Musculoskeletal: arthralgia, arthritis, bone necrosis, bone pain, leg cramps, myalgia, myasthenia, myopathy, osteomalacia, osteoporosis

Nervous system: abnormal dreams, acute brain syndrome, agitation, akathisia, amnesia, anxiety, ataxia, brain edema, coma, confusion, convulsion, delirium, dementia, depersonalization, depression, diplopia, encephalitis, encephalopathy, euphoria, Extrapyramidal Syndrome, grand mal convulsion, Guillain-Barré syndrome, hypertonia, hypesthesia, insomnia, intracranial hypertension, libido decreased, neuralgia, neuropathy, nystagmus, oculogyric crisis, paresthesia, psychosis, somnolence, suicidal ideation, tremor, vertigo

Respiratory system: cough increased, dyspnea, epistaxis, hemoptysis, hypoxia, lung edema, pharyngitis, pleural effusion, pneumonia, respiratory disorder, respiratory distress syndrome, respiratory tract infection, rhinitis, sinusitis, voice alteration

Skin and Appendages: alopecia, angioedema, contact dermatitis, discoid lupus erythematosis, eczema, erythema multiforme, exfoliative dermatitis, fixed drug eruption, furunculosis, herpes simplex, melanosis, photosensitivity skin reaction, psoriasis, skin discoloration, skin disorder, skin dry, Stevens-Johnson syndrome, sweating, toxic epidermal necrolysis, urticaria

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

Urogenital: anuria, blighted ovum, creatinine clearance decreased, dysmenorrhea, dysuria, epididymitis, glycosuria, hemorrhagic cystitis, hematuria, hydronephrosis, impotence, kidney pain, kidney tubular necrosis, metrorrhagia, nephritis, nephrosis, oliguria, scrotal edema, urinary incontinence, urinary retention, urinary tract infection, uterine hemorrhage, vaginal hemorrhage

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. Increased incidence of 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 including cases of jaundice and rare cases of hepatitis and hepatic failure leading to death. Most of these patients had other serious underlying conditions.

Liver function tests should be evaluated at the start of and during the course of VFEND therapy. 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 WARNINGS and PRECAUTIONS-Laboratory Tests).

Acute renal failure has been observed in severely ill patients undergoing treatment with VFEND. Patients being treated with voriconazole are likely to be treated concomitantly with nephrotoxic medications and have concurrent conditions that may result in decreased renal function. It is recommended that patients are monitored for the development of abnormal renal function. This should include laboratory evaluation, particularly serum creatinine.

Tables 9 and 10 show the number of patients with hypokalemia and clinically significant changes in renal and liver function tests in two randomized, comparative multicenter studies. In study 305, patients were randomized to either oral voriconazole or oral fluconazole to evaluate an indication other than invasive aspergillosis in immunocompromised patients. In study 307/602, patients with definite or probable invasive aspergillosis were randomized to either voriconazole or amphotericin B therapy.

Table 9
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

Table 10
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)
Creatinine	>1.3x ULN	39/182 (21.4)	102/177 (57.6)
Potassium	<0.9x LLN	30/181 (16.6)	70/178 (39.3)

* 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

OVERDOSE

In clinical trials, there were three cases of accidental overdose. All occurred in pediatric patients who received up to five times the recommended intravenous dose of voriconazole. A single adverse event of photophobia of 10 minutes duration was reported.

There is no known antidote to voriconazole.

Voriconazole is hemodialyzed with clearance of 121 mL/min. The intravenous vehicle, SBECD, is hemodialyzed with clearance of 55 mL/min. In an overdose, hemodialysis may assist in the removal of voriconazole and SBECD from the body.

The minimum lethal oral dose in mice and rats was 300 mg/kg (equivalent to 4 and 7 times the recommended maintenance dose (RMD), based on body surface area). At this dose, clinical signs observed in both mice and rats included salivation, mydriasis, titubation (loss of balance while moving), depressed behavior, prostration, partially closed eyes, and dyspnea. Other signs in mice were convulsions, corneal opacification and swollen abdomen.

DOSAGE AND ADMINISTRATION

Administration

VFEND Tablets should be taken at least one hour before, or one hour following, a meal.

VFEND I.V. for Injection requires reconstitution to 10 mg/mL and subsequent dilution to 5 mg/mL or less prior to administration as an infusion, at a maximum rate of 3 mg/kg per hour over 1-2 hours (see Intravenous Administration).
NOT FOR IV BOLUS INJECTION

Use In Adults

Therapy must be initiated with the specified loading dose regimen of intravenous VFEND to achieve plasma concentrations on Day 1 that are close to steady state. On the basis of high oral bioavailability, switching between intravenous and oral administration is appropriate when clinically indicated (see CLINICAL PHARMACOLOGY).

For the treatment of adults with invasive aspergillosis and infections due to *Fusarium* spp. and *Scedosporium apiospermum*, the recommended dosing regimen of VFEND is as follows:

Loading dose of 6 mg/kg VFEND I.V. every 12 hours for two doses, followed by a maintenance dose of 4 mg/kg VFEND I.V. every 12 hours.

Once the patient can tolerate medication given by mouth, the oral tablet form of voriconazole may be utilized. Patients who weigh more than 40 kg should receive an oral maintenance dose of 200 mg VFEND tablet every 12 hours. Adult patients who weigh less than 40 kg should receive an oral maintenance dose of 100 mg every 12 hours.

Dosage Adjustment

If patient response is inadequate, the oral maintenance dose may be increased from 200 mg every 12 hours to 300 mg every 12 hours. For adult patients weighing less than 40 kg, the oral maintenance dose may be increased from 100 mg every 12 hours to 150 mg every 12 hours.

If patients are unable to tolerate treatment, reduce the intravenous maintenance dose to 3 mg/kg every 12 hours and the oral maintenance dose by 50 mg steps to a minimum of 200 mg every 12 hours (or to100 mg every 12 hours for adult patients weighing less than 40 kg).

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 200 mg to 400 mg every 12 hours orally (100 mg to 200 mg every 12 hours orally in adult patients weighing less than 40kg) (see CLINICAL PHARMACOLOGY, PRECAUTIONS-Drug Interactions).

Duration of therapy should be based on the severity of the patient's underlying disease, recovery from immunosuppression, and clinical response.

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Use In Geriatric Patients

No dose adjustment is necessary for geriatric patients.

Use In Patients With Hepatic Insufficiency

In the clinical program, patients were included who had baseline liver function tests (ALT, AST) up to 5 times the upper limit of normal. No dose adjustment is necessary in patients with this degree of abnormal liver function, but continued monitoring of liver function tests for further elevations is recommended (see WARNINGS).

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 Class A and B).

VFEND has not been studied in patients with severe hepatic cirrhosis (Child-Pugh Class C) or in patients with chronic hepatitis B or chronic hepatitis C disease. 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.

Use In Patients With Renal Insufficiency

The pharmacokinetics of orally administered VFEND are not significantly affected by renal insufficiency. Therefore, no adjustment is necessary for oral dosing in patients with mild to severe renal impairment (see CLINICAL PHARMACOLOGY - Special Populations)

In patients with moderate or severe renal insufficiency (creatinine clearance <50 mL/min), accumulation of the intravenous vehicle, SBECD, occurs. Oral voriconazole should be administered to these patients, unless an assessment of the benefit/risk to the patient justifies the use of intravenous voriconazole. Serum creatinine levels should be closely monitored in these patients, and, if increases occur, consideration should be given to changing to oral voriconazole therapy (see DOSAGE and ADMINISTRATION).

Voriconazole is hemodialyzed with clearance of 121 mL/min. The intravenous vehicle, SBECD, is hemodialyzed with clearance of 55 mL/min. A 4-hour hemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment.

Intravenous Administration

VFEND I.V. For Injection:

Reconstitution

The powder is reconstituted with 19 mL of Water for Injection to obtain an extractable volume of 20 mL of clear concentrate containing 10 mg/mL of voriconazole. It is recommended that a standard 20 mL (non-automated) syringe be used to ensure that the exact amount (19.0 mL) of water for injection is dispensed. Discard the vial if a vacuum does not pull the diluent into the vial. Shake the vial until all the powder is dissolved.

Dilution

VFEND must be infused over 1–2 hours, at a concentration of 5 mg/mL or less. Therefore, the required volume of the 10 mg/mL VFEND concentrate should be further diluted as follows (appropriate diluents listed below):

1. Calculate the volume of 10 mg/mL VFEND concentrate required based on the patient's weight (see Table 11).

2. In order to allow the required volume of VFEND concentrate to be added, withdraw and discard at least an equal volume of diluent from the infusion bag or bottle to be used. The volume of diluent remaining in the bag or bottle should be such that when the 10 mg/mL VFEND concentrate is added, the final concentration is not less than 0.5 mg/mL nor greater than 5 mg/mL.

3. Using a suitable size syringe and aseptic technique, withdraw the required volume of VFEND concentrate from the appropriate number of vials and add to the infusion bag or bottle. DISCARD PARTIALLY USED VIALS.

The final VFEND solution must be infused over 1-2 hours at a maximum rate of 3 mg/kg per hour.

Table 11 RequiredVolumes of 10mg/mL VFEND Concentrate

Body Weight (kg)	Volume of VFEND Concentrate (10 mg/mL) required for:		
	3 mg/kg dose (number of vials)	4 mg/kg dose (number of vials)	6 mg/kg dose (number of vials)
30	9.0 mL (1)	12 mL (1)	18 mL (1)
35	10.5 mL (1)	14 mL (1)	21 mL (2)
40	12.0 mL (1)	16 mL (1)	24 mL (2)
45	13.5 mL (1)	18 mL (1)	27 mL (2)
50	15.0 mL (1)	20 mL (1)	30 mL (2)
55	16.5 mL (1)	22 mL (2)	33 mL (2)
60	18.0 mL (1)	24 mL (2)	36 mL (2)
65	19.5 mL (1)	26 mL (2)	39 mL (2)
70	21.0 mL (2)	28 mL (2)	42 mL (3)
75	22.5 mL (2)	30 mL (2)	45 mL (3)
80	24.0 mL (2)	32 mL (2)	48 mL (3)
85	25.5 mL (2)	34 mL (2)	51 mL (3)
90	27.0 mL (2)	36 mL (2)	54 mL (3)
95	28.5 mL (2)	38 mL (2)	57 mL (3)
100	30.0 mL (2)	40 mL (2)	60 mL (3)

VFEND is a single dose unpreserved sterile lyophile. Therefore, from a microbiological point of view, once reconstituted, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2° to 8°C (37° to 46°F). This medicinal product is for single use only and any unused solution should be discarded. Only clear solutions without particles should be used.

The reconstituted solution can be diluted with:

9 mg/mL (0.9%) Sodium Chloride USP
Lactated Ringers USP
5% Dextrose and Lactated Ringers USP
5% Dextrose and 0.45% Sodium Chloride, USP
5% Dextrose USP
5% Dextrose and 20 mEq Potassium Chloride, USP
0.45% Sodium Chloride USP
5% Dextrose and 0.9% Sodium Chloride, USP

The compatibility of VFEND I.V. with diluents other than those described above is unknown (see Incompatibilities below).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Incompatibilities:

VFEND I.V. must not be infused into the same line or cannula concomitantly with other drug infusions, including parenteral nutrition, e.g., Aminofusin 10% Plus. Aminofusin 10% Plus is physically incompatible, with an increase in sub-visible particulate matter after 24 hours storage at 4ºC.

Infusions of blood products and any electrolyte supplementation must not occur simultaneously with VFEND I.V.

VFEND I.V. must not be diluted with 4.2% Sodium Bicarbonate Infusion. The mildly alkaline nature of this diluent caused slight degradation of VFEND after 24 hours storage at room temperature. Although refrigerated storage is recommended following reconstitution, use of this diluent is not recommended as a precautionary measure. Compatibility with other concentrations is unknown.

Stability

VFEND Tablets: Store at controlled room temperature 15° - 30°C (59° - 86°F).

VFEND I.V. for Injection: Store at controlled room temperature 15° - 30°C (59° - 86°F).

HOW SUPPLIED

Tablets

VFEND 50 mg tablets - white, film-coated, round, debossed with “Pfizer” on one side and “VOR50” on the reverse.
Bottles of 30 (NDC XXXX-3170-30)

VFEND 200 mg tablets – white, film coated, capsule shaped, debossed with “Pfizer” on one side and “VOR200” on the reverse.
Bottles of 30 (NDC XXXX-3180-30)

Powder for Solution for Injection

VFEND I.V. for injection is supplied in a single use vial as a sterile lyophilized powder equivalent to 200 mg VFEND and 3200 mg sulfobutyl ether beta-cyclodextrin sodium (SBECD).

Individually packaged vials of 200 mg VFEND I.V. (NDC XXXX-3190-XX)

Storage

VFEND Tablets should be stored at controlled room temperature 15° - 30°C (59° - 86°F).

Unreconstituted vials should be stored at controlled room temperature 15° - 30°C (59° - 86°F). VFEND is a single dose unpreserved sterile lyophile. From a microbiological point of view, following reconstitution of the lyophile with Water for Injection, the reconstituted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°to 8°C (37° to 46°F). Chemical and physical in-use stability has been demonstrated for 24 hours at 2° to 8°C (37° to 46°F). This medicinal product is for single use only and any unused solution should be discarded. Only clear solutions without particles should be used (see DOSAGE AND ADMINISTRATION - Intravenous Administration).

REFERENCES

1. National Committee for Clinical Laboratory Standards. Reference method for broth dilution antifungal susceptibility testing of conidium-forming filamentous fungi. Approved Standard M38-P. National Committee for Clinical Laboratory Standards, Villanova, Pa.

/s/

Mark Goldberger
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