

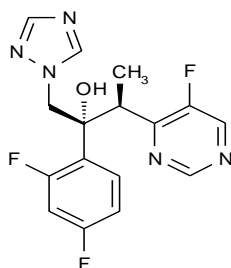
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Trade Name: **VFEND®**
CDS Effective Date: January 13, 2021
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PT. PFIZER INDONESIA
Local Product Document

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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-(1H-1,2,4-triazol-1-yl)-2-butanol with an empirical formula of C₁₆H₁₄F₃N₅O and a molecular weight of 349.3.

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

VFEND Tablets contain 200 mg of voriconazole. The inactive ingredients include lactose monohydrate, pre-gelatinized 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 Section **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 an approximately 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}^* ($\mu\text{g}\cdot\text{h/mL}$) (CV%)	19.86 (94%)	50.32 (74%)	21.81 (100%)	50.40 (83%)

* Mean AUC_{τ} 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}^* ($\mu\text{g}\cdot\text{h/mL}$) (CV%)	20.31 (69%)	36.51 (45%)
C_{\max}^* ($\mu\text{g/mL}$) (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 $\mu\text{g/mL}$ (inter-quartile range 0.28 to 2.73 $\mu\text{g/mL}$). In 17 adolescent patients for whom mean plasma concentrations were calculated following a

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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, 1 st dose	Day 10	Day 1, 1 st 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. Voriconazole is rapidly and almost completely absorbed following oral administration, with maximum plasma concentrations (C_{max}) achieved 1 to 2 hours after dosing. 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%). Bioequivalence was established between the 200 mg tablet and the 40 mg/mL oral suspension when administered as a 400 mg every 12 hours loading dose followed by a 200 mg every 12 hours maintenance dose.

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, when administered as a tablet (see Section **DOSAGE AND ADMINISTRATION**).

In healthy subjects, the absorption of voriconazole is not affected by co-administration 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.

Cerebrospinal fluid samples from eight patients in a compassionate programme showed detectable voriconazole concentrations in all patients.

Metabolism

In vitro studies showed that voriconazole is metabolised by the human hepatic cytochrome P450 enzymes, CYP2C19, CYP2C9 and CYP3A4 (see Section **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 metabolisers. For Caucasians and Blacks, the prevalence of poor metabolisers is 3%-5%. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolisers have, on average, 4-fold higher voriconazole exposure (AUC_{τ}) than their homozygous extensive metaboliser counterparts. Subjects who are heterozygous extensive metabolisers have, on average, 2-fold higher voriconazole exposure than their homozygous extensive metaboliser 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 Section **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 a similar study, after dosing with the oral suspension, the mean AUC for healthy young females was 45% higher than in healthy young males, whereas the mean C_{max} was comparable between genders. The steady state trough voriconazole concentrations (C_{min}) seen in females were 100% and 91% higher than in males receiving the tablet and the oral suspension, respectively.

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

The recommended intravenous dose in pediatric patients is based on a population pharmacokinetic analysis of data pooled from 82 immunocompromised pediatric patients aged 2 to < 12 years old who were evaluated in three pharmacokinetic studies (examining single intravenous doses of 3 and 4 mg/kg twice daily, multiple intravenous doses of 3,

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4, 6 and 8 mg/kg twice daily and multiple oral suspension doses of 4 and 6 mg/kg twice daily).

The majority of patients received more than one dose level with a maximum duration of dosing of 30 days. A comparison of the pediatric and adult population pharmacokinetic data indicated that in order to obtain comparable exposures to those obtained in adults following intravenous maintenance doses of 4 mg/kg twice daily, intravenous maintenance doses of 7 mg/kg twice daily are required in pediatric patients.

The higher intravenous maintenance dose in pediatric patients relative to adults reflects the higher elimination capacity in pediatric patients due to a greater liver mass to body mass ratio. In order to obtain comparable exposures to those obtained in adults following intravenous maintenance doses of 3 mg/kg twice daily, intravenous maintenance doses of 4 mg/kg twice daily are required in pediatric patients. Based on the population pharmacokinetic analysis, no loading dose or dosage adjustment according to age is warranted in patients aged 2 to <12 years old.

The recommended oral dose in pediatrics is based on a population pharmacokinetic analysis data obtained from 47 immunocompromised pediatric patients aged 2 to <12 years old who were evaluated in a pharmacokinetic study examining multiple oral suspension doses of 4 to 6 mg/kg twice daily. A comparison of the pediatric and adult population pharmacokinetic data indicated that in order to obtain comparable exposures to those obtained in adults following a maintenance dose of 200 mg twice daily, the same dose of 200 mg of oral solution twice daily is required in pediatric patients, independent of body weight. In pediatric patients there is a general trend towards low bioavailability at lower body weights and high bioavailability at higher body weights (towards the extent demonstrated in adults). Based on the population pharmacokinetic analysis, no dosage adjustment according to age or weight is warranted in patients aged 2 to <12 years old at the 200 mg bid oral solution dosing regimen. A loading dose is not indicated in pediatric patients. Oral bioavailability may however be limited in pediatric patients with malabsorption and very low body weight for their age. In that case, intravenous voriconazole administration is recommended.

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. Protein binding of voriconazole was not affected by impaired 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 Section **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 Section **DOSAGE AND ADMINISTRATION - Dosage Adjustment**).

A pharmacokinetic study in subjects with renal failure undergoing hemodialysis showed that voriconazole is dialyzed 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.

Preclinical Safety Data

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/m² 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/m² 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.

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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.

Repeated-dose toxicity studies with voriconazole indicated the liver to be the target organ. Hepatotoxicity occurred at plasma exposures similar to those obtained at therapeutic doses in humans, in common with other antifungal agents. In rats, mice and dogs, voriconazole also induced minimal adrenal changes. Conventional studies of safety pharmacology, genotoxicity or carcinogenic potential did not reveal a special hazard for humans.

In reproduction studies, voriconazole was shown to be teratogenic in rats and embryotoxic in rabbits at systemic exposures equal to those obtained in humans with therapeutic doses. In the pre- and post-natal development study in rats at exposures lower than those obtained in humans with therapeutic doses, voriconazole prolonged the duration of gestation and labor and produced dystocia with consequent maternal mortality and reduced perinatal survival of pups. The effects on parturition are probably mediated by species-specific mechanisms, involving reduction of estradiol levels, and are consistent with those observed with other azole antifungal agents. Voriconazole administration induced no impairment of male or female fertility in rats at exposures similar to those obtained in humans at therapeutic doses.

Preclinical data on the intravenous vehicle, SBECD indicated that the main effects were vacuolation of urinary tract epithelium and activation of macrophages in the liver and lungs in the repeated-dose toxicity studies.

Drug Interactions

Effects of Other Drugs on Voriconazole

Voriconazole is metabolised by, and inhibits the activity of, cytochrome P450 isoenzymes, CYP2C19, CYP2C9, and CYP3A4. Inhibitors or inducers of these isoenzymes may increase or decrease voriconazole plasma concentrations, respectively, and there is potential for voriconazole to increase the plasma concentrations of substances metabolised by these CYP450 isoenzymes, in particular for substances metabolised by CYP3A4 since voriconazole is a strong CYP3A4 inhibitor though the increase in AUC is substrate dependent (see Interaction Table below).

Unless otherwise specified, drug interaction studies have been performed in healthy adult male subjects using multiple dosing to steady state with oral voriconazole at 200 mg twice daily (BID). These results are relevant to other populations and routes of administration.

Voriconazole should be administered with caution in patients with concomitant medication that is known to prolong QT interval. When there is also a potential for

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voriconazole to increase the plasma concentrations of substances metabolised by CYP3A4 isoenzymes (certain antihistamines, quinidine, cisapride, pimozone and ivabradine) co-administration is contraindicated (see below and Section **CONTRAINDICATIONS**).

Interaction Table

Interactions between voriconazole and other medicinal products are listed in the table below (once daily as “QD”, twice daily as “BID”, three times daily as “TID” and not determined as “ND”). The direction of the arrow for each pharmacokinetic parameter is based on the 90% confidence interval of the geometric mean ratio being within (\leftrightarrow), below (\downarrow) or above (\uparrow) the 80%-125% range. The asterisk (*) indicates a two-way interaction. AUC_τ, AUC_t and AUC_{0-∞} represent area under the curve over a dosing interval, from time zero to the time with detectable measurement and from time zero to infinity, respectively.

The interactions in the table are presented in the following order: contraindications, those requiring dose adjustment and careful clinical and/or biological monitoring, and finally those that have no significant pharmacokinetic interaction but may be of clinical interest in this therapeutic field.

Table 4

Medicinal product [Mechanism of Interaction]	Interaction Geometric mean changes (%)	Recommendations concerning co-administration
Astemizole, cisapride, pimozone, quinidine, terfenadine and ivabradine [CYP3A4 substrates]	Although not studied, increased plasma concentrations of these medicinal products can lead to QTc prolongation and rare occurrences of <i>torsades de pointes</i> .	Contraindicated (see Section CONTRAINDICATIONS)
Carbamazepine and long-acting barbiturates (e.g., phenobarbital, mephobarbital) [potent CYP450 inducers]	Although not studied, carbamazepine and long-acting barbiturates are likely to significantly decrease plasma voriconazole concentrations.	Contraindicated (see Section CONTRAINDICATIONS)
Efavirenz (a non-nucleoside reverse transcriptase inhibitor) [CYP450 inducer; CYP3A4 inhibitor and substrate] Efavirenz 400 mg QD, co-administered with voriconazole 200 mg BID	<p> Efavirenz C_{max} \uparrow 38% Efavirenz AUC_τ \uparrow 44% Voriconazole C_{max} \downarrow 61% Voriconazole AUC_τ \downarrow 77% </p> <p> Compared to efavirenz 600 mg QD, Efavirenz C_{max} \leftrightarrow Efavirenz AUC_τ \uparrow 17% </p>	<p>Standard doses of voriconazole and standard doses of efavirenz (400 mg QD or above) is contraindicated (see Section CONTRAINDICATIONS).</p> <p>Voriconazole may be co-administered with efavirenz if the voriconazole maintenance dose is increased to 400 mg BID and the efavirenz dose is decreased to</p>

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Medicinal product [Mechanism of Interaction]	Interaction Geometric mean changes (%)	Recommendations concerning co-administration
Efavirenz 300 mg QD, co-administered with voriconazole 400 mg BID*	Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 23% Voriconazole AUC_{τ} ↓ 7%	300 mg QD. When voriconazole treatment is stopped, the initial dose of efavirenz should be restored (see Section DOSAGE AND ADMINISTRATION).
Ergot alkaloids (e.g., ergotamine and dihydroergotamine) [CYP3A4 substrates]	Although not studied, voriconazole is likely to increase the plasma concentrations of ergot alkaloids and lead to ergotism.	Contraindicated (see Section CONTRAINDICATIONS)
Lurasidone [CYP3A4 substrate]	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of lurasidone.	Contraindicated (see Section CONTRAINDICATIONS)
Naloxegol [CYP3A4 substrate]	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of naloxegol.	Contraindicated (see Section CONTRAINDICATIONS)
Rifabutin [potent CYP450 inducer] 300 mg QD 300 mg QD (co-administered with voriconazole 400 mg BID)*	Voriconazole C_{max} ↓ 69% Voriconazole AUC_{τ} ↓ 78% Rifabutin C_{max} ↑ 195% Rifabutin AUC_{τ} ↑ 331% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 104% Voriconazole AUC_{τ} ↑ 87%	Contraindicated (see Section CONTRAINDICATIONS)
Rifampicin (600 mg QD) [potent CYP450 inducer]	Voriconazole C_{max} ↓ 93% Voriconazole AUC_{τ} ↓ 96%	Contraindicated (see Section CONTRAINDICATIONS)
Ritonavir (protease inhibitor) [potent CYP450 inducer; CYP3A4 inhibitor and substrate] High dose (400 mg BID) Low dose (100 mg BID)*	Ritonavir C_{max} and AUC_{τ} ↔ Voriconazole C_{max} ↓ 66% Voriconazole AUC_{τ} ↓ 82% Ritonavir C_{max} ↓ 25% Ritonavir AUC_{τ} ↓ 13% Voriconazole C_{max} ↓ 24% Voriconazole AUC_{τ} ↓ 39%	Co-administration of voriconazole and high doses of ritonavir (400 mg and above BID) is contraindicated (see Section CONTRAINDICATIONS). Co-administration of voriconazole and low dose ritonavir (100 mg BID) should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.
St. John's Wort [CYP450 inducer; P-gp inducer]		

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Medicinal product [Mechanism of Interaction]	Interaction Geometric mean changes (%)	Recommendations concerning co-administration
300 mg TID (co-administered with voriconazole 400 mg single dose)	In an independent published study, Voriconazole AUC _{0-∞} ↓ 59%	Contraindicated (see Section CONTRAINDICATIONS)
Tolvaptan [CYP3A substrate]	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of tolvaptan.	Contraindicated (see Section CONTRAINDICATIONS)
Venetoclax [CYP3A substrate]	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of venetoclax.	Concomitant administration of voriconazole is contraindicated at initiation and during venetoclax dose titration phase (see Section CONTRAINDICATIONS). Dose reduction of venetoclax is required as instructed in venetoclax prescribing information during steady daily dosing; close monitoring for signs of toxicity is recommended.
Fluconazole (200 mg QD) [CYP2C9, CYP2C19 and CYP3A4 inhibitor]	Voriconazole C _{max} ↑ 57% Voriconazole AUC _τ ↑ 79% Fluconazole C _{max} ND Fluconazole AUC _τ ND	The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole-associated adverse events is recommended if voriconazole is used sequentially after fluconazole.
Phenytoin [CYP2C9 substrate and potent CYP450 inducer] 300 mg QD 300 mg QD (co-administered with voriconazole 400 mg BID)*	Voriconazole C _{max} ↓ 49% Voriconazole AUC _τ ↓ 69% Phenytoin C _{max} ↑ 67% Phenytoin AUC _τ ↑ 81% Compared to voriconazole 200 mg BID, Voriconazole C _{max} ↑ 34% Voriconazole AUC _τ ↑ 39%	Concomitant use of voriconazole and phenytoin should be avoided unless the benefit outweighs the risk. Careful monitoring of phenytoin plasma levels is recommended. Phenytoin may be co-administered with voriconazole if the maintenance dose of voriconazole is increased to 5 mg/kg IV BID or from 200 mg to 400 mg oral BID, (100 mg to 200 mg oral BID in patients less than 40 kg) (see Section DOSAGE AND ADMINISTRATION).
Letermovir [CYP2C9 and CYP2C19 inducer]	Voriconazole C _{max} ↓ 39% Voriconazole AUC ₀₋₁₂ ↓ 44% Voriconazole C ₁₂ ↓ 51%	If concomitant administration of voriconazole with letermovir cannot be avoided,

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Medicinal product [Mechanism of Interaction]	Interaction Geometric mean changes (%)	Recommendations concerning co-administration
		monitor for loss of voriconazole effectiveness.
Anticoagulants Warfarin (30 mg single dose, co-administered with 300 mg BID voriconazole) [CYP2C9 substrate] Other oral coumarins (e.g., phenprocoumon, acenocoumarol) [CYP2C9 and CYP3A4 substrates]	Maximum increase in prothrombin time was approximately 2-fold Although not studied, voriconazole may increase the plasma concentrations of coumarins that may cause an increase in prothrombin time.	Close monitoring of prothrombin time or other suitable anticoagulation tests is recommended, and the dose of anticoagulants should be adjusted accordingly.
Ivacaftor [CYP3A4 substrate]	Although not studied, voriconazole is likely to increase the plasma concentrations of ivacaftor with risk of increased adverse effects.	Dose reduction of ivacaftor is recommended.
Benzodiazepines [CYP3A4 substrates] Midazolam (0.05 mg/kg IV single dose) Midazolam (7.5 mg oral single dose) Other benzodiazepines (e.g., triazolam, alprazolam)	In an independent published study, Midazolam AUC _{0-∞} ↑ 3.6-fold In an independent published study, Midazolam C _{max} ↑ 3.8-fold Midazolam AUC _{0-∞} ↑ 10.3-fold Although not studied, voriconazole is likely to increase the plasma concentrations of other benzodiazepines that are metabolised by CYP3A4 and lead to a prolonged sedative effect.	Dose reduction of benzodiazepines should be considered.
Immunosuppressants [CYP3A4 substrates] Sirolimus (2 mg single dose) Everolimus [also P-gp substrate]	In an independent published study, Sirolimus C _{max} ↑ 6.6-fold Sirolimus AUC _{0-∞} ↑ 11-fold Although not studied, voriconazole is likely to significantly increase the plasma concentrations of everolimus.	Co-administration of voriconazole and sirolimus is contraindicated (see Section CONTRAINDICATIONS). Co-administration of voriconazole and everolimus is not recommended because voriconazole is expected to significantly increase everolimus concentrations (see

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Medicinal product [Mechanism of Interaction]	Interaction Geometric mean changes (%)	Recommendations concerning co-administration
Ciclosporin (In stable renal transplant recipients receiving chronic ciclosporin therapy)	Ciclosporin C_{max} ↑ 13% Ciclosporin AUC_{τ} ↑ 70%	Section WARNINGS AND PRECAUTIONS . When initiating voriconazole in patients already on ciclosporin it is recommended that the ciclosporin dose be halved and ciclosporin level carefully monitored. Increased ciclosporin levels have been associated with nephrotoxicity. <u>When voriconazole is discontinued, ciclosporin levels must be carefully monitored and the dose increased as necessary.</u>
Tacrolimus (0.1 mg/kg single dose)	Tacrolimus C_{max} ↑ 117% Tacrolimus AUC_{τ} ↑ 221%	When initiating voriconazole in patients already on tacrolimus, it is recommended that the tacrolimus dose be reduced to a third of the original dose and tacrolimus level carefully monitored. Increased tacrolimus levels have been associated with nephrotoxicity. <u>When voriconazole is discontinued, tacrolimus levels must be carefully monitored and the dose increased as necessary.</u>
Long Acting Opiates [CYP3A4 substrates] Oxycodone (10 mg single dose)	In an independent published study, Oxycodone C_{max} ↑ 1.7-fold Oxycodone $AUC_{0-\infty}$ ↑ 3.6-fold	Dose reduction in oxycodone and other long-acting opiates metabolised by CYP3A4 (e.g., hydrocodone) should be considered. Frequent monitoring for opiate-associated adverse events may be necessary.
Methadone (32-100 mg QD) [CYP3A4 substrate]	R-methadone (active) C_{max} ↑ 31% R-methadone (active) AUC_{τ} ↑ 47% S-methadone C_{max} ↑ 65% S-methadone AUC_{τ} ↑ 103%	Frequent monitoring for adverse events and toxicity related to methadone, including QT prolongation, is recommended. Dose reduction of methadone may be needed.
Non-steroidal Anti-inflammatory Drugs (NSAIDs) [CYP2C9 substrates] Ibuprofen (400 mg single dose) Diclofenac (50 mg single dose)	S-Ibuprofen C_{max} ↑ 20% S-Ibuprofen $AUC_{0-\infty}$ ↑ 100% Diclofenac C_{max} ↑ 114% Diclofenac $AUC_{0-\infty}$ ↑ 78%	Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Dose reduction of NSAIDs may be needed.

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Medicinal product <i>[Mechanism of Interaction]</i>	Interaction Geometric mean changes (%)	Recommendations concerning co-administration
Omeprazole (40 mg QD)* <i>[CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate]</i>	Omeprazole C_{max} ↑ 116% Omeprazole AUC_{τ} ↑ 280% Voriconazole C_{max} ↑ 15% Voriconazole AUC_{τ} ↑ 41% Other proton pump inhibitors that are CYP2C19 substrates may also be inhibited by voriconazole and may result in increased plasma concentrations of these medicinal products.	No dose adjustment of voriconazole is recommended. When initiating voriconazole in patients already receiving omeprazole doses of 40 mg or above, it is recommended that the omeprazole dose be halved.
Oral Contraceptives* <i>[CYP3A4 substrate; CYP2C19 inhibitor]</i> Norethisterone/ethinylestradiol (1 mg/0.035 mg QD)	Ethinylestradiol C_{max} ↑ 36% Ethinylestradiol AUC_{τ} ↑ 61% Norethisterone C_{max} ↑ 15% Norethisterone AUC_{τ} ↑ 53% Voriconazole C_{max} ↑ 14% Voriconazole AUC_{τ} ↑ 46%	Monitoring for adverse events related to oral contraceptives, in addition to those for voriconazole, is recommended.
Short Acting Opiates <i>[CYP3A4 substrates]</i> Alfentanil (20 µg/kg single dose, with concomitant naloxone) Fentanyl (5 µg/kg single dose)	In an independent published study, Alfentanil $AUC_{0-\infty}$ ↑ 6-fold In an independent published study, Fentanyl $AUC_{0-\infty}$ ↑ 1.34-fold	Dose reduction of alfentanil, fentanyl and other short acting opiates similar in structure to alfentanil and metabolised by CYP3A4 (e.g., sufentanil) should be considered. Extended and frequent monitoring for respiratory depression and other opiate-associated adverse events is recommended.
Statins (e.g., lovastatin) <i>[CYP3A4 substrates]</i>	Although not studied, voriconazole is likely to increase the plasma concentrations of statins that are metabolised by CYP3A4 and could lead to rhabdomyolysis.	If concomitant administration of voriconazole with statins metabolised by CYP3A4 cannot be avoided, dose reduction of the statin should be considered.
Sulphonylureas (e.g., tolbutamide, glipizide, glyburide) <i>[CYP2C9 substrates]</i>	Although not studied, voriconazole is likely to increase the plasma concentrations of sulphonylureas and cause hypoglycaemia.	Careful monitoring of blood glucose is recommended. Dose reduction of sulphonylureas should be considered.
Vinca Alkaloids (e.g., vincristine and vinblastine) <i>[CYP3A4 substrates]</i>	Although not studied, voriconazole is likely to increase the plasma concentrations of vinca alkaloids and lead to neurotoxicity.	Dose reduction of vinca alkaloids should be considered.
Other HIV Protease Inhibitors (e.g., saquinavir, amprenavir and nelfinavir)* <i>[CYP3A4 substrates and inhibitors]</i>	Not studied clinically. <i>In vitro</i> studies show that voriconazole may inhibit the metabolism of HIV protease inhibitors and the metabolism of voriconazole	Careful monitoring for any occurrence of drug toxicity and/or lack of efficacy, and dose adjustment may be needed.

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Medicinal product [Mechanism of Interaction]	Interaction Geometric mean changes (%)	Recommendations concerning co-administration
	may also be inhibited by HIV protease inhibitors.	
Other Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (e.g., delavirdine, nevirapine)* [CYP3A4 substrates, inhibitors or CYP450 inducers]	Not studied clinically. <i>In vitro</i> studies show that the metabolism of voriconazole may be inhibited by NNRTIs and voriconazole may inhibit the metabolism of NNRTIs. The findings of the effect of efavirenz on voriconazole suggest that the metabolism of voriconazole may be induced by a NNRTI.	Careful monitoring for any occurrence of drug toxicity and/or lack of efficacy, and dose adjustment may be needed.
Cimetidine (400 mg BID) [non-specific CYP450 inhibitor and increases gastric pH]	Voriconazole C_{max} ↑ 18% Voriconazole AUC_{τ} ↑ 23%	No dose adjustment
Digoxin (0.25 mg QD) [P-gp substrate]	Digoxin C_{max} ↔ Digoxin AUC_{τ} ↔	No dose adjustment
Indinavir (800 mg TID) [CYP3A4 inhibitor and substrate]	Indinavir C_{max} ↔ Indinavir AUC_{τ} ↔ Voriconazole C_{max} ↔ Voriconazole AUC_{τ} ↔	No dose adjustment
Macrolide antibiotics Erythromycin (1 g BID) [CYP3A4 inhibitor] Azithromycin (500 mg QD)	Voriconazole C_{max} and AUC_{τ} ↔ Voriconazole C_{max} and AUC_{τ} ↔ The effect of voriconazole on either erythromycin or azithromycin is unknown.	No dose adjustment
Mycophenolic acid (1 g single dose) [UDP-glucuronyl transferase substrate]	Mycophenolic acid C_{max} ↔ Mycophenolic acid AUC_{τ} ↔	No dose adjustment
Corticosteroids Prednisolone (60 mg single dose) [CYP3A4 substrate]	Prednisolone C_{max} ↑ 11% Prednisolone $AUC_{0-\infty}$ ↑ 34%	No dose adjustment Patients on long-term treatment with voriconazole and corticosteroids (including inhaled corticosteroids e.g. budesonide) should be carefully monitored for adrenal cortex dysfunction both during treatment and when voriconazole is discontinued (see Section

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Medicinal product [Mechanism of Interaction]	Interaction Geometric mean changes (%)	Recommendations concerning co-administration
		WARNINGS AND PRECAUTIONS).
Ranitidine (150 mg BID) [increases gastric pH]	Voriconazole C _{max} and AUC _τ ↔	No dose adjustment

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 metabolised by CYP3A4. Frequent monitoring for adverse events and toxicity related to calcium channel blockers is recommended during co-administration. Dose adjustment of the calcium channel blocker may be needed (see Section **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

In vitro, voriconazole displays broad-spectrum antifungal activity with antifungal potency against *Candida* species (including fluconazole resistant *C. krusei* and resistant strains of *C. glabrata* and *C. albicans*). 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 Sections **INDICATIONS AND USAGE** and **CLINICAL STUDIES - Invasive Aspergillosis**).

Other treated fungal infections (with often partial or complete response) included isolated cases of *Alternaria* spp., *Blastomyces dermatitidis*, *Blastoschizomyces capitatus*, *Cladosporium* spp., *Coccidioides immitis*, *Conidiobolus coronatus*, *Cryptococcus neoformans*, *Exserohilum rostratum*, *Exophiala spinifera*, *Fonsecaea pedrosoi*, *Madurella mycetomatis*, *Paecilomyces lilacinus*, *Penicillium* spp. including *P. marneffe*, *Phialophora richardsiae*, *Scopulariopsis brevicaulis* and *Trichosporon* spp. including *T. beigelii* infections.

In vitro activity against clinical isolates has been observed for *Acremonium* spp., *Alternaria* spp., *Bipolaris* spp., *Cladophialophora* spp., *Histoplasma capsulatum*, with

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most strains being inhibited by concentrations of voriconazole in the range 0.05 to 2 mcg/mL.

In vitro activity against the following pathogens has been shown, but the clinical significance is unknown: *Curvularia* spp. and *Sporothrix* spp.

Breakpoints

The species most frequently involved in causing human infections include *C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata* and *C. krusei*, all of which usually exhibit minimum inhibitory concentrations (MICs) of less than 1 mg/L for voriconazole.

However, the *in vitro* activity of voriconazole against *Candida* species is not uniform. Specifically, for *C. glabrata*, the MICs of voriconazole for fluconazole-resistant isolates are proportionally higher than are those of fluconazole-susceptible isolates. Therefore, every attempt should be made to identify *Candida* to species level. If antifungal susceptibility testing is available, the MIC results may be interpreted using breakpoint criteria.

European Committee on Antimicrobial Susceptibility Testing (EUCAST) Breakpoints

Candida species: The interpretive standards for voriconazole against *Candida* species are applicable only to tests performed using EUCAST microbroth dilution reference method for minimum inhibitory concentrations (MICs) read at 24 hours.

Table 5. Breakpoint criteria established by EUCAST

Candida Species	MIC breakpoint (mg/L)	
	≤S (Susceptible)	>R (Resistant)
<i>Candida albicans</i> ¹	0.125	0.125
<i>Candida tropicalis</i> ¹	0.125	0.125
<i>Candida parapsilosis</i> ¹	0.125	0.125
<i>Candida glabrata</i> ²	Insufficient evidence	
<i>Candida krusei</i> ³	Insufficient evidence	
Other <i>Candida</i> spp. ⁴	Insufficient evidence	

¹ Strains with MIC values above the Susceptible (S) breakpoint are rare, or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory.

² In clinical studies, response to voriconazole in patients with *C. glabrata* infections was 21% lower compared to *C. albicans*, *C. parapsilosis* and *C. tropicalis*. However, this reduced response was not correlated with elevated MICs.

³ In clinical studies, response to voriconazole in *C. krusei* infections was similar to *C. albicans*, *C. parapsilosis* and *C. tropicalis*. However, as there were only 9 cases available for EUCAST analysis, there is currently insufficient evidence to set clinical breakpoints for *C. krusei*.

⁴ EUCAST has not determined non-species related breakpoints for voriconazole.

Clinical and Laboratory Standards Institute (CLSI) Breakpoints Breakpoint criteria established by CLSI

Susceptibility Testing Methods

Aspergillus species and other filamentous fungi: No interpretive criteria have been established for *Aspergillus* species and other filamentous fungi.

Candida species: The interpretive standards for voriconazole against *Candida* species are applicable only to tests performed using Clinical and Laboratory Standards Institute (CLSI) microbroth dilution reference method M27 for MIC read at 48 hours or disk diffusion reference method M44 for zone diameter read at 24 hours.

Broth Dilution Techniques: Quantitative methods are used to determine antifungal MICs. These MICs provide estimates of the susceptibility of *Candida* species to antifungal agents. MICs should be determined using a standardized procedure at 48 hours. Standardized procedures are based on a microdilution method (broth) with standardized inoculum concentrations and standardized concentrations of voriconazole powder. The MIC values should be interpreted according to the criteria provided in the table below.

Diffusion Techniques: Qualitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of *Candida* species to an antifungal agent. One such standardized procedure requires the use of standardized inoculum concentrations. This procedure uses paper discs impregnated with 1 microgram of voriconazole to test the susceptibility of yeasts to voriconazole. Disc diffusion interpretive criteria are also provided in the table below.

Table 6. Susceptibility Interpretive Criteria for Voriconazole

	Broth Dilution at 48 hours (MIC in µg/mL)			Disk Diffusion at 24 hours (Zone diameters in mm)		
	Susceptible (S)	Susceptible-dose dependent (S-DD)	Resistant (R)	Susceptible (S)	Susceptible-dose dependent (S-DD)	Resistant (R)
Voriconazole	≤1.0	2.0	≥4.0	≥17	14-16	≤13

Note 1: Shown are the breakpoints (µg/mL) for voriconazole against *Candida* species. If MICs are measured using a scale that yields results falling between categories, the next higher category is implied. Thus, an isolate with a voriconazole MIC of 1.5 µg/mL would be placed in the S-DD category.

The susceptible category implies that isolates are inhibited by the usually achievable concentrations of antifungal agent tested when the recommended dosage is used for the site of infection. The susceptible-dose dependent category implies that an infection due to the isolate may be appropriately treated in body sites where the drugs are physiologically concentrated or when a high dosage of drug is used. The resistant category implies that isolates are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies.

Quality Control

Standardized susceptibility test procedures require the use of quality control organisms to control the technical aspects of the test procedures. Standard voriconazole powder and 1 µg discs should provide the following range of values noted in the table below.

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NOTE: Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within fungi; the specific strains used for microbiological control are not clinically significant.

Table 7. Acceptable Quality Control Ranges for Voriconazole to be Used in Validation of Susceptibility Test Results

	Broth Dilution (MIC in µg/mL)		Disk Diffusion (Zone diameter in mm) @ 24-hour
	@ 24-hour	@ 48-hour	
QC Strain			
<i>Candida parapsilosis</i> ATCC 22019	0.016-0.12	0.03-0.25	28-37
<i>Candida krusei</i> ATCC 6258	0.06-0.5	0.12-1.0	16-25
<i>Candida albicans</i> ATCC 90028	*	*	31-42

* Quality control ranges have not been established for this strain/antifungal agent combination due to their extensive inter-laboratory variation during initial quality control studies.

ATCC is a registered trademark of the American Type Culture Collection.

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:

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Treatment of invasive aspergillosis. In clinical trials, the majority of isolates recovered were *Aspergillus fumigatus*. There were a small number of cases of culture-proven disease due to species of *Aspergillus* other than *A. fumigatus* (see Sections **CLINICAL STUDIES** and **MICROBIOLOGY**).

Treatment of candidemia in non-neutropenic patients;

Treatment of serious invasive *Candida* infections (including *C. krusei*);

Treatment of esophageal candidiasis;

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).

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Voriconazole was administered intravenously with a loading dose of 6 mg/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 8). 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 8).

This study confirmed findings from an earlier, prospectively designed study where there was a positive outcome in subjects with risk factors for a poor prognosis, including graft versus host disease, and, in particular, cerebral infections (normally associated with almost 100% mortality).

Table 8 also summarizes the response (success) based on mycological confirmation and species.

Table 8. Overall Efficacy and Success by Species in the Primary Treatment 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%)
<u>Success by Species</u>			
	Success n/N (%)		
<u>Overall success</u>	76/144 (53)	42/133 (32)	

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Mycologically confirmed ^c	37/84 (44)	16/67 (24)	
<i>Aspergillus</i> spp. ^f			
<i>A. fumigatus</i>	28/63 (44)	12/47 (26)	
<i>A. flavus</i>	3/6	4/9	
<i>A. terreus</i>	2/3	0/3	
<i>A. niger</i>	1/4	0/9	
<i>A. nidulans</i>	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 9.

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 9. 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 9.

Table 9. Combined Response Data in Salvage Patients with Single *Aspergillus* Species (Studies 304 and 309/604)

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

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

Candidemia in non-neutropenic patients and other deep tissue *Candida* infections

The efficacy of voriconazole was compared to the regimen of amphotericin B followed by fluconazole in Study 608, an open label, comparative study in non-neutropenic patients with candidemia associated with clinical signs of infection, of which 248 were treated with voriconazole. The patient population was seriously ill, with approximately 50% of subjects in the intensive care unit and 40% mechanically ventilated at baseline. The median treatment duration was 15 days in both treatment arms. Patients were randomized in 2:1 ratio to receive either voriconazole (n=283) or the regimen of amphotericin B followed by fluconazole (n=139). Patients were treated with randomized study drug for a median of 15 days. Most of the candidemia in patients evaluated for efficacy was caused by *C. albicans* (46%), followed by *C. tropicalis* (19%), *C. parapsilosis* (17%), *C. glabrata* (15%), and *C. krusei* (1%).

An independent Data Review Committee (DRC), blinded to study treatment, reviewed the clinical and mycological data from this study, and generated one assessment of response for each patient. A successful response required all of the following: resolution or improvement in all clinical signs and symptoms of infection, blood cultures negative for *Candida*, infected deep tissue sites negative for *Candida* or resolution of all local signs of infection, and no systemic antifungal therapy other than study drug. The primary analysis, which counted DRC-assessed successes at the fixed time point (12 weeks after End of Therapy [EOT]), demonstrated that voriconazole was comparable to the regimen of amphotericin B followed by fluconazole (response rates of 41% and 41%, respectively) in the treatment of candidemia. Patients who did not have a 12-week assessment for any reason were considered a treatment failure.

The overall clinical and mycological success rates by *Candida* species in Study 150-608 are presented in Table 10.

Table 10. Overall Success Rates Sustained from EOT to the Fixed 12-Week Follow-up Time Point by Baseline Pathogen^{a,b}

Baseline Pathogen	Clinical and Mycological Success (%)	
	Voriconazole	Amphotericin B --> Fluconazole
<i>C. albicans</i>	46/107 (43%)	30/63 (48%)
<i>C. tropicalis</i>	17/53 (32%)	1/16 (6%)
<i>C. parapsilosis</i>	24/45 (53%)	10/19 (53%)
<i>C. glabrata</i>	12/36 (33%)	7/21 (33%)
<i>C. krusei</i>	1/4	0/1

^a A few patients had more than one pathogen at baseline.

^b Patients who did not have a 12-week assessment for any reason were considered a treatment failure.

In a secondary analysis, which counted DRC-assessed successes at any time point (EOT, or 2, 6, or 12 weeks after EOT), the response rates were 65% for voriconazole and 71% for the regimen of amphotericin B followed by fluconazole.

In Studies 608 and 309/604 (non-comparative study in patients with invasive fungal infections who were refractory to, or intolerant of, other antifungal agents), voriconazole was evaluated in 35 patients with deep tissue *Candida* infections. A favorable response was seen in 4 of 7 patients with intraabdominal infections, 5 of 6 patients with kidney and

bladder wall infections, 3 of 3 patients with deep tissue abscess or wound infection, 1 of 2 patients with pneumonia/pleural space infections, 2 of 4 patients with skin lesions, 1 of 1 patients with mixed intraabdominal and pulmonary infection, 1 of 2 patients with suppurative phlebitis, 1 of 3 patients with hepatosplenic infection, 1 of 5 patients with osteomyelitis, 0 of 1 with liver infection, and 0 of 1 with cervical lymph node infection.

Esophageal Candidiasis

The efficacy of oral voriconazole 200 mg bid compared to oral fluconazole 200 mg od in the primary treatment of esophageal candidiasis was demonstrated in Study 150-305, a double-blind, double-dummy study in immunocompromised patients with endoscopically-proven esophageal candidiasis. Patients were treated for a median of 15 days (range 1 to 49 days). Outcome was assessed by repeat endoscopy at end of treatment (EOT). A successful response was defined as a normal endoscopy at EOT or at least a 1 grade improvement over baseline endoscopic score. For patients in the Intent to Treat (ITT) population with only a baseline endoscopy, a successful response was defined as symptomatic cure or improvement at EOT compared to baseline. Voriconazole and fluconazole (200 mg od) showed comparable efficacy rates against esophageal candidiasis, as presented in Table 11.

Table 11. Success Rates in Patients Treated for Esophageal Candidiasis

Population	Voriconazole	Fluconazole	Difference % (95% CI) ^a
PP ^b	113/115 (98.2%)	134/141 (95.0%)	3.2 (-1.1, 7.5)
ITT ^c	175/200 (87.5%)	171/191 (89.5%)	-2.0 (-8.3, 4.3)

^a Confidence Interval for the difference (Voriconazole – Fluconazole) in success rates.

^b PP (Per Protocol) patients had confirmation of *Candida* esophagitis by endoscopy, received at least 12 days of treatment, and had a repeat endoscopy at EOT (end of treatment).

^c ITT (Intent to Treat) patients without endoscopy or clinical assessment at EOT were treated as failures.

Microbiologic success rates by *Candida* species are presented in Table 12.

Table 12. Clinical and mycological outcome by baseline pathogen in patients with esophageal candidiasis (Study 150-305).

Pathogen ^a	Voriconazole		Fluconazole	
	Favorable endoscopic response ^b	Mycological eradication ^b	Favorable endoscopic response ^b	Mycological eradication ^b
	Success/Total (%)	Eradication/Total (%)	Success/Total (%)	Eradication/Total (%)
<i>C. albicans</i>	134/140 (96%)	90/107 (84%)	147/156 (94%)	91/115 (79%)
<i>C. glabrata</i>	8/8 (100%)	4/7 (57%)	4/4 (100%)	1/4 (25%)
<i>C. krusei</i>	1/1	1/1	2/2 (100%)	0/0

^a Some patients had more than one species isolated at baseline

^b Patients with endoscopic and/or mycological assessment at end of therapy

Serious refractory *Candida* infections

The study comprised 55 patients with serious refractory systemic *Candida* infections (including candidemia, disseminated and other invasive candidiasis) where prior antifungal treatment, particularly with fluconazole, had been ineffective. Successful response was seen in 24 patients (15 complete, 9 partial responses). In fluconazole-resistant non-*albicans* species, a successful outcome was seen in 3/3 *C. krusei* (complete responses) and 6/8 *C. glabrata* (5 complete, 1 partial response) infections. The clinical efficacy data were supported by limited susceptibility data.

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%) with *S. apiospermum* and in 2 of 7 patients (29%) with *S. prolificans* infection. 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.

The majority of patients receiving voriconazole treatment of the above-mentioned rare infections were intolerant of, or refractory to, prior antifungal therapy.

Duration of Treatment

Intravenous and oral voriconazole allows flexibility in patient care and the possibility of prolonged treatment where indicated. In clinical trials, 714 patients received voriconazole therapy for greater than 12 weeks, with 155 subjects receiving voriconazole for over 6 months.

Clinical Studies in Children

Fifty-three pediatric patients aged 2 to <18 years were treated with voriconazole in two prospective, open-label, non-comparative, multi-center clinical trials. One study enrolled 31 patients with possible, proven or probable invasive aspergillosis (IA), of whom 14 patients had proven or probable IA and were included in the MITT efficacy analyses. The second study enrolled 22 patients with invasive candidiasis including candidaemia (ICC), and esophageal candidiasis (EC) requiring either primary or salvage therapy, of whom 17 were included in the MITT efficacy analyses. Of the total of 31 patients included in the MITT analyses, 14 were 2 to <12 years old (5 patients with IA and 9 with ICC or EC)

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and 17 were 12 to <18 years old (9 patients with IA and 8 with ICC and EC). The overall rates of global response were 64.3% (9/14) at 6 weeks for patients with IA, 85.7% (6/7) at EOT for patients with ICC and 70% (7/10) at EOT for patients with EC. In subjects with IA, the success rate was 40% (2/5) for patients 2 to <12 years and 77.8% (7/9) for patients 12 to <18 years of age.

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.

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

Co-administration of VFEND with sirolimus is contraindicated because VFEND significantly increases sirolimus concentrations in healthy subjects (see Section **Drug Interactions**).

Co-administration of VFEND with rifabutin, rifampin, carbamazepine, long-acting barbiturates and St John's Wort is contraindicated since these drugs are likely to decrease plasma voriconazole concentrations significantly (see Section **Drug Interactions**).

Co-administration of standard doses of voriconazole with efavirenz doses of 400 mg QD or higher is contraindicated, because efavirenz significantly decreases plasma voriconazole concentrations in healthy subjects at these doses. Voriconazole also significantly increases efavirenz plasma concentrations (see Sections **Drug Interactions** for lower doses and **WARNINGS AND PRECAUTIONS**).

Co-administration of voriconazole with ritonavir (400 mg every 12 hours) is contraindicated because ritonavir significantly decreased plasma voriconazole concentrations in healthy subjects.

Co-administration 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.

Coadministration of voriconazole with naloxegol is contraindicated because voriconazole may significantly increase plasma concentrations of naloxegol which may precipitate opioid withdrawal symptoms (see Section **Drug Interactions**).

Coadministration of voriconazole with tolvaptan is contraindicated because voriconazole may significantly increase plasma concentrations of tolvaptan (see Section **Drug Interactions**).

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Coadministration of voriconazole with venetoclax at initiation and during the venetoclax dose titration phase since voriconazole is likely to significantly increase plasma concentrations of venetoclax and increase risk of tumour lysis syndrome (see Section **Drug Interactions**).

Coadministration of voriconazole with lurasidone is contraindicated since it may result in significant increases in lurasidone exposure and the potential for serious adverse reactions (see Section **Drug Interactions**).

WARNINGS AND PRECAUTIONS

Hypersensitivity: Caution should be used in prescribing voriconazole to patients with hypersensitivity to other azoles.

Cardiac adverse events: Some azoles, including voriconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During clinical development and post-marketing surveillance, there have been rare cases of *torsade de pointes* in patients taking voriconazole. These cases involved seriously ill patients with multiple confounding risk factors, such as history of cardiotoxic chemotherapy, cardiomyopathy, hypokalemia and concomitant medications that may have been contributory. Voriconazole should be administered with caution to patients with potentially proarrhythmic conditions, such as:

- Congenital or acquired QT-prolongation;
- Cardiomyopathy, in particular when heart failure is present;
- Sinus bradycardia;
- Existing symptomatic arrhythmias;
- Concomitant medication that is known to prolong QT interval (see Section **Drug Interactions**).

Electrolyte disturbances such as hypokalemia, hypomagnesemia and hypocalcemia should be monitored and corrected, if necessary, prior to initiation of and during voriconazole therapy (see Section **DOSAGE AND ADMINISTRATION**).

A study has been conducted in healthy volunteers which examined the effect on QT interval of single doses of voriconazole up to 4 times the usual daily dose. No subject in any group had an increase in QTc of ≥ 60 msec from baseline. No subject experienced an interval exceeding the potentially clinically relevant threshold of 500 msec (see Section **MICROBIOLOGY**).

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.

Hepatic toxicity: In clinical trials, there have been 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 Sections **WARNINGS AND PRECAUTIONS – Laboratory Tests** and **ADVERSE REACTIONS – Clinical Laboratory Values**).

Monitoring of hepatic function: Patients receiving voriconazole must be carefully monitored for hepatic toxicity. Clinical management should include laboratory evaluation of hepatic function (specifically AST and ALT) at the initiation of treatment with voriconazole and at least weekly for the first month of treatment. If treatment is continued, monitoring frequency can be reduced to monthly if there are no changes in the liver function tests.

If the liver function tests become markedly elevated, voriconazole should be discontinued, unless the medical judgment of the risk-benefit of the treatment for the patient justifies continued use (see Section **DOSAGE AND ADMINISTRATION**).

Visual adverse events: There have been post-marketing reports of prolonged visual adverse events, including optic neuritis and papilledema. These events occurred primarily in severely ill patients who had underlying conditions and/or concomitant medications which may have caused or contributed to these events (see Section **ADVERSE REACTIONS**).

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 may 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.

Monitoring of pancreatic function: Adults and children with risk factors for acute pancreatitis (e.g., recent chemotherapy, hematopoietic stem cell transplantation [HSCT]), should be monitored for development of pancreatitis during voriconazole treatment.

Dermatological adverse events: During treatment with VFEND, patients have developed severe cutaneous reactions (SCARs), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) which can be life-threatening or fatal (see Section **ADVERSE REACTIONS**). If a patient develops a severe cutaneous adverse reaction voriconazole should be discontinued.

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In addition voriconazole has been associated with photosensitivity skin reaction. It is recommended that patients, including children avoid exposure to direct sunlight during voriconazole treatment and use measures such as protective clothing and sunscreen with high sun protection factor (SPF).

Adrenal events: Reversible cases of adrenal insufficiency have been reported in patients receiving azoles, including voriconazole. Adrenal insufficiency has been reported in patients receiving azoles with or without concomitant corticosteroids. In patients receiving azoles without corticosteroids, adrenal insufficiency is related to direct inhibition of steroidogenesis by azoles. In patients taking corticosteroids, voriconazole associated CYP3A4 inhibition of their metabolism may lead to corticosteroid excess and adrenal suppression (see Section **Drug Interactions**). Cushing's syndrome with and without subsequent adrenal insufficiency has also been reported in patients receiving voriconazole concomitantly with corticosteroids.

Patients on long-term treatment with voriconazole and corticosteroids (including inhaled corticosteroids e.g. budesonide) should be carefully monitored for adrenal cortex dysfunction both during treatment and when voriconazole is discontinued (see Section **Drug Interactions**). Patients should be instructed to seek immediate medical care if they develop signs and symptoms of Cushing's syndrome or adrenal insufficiency.

Long-term treatment

The following severe adverse events have been reported in relation with long-term voriconazole treatment:

Squamous cell carcinoma of the skin (SCC): In patients with photosensitivity skin reactions and additional risk factors, squamous cell carcinoma of the skin and melanoma have been reported during long-term therapy. If phototoxic reactions occur, multidisciplinary advice should be sought and the patient should be referred to a dermatologist. Voriconazole discontinuation should be considered. Dermatologic evaluation should be performed on a systematic and regular basis, whenever voriconazole is continued despite the occurrence of phototoxicity-related lesions, to allow early detection and management of premalignant lesions.

If a patient develops a skin lesion consistent with squamous cell carcinoma or melanoma, voriconazole discontinuation should be considered.

Non-infectious periostitis: Periostitis has been reported in transplant patients during long-term voriconazole therapy. If a patient develops skeletal pain and radiologic findings compatible with periostitis, voriconazole should be discontinued.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 2 years have not been established. Voriconazole is indicated for pediatric patients aged two years or older. A higher frequency of liver enzyme elevations was observed in the pediatric population (see Section **ADVERSE REACTIONS**). Hepatic function should be monitored in both children and adults. Oral bioavailability may be limited in pediatric

patients 2 to 12 years with malabsorption and very low body weight for age. In that case, intravenous voriconazole administration is recommended.

The frequency of phototoxicity reactions is higher in the pediatric population. As an evolution towards SCC has been reported, stringent measures for the photoprotection are warranted in this population of patients. In children experiencing photoaging injuries such as lentigines or ephelides, sun avoidance and dermatologic follow-up are recommended even after treatment discontinuation.

Everolimus (CYP3A4 substrate, P-gp substrate): Co-administration of voriconazole with everolimus is not recommended because voriconazole is expected to significantly increase everolimus concentrations. Currently there are insufficient data to allow dosing recommendations in this situation (see Section **Drug Interactions**).

Fluconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor): Co-administration of oral voriconazole and oral fluconazole resulted in a significant increase in C_{max} and AUC_{τ} of voriconazole in healthy subjects. The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole associated adverse events is recommended if voriconazole is used sequentially after fluconazole (see Section **Drug Interactions**).

Efavirenz (CYP450 inducer; CYP3A4 inhibitor and substrate): When voriconazole is co-administered with efavirenz the dose of voriconazole should be increased to 400 mg every 12 hours and that of efavirenz should be decreased to 300 mg every 24 hours (see Sections **DOSAGE AND ADMINISTRATION**, **CONTRAINDICATIONS** and **Drug Interactions**).

Phenytoin (CYP2C9 substrate and potent CYP450 inducer): Careful monitoring of phenytoin levels is recommended when phenytoin is co-administered with voriconazole. Concomitant use of voriconazole and phenytoin should be avoided unless the benefit outweighs the risk (see Section **Drug Interactions**).

Ritonavir (potent CYP450 inducer, CYP3A4 inhibitor and substrate): Co-administration of voriconazole and low dose ritonavir (100 mg twice daily) should be avoided unless an assessment of the benefit/risk justifies the use of voriconazole (see Section **Drug Interactions**, for higher doses see Section **CONTRAINDICATIONS**).

Methadone (CYP3A4 substrate): Increased plasma concentrations of methadone have been associated with toxicity including QT prolongation. Frequent monitoring for adverse events and toxicity related to methadone is recommended during co-administration. Dose reduction of methadone may be needed (see Section **Drug Interactions**).

Short Acting Opiates (CYP3A4 substrate): Reduction in the dose of alfentanil, fentanyl and other short acting opiates similar in structure to alfentanil and metabolised by CYP3A4 (e.g., sufentanil) should be considered when co-administered with voriconazole (see Section **Drug Interactions**). As the half-life of alfentanil is prolonged in a 4-fold manner when alfentanil is co-administered with voriconazole and in an independent

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published study, concomitant use of voriconazole with fentanyl resulted in an increase in the mean $AUC_{0-\infty}$ of fentanyl by 1.4-fold, frequent monitoring for opiate-associated adverse events (including a longer respiratory monitoring period) may be necessary.

Long Acting Opiates (CYP3A4 substrate): Reduction in the dose of oxycodone and other long-acting opiates metabolised by CYP3A4 (e.g., hydrocodone) should be considered when co-administered with voriconazole. Frequent monitoring for opiate-associated adverse events may be necessary (see Section **Drug Interactions**).

Pregnancy and Lactation

Pregnancy

No adequate information on the use of voriconazole in pregnant women is available.

Studies in animals have shown reproductive toxicity at high doses (see Section **Preclinical Safety Data**). The potential risk to humans is unknown.

Voriconazole must not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the fetus.

Women of child-bearing potential

Women of child-bearing potential must always use effective contraception during treatment.

Nursing Mothers

The excretion of voriconazole in breast milk has not been investigated. Breast-feeding must be stopped on initiation of treatment with voriconazole.

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 Section **CLINICAL PHARMACOLOGY - Pharmacokinetics, General Pharmacokinetic Characteristics**).

Effects on Ability to Drive and Use Machines

Voriconazole may cause transient and reversible changes to vision, including blurring, altered/enhanced visual perception, and/or photophobia. Patients must avoid potentially hazardous tasks, such as driving or operating machinery while experiencing these symptoms. Patients should not drive at night while taking voriconazole.

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.

Information for Patients

Patients should be advised:

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- 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

Electrolyte disturbances such as hypokalemia, hypomagnesemia and hypocalcemia should be corrected prior to initiation of VFEND therapy.

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

ADVERSE REACTIONS

The safety profile of voriconazole in adults is based on an integrated safety database of more than 2,000 subjects (1,603 adult patients in therapeutic studies). This represents a heterogeneous population, containing patients with hematological malignancy, HIV infected patients with esophageal candidiasis and refractory fungal infections, non-neutropenic patients with candidemia or aspergillosis and healthy volunteers.

In addition, the safety of voriconazole was investigated in 279 patients (including 270 adults) who were treated with voriconazole in prophylaxis studies. The adverse event profile in these prophylaxis studies was similar to the established safety profile from 2,000 subjects in voriconazole clinical trials.

The table below includes all causality adverse reactions in 1,873 adults from pooled therapeutic(1,603) and prophylaxis (270) studies. The most commonly reported adverse events were visual impairment, liver function test abnormal, pyrexia, rash, vomiting, nausea, diarrhea, headache, peripheral edema and abdominal pain. The severity of the adverse events was generally mild to moderate. No clinically significant differences were seen when the safety data were analyzed by age, race, or gender.

Table 13. ADRs by SOC and CIOMS frequency category listed in order of decreasing medical seriousness within each frequency category and SOC.

System organ class	Very common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Frequency not known (cannot be estimated from the available data)
Infections and infestations		sinusitis	pseudomembranous colitis		
Neoplasms benign, malignant and unspecified (including cysts and polyps)					squamous cell carcinoma* ^g
Blood and lymphatic system disorders		agranulocytosis ^a , pancytopenia, thrombocytopenia ^b , leukopenia, anaemia	bone marrow failure, lymphadenopathy, eosinophilia	disseminated intravascular coagulation	
Immune system disorders			hypersensitivity	anaphylactoid reaction	
Endocrine disorders			adrenal insufficiency, hypothyroidism	hyperthyroidism	
Metabolism and nutrition disorders	oedema peripheral	hypoglycaemia, hypokalaemia, hyponatraemia* ^c			
Psychiatric disorders		depression, hallucination, anxiety, insomnia, agitation, confusional state			
Nervous system disorders	headache	syncope, tremor, hypertonia ^e , paraesthesia, somnolence, dizziness	brain oedema, encephalopathy ^c , extrapyramidal disorder ^d , neuropathy peripheral, ataxia, hypoaesthesia, dysgeusia	hepatic encephalopathy, Guillain-Barré syndrome, nystagmus	
Eye disorders	visual impairment ^h	retinal haemorrhage	optic nerve disorder ^f , papilloedema ^g , oculogyric crisis, diplopia,	optic atrophy, corneal opacity	

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System organ class	Very common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Frequency not known (cannot be estimated from the available data)
			scleritis, blepharitis		
Ear and labyrinth disorders			hypoacusis, vertigo, tinnitus		
Cardiac disorders		arrhythmia supra ventricular, tachycardia, bradycardia	ventricular fibrillation, ventricular extrasystoles, ventricular tachycardia, electrocardiogram prolonged, supra ventricular tachycardia	<i>torsades de pointes</i> , atrioventricular block complete, bundle branch block, nodal rhythm	
Vascular disorders		hypotension, phlebitis	thrombophlebitis, lymphangitis		
Respiratory, thoracic and mediastinal disorders		acute respiratory distress syndrome, pulmonary oedema			
Gastrointestinal disorders	diarrhoea, vomiting, abdominal pain, nausea	cheilitis, dyspepsia, constipation, gingivitis	peritonitis, pancreatitis, swollen tongue, duodenitis, gastroenteritis, glossitis		
Hepatobiliary disorders	liver function test abnormal	jaundice, jaundice cholestatic, hepatitis ¹	hepatic failure, hepatomegaly, cholecystitis, cholelithiasis		
Skin and subcutaneous tissue disorders	Rash	dermatitis exfoliative, alopecia, rash maculo-papular, pruritus	Stevens-Johnson syndrome ^g , photosensitivity reaction, purpura, urticaria, eczema	toxic epidermal necrolysis ^g , angioedema, pseudoporphyria, erythema multiforme, psoriasis, drug eruption	cutaneous lupus erythematosus*, drug reaction with eosinophilia and systemic symptoms* ^g
Musculoskeletal and connective		back pain	arthritis		

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System organ class	Very common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Frequency not known (cannot be estimated from the available data)
tissue disorders					
Renal and urinary disorders		renal failure acute, haematuria	renal tubular necrosis, proteinuria, nephritis		
General disorders and administration site conditions	pyrexia	chest pain, face oedema ⁱ , asthenia, chills	infusion site reaction, influenza like illness		
Investigations		blood creatinine increased	blood urea increased, blood cholesterol increased		

*ADR identified post-marketing

^a Includes febrile neutropenia and neutropenia.

^b Includes immune thrombocytopenic purpura.

^c Includes hypoxic-ischaemic encephalopathy and metabolic encephalopathy.

^d Includes akathisia and parkinsonism.

^e Includes nuchal rigidity and tetany.

^f Prolonged optic neuritis has been reported post-marketing. See Section **WARNINGS AND PRECAUTIONS**.

^g See Section **WARNINGS AND PRECAUTIONS**.

^h See “Visual impairments” paragraph in Section **ADVERSE REACTIONS**.

ⁱ Includes drug-induced liver injury, hepatitis toxic, hepatocellular injury and hepatotoxicity.

^j Includes periorbital oedema, lip oedema, and oedema mouth.

Visual Impairments

In clinical trials, visual impairments (including blurred vision, photophobia, chloropsia, chromatopsia, color blindness, cyanopsia, eye disorder, halo vision, night blindness, oscillopsia, photopsia, scintillating scotoma, visual acuity reduced, visual brightness, visual field defect, vitreous floaters, and xanthopsia) with voriconazole were very common.

These visual impairments were transient and fully reversible, with the majority spontaneously resolving within 60 minutes. There was evidence of attenuation with repeated doses of voriconazole. The visual impairments were generally mild, rarely resulted in discontinuation and were not associated with long-term sequelae. Visual impairments may be associated with higher plasma levels and/or doses.

There have been post-marketing reports of prolonged visual adverse events (see Section **WARNINGS AND PRECAUTIONS**).

The mechanism of action is unknown, although the site of action is most likely to be within the retina.

In a study in healthy volunteers investigating the impact of voriconazole on retinal function, voriconazole caused a decrease in the electroretinogram (ERG) waveform amplitude. The ERG measures electrical currents in the retina. The ERG changes did not progress over 29 days of administration and were fully reversible on withdrawal of voriconazole.

The long-term effect of voriconazole (median 169 days; range 5-353 days) on visual function was evaluated in subjects with paracoccidioidomycosis. Voriconazole had no clinically relevant effect on visual function as assessed by testing of visual acuity, visual fields, color vision and contrast sensitivity. There were no signs of retinal toxicity. 17/35 voriconazole subjects experienced visual adverse events. These events did not lead to discontinuation, were generally mild, occurred during the first week of therapy and resolved during continued voriconazole therapy.

Dermatological Reactions

Dermatological reactions were very common in patients treated with voriconazole in clinical trials, but these patients had serious underlying diseases and were receiving multiple concomitant medications. The majority of rashes were of mild to moderate severity. Patients have developed severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (uncommon), toxic epidermal necrolysis (rare), drug reaction with eosinophilia and systemic symptoms (DRESS) which was reported post-marketing (not known), and erythema multiforme (rare) during treatment with voriconazole (see Section **WARNINGS AND PRECAUTIONS**).

If patients develop a rash they should be monitored closely voriconazole discontinued if lesions progress. Patients receiving long-term voriconazole therapy have developed photosensitive skin reactions (see Section **WARNINGS AND PRECAUTIONS**).

Dermatological adverse reactions potentially related to phototoxicity (pseudoporphyria, cheilitis, and cutaneous lupus erythematosus) are also reported with voriconazole. Sun avoidance and photoprotection are recommended for all patients. If phototoxicity occurs, voriconazole discontinuation and dermatological evaluation should be considered (see Section **WARNINGS AND PRECAUTIONS**).

Less Common Adverse Events

The following adverse events occurred in <2% 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 13 above and does not include every event reported in the voriconazole clinical program.

Body as a whole: Abdominal pain, abdomen enlarged, allergic reaction, anaphylactoid reaction (see Section **WARNINGS AND 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

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site infection/inflammation, mucous membrane disorder, multi-organ failure, pain, pelvic pain, peritonitis, sepsis, substernal chest pain.

Cardiovascular: Supraventricular extrasystoles, 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 *torsade de pointes*).

Digestive: Diarrhea and jaundice, 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, leucopenia, thrombocytopenia and pancytopenia.

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, hypomagnesemia and peripheral edema.

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, dizziness.

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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 erythematosus, 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, maculopapular rash.

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, eye hemorrhage and hypoacusis.

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.

Liver Function Tests

The overall incidence of transaminase increases $>3 \times$ ULN (not necessarily comprising an adverse event) in the voriconazole clinical program was 18.0% (319/1,768) in adults and 25.8% (73/283) in pediatric subjects who received voriconazole for pooled therapeutic and prophylaxis use. Liver function test abnormalities may be associated with higher plasma levels 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 associated with cases of serious hepatic toxicity, in patients with other serious underlying conditions. This includes cases of jaundice, hepatitis and hepatic failure leading to death.

Pediatric Use

The safety of voriconazole was investigated in 288 pediatric patients aged 2 to <12 years (169) and 12 to <18 years (119) who received voriconazole therapeutic use (105). The adverse event profile in these 288 pediatric patients was similar to that in adults. A higher frequency of liver enzyme elevations reported as adverse events (14.2% transaminases increased in pediatrics compared to 5.3% in adults) was observed in pediatric patients as compared to adults. The safety of voriconazole was investigated in additional pediatric patients aged 2 to <12 years who were observed in compassionate use programs (158 pediatric patients). The adverse event profile in these pediatric patients was similar to that observed in adults. Although post-marketing data suggest there might be a higher occurrence of skin reactions in the pediatric population compared to adults.

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There have been post-marketing reports of pancreatitis in pediatric patients.

Infusion-related Reactions

Infusion-related reactions, predominantly flushing and nausea, have been observed during administration of the intravenous formulation of voriconazole. Depending on the severity of symptoms, consideration should be given to stopping treatment.

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; it is recommended that treatment of overdose be symptomatic and supportive.

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 1-3 hours (see Section **Intravenous Administration**).

NOT FOR IV BOLUS INJECTION

Electrolyte disturbances such as hypokalemia, hypomagnesemia and hypocalcemia should be corrected prior to initiation of VFEND therapy (see Section **WARNINGS AND PRECAUTIONS**).

Use in Adults

Therapy must be initiated with the specified intravenous loading dose regimen of VFEND to achieve adequate plasma concentrations on Day 1. Intravenous treatment should be continued for at least 7 days before switching to oral treatment (see Section **CLINICAL STUDIES**). Once the patient is clinically improved and can tolerate medication given by

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mouth, the oral tablet form or oral suspension form of voriconazole may be utilized. On the basis of high oral bioavailability, switching between intravenous and oral administration is appropriate when clinically indicated (see Section **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.

Detailed information on dosage recommendations is provided in the following table:

Table 14

	Intravenous	Oral ^a	
		Patients 40 kg and above	Patients less than 40 kg
<u>Loading Dose Regimen for All Indications (first 24 hours)</u>	6 mg/kg every 12 hours	-	-
<u>Maintenance Dose (after first 24 hours)</u> Invasive aspergillosis / <i>Scedosporium</i> and <i>Fusarium</i> infections / Other serious mould Infections ^b	4 mg/kg every 12 hours	200 mg every 12 hours	100 mg every 12 hours
Candidemia in non-neutropenic patients	3-4 mg/kg every 12 hours ^c	200 mg every 12 hours	100 mg every 12 hours
Esophageal candidiasis	Not evaluated	200 mg every 12 hours	100 mg every 12 hours

a: In healthy volunteer studies, the 200 mg oral every 12 hours dose provided an exposure (AUC_τ) similar to a 3 mg/kg IV every 12 hours dose, the 300 mg oral every 12 hours dose provided an exposure (AUC_τ) similar to a 4 mg/kg IV every 12 hours dose (see Section **CLINICAL PHARMACOLOGY**).

b: In the pivotal clinical study of invasive aspergillosis, the median duration of IV voriconazole therapy was 10 days (range 2-85 days). The median duration of oral voriconazole therapy was 76 days (range 2-232 days) (see Section **CLINICAL STUDIES**).

c: In clinical trials, patients with candidemia received 3 mg/kg every 12 hours as primary therapy, while patients with other deep tissue *Candida* infections received 4 mg/kg as salvage therapy. Appropriate dose should be based on severity and nature of the infection.

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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 (similar to 4 mg/kg IV every 12 hours) for oral administration. 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 patient response at 3 mg/kg every 12 hours is inadequate, the intravenous maintenance dose may be increased to 4 mg/kg 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 to 100 mg every 12 hours for adult patients weighing less than 40 kg).

Phenytoin may be co-administered 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 40 kg) (see Section **Drug Interactions**).

When voriconazole is co-administered with adjusted doses of efavirenz, voriconazole maintenance dose should be increased to 400 mg every 12 hours (see Sections **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS** and **Drug Interactions**).

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

Use in Geriatric Patients

No dose adjustment is necessary for geriatric patients.

Use in Pediatrics

Safety and effectiveness in pediatric patients below the age of 2 years has not been established (see also Section **CLINICAL STUDIES**). Therefore, voriconazole is not recommended for children less than 2 years of age.

Use in children (2 to <12 years) and young adolescents (12 to 14 years and <50 kg)

The recommended dosing regimen is as follows:

Table 15

	Intravenous	Oral
Loading Dose Regimen (first 24 hours)	9 mg/kg every 12 hours	Not recommended
Maintenance Dose (after first 24 hours)	8 mg/kg twice daily	9 mg/kg twice daily (a maximum dose of 350 mg twice daily)
Note: Based on a population pharmacokinetic analysis in 112 immunocompromised patients aged 2 to <12 years and 26 immunocompromised patients aged 12 to <17 years		

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It is recommended to initiate the therapy with intravenous regimen, and oral regimen should be considered only after there is a significant clinical improvement. It should be noted that an 8 mg/kg intravenous dose will provide voriconazole exposure approximately 2-fold higher than a 9 mg/kg oral dose.

Use in pediatric patients aged 2 to <12 years with hepatic or renal insufficiency has not been studied (see Section **ADVERSE REACTIONS** and Section **Pharmacokinetics**).

The oral dose recommendation for children is based on studies in which voriconazole was administered as the powder for oral suspension formulation. Bioequivalence between the powder for oral suspension and tablets has not been investigated in a pediatric population. Considering the assumed limited gastro-enteric transit time in pediatrics, the absorption of tablets may be different in pediatric compared to adult patients.

Use in all other adolescents (12 to 14 years and ≥ 50 kg; 15 to 16 years regardless of body weight)

Voriconazole should be dosed as adults.

Dose adjustment

If patient response is inadequate, the dose may be increased by 1 mg/kg steps (or by 50 mg steps if the maximum oral dose of 350 mg was used initially). If patients are unable to tolerate treatment, reduce the dose by 1 mg/kg steps (or by 50 mg steps if the maximum oral dose of 350 mg was used initially).

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 Section **WARNINGS AND PRECAUTIONS**).

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 Section **CLINICAL PHARMACOLOGY - Special Populations**).

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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 Section **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 16).
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 1-3 hours at a maximum rate of 3 mg/kg per hour.

Table 16. Required Volumes of 10 mg/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)	8 mg/kg dose (number of vials)	9 mg/kg dose (number of vials)
10	-	4.0 mL (1)	-	8.0 mL (1)	9.0 mL (1)
15	-	6.0 mL (1)	-	12.0 mL (1)	13.5 mL (1)

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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)	8 mg/kg dose (number of vials)	9 mg/kg dose (number of vials)
20	-	8.0 mL (1)	-	16.0 mL (1)	18.0 mL (1)
25	-	10.0 mL (1)	-	20.0 mL (1)	22.5 mL (2)
30	9.0 mL (1)	12 mL (1)	18 mL (1)	24.0 mL (2)	27.0 mL (2)
35	10.5 mL (1)	14 mL (1)	21 mL (2)	28.0 mL (2)	31.5 mL (2)
40	12.0 mL (1)	16 mL (1)	24 mL (2)	32.0 mL (2)	36.0 mL (2)
45	13.5 mL (1)	18 mL (1)	27 mL (2)	36.0 mL (2)	40.5 mL (3)
50	15.0 mL (1)	20 mL (1)	30 mL (2)	40.0 mL (2)	45.0 mL (3)
55	16.5 mL (1)	22 mL (2)	33 mL (2)	44.0 mL (3)	49.5 mL (3)
60	18.0 mL (1)	24 mL (2)	36 mL (2)	48.0 mL (3)	54.0 mL (3)
65	19.5 mL (1)	26 mL (2)	39 mL (2)	52.0 mL (3)	58.5 mL (3)
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°C to 8°C. 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 subvisible particulate matter after 24 hours storage at 4°C.

Infusions of blood products must not occur simultaneously with VFEND I.V.

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Infusions of total parenteral nutrition can occur simultaneously with VFEND I.V.

Blood Products and Concentrate Electrolyte

Voriconazole must not be infused concomitantly with any blood product or any short-term infusion of concentrated electrolytes, even if the two infusions are running in separate intravenous lines (or cannulas). Electrolyte disturbances such as hypokalemia, hypomagnesemia and hypocalcemia should be corrected prior to initiation of voriconazole therapy (see Sections **DOSAGE AND ADMINISTRATION** and **WARNINGS AND PRECAUTIONS**).

Intravenous solutions containing (non-concentrated) electrolytes

Voriconazole can be infused at the same time as other intravenous solutions containing (non-concentrated) electrolytes, but must be infused through a separate line.

Total parenteral nutrition (TPN)

Voriconazole can be infused at the same time as total parenteral nutrition, but must be infused in a separate line. If infused through a multiple-lumen catheter, TPN needs to be administered using a different port from the one used for voriconazole.

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 temperature maximum 30°C.

VFEND I.V. for Injection: Store at temperature maximum 30°C. Reconstituted concentrate: store at 2°C-8°C up to 24 hours (in a refrigerators).

HOW SUPPLIED

Tablets

VFEND 200 mg film coated tablets – Box contains of 1 blister @ 10 film-coated tablets; Reg. No. DKI2054201017A1

Powder for Solution for Injection

VFEND I.V. 200 mg; Box contains of 1 vial; Reg. No.: DKI1590401144A1

Storage

VFEND Tablets should be stored at temperature maximum 30°C.

Unreconstituted vials should be stored at temperature maximum 30°C. VFEND is a single dose unpreserved sterile lyophile. From a microbiological point of view, following

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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°C to 8°C. Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C. This medicinal product is for single use only and any unused solution should be discarded. Only clear solutions without particles should be used (see Section **DOSAGE AND ADMINISTRATION - Intravenous Administration**).

HARUS DENGAN RESEP DOKTER

VFEND IV 200 mg:

Produced by:
Pharmacia & Upjohn Company LLC
Kalamazoo, Michigan, USA

Packed and released by:
Fareva Amboise,
Pocé-sur-Cisse, France

Imported by:
PT. Pfizer Indonesia
Jakarta, Indonesia

VFEND Film-coated Tablets:

Produced by:
Pfizer Italia S.r.l.
Ascoli Piceno, Italy

Imported by:
PT. Pfizer Indonesia
Jakarta, Indonesia