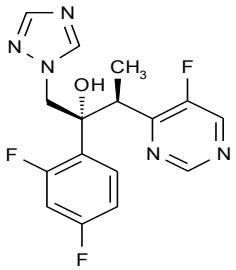
PT. PFIZER INDONESIA
Local Product Document

Generic Name: Voriconazole
Trade Name: **VFEND®**
200 mg Film-coated Tablet
CDS Effective Date: October 28, 2022
Supersedes: February 28, 2022

DESCRIPTION

VFEND® (voriconazole), a triazole antifungal agent, is available as film-coated tablets for oral administration. The structural formula is:



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

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

VFEND Tablets contain 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.

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* (µg•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* (µg•h/mL) (CV%)	20.31 (69%)	36.51 (45%)
C_{max}* (µg/mL) (CV%)	3.00 (51%)	4.66 (35%)

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

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

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

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

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

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

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

Absorption
The pharmacokinetic properties of voriconazole are similar following administration by the intravenous and oral routes. 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, 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.

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/m^2 basis. Hepatocellular adenomas were detected in females at 50 mg/kg and hepatocellular carcinomas were found in males at 6 and 50 mg/kg. Mice were given oral doses of 10, 30 or 100 mg/kg voriconazole, or 0.1, 0.4, or 1.4 times the RMD on a mg/m^2 basis. In mice, hepatocellular adenomas were detected in males and females and hepatocellular carcinomas were detected in males at 1.4 times the RMD of voriconazole.

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

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

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 voriconazole to increase the plasma concentrations of substances metabolised by CYP3A4 isoenzymes (certain antihistamines, quinidine, cisapride, pimozide 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 (↔), below (↓) or above (↑) the 80%-125% range. The asterisk (*) indicates a two-way interaction. AUC_{τ}, AUC_t and $AUC_{0-\infty}$ 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, pimozide, 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 *torsades de pointes*.	**Contraindicated** (see Section **CONTRAINDICATIONS**)
Carbamazepine and long-acting barbiturates (including but not limited to: 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 Efavirenz 300 mg QD, co-administered with voriconazole 400 mg BID*	Efavirenz C_{max} ↑ 38% Efavirenz AUC_{τ} ↑ 44% Voriconazole C_{max} ↓ 61% Voriconazole AUC_{τ} ↓ 77% Compared to efavirenz 600 mg QD, Efavirenz C_{max} ↔ Efavirenz AUC_{τ} ↑ 17% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 23% Voriconazole AUC_{τ} ↓ 7%	Standard doses of voriconazole and standard doses of efavirenz (400 mg QD or above) is **contraindicated** (see Section **CONTRAINDICATIONS**). 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 300 mg QD. When voriconazole treatment is stopped, the initial dose of efavirenz should be restored (see Section **DOSAGE AND ADMINISTRATION**).

Medicinal product ***[Mechanism of Interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
Ergot alkaloids (including but not limited to: 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]* 300 mg TID (co-administered with voriconazole 400 mg single dose)	In an independent published study, Voriconazole $AUC_{0-\infty}$ ↓ 59%	**Contraindicated** (see Section **CONTRAINDICATIONS**)
Tolvaptan *[CYP3A substrate]*	Although not studied, voriconazole is likely to significantly increase the	**Contraindicated** (see Section **CONTRAINDICATIONS**)

Medicinal product ***[Mechanism of Interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
	plasma concentrations of tolvaptan.	
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 $AUC_{0\text{-}12}$ ↓ 44% Voriconazole C_{12} ↓ 51%	If concomitant administration of voriconazole with letermovir cannot be avoided, monitor for loss of voriconazole effectiveness.
Lemborexant *[CYP3A4 substrate]*	Although not studied, voriconazole is likely to increase the plasma concentrations of lemborexant	Concomitant use of voriconazole and lemborexant should be avoided.

Medicinal product ***[Mechanism of Interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
Glasdegib *[CYP3A4 substrate]*	Although not studied, voriconazole is likely to increase the plasma concentrations of glasdegib and increase risk of QTc prolongation.	If concomitant use cannot be avoided, frequent ECG monitoring is recommended.
Tyrosine kinase inhibitors (including but not limited to: axitinib, bosutinib, cabozantinib, ceritinib, cobimetinib, dabrafenib, dasatinib, nilotinib, sunitinib, ibrutinib, ribociclib) *[CYP3A4 substrates]*	Although not studied, voriconazole may increase plasma concentrations of tyrosine kinase inhibitors metabolized by CYP3A4.	If concomitant use cannot be avoided, dose reduction of the tyrosine kinase inhibitor and close clinical monitoring is recommended.
Anticoagulants Warfarin (30 mg single dose, co- administered with 300 mg BID voriconazole) *[CYP2C9 substrate]* Other oral coumarins (including but not limited to: 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 reactions.	Dose reduction of ivacaftor is recommended.
Eszopiclone *[CYP3A4 substrate]*	Although not studied, voriconazole is likely to increase the plasma concentrations and sedative effect of eszopiclone.	Dose reduction of eszopiclone is recommended.
Benzodiazepines *[CYP3A4 substrates]* Midazolam (0.05 mg/kg IV single dose) Midazolam (7.5 mg oral single dose) Other benzodiazepines (including but not limited to: triazolam, alprazolam)	 In an independent published study, Midazolam $AUC_{0-\infty}$ ↑ 3.7-fold In an independent published study, Midazolam C_{max} ↑ 3.8-fold Midazolam $AUC_{0-\infty}$ ↑ 10.3-fold Although not studied clinically, voriconazole is likely to increase the plasma	Dose reduction of benzodiazepines should be considered.

Medicinal product *[Mechanism of Interaction]*	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
	concentrations of other benzodiazepines that are metabolised by CYP3A4 and lead to a prolonged sedative effect.	
Immunosuppressants *[CYP3A4 substrates]*		
Sirolimus (2 mg single dose)	In an independent published study, Sirolimus C_{max} ↑ 6.6-fold Sirolimus $AUC_{0-\infty}$ ↑ 11-fold	Co-administration of voriconazole and sirolimus is **contraindicated** (see Section **CONTRAINDICATIONS**).
Everolimus *[also P-gp substrate]*	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of everolimus.	Co-administration of voriconazole and everolimus is not recommended because voriconazole is expected to significantly increase everolimus concentrations (see Section **WARNINGS AND PRECAUTIONS**).
Ciclosporin (In stable renal transplant recipients receiving chronic ciclosporin therapy)	Ciclosporin C_{max} ↑ 13% Ciclosporin AUC_{τ} ↑ 70%	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. When voriconazole is discontinued, ciclosporin levels must be carefully monitored and the dose increased as necessary.
Tacrolimus (0.1 mg/kg single dose)	Tacrolimus C_{max} ↑ 117% Tacrolimus AUC_t ↑ 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. When voriconazole is discontinued, tacrolimus levels must be carefully monitored and the dose increased as necessary.
Long Acting Opiates *[CYP3A4 substrates]*		Dose reduction in oxycodone and other long-acting opiates metabolised by CYP3A4

Medicinal product ***[Mechanism of Interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
Oxycodone (10 mg single dose)	In an independent published study, Oxycodone C_{max} ↑ 1.7-fold Oxycodone $AUC_{0-\infty}$ ↑ 3.6-fold	(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.
Omeprazole (40 mg QD)* *[CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate]*	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* *[CYP3A4 substrate; CYP2C19 inhibitor]* 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 *[CYP3A4 substrates]* 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) *[CYP3A4 substrates]*	Although not studied, voriconazole is likely to increase the plasma	If concomitant administration of voriconazole with statins metabolised by CYP3A4

Medicinal product ***[Mechanism of Interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
	concentrations of statins that are metabolised by CYP3A4 and could lead to rhabdomyolysis.	cannot be avoided, dose reduction of the statin should be considered.
Sulphonylureas (including but not limited to: tolbutamide, glipizide, glyburide) *[CYP2C9 substrates]*	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 sulfonylureas should be considered.
Vinca Alkaloids (including but not limited to: vincristine and vinblastine) *[CYP3A4 substrates]*	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 (including but not limited to: saquinavir, amprenavir and nelfinavir)* *[CYP3A4 substrates and inhibitors]*	Not studied clinically. *In vitro* studies show that voriconazole may inhibit the metabolism of HIV protease inhibitors and the metabolism of voriconazole may also be inhibited by HIV protease inhibitors.	Careful monitoring for any occurrence of drug toxicity and/or lack of efficacy, and dose adjustment may be needed.
Tretinoin *[CYP3A4 substrate]*	Although not studied, voriconazole may increase tretinoin concentrations and increase risk of adverse reactions (pseudotumor cerebri, hypercalcaemia).	Dose adjustment of tretinoin is recommended during treatment with voriconazole and after its discontinuation.
Other Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (including but not limited to: delavirdine, nevirapine)* *[CYP3A4 substrates, inhibitors or CYP450 inducers]*	Not studied clinically. *In vitro* 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]*	Voriconazole C_{max} and AUC_{τ} ↔	No dose adjustment

Medicinal product ***[Mechanism of Interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
Azithromycin (500 mg QD)	Voriconazole C_{max} and AUC_{τ} ↔ The effect of voriconazole on either erythromycin or azithromycin is unknown.	
Mycophenolic acid (1 g single dose) *[UDP-glucuronyl transferase substrate]*	Mycophenolic acid C_{max} ↔ Mycophenolic acid AUC_t ↔	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 **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. marneffei, 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 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 and Aspergillus Species	Minimal Inhibitory Concentration (MIC) breakpoint (mg/L)	
	≤S (Susceptible)	>R (Resistant)
Candida albicans[1]	0.06	0.25
Candida glabrata	Insufficient evidence (IE)	IE
Candida krusei	IE	IE
Candida parapsilosis[1]	0.125	0.25
Candida tropicalis[1]	0.125	0.25
Non-species related breakpoints for *Candida*[2]	IE	IE
Aspergillus fumigatus[3]	1	1
Aspergillus nidulans[3]	1	1
Aspergillus flavus	IE[4]	IE[4]
Aspergillus niger	IE[4]	IE[4]
Aspergillus terreus	IE[4]	IE[4]
Non-species related breakpoints[5]	IE	IE

[1] Strains with MIC values above the Susceptible/Intermediate (S/I) breakpoint are rare or not yet reported. The identification and antifungal susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint they should be reported resistant. A clinical response of 76% was achieved in infections caused by the species listed below when MICs were lower than or equal to the epidemiological cut-offs. Therefore, wild type populations of *C. albicans, C. parapsilosis* and *C. tropicalis* are considered susceptible.
[2] Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific *Candida* species. They are for use only for organisms that do not have specific breakpoints.
[3] Area of technical uncertainty (ATU) is 2. Report as R with the following comment: "In some clinical situations (non-invasive infections forms) voriconazole can be used provided sufficient exposure is ensured".
[4] The ECOFFs for these species are in general one two-fold dilution higher than for *A. fumigatus*.
[5] Non-species related breakpoints have not been determined.

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 inoculums 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.

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			
Candida parapsilosis ATCC 22019	0.016-0.12	0.03-0.25	28-37
Candida krusei ATCC 6258	0.06-0.5	0.12-1.0	16-25
Candida albicans 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:

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).

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%)
Success by Species			
	Success n/N (%)		
Overall success	76/144 (53)	42/133 (32)	
Mycologically confirmed[e]	37/84 (44)	16/67 (24)	
Aspergillus spp.[f]			

A. fumigatus	28/63 (44)	12/47 (26)	
A. flavus	3/6	4/9	
A. terreus	2/3	0/3	
A. niger	1/4	0/9	
A. nidulans	1/1	0/0	

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

Study 304
The results of this comparative trial (Study 307/602) confirmed the results of an earlier trial in the primary and salvage treatment of patients with acute invasive aspergillosis (Study 304). In this earlier study, an overall success rate of 52% (26/50) was seen in patients treated with voriconazole for primary therapy. Success was seen in 17/29 (59%) with *Aspergillus fumigatus* infections and 3/6 (50%) patients with infections due to non-*fumigatus* species [*A. flavus* (1/1); *A. nidulans* (0/2); *A. niger* (2/2); *A. terreus* (0/1)]. Success in patients who received voriconazole as salvage therapy is presented in Table 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
A. fumigatus	43/97 (44%)
A. flavus	5/12
A. nidulans	1/3
A. niger	4/5
A. terreus	3/8
A. versicolor	0/1

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

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
C. albicans	46/107 (43%)	30/63 (48%)
C. tropicalis	17/53 (32%)	1/16 (6%)
C. parapsilosis	24/45 (53%)	10/19 (53%)
C. glabrata	12/36 (33%)	7/21 (33%)
C. krusei	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 (%)
C. albicans	134/140 (96%)	90/107 (84%)	147/156 (94%)	91/115 (79%)
C. glabrata	8/8 (100%)	4/7 (57%)	4/4 (100%)	1/4 (25%)
C. krusei	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) 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.

Co-administration of 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**).

Coadministration of voriconazole with venetoclax is contraindicated 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**).

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.

In addition voriconazole has been associated with photosensitivity skin reaction. An increased risk of skin toxicity with concomitant use of methotrexate, a drug associated with ultraviolet (UV) reactivation has been observed. There is a potential for this risk to be observed with other drugs associated with UV reactivation. 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 (including cutaneous SCC *in situ*, or Bowen's disease) 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**).

Glasdegib (CYP3A4 substrate): Coadministration of voriconazole is expected to increase glasdegib plasma concentrations and increase the risk of QTc prolongation (see Section **Drug Interactions**). If concomitant use cannot be avoided, frequent ECG monitoring is recommended.

Tyrosine kinase inhibitors (CYP3A4 substrate): Coadministration of voriconazole with tyrosine kinase inhibitors metabolised by CYP3A4 is expected to increase tyrosine kinase inhibitor plasma concentrations and the risk of adverse reactions. If concomitant use cannot be avoided, dose reduction of the tyrosine kinase inhibitor and close clinical monitoring is recommended (see Section **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 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:

- 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 (including cutaneous SCC *in situ*, or Bowen's disease)*,[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*,			
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, scleritis, blepharitis	optic atrophy, corneal opacity	

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)**
Ear and labyrinth disorders			hypoacusis, vertigo, tinnitus		
Cardiac disorders		arrhythmia supraventricular, tachycardia, bradycardia	ventricular fibrillation, ventricular extrasystoles, ventricular tachycardia, electrocardiogram QT prolonged, supraventricular tachycardia	*torsades de pointes*, 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[i]	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 tissue disorders		back pain	arthritis		

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)
Renal and urinary disorders		renal failure acute, haematuria	renal tubular necrosis, proteinuria, nephritis		
General disorders	pyrexia	chest pain, face oedema[j], asthenia, chills	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, 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.

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 x 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.

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

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 is also available as 200 mg powder for solution for infusion, which is **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 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
Loading Dose Regimen for All Indications (first 24 hours)	6 mg/kg every 12 hours	-	-
Maintenance Dose (after first 24 hours)			
Invasive aspergillosis / *Scedosporium* and *Fusarium* 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 (AUCτ) similar to a 3 mg/kg IV every 12 hours dose, the 300 mg oral every 12 hours dose provided an exposure (AUCτ) 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.

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 in adequate, 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		

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**).

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.

Stability
VFEND Tablets: Store at temperature maximum 30°C.

HOW SUPPLIED

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

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

HARUS DENGAN RESEP DOKTER

VFEND Film-coated Tablets:
Produced by:
Pfizer Italia S.r.l.
Ascoli Piceno, Italy

Imported by:
PT. Pfizer Indonesia
Jakarta, Indonesia

Leaflet kemasan: Informasi bagi pengguna

VFEND® 200 mg tablet salut selaput

Vorikonazol

Baca seluruh bagian leaflet ini dengan cermat sebelum Anda diberi obat ini karena berisi informasi penting bagi Anda atau anak Anda.
- Simpan leaflet ini. Anda mungkin perlu membacanya kembali.
- Jika ada pertanyaan lebih lanjut, hubungi dokter atau perawat Anda.
- Obat ini telah diresepkan hanya untuk Anda. Jangan berikan kepada orang lain. Obat ini dapat membahayakan mereka, sekali pun tanda-tanda penyakit mereka sama dengan Anda.
- Jika Anda mengalami efek samping apa pun, konsultasikan dengan dokter atau perawat Anda. Ini termasuk segala kemungkinan efek samping yang tidak tercantum di dalam leaflet ini. Lihat bagian 9.

Isi leaflet ini:

1. Nama Produk

VFEND® 200 mg tablet salut selaput

2. Deskripsi Produk

VFEND® adalah obat antijamur. Cara kerjanya adalah dengan mematikan atau menghentikan pertumbuhan jamur penyebab infeksi.

3. Apa kandungan obat ini?

Tablet **VFEND®** mengandung 200 mg vorikonazol. Bahan tidak aktif yang terkandung meliputi laktosa monohidrat, pati pragelatinisasi, natrium kroskarmelosa, povidon,

magnesium stearat, dan pelapis yang mengandung hidroksipropil metilselulosa, titanium dioksida, laktosa monohidrat, dan triasetin.

4. Kekuatan obat

200 mg

5. Apa kegunaan obat ini?

Obat ini digunakan untuk mengobati infeksi jamur berikut:

- Aspergilosis invasif (sejenis infeksi jamur yang disebabkan oleh *Aspergillus* spp.)
- Kandidemia (sejenis infeksi jamur yang disebabkan oleh *Candida* spp.) pada pasien non-neutropenik (pasien tanpa jumlah sel darah putih yang rendah secara abnormal)
- Infeksi *Candida* invasif serius (termasuk *C. krusei*)
- Kandidiasis esofagus
- Infeksi jamur serius yang disebabkan oleh *Scedosporium apiospermum* (bentuk aseksual dari *Pseudallescheria boydii*) atau *Fusarium* spp. termasuk *Fusarium solani* (dua spesies jamur yang berbeda) pada pasien yang tidak toleran terhadap atau tidak merespons terapi lainnya.

6. Berapa banyak dan seberapa sering Anda seharusnya menggunakan obat ini?

VFEND® harus diminum setidaknya satu jam sebelum, atau satu jam sesudah makan. Telan tablet utuh bersama air.

Dokter akan menentukan dosis Anda bergantung pada berat badan dan jenis infeksi yang Anda alami. Selalu minum obat ini sesuai dengan petunjuk dokter Anda. Tanyakan kepada dokter atau apoteker jika Anda merasa tidak yakin.

Dokter dapat mengubah dosis bergantung pada kondisi Anda.

Penggunaan pada Orang Dewasa

Dosis yang disarankan untuk dewasa (termasuk pasien lanjut usia) adalah sebagai berikut:

	Tablet	
	Pasien dengan berat badan 40 kg atau lebih	**Pasien dengan berat badan kurang dari 40 kg**
Regimen Dosis Awal untuk Semua Indikasi (24 jam pertama)	Pengobatan Anda akan dimulai dalam bentuk infus	Pengobatan Anda akan dimulai dalam bentuk infus
Dosis Pemeliharaan (setelah 24 jam pertama)	200 mg setiap 12 jam	100 mg setiap 12 jam

Bergantung pada respons Anda terhadap pengobatan, dokter dapat meningkatkan dosis harian menjadi 300 mg dua kali sehari.

Dokter dapat memutuskan untuk menurunkan dosis jika Anda menderita sirosis ringan hingga sedang.

Penggunaan pada Anak-anak dan Remaja

Tablet hanya boleh diberikan jika anak dapat menelan tablet.

	Tablet	
	Anak-anak berusia 2 hingga kurang dari 12 tahun dan remaja berusia 12 hingga 14 tahun dengan berat badan kurang dari 50 kg	Remaja berusia 12 hingga 14 tahun dengan berat badan 50 kg atau lebih; dan semua remaja berusia lebih dari 14 tahun
Regimen Dosis Awal (24 jam pertama)	Pengobatan Anda akan dimulai dalam bentuk infus	Pengobatan Anda akan dimulai dalam bentuk infus
Dosis Pemeliharaan (setelah 24 jam pertama)	9 mg/kg dua kali sehari (dosis maksimum 350 mg dua kali sehari)	200 mg setiap 12 jam

Bergantung pada respons Anda terhadap pengobatan, dokter dapat meningkatkan atau menurunkan dosis harian Anda.

7. Kapan seharusnya Anda tidak menggunakan obat ini?

Jangan gunakan **VFEND®** jika Anda alergi terhadap vorikonazol atau bahan lain yang terkandung dalam obat ini (lihat daftar pada bagian 3).

Penting kiranya agar Anda menginformasikan dokter jika Anda sedang meminum atau telah meminum obat-obatan lainnya, bahkan yang diperoleh tanpa resep, atau obat-obatan herbal.

Obat-obatan dalam daftar berikut ini tidak boleh diminum selama menjalani pengobatan dengan **VFEND®**:

- Terfenadin
- Astemizol
- Cisaprid
- Pimozid
- Kuinidin
- Ivabradin
- Sirolimus
- Rifabutin
- Rifampin
- Karbamazepin
- Barbiturat kerja panjang
- Efavirenz dengan dosis 400 mg atau lebih, satu kali sehari
- Ritonavir dengan dosis 400 mg setiap 12 jam atau lebih
- Alkaloid ergot (misalnya ergotamin, dihidroergotamin)
- St. John’s Wort
- Naloxegol
- Tolvaptan
- Lurasidone

8. Apa saja yang perlu diperhatikan saat menggunakan obat ini?

Konsultasikan dengan dokter Anda sebelum menggunakan **VFEND®** jika:

- Anda pernah mengalami reaksi alergi terhadap azol lainnya.
- Anda menderita, atau pernah menderita penyakit hati. Jika Anda menderita penyakit hati, dokter mungkin akan meresepkan **VFEND®** dengan dosis yang lebih rendah. Dokter juga akan memantau fungsi hati Anda selama menjalani pengobatan dengan **VFEND®** melalui tes darah.
- Anda diketahui menderita kardiomiopati, denyut jantung tidak teratur, detak jantung lemah, atau abnormalitas elektrokardiogram (EKG) yang disebut 'sindrom QTc panjang'.

Anda harus menghindari paparan matahari dan sinar matahari selama pengobatan. Penting kiranya untuk menutup bagian-bagian kulit yang terpapar matahari dan menggunakan tabir surya dengan faktor perlindungan matahari (SPF) yang tinggi, karena dapat terjadi peningkatan kepekaan kulit terhadap sinar UV matahari. Kondisi ini dapat terjadi dengan atau tanpa meminum obat-obatan lain seperti metotreksat. Langkah-langkah pencegahan ini juga berlaku untuk anak-anak.

Selama menjalani pengobatan dengan **VFEND®**, segera beri tahu dokter Anda jika Anda mengalami

- luka bakar matahari
- ruam kulit atau lepuh yang parah
- nyeri pada tulang

Jika Anda mengalami gangguan kulit sebagaimana diuraikan di atas, dokter dapat merujuk Anda ke dokter spesialis kulit, yang setelah melakukan konsultasi dapat memutuskan apakah Anda perlu diperiksa secara rutin. Ada kemungkinan kecil timbulnya kanker kulit jika **VFEND®** digunakan untuk jangka panjang.

Gangguan penglihatan jangka panjang juga terjadi seperti peradangan dan pembengkakan pada saraf optik mata.

Jika Anda mengalami tanda-tanda 'insufisiensi adrenal' yaitu kondisi kelenjar adrenal yang tidak memproduksi hormon steroid tertentu dalam jumlah yang memadai seperti kortisol (kelelahan kronis atau berkepanjangan, kelemahan otot, hilangnya nafsu makan, penurunan berat badan, nyeri abdomen), harap beri tahu dokter Anda.

Dokter harus memantau fungsi hati dan ginjal Anda dengan melakukan tes darah.

Pasien anak-anak dan remaja
VFEND tidak boleh diberikan kepada anak-anak berusia kurang dari 2 tahun.

Kehamilan dan menyusui
VFEND tidak boleh digunakan selama kehamilan, kecuali jika diindikasikan oleh dokter. Kontrasepsi yang efektif harus digunakan pada wanita yang berpotensi untuk mengandung. Segera hubungi dokter jika Anda kemudian mengandung selama diobati dengan **VFEND®**.

Jika Anda hamil atau menyusui, menduga bahwa diri Anda sedang hamil, atau berencana untuk hamil, mintalah saran dokter Anda sebelum meminum obat ini.

Mengemudi dan menggunakan mesin
VFEND® dapat menyebabkan penglihatan kabur atau sensitivitas terhadap cahaya yang terasa tidak nyaman. Saat mengalami efek tersebut, jangan mengemudi atau mengoperasikan peralatan atau mesin apa pun. Beri tahu dokter jika Anda mengalami hal ini.

VFEND® mengandung laktosa
Jika Anda telah diberi tahu oleh dokter bahwa Anda mempunyai intoleransi terhadap jenis gula tertentu, laporkan kepada dokter sebelum meminum **VFEND®**.

9. Efek yang tidak diinginkan

Seperti semua obat-obatan yang ada, obat ini bisa menimbulkan efek samping, meskipun tidak semua orang mengalaminya.

Efek samping yang timbul sebagian besar ringan dan sementara. Namun demikian beberapa efek samping mungkin serius dan memerlukan penanganan medis.

Kejadian merugikan yang paling sering dilaporkan adalah gangguan penglihatan, demam, ruam, muntah, mual, diare, sakit kepala, edema perifer, dan nyeri abdomen. Tingkat keparahan kejadian merugikan umumnya ringan hingga sedang.

Efek samping serius – Hentikan penggunaan VFEND® dan segera kunjungi dokter
- Ruam
- Penyakit kuning; Perubahan hasil tes darah untuk fungsi hati
- Pankreatitis

Efek samping lainnya

Sangat umum: dapat dialami lebih dari 1 di antara 10 orang

- Gangguan penglihatan (perubahan penglihatan termasuk penglihatan yang kabur, perubahan warna visual, intoleransi abnormal terhadap persepsi visual cahaya, buta warna, gangguan mata, penglihatan halo, rabun senja, penglihatan bergoyang, melihat percikan api, aura visual, penurunan akuitas penglihatan, penglihatan terlalu terang, hilangnya sebagian bidang pandang yang biasa, bintik-bintik di depan mata)
- Demam
- Ruam
- Mual, muntah, diare
- Sakit kepala
- Pembengkakan anggota gerak
- Sakit perut
- Peningkatan enzim hati

Umum: dapat dialami hingga 1 di antara 10 orang

- Peradangan sinus, peradangan gusi, menggigil, merasa lemah
- Jumlah beberapa jenis sel darah yang rendah, termasuk jumlah sel darah merah (kadang-kadang berkaitan dengan imun) dan/atau sel darah putih (kadang-kadang disertai

demam) yang sangat rendah, jumlah sel-sel yang disebut trombosit yang membantu pembekuan darah juga rendah
- Kadar gula darah rendah, kadar kalium darah rendah, kadar natrium darah rendah
- Cemas, depresi, kebingungan, agitasi, sulit tidur, halusinasi
- Kejang, tremor atau gerakan otot yang tidak terkendali, kesemutan atau sensasi tidak normal pada kulit, peningkatan tonus otot, mengantuk, pusing
- Perdarahan pada mata
- Gangguan irama jantung, termasuk denyut jantung yang sangat cepat, denyut jantung yang sangat lambat, pingsan
- Tekanan darah rendah, peradangan pembuluh vena (yang dapat dikaitkan dengan pembentukan bekuan darah)
- Kesulitan bernapas akut, nyeri dada, pembengkakan wajah (mulut, bibir, dan di sekitar mata), akumulasi cairan di dalam paru-paru
- Konstipasi, gangguan pencernaan, peradangan bibir-
- Penyakit kuning, peradangan hati, dan cedera hati
- Ruam kulit yang dapat menimbulkan lepuh dan pengelupasan kulit parah yang ditandai dengan area yang datar dan memerah pada kulit yang diliputi dengan bentol-bentol yang konfluen, kemerahan pada kulit
- Gatal-gatal
- Rambut rontok
- Sakit punggung
- Gagal ginjal, darah dalam air seni, perubahan hasil tes fungsi ginjal

Tidak umum: dapat dialami hingga 1 di antara 100 orang

- Gejala menyerupai flu, iritasi dan peradangan saluran pencernaan, peradangan saluran pencernaan yang menyebabkan diare yang terkait antibiotik, peradangan pembuluh limfatik
- Peradangan jaringan tipis yang melapisi dinding dalam abdomen dan membungkus organ-organ abdomen
- Pembesaran kelenjar limfa (kadang-kadang terasa sakit), kegagalan sumsum tulang, peningkatan eosinofil
- Penurunan fungsi kelenjar adrenal, kelenjar tiroid kurang aktif
- Fungsi otak tidak normal, gejala menyerupai Parkinson, cedera saraf yang menyebabkan kebas, rasa nyeri, kesemutan, atau rasa terbakar pada tangan atau kaki
- Gangguan keseimbangan atau koordinasi
- Pembengkakan otak
- Penglihatan ganda, kondisi serius pada mata yang mencakup: nyeri dan peradangan mata dan kelopak mata, gerakan mata yang tidak normal, kerusakan saraf optik yang menyebabkan gangguan penglihatan, pembengkakan cakram optik
- Penurunan sensitivitas terhadap sentuhan
- Indera pengecap tidak normal
- Kesulitan mendengar, telinga berdenging, vertigo
- Peradangan organ-organ dalam tertentu, seperti pankreas dan usus dua belas jari, pembengkakan dan peradangan lidah
- Pembesaran hati, gagal hati, penyakit kantong empedu, batu empedu
- Peradangan sendi, peradangan pembuluh vena di bawah kulit (yang mungkin berkaitan dengan pembentukan bekuan darah)
- Peradangan ginjal, protein dalam air seni, kerusakan ginjal

- Denyut jantung sangat cepat atau denyut jantung terlewat, kadang-kadang disertai impuls listrik yang tidak menentu
- Hasil elektrokardiogram (EKG) abnormal
- Peningkatan kadar kolesterol dalam darah, peningkatan urea dalam darah
- Reaksi alergi pada kulit (kadang-kadang parah), termasuk kondisi kulit yang mengancam jiwa yang menimbulkan lepuh dan luka yang terasa sakit pada kulit dan membran mukosa, khususnya di dalam mulut, peradangan kulit, kaligata, luka bakar matahari, atau reaksi kulit yang berat setelah terpapar cahaya atau matahari, kulit kemerahan dan iritasi, perubahan warna kulit menjadi merah atau ungu yang dapat disebabkan oleh jumlah trombosit yang rendah, eksema
- Reaksi alergi atau respons imun yang berlebihan

Jarang: dapat dialami hingga 1 di antara 1000 orang

- Kelenjar tiroid terlalu aktif
- Penurunan fungsi otak yang merupakan komplikasi serius penyakit hati
- Hilangnya sebagian besar serat dalam saraf optik, kornea menjadi keruh, gerakan mata tanpa disengaja
- Fotosensitivitas bulosa
- Gangguan berupa serangan sistem imun tubuh terhadap sebagian sistem saraf perifer
- Masalah irama atau konduksi jantung (kadang-kadang mengancam jiwa)
- Reaksi alergi yang mengancam jiwa
- Gangguan sistem pembekuan darah
- Reaksi alergi pada kulit (kadang-kadang bersifat parah), termasuk pembengkakan yang cepat (edema) pada dermis, jaringan subkutan, jaringan mukosa dan submukosa, bercak-bercak tebal yang gatal atau nyeri, kulit memerah disertai sisik-sisik keperakan pada kulit, iritasi kulit dan membran mukosa, kondisi kulit yang mengancam jiwa yang menyebabkan sebagian besar epidermis, lapisan kulit paling luar, terlepas dari lapisan kulit di bawahnya
- Bercak-bercak kecil yang kering dan bersisik pada kulit kadang-kadang menebal dengan bagian-bagian yang runcing atau ‘bertanduk’

Efek samping dengan frekuensi yang tidak diketahui:
- Bintik-bintik dan bercak berpigmen

Efek samping signifikan lainnya yang frekuensinya tidak diketahui, tetapi harus segera dilaporkan kepada dokter Anda:
- Kanker kulit
- Peradangan jaringan di sekitar tulang
- Bercak-bercak memerah dan bersisik atau lesi kulit berbentuk cincin yang dapat merupakan gejala penyakit autoimun yang disebut lupus eritematosus diskoid
- Lepuh pada kulit, rasa tidak enak, dan demam dalam konteks kondisi yang disebut reaksi obat dengan gejala eosinofilia dan sistemik (DRESS)

Karena **VFEND®** telah diketahui dapat memengaruhi hati dan ginjal, dokter Anda harus memantau fungsi hati dan ginjal Anda dengan melakukan tes darah. Harap beri tahu dokter Anda jika Anda merasa sakit perut atau jika feses Anda mengalami perubahan konsistensi.

Telah dilaporkan terjadinya kasus kanker kulit pada pasien yang diterapi dengan **VFEND®** untuk jangka waktu yang lama.

Luka bakar matahari atau reaksi kulit berat setelah terpapar pada cahaya atau matahari lebih banyak dialami oleh anak-anak. Jika Anda atau anak Anda mengalami gangguan kulit, dokter dapat merujuk Anda ke dokter spesialis kulit, yang setelah melakukan konsultasi dapat memutuskan apakah Anda atau anak Anda perlu diperiksa secara rutin.

Jika ada efek samping yang berlanjut atau mengganggu, harap beri tahu dokter Anda.

Melaporkan efek samping
Jika Anda mengalami efek samping apa pun, konsultasikan dengan dokter, apoteker, atau perawat Anda. Ini termasuk segala kemungkinan efek samping yang tidak tercantum di dalam leaflet ini. Dengan melaporkan efek samping, Anda bisa membantu memberikan informasi lebih lanjut mengenai keamanan obat ini.

10. Apa saja obat lain atau makanan yang harus dihindari selama menggunakan obat ini?

Beri tahu dokter jika Anda sedang meminum, baru-baru ini telah meminum, atau mungkin meminum obat-obatan lainnya.

- Beberapa jenis obat, jika diminum bersama dengan **VFEND®**, dapat memengaruhi cara kerja **VFEND®** atau **VFEND®** dapat memengaruhi cara kerja obat-obatan tersebut.

Beri tahu dokter jika Anda meminum obat-obatan berikut, karena pengobatan dengan **VFEND®** pada saat yang sama sedapat mungkin harus dihindari:

- Ritonavir (digunakan untuk mengobati HIV) dengan dosis 100 mg dua kali sehari
- Glasdegib (digunakan untuk mengobati kanker) - jika Anda perlu menggunakan kedua obat, dokter Anda akan sering memantau ritme jantung Anda
- Lemborexant (digunakan untuk mengobati insomnia pada orang dewasa)

Beri tahu dokter jika Anda meminum salah satu obat-obatan berikut, karena pengobatan dengan **VFEND®** pada saat yang sama harus sedapat mungkin dihindari, dan penyesuaian dosis vorikonazol mungkin perlu dilakukan:

- Fenitoin (digunakan untuk mengobati epilepsi). Jika Anda sudah dirawat dengan fenitoin maka konsentrasi fenitoin dalam darah perlu dipantau selama pengobatan dengan **VFEND®** dan dosis Anda mungkin disesuaikan.

Laporkan kepada dokter jika Anda meminum obat-obatan berikut, karena penyesuaian atau pemantauan dosis mungkin diperlukan untuk memeriksa apakah obat-obatan dan/atau **VFEND®** masih memberikan efek yang diharapkan:

- Warfarin dan antikoagulan lainnya (misalnya fenprokoumon, asenokumarol; yang digunakan untuk memperlambat pembekuan darah)
- Siklosporin (digunakan pada pasien transplantasi)
- Takrolimus (digunakan pada pasien transplantasi)
- Sulfonilurea (misalnya tolbutamid, glipizid, dan gliburid) (digunakan untuk diabetes)

- Statin (misalnya atorvastatin, simvastatin) (digunakan untuk menurunkan kolesterol)
- Benzodiazepin (misalnya midazolam, triazolam) (digunakan untuk insomnia berat dan stres)
- Eszopiclone (digunakan untuk mengobati insomnia)
- Omeprazol (digunakan untuk mengobati ulkus)
- Kontrasepsi oral (jika Anda menggunakan **VFEND®** sambil menggunakan kontrasepsi oral, maka Anda dapat mengalami efek samping seperti mual dan gangguan menstruasi)
- Alkaloid vinka (misalnya vinkristin dan vinblastin) (digunakan untuk mengobati kanker)
- Inhibitor kinase tyrosin (misalnya, axitinib, bosutinib, cabozantinib, ceritinib, cobimetinib, dabrafenib, dasatinib, nilotinib, sunitinib, ibrutinib, ribociclib) (digunakan untuk mengobati kanker)
- Tretinoin (digunakan untuk mengobati leukaemia)
- Penghambat protease HIV lainnya (misalnya sakuinavir, amprenavir, nelfinavir) (digunakan untuk mengobati HIV)
- Penghambat transkriptase balik nonnukleosida lainnya (misalnya delavirdin, nevirapin) (digunakan untuk mengobati HIV)
- Metadon (digunakan untuk mengobati ketergantungan heroin)
- Alfentanil dan fentanil dan opiat kerja pendek lainnya seperti sufentanil (pereda nyeri digunakan untuk prosedur pembedahan)
- Oksikodon dan opiat kerja panjang lainnya seperti hidrokodon (digunakan untuk nyeri sedang hingga berat)
- Obat-obatan anti peradangan nonsteroid (misalnya ibuprofen, diklofenak) (digunakan untuk mengobati nyeri dan peradangan)
- Flukonazol (digunakan untuk infeksi jamur)
- Everolimus (digunakan untuk mengobati kanker ginjal stadium lanjut dan pada pasien transplantasi)
- Venetoklaks (digunakan untuk mengobati beberapa jenis kanker (leukemia limfositik kronis-CLL, limfoma limfositik kecil-SLL, leukemia mieloid akut-AML))
- Ivacaftor
- Kortikosteroid (termasuk kortikosteroid hirup mis., budesonid)
- Letermovir (digunakan untuk mencegah penyakit sitomegalovirus (CMV) setelah transplantasi sumsum tulang)

11. Bagaimana cara menyimpan obat ini?

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan gunakan obat ini setelah melewati tanggal kedaluwarsa yang tertera pada labelnya. Tanggal kedaluwarsa mengacu pada hari terakhir dari bulan yang tertera.

Simpan pada suhu maksimum 30 °C.

Jangan buang obat melalui saluran pembuangan air atau bersama sampah rumah tangga. Tanyakan kepada dokter tentang cara membuang obat yang sudah tidak dibutuhkan. Langkah-langkah ini akan membantu melindungi lingkungan.

12. Tanda-tanda dan gejala-gejala overdosis

Tidak ada informasi spesifik yang tersedia mengenai penanganan jika terjadi overdosis vorikonazol. Jika Anda meminum tablet melebihi yang diresepkan (atau jika ada orang lain yang meminum tablet Anda), Anda dapat mengalami intoleransi abnormal terhadap cahaya dikarenakan meminum **VFEND®** melebihi dosis yang seharusnya. Efek samping mana pun yang disebutkan di atas mungkin terjadi.

13. Apa yang harus dilakukan jika Anda menggunakan lebih dari dosis yang dianjurkan?

Jika Anda khawatir mungkin telah menerima **VFEND®** melebihi dosis yang seharusnya, segera beri tahu dokter Anda.

14. Kapan sebaiknya Anda berkonsultasi dengan dokter?

Jika Anda memiliki pertanyaan lebih lanjut atau Anda mengalami situasi yang sama seperti yang tercantum dalam leaflet ini, konsultasikan dengan dokter Anda.

15. Nama produsen/importir/Pemegang Hak Pemasaran

VFEND® 200 mg tablet salut selaput – Dus berisi 1 blister @10 tablet salut selaput; No. Reg. DKI2054201017A1

HARUS DENGAN RESEP DOKTER

Diproduksi oleh:
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Ascoli Piceno, Italia

Diimpor oleh:
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Jakarta, Indonesia

16. Tanggal Revisi

12/2022