ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VFEND 50mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50mg voriconazole.
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White, round tablets, debossed “Pfizer” on one side and “VOR50”on the reverse.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VFEND, voriconazole, is a broad spectrum, triazole antifungal agent and is indicated as follows:

Treatment of invasive aspergillosis.

Treatment of candidemia in non-neutropenic patients

Treatment of fluconazole-resistant serious invasive *Candida* infections (including *C. krusei*).

Treatment of serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp.

VFEND should be administered primarily to patients with progressive, possibly life-threatening infections.

4.2 Posology and method of administration

VFEND film-coated tablets are to be taken at least one hour before, or one hour following, a meal.

Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy (see section 4.4).

VFEND is also available as 200mg film-coated tablets, 200mg powder for solution for infusion and 40mg/ml powder for oral suspension.

Use in adults
Therapy must be initiated with the specified loading dose regimen of either intravenous or oral VFEND to achieve plasma concentrations on Day 1 that are close to steady state. On the basis of the high oral bioavailability (96 %; see section 5.2), switching between intravenous and oral administration is appropriate when clinically indicated.

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

	Intravenous	**Oral**	
		Patients 40kg and above	Patients less than 40kg
Loading Dose Regimen (first 24 hours)	6mg/kg every 12 hours (for the first 24 hours)	400mg every 12 hours (for the first 24 hours)	200mg every 12 hours (for the first 24 hours)
Maintenance Dose (after first 24 hours)	4mg/kg twice daily	200mg twice daily	100mg twice daily

Dosage adjustment
If patient response is inadequate, the maintenance dose may be increased to 300mg twice daily for oral administration. For patients less than 40kg the oral dose may be increased to 150mg twice daily.

If patients are unable to tolerate treatment at these higher doses reduce the oral dose by 50mg steps to the 200mg twice daily (or 100mg twice daily for patients less than 40kg) maintenance dose.

Phenytoin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased from 200mg to 400mg orally, twice daily (100mg to 200mg orally, twice daily in patients less than 40kg), see sections 4.4 and 4.5.

Rifabutin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased from 200mg to 350mg orally, twice daily (100mg to 200mg orally, twice daily in patients less than 40kg), see sections 4.4 and 4.5.

Treatment duration depends upon patients' clinical and mycological response.

Use in the elderly
No dose adjustment is necessary for elderly patients (see section 5.2).

Use in patients with renal impairment
The pharmacokinetics of orally administered voriconazole are not affected by renal impairment. Therefore, no adjustment is necessary for oral dosing for patients with mild to severe renal impairment (see section 5.2).

Voriconazole is haemodialysed with a clearance of 121ml/min. A four hour haemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment.

Use in patients with hepatic impairment
No dose adjustment is necessary in patients with acute hepatic injury, manifested by elevated liver function tests (ALAT, ASAT) (but continued monitoring of liver function tests for further elevations is recommended).

It is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B) receiving VFEND (see section 5.2).

VFEND has not been studied in patients with severe chronic hepatic cirrhosis (Child-Pugh C).

VFEND has been associated with elevations in liver function tests and clinical signs of liver damage, such as jaundice, and must only be used in patients with severe hepatic impairment if the benefit outweighs the potential risk. Patients with hepatic impairment must be carefully monitored for drug toxicity (see also section 4.8).

Use in children
Safety and effectiveness in paediatric subjects below the age of 2 years has not been established (see also section 5.1). Therefore voriconazole is not recommended for children less than 2 years of age. Limited data are currently available to determine the optimal posology. However, the following regimen has been used in paediatric studies.

Children aged 2 to < 12 years:

	Intravenous	**Oral**
Loading Dose Regimen (first 24 hours)	6mg/kg every 12 hours (for the first 24 hours)	6mg/kg every 12 hours (for the first 24 hours)
Maintenance Dose (after first 24 hours)	4mg/kg twice daily	4mg/kg twice daily

If a child is able to swallow tablets, the dose should be administered to the nearest mg/kg dose possible using whole 50mg tablets.

The pharmacokinetics and tolerability of higher doses have not been characterised in paediatric populations.

Adolescents (12 to 16 years of age): should be dosed as adults.

4.3 Contraindications

VFEND is contraindicated in patients with known hypersensitivity to voriconazole or to any of the excipients.

Coadministration of the CYP3A4 substrates, terfenadine, astemizole, cisapride, pimozide or quinidine with VFEND is contraindicated since increased plasma concentrations of these medicinal products can lead to QTc prolongation and rare occurrences of *torsades de pointes* (see section 4.5).

Coadministration of VFEND with rifampicin, carbamazepine and phenobarbital is contraindicated since these medicinal products are likely to decrease plasma voriconazole concentrations significantly (see section 4.5).

Coadministration of VFEND with efavirenz is contraindicated because efavirenz significantly decreases voriconazole plasma concentrations while VFEND also significantly increases efavirenz plasma concentrations (see section 4.5).

Coadministration of VFEND with ritonavir (400mg and above twice daily) is contraindicated because ritonavir significantly decreases plasma voriconazole concentrations in healthy subjects (see section 4.5).

Coadministration of ergot alkaloids (ergotamine, dihydroergotamine), which are CYP3A4 substrates, is contraindicated since increased plasma concentrations of these medicinal products can lead to ergotism (see section 4.5).

Coadministration of voriconazole and sirolimus is contraindicated, since voriconazole is likely to increase plasma concentrations of sirolimus significantly (see section 4.5).

4.4 Special warnings and special precautions for use

Hypersensitivity: Caution should be used in prescribing VFEND to patients with hypersensitivity to other azoles (see also section 4.8).

Cardiovascular:
Some azoles, including voriconazole have been associated with QT interval prolongation. There have been rare cases of torsade de pointes in patients taking voriconazole who had risk factors, such as history of cardiotoxic chemotherapy, cardiomyopathy, hypokalaemia 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

Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy (see section 4.2). 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 experienced an interval exceeding the potentially clinically relevant threshold of 500msec (see section 5.1).

Hepatic toxicity: In clinical trials, there have been uncommon cases of serious hepatic reactions during treatment with VFEND (including clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities). Instances of hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly haematological malignancy). Transient 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 section 4.8).

Monitoring of hepatic function: Patients at the beginning of therapy with voriconazole and patients who develop abnormal liver function tests during VFEND therapy must be routinely monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of VFEND should be considered if clinical signs and symptoms are consistent with liver disease development.

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 (see section 4.8).

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

Dermatological reactions: Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome, during treatment with VFEND. If patients develop a rash they should be monitored closely and VFEND discontinued if lesions progress. In addition VFEND has been associated with photosensitivity skin reaction especially during long term therapy. It is recommended that patients should be informed to avoid sunlight during the treatment.

Paediatric use: Safety and effectiveness in paediatric subjects below the age of two years has not been established (see also section 5.1).

Phenytoin (CYP2C9 substrate and potent CYP450 inducer): Careful monitoring of phenytoin levels is recommended when phenytoin is coadministered with voriconazole. Concomitant use of voriconazole and phenytoin should be avoided unless the benefit outweighs the risk (see section 4.5).

Rifabutin (CYP450 inducer): Careful monitoring of full blood counts and adverse events to rifabutin (e.g. uveitis) is recommended when rifabutin is coadministered with voriconazole. Concomitant use of voriconazole and rifabutin should be avoided unless the benefit outweighs the risk (see section 4.5).

Methadone (CYP3A4 substrate). Frequent monitoring for adverse events and toxicity related to methadone, including QTc prolongation, is recommended when coadministered with voriconazole since methadone levels increased following co-administration of voriconazole. Dose reduction of methadone may be needed (see section 4.5).

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.

4.5 Interaction with other medicinal products and other forms of interaction

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

This section addresses the effects of other medicinal products on voriconazole, the effects of voriconazole on other medicinal products and two-way interactions. The interactions for the first two sections are presented in the following order: contraindications, those requiring dosage 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.

Effects of other medicinal products on voriconazole

Voriconazole is metabolised by cytochrome P450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4. Inhibitors or inducers of these isoenzymes may increase or decrease voriconazole plasma concentrations respectively.

Rifampicin (CYP450 inducer): Rifampicin (600 mg once daily) decreased the C_{max} (maximum plasma concentration) and AUC_{τ} (area under the plasma concentration time curve within a dose interval) of voriconazole by 93 % and 96 %, respectively. Coadministration of voriconazole and rifampicin is contraindicated (see section 4.3)**.**

Ritonavir (potent CYP450 inducer; CYP3A4 inhibitor and substrate): Ritonavir (400mg twice daily) decreased the steady state C_{max} and AUC_{τ} of oral voriconazole by an average of 66% and 82%, respectively, in healthy subjects with the exception of one subject in whom a 2.5 fold increases in AUC_{τ} was observed. No extrapolation can be made for ritonavir doses lower than 400mg. Repeat oral administration of voriconazole did not have a significant effect on steady state C_{max} and AUC_{τ} of ritonavir following repeat dose administration in healthy subjects. Coadministration of voriconazole and ritonavir (400mg and above twice daily) is contraindicated (see section 4.3).

Carbamazepine and phenobarbital (potent CYP450 inducers): Although not studied, carbamazepine or phenobarbital are likely to significantly decrease plasma voriconazole concentrations. Coadministration of voriconazole with carbamazepine and phenobarbital is contraindicated (see section 4.3).

Cimetidine (non-specific CYP450 inhibitor and increases gastric pH): Cimetidine (400mg twice daily) increased voriconazole C_{max} and AUC_{τ} by 18 % and 23 %, respectively. No dosage adjustment of voriconazole is recommended.

Ranitidine (increases gastric pH): Ranitidine (150mg twice daily) had no significant effect on voriconazole C_{max} and AUC_{τ}.

Macrolide antibiotics: Erythromycin (CYP3A4 inhibitor; 1g twice daily) and azithromycin (500mg once daily) had no significant effect on voriconazole C_{max} and AUC_{τ}.

Effects of voriconazole on other medicinal products

Voriconazole inhibits the activity of cytochrome P450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4. Therefore there is potential for voriconazole to increase the plasma levels of substances metabolised by these CYP450 isoenzymes.

Terfenadine, astemizole, cisapride, pimozide and quinidine (CYP3A4 substrates): Although not studied, coadministration of voriconazole with terfenadine, astemizole, cisapride, pimozide, or quinidine is contraindicated, since increased plasma concentrations of these medicinal products can lead to QTc prolongation and rare occurrences of *torsades de pointes* (see section 4.3).

Sirolimus (CYP3A4 substrate): Voriconazole increased sirolimus (2mg single dose) C_{max} and AUC_{τ} by 556 % and 1014 %, respectively. Coadministration of voriconazole and sirolimus is contraindicated (see section 4.3).

Ergot alkaloids (CYP3A4 substrates): Although not studied, voriconazole may increase the plasma concentrations of ergot alkaloids (ergotamine and dihydroergotamine) and lead to ergotism. Coadministration of voriconazole with ergot alkaloids is contraindicated (see section 4.3).

Cyclosporin (CYP3A4 substrate): In stable, renal transplant recipients, voriconazole increased cyclosporin C_{max} and AUC_{τ} by at least 13 % and 70 % respectively. When initiating voriconazole in patients already receiving cyclosporin it is recommended that the cyclosporin dose be halved and cyclosporin level carefully monitored. Increased cyclosporin levels have been associated with nephrotoxicity. When voriconazole is discontinued, cyclosporin levels must be carefully monitored and the dose increased as necessary.

Methadone (CYP3A4 substrate): In subjects receiving a methadone maintenance dose (32-100mg once daily) coadministration of oral voriconazole (400mg twice daily for 1 day, then 200mg twice daily for four days) increased the C_{max} and AUC_{τ} of pharmacologically active R-methadone by 31% and 47%, respectively, whereas the C_{max} and AUC_{τ} of the S-enantiomer increased by approximately 65% and 103%, respectively. Voriconazole plasma concentrations during coadministration of methadone were comparable to voriconazole levels (historical data) in healthy subjects without any comedication. Frequent monitoring for adverse events and toxicity related to increased plasma concentrations of methadone, including QT prolongation, is recommended during coadministration. Dose reduction of methadone may be needed.

Tacrolimus (CYP3A4 substrate): Voriconazole increased tacrolimus (0.1mg/kg single dose) C_{max} and AUC_t (area under the plasma concentration time curve to the last quantifiable measurement) by 117% and 221%, respectively. When initiating voriconazole in patients already receiving 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.

Oral anticoagulants:
Warfarin (CYP2C9 substrate): Coadministration of voriconazole (300mg twice daily) with warfarin (30mg single dose) increased maximum prothrombin time by 93%. Close monitoring of prothrombin time is recommended if warfarin and voriconazole are coadministered.
Other oral anticoagulants e.g. phenprocoumon, acenocoumarol (CYP2C9, CYP3A4 substrates): Although not studied, voriconazole may increase the plasma concentrations of coumarins and therefore may cause an increase in prothrombin time. If patients receiving coumarin preparations are treated simultaneously with voriconazole, the prothrombin time should be monitored at close intervals and the dosage of anticoagulants adjusted accordingly.

Sulphonylureas (CYP2C9 substrates): Although not studied, voriconazole may increase the plasma levels of sulphonylureas, (e.g. tolbutamide, glipizide, and glyburide) and therefore cause hypoglycaemia. Careful monitoring of blood glucose is recommended during coadministration.

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

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

Vinca Alkaloids (CYP3A4 substrates): Although not studied, voriconazole may increase the plasma levels of the vinca alkaloids (e.g. vincristine and vinblastine) and lead to neurotoxicity.

Prednisolone (CYP3A4 substrate): Voriconazole increased C_{max} and AUC_{τ} of prednisolone (60 mg single dose) by 11% and 34%, respectively. No dosage adjustment is recommended.

Digoxin (P-glycoprotein mediated transport): Voriconazole had no significant effect on C_{max} and AUC_{τ} of digoxin (0.25mg once daily).

Mycophenolic acid (UDP-glucuronyl transferase substrate): Voriconazole had no effect on the C_{max} and AUC_{t} of mycophenolic acid (1g single dose).

Two-way interactions

Phenytoin (CYP2C9 substrate and potent CYP450 inducer): Concomitant use of voricoazole and phenytoin should be avoided unless the benefit outweighs the risk.
Phenytoin (300mg once daily) decreased the C_{max} and AUC_{τ} of voriconazole by 49% and 69%, respectively. Voriconazole (400mg twice daily, see section 4.2) increased C_{max} and AUC_{τ} of phenytoin (300 mg once daily) by 67% and 81%, respectively. Careful monitoring of phenytoin plasma levels is recommended when phenytoin is coadministered with voriconazole.

Phenytoin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased to 5 mg /kg intravenously twice daily or from 200mg to 400mg orally, twice daily (100mg to 200mg orally, twice daily in patients less than 40kg), see section 4.2.

Rifabutin (CYP450 inducer): Concomitant use of voriconazole and rifabutin should be avoided unless the benefit outweighs the risk.
Rifabutin (300 mg once daily) decreased the C_{max} and AUC_{τ} of voriconazole at 200mg twice daily by 69% and 78%, respectively. During coadministration with rifabutin, the C_{max} and AUC_{τ} of voriconazole at 350mg twice daily were 96% and 68% of the levels when administered alone at 200mg twice daily. At a voriconazole dose of 400mg twice daily C_{max} and AUC_{τ} were 104% and 87% higher, respectively, compared with voriconazole alone at 200mg twice daily. Voriconazole at 400mg twice daily increased C_{max} and AUC_{τ} of rifabutin by 195% and 331%, respectively.

If rifabutin coadministration with voriconazole is justified then the maintenance dose of voriconazole may be increased to 5mg/kg intravenously twice daily or from 200mg to 350mg orally, twice daily (100mg to 200mg orally, twice daily in patients less than 40kg) (see section 4.2). Careful monitoring of full blood counts and adverse events to rifabutin (e.g. uveitis) is recommended when rifabutin is coadministered with voriconazole.

Omeprazole (CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate): Omeprazole (40mg once daily) increased voriconazole C_{max} and AUC_{τ} by 15% and 41%, respectively. No dosage adjustment of voriconazole is recommended.Voriconazole increased omeprazole C_{max} and AUC_{τ} by 116% and 280%, respectively. When initiating voriconazole in patients already receiving omeprazole, it is

recommended that the omeprazole dose be halved. The metabolism of other proton pump inhibitors which are CYP2C19 substrates may also be inhibited by voriconazole.

Indinavir (CYP3A4 inhibitor and substrate): Indinavir (800 mg three times daily) had no significant effect on voriconazole C_{max} , C_{min} and AUC_{τ}.
Voriconazole did not have a significant effect on C_{max} and AUC_{τ} of indinavir (800mg three times daily).

Efavirenz (a non-nucleoside reverse transcriptase inhibitor (CYP450 inducer; CYP3A4 inhibitor and substrate)): Steady-state efavirenz (400mg orally once daily) decreased the steady state C_{max} and AUC_{τ} of voriconazole by an average of 61% and 77%, respectively, in healthy subjects. In the same study voriconazole at steady state increased the steady state C_{max} and AUC_{τ} of efavirenz by an average of 38% and 44% respectively, in healthy subjects. Coadministration of voriconazole and efavirenz is contraindicated (see section 4.3).

Other HIV protease inhibitors (CYP3A4 inhibitors): *In vitro* studies suggest that voriconazole may inhibit the metabolism of HIV protease inhibitors (e.g. saquinavir, amprenavir and nelfinavir*). In vitro* studies also show that the metabolism of voriconazole may be inhibited by HIV protease inhibitors. However results of the combination of voriconazole with other HIV protease inhibitors cannot be predicted in humans only from *in vitro* studies. Patients should be carefully monitored for any occurrence of drug toxicity and/or loss of efficacy during the co-administration of voriconazole and HIV protease inhibitors.

Non-nucleoside reverse transcriptase inhibitors (NNRTI) (CYP3A4 substrates, inhibitors or CYP450 inducers): *In vitro* studies show that the metabolism of voriconazole may be inhibited by delavirdine. Although not studied, the metabolism of voriconazole may be induced by nevirapine. An in-vivo study showed that voriconazole inhibited the metabolism of efavirenz. Voriconazole may also inhibit the metabolism of NNRTIs besides efavirenz. Patients should be carefully monitored for any occurrence of drug toxicity and/or lack of efficacy during the coadministration of voriconazole and NNRTIs. Coadministration of voriconazole with efavirenz is contraindicated (see section 4.3)

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 levels of substances metabolised by CYP3A4 isoenzymes (certain antihistamines, quinidine, cisapride, pimozide) co-administration is contraindicated (see section 4.3).

4.6 Pregnancy and lactation

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

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk to humans is unknown.

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

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

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

4.7 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.

4.8 Undesirable effects

The safety profile of voriconazole is based on an integrated safety database of more than 2000 subjects (1655 patients in therapeutic trials). This represents a heterogeneous population, containing patients with haematological malignancy, HIV infected patients with oesophageal candidiasis and refractory fungal infections, non-neutropenic patients with candidaemia or aspergillosis and healthy volunteers. Five hundred and sixty one patients had a duration of voriconazole therapy of greater than 12 weeks, with 136 patients receiving voriconazole for over 6 months.

In the table below, since the majority of the studies were of an open nature all causality adverse events, by system organ class and frequency (very common >1/10, common >1/100 and <1/10, uncommon >1/1000 and <1/100 and rare, <1/1000) if possibly causally related are listed. The most commonly reported adverse events were visual disturbances, fever, rash, vomiting, nausea, diarrhoea, headache, peripheral oedema 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 analysed by age, race, or gender.

Undesirable effects reported in subjects receiving voriconazole

Body System	**Adverse Drug Reactions**
Body as a whole	
Very common	Fever, headache, abdominal pain
Common	Chills, asthenia, back pain, chest pain, injection site reaction/inflammation, face oedema, flu syndrome
Uncommon	Allergic reaction, anaphylactoid reaction, angioedema, peritonitis
Cardiovascular	
Common	Hypotension, thrombophlebitis, phlebitis
Uncommon	Atrial arrhythmia, bradycardia, syncope, tachycardia, ventricular arrhythmia, ventricular fibrillation, supraventricular tachycardia, QT interval prolongation
Rare	AV complete block, bundle branch block, nodal arrhythmia, ventricular tachycardia, torsade de pointes
Digestive	
Very common	Nausea, vomiting, diarrhoea
Common	Elevated liver function tests (includingASAT, ALAT, alkaline phosphatase, GGT, LDH, bilirubin), jaundice, cheilitis, cholestatic jaundice, gastroenteritis
Uncommon	Cholecystitis, cholelithiasis, constipation, duodenitis, dyspepsia, enlarged liver, gingivitis, glossitis, hepatitis, hepatic failure, pancreatitis, tongue oedema
Rare	Pseudomembranous colitis, hepatic coma
Endocrine	
Uncommon	Adrenal cortex insufficiency

Haemic and lymphatic	
Common	Thrombocytopenia, anaemia (including macrocytic, microcytic, normocytic, megaloblastic, aplastic), leukopenia, pancytopenia, purpura
Uncommon	Lymphadenopathy, agranulocytosis, eosinophilia, disseminated intravascular coagulation, marrow depression
Rare	Lymphangitis
Metabolic and nutritional	
Very common	Peripheral oedema
Common	Hypokalaemia, creatinine increased, hypoglycaemia
Uncommon	BUN increased, albuminuria, hypercholesterolaemia
Rare	Hyperthyroidism, hypothyroidism
Musculoskeletal	
Uncommon	Arthritis
Nervous	

Common	Dizziness, hallucinations, confusion, depression, anxiety, tremor, agitation, paraesthesia
Uncommon	Ataxia, brain oedema, diplopia, hypoaesthesia, nystagmus, vertigo
Rare	Guillain-Barre syndrome, oculogyric crisis, hypertonia, Extrapyramidal syndrome, insomnia, encephalopathy, somnolence during infusion
Respiratory	
Common	Respiratory distress syndrome, lung oedema, sinusitis
Skin and appendages	
Very common	Rash
Common	Pruritus, maculopapular rash, photosensitivity skin reaction, alopecia, exfoliative dermatitis
Uncommon	Fixed drug eruption, eczema, psoriasis, Stevens-Johnson syndrome, urticaria
Rare	Discoid lupus erythematosis, erythema multiforme, toxic epidermal necrolysis
Special senses	
Very Common	Visual disturbances (including altered/enhanced visual perception, decrease in ERG amplitude,blurred vision, colour vision change, photophobia)
Uncommon	Blepharitis, optic neuritis, papilloedema, scleritis, altered taste perception
Rare	Retinal haemorrhage, corneal opacity, optic atrophy, hypoacusis, tinnitus
Urogenital	
Common	Acute kidney failure, haematuria
Uncommon	Nephritis
Rare	Kidney tubular necrosis

Visual disturbances

Voriconazole treatment-related visual disturbances were very common. In clinical trials, short-term as well as long-term treatment, approximately 30% of subjects experienced altered/enhanced visual perception, blurred vision, colour vision change or photophobia. The visual disturbances are transient and fully reversible, with the majority spontaneously resolving within 60 minutes and no clinically significant long-term visual effects were observed. There is evidence of attenuation with repeated doses of voriconazole. The visual disturbance is generally mild, rarely results in discontinuation and has not been associated with long-term sequelae. Visual disturbances may be associated with higher plasma concentrations and/or doses.

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 treatment and were fully reversible on withdrawal of voriconazole.

Dermatological reactions

Dermatological reactions were 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 rarely developed serious cutaneous reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme during treatment with VFEND.

If patients develop a rash they should be monitored closely and VFEND discontinued if lesions progress. Photosensitivity reactions have been reported, especially during long-term therapy (see also section 4.4).

Liver Function Tests

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

Voriconazole has been infrequently associated with cases of serious hepatic toxicity in patients with other serious underlying conditions. This includes cases of jaundice, and rare cases of hepatitis and hepatic failure leading to death (see section 4.4).

4.9 Overdose

In clinical trials there were 3 cases of accidental overdose. All occurred in paediatric patients, who received up to five times the recommended intravenous dose of voriconazole. A single adverse event of photophobia of 10 minutes duration was reported.

There is no known antidote to voriconazole.

Voriconazole is haemodialysed with a clearance of 121 ml/min. In an overdose, haemodialysis may assist in the removal of voriconazole from the body.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC code: J02A C03
Antimycotics for Systemic Use – Triazole derivatives

Mechanism of action

I*n 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*) and fungicidal activity against all *Aspergillus* species tested. In addition voriconazole shows *in vitro* fungicidal activity against emerging fungal pathogens, including those such as *Scedosporium* or *Fusarium* which have limited susceptibility to existing antifungal agents. Its mode of action is inhibition of fungal cytochrome P450-mediated 14α-sterol demethylation, an essential step in ergosterol biosynthesis.

In animal studies there is a correlation between minimum inhibitory concentration values and efficacy against experimental mycoses. By contrast, in clinical studies, there appears to be no correlation between minimum inhibitory concentration values and clinical outcome. Furthermore, there does not appear to be a correlation between plasma levels and clinical outcome. This is typical of azole antimycotics.

Microbiology

Clinical efficacy (with partial or complete response, see below under Clinical Experience) has been demonstrated for *Aspergillus* spp. including *A. flavus, A. fumigatus, A. terreus, A. niger, A. nidulans, Candida* spp., including *C. albicans, C. glabrata, C. krusei, C. parapsilosis and C. tropicalis* and limited numbers of *C. dubliniensis, C. inconspicua,* and *C. guilliermondii, Scedosporium* spp., including *S. apiospermum, S. prolificans and Fusarium* spp.

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 μg/ml.

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

Specimens for fungal culture and other relevant laboratory studies (serology, histopathology) should be obtained prior to therapy to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.

Clinical isolates with decreased susceptibility to voriconazole have been identified. However, elevated minimum inhibitory concentrations did not always correlate with clinical failure and clinical success has been observed in patients infected with organisms resistant to other azoles. Correlation of *in vitro* activity with clinical outcome is difficult owing to the complexity of the patients studied in clinical trials; breakpoints for voriconazole remain to be established.

Clinical Experience

Successful outcome in this section is defined as complete or partial response.

Aspergillus infections – efficacy in aspergillosis patients with poor prognosis
Voriconazole has *in vitro* fungicidal activity against *Aspergillus* spp. The efficacy and survival benefit of voriconazole versus conventional amphotericin B in the primary treatment of acute invasive aspergillosis was demonstrated in an open, randomised, multicentre study in 277 immunocompromised patients treated for 12 weeks. A satisfactory global response (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 31% of patients treated with comparator. The 84-day survival rate for voriconazole was statistically significantly higher than that for the comparator and a clinically and statistically significant benefit was shown in favour of voriconazole for both time to death and time to discontinuation due to toxicity.

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).

The studies included cerebral, sinus, pulmonary and disseminated aspergillosis in patients with bone marrow and solid organ transplants, haematological malignancies, cancer and AIDS.

Candidaemia in non-neutropenic patients.

The efficacy of voriconazole compared to the regimen of amphotericin B followed by fluconazole in the primary treatment of candidaemia was demonstrated in an open, comparative study. Three hundred and seventy non-neutropenic patients (above 12 years of age) with documented candidaemia were included in the study, of whom 248 were treated with voriconazole. Nine subjects in the voriconazole group and five in the amphotericin B followed by fluconazole group also had mycologically proven infection in deep tissue. Patients with renal failure were excluded from this study. The median treatment duration was 15 days in both treatment arms. In the primary analysis, successful response as assessed by a Data Review Committee (DRC) blinded to study medication was defined as resolution/improvement in all clinical signs and symptoms of infection with eradication of *Candida* from blood and infected deep tissue sites at 12 weeks after the end of therapy (EOT). Patients who did not have an assessment 12 weeks after EOT were counted as failures. In this analysis a successful response was seen in 41% of patients in both treatment arms.

In a secondary analysis, which utilised *DRC* assessments at the latest evaluable time point (EOT, or 2, 6, or 12 weeks after EOT) voriconazole and the regimen of amphotericin B followed by fluconazole had successful response rates of 65% and 71%, respectively. The Investigator's assessment of successful outcome at each of these time points is shown in the following table.

Timepoint	*Voriconazole (N=248)*	*Amphotericin B → fluconazole (N=122)*
EOT	***178 (72%)***	***88 (72%)***
2 weeks after EOT	***125 (50%)***	***62 (51%)***
6 weeks after EOT	***104 (42%)***	***55 (45%)***
12 weeks after EOT	***104 (42%)***	***51 (42%)***

There are no data in children below the age of 12 years for this indication.

Serious refractory *Candida* infections
The study comprised 55 patients with serious refractory systemic *Candida* infections (including candidaemia, 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.

Scedosporium and *Fusarium* infections
Voriconazole was shown to be effective against the following rare fungal pathogens:

Scedosporium spp.: Successful response to voriconazole therapy was seen in 16 (6 complete, 10 partial responses) of 28 patients with *S. apiospermum* and in 2 (both partial responses) of 7 patients with *S. prolificans* infection. In addition, a successful response was seen in 1 of 3 patients with infections caused by more than one organism including *Scedosporium* spp.

Fusarium spp.: Seven (3 complete, 4 partial responses) of 17 patients were successfully treated with voriconazole. Of these 7 patients, 3 had eye, 1 had sinus, and 3 had disseminated infection. Four additional patients with fusariosis had an infection caused by several organisms; two of them had a successful outcome.

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
In clinical trials, 561 patients received voriconazole therapy for greater than 12 weeks, with 136 patients receiving voriconazole for over 6 months.

Experience in paediatric patients
Sixty one paediatric patients aged 9 months up to 15 years who had definite or probable invasive fungal infections, were treated with voriconazole. This population included 34 patients 2 to < 12 years old and 20 patients 12-15 years of age.

The majority (57/61) had failed previous antifungal therapies. Therapeutic studies included 5 patients aged 12-15 years, the remaining patients received voriconazole in the compassionate use programmes. Underlying diseases in these patients included haematological malignancies and aplastic anaemia (27 patients) and chronic granulomatous disease (14 patients). The most commonly treated fungal infection was aspergillosis (43/61; 70 %).

Clinical Studies Examining QT Interval
A placebo-controlled, randomized, single-dose, crossover study to evaluate the effect on the QT interval of healthy volunteers was conducted with three oral doses of voriconazole and ketoconazole. The placebo-adjusted mean maximum increases in QTc from baseline after 800, 1200 and 1600 mg of voriconazole were 5.1, 4.8, and 8.2 msec, respectively and 7.0 msec for ketoconazole 800 mg. 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 500msec.

5.2 Pharmacokinetic properties

General pharmacokinetic characteristics
The pharmacokinetics of voriconazole have been characterised in healthy subjects, special populations and patients. During oral administration of 200mg or 300mg twice daily for 14 days in patients at risk of aspergillosis (mainly patients with malignant neoplasms of lymphatic or haematopoietic tissue), the observed pharmacokinetic characteristics of rapid and consistent absorption, accumulation and non-linear pharmacokinetics were in agreement with those observed in healthy subjects.

The pharmacokinetics of voriconazole are non-linear due to saturation of its metabolism. Greater than proportional increase in exposure is observed with increasing dose. It is estimated that, on average, increasing the oral dose from 200mg twice daily to 300mg twice daily leads to a 2.5-fold increase in exposure (AUCτ). When the recommended intravenous or oral loading dose regimens are administered, 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 plasma voriconazole concentrations being achieved by day 6 in the majority of subjects.

Absorption
Voriconazole is rapidly and almost completely absorbed following oral administration, with maximum plasma concentrations (C_{max}) achieved 1-2 hours after dosing. The absolute bioavailability of voriconazole after oral administration is estimated to be 96%. When multiple doses of voriconazole are administered with high fat meals, C_{max} and AUC_{τ} are reduced by 34% and 24%, respectively. The absorption of voriconazole is not affected by changes in gastric pH.

Distribution
The volume of distribution at steady state for voriconazole is estimated to be 4.6l/kg, suggesting extensive distribution into tissues. Plasma protein binding is estimated to be 58%.
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 hepatic cytochrome P450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4.

The inter-individual variability of voriconazole pharmacokinetics is high.

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. This metabolite has minimal antifungal activity and 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 radiolabelled dose of voriconazole, approximately 80% of the radioactivity is recovered in the urine after multiple intravenous dosing and 83% in the urine after multiple oral

dosing. The majority (> 94%) of the total radioactivity is excreted in the first 96 hours after both oral and intravenous dosing.

The terminal half-life of voriconazole depends on dose and is approximately 6 hours at 200mg (orally). Because of non-linear pharmacokinetics, the terminal half-life is not useful in the prediction of the accumulation or elimination of voriconazole.

Pharmacokinetic-Pharmacodynamic relationships
In 10 therapeutic studies, the median for the average and maximum plasma concentrations in individual subjects across the studies was 2425ng/ml (inter-quartile range 1193 to 4380ng/ml) and 3742ng/ml (inter-quartile range 2027 to 6302ng/ml), respectively. A positive association between mean, maximum or minimum plasma voriconazole concentration and efficacy in therapeutic studies was not found.

Pharmacokinetic-Pharmacodynamic analyses of clinical trial data identified positive associations between plasma voriconazole concentrations and both liver function test abnormalities and visual disturbances.

Pharmacokinetics in special patient groups

Gender
In an oral multiple dose study, 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 C_{max} and AUC_{τ} were observed between healthy elderly males and healthy elderly females (≥ 65 years).

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

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

In the therapeutic studies no dosage adjustment was made on the basis of age. A relationship between plasma concentrations and age was observed. The safety profile of voriconazole in young and elderly patients was similar and, therefore, no dosage adjustment is necessary for the elderly (see section 4.2).

Renal impairment
In an oral single dose (200mg) study in subjects with normal renal function and mild (creatinine clearance 41-60ml/min) to severe (creatinine clearance <20 ml/min) renal impairment, the pharmacokinetics of voriconazole were not significantly affected by renal impairment. The plasma protein binding of voriconazole was similar in subjects with different degrees of renal impairment. See dosing and monitoring recommendations under sections 4.2 and 4.4.

Hepatic impairment
After an oral single dose (200mg), AUC was 233% higher in subjects with mild to moderate hepatic cirrhosis (Child-Pugh A and B) compared with subjects with normal hepatic function. Protein binding of voriconazole was not affected by impaired hepatic function.

In an oral multiple dose study, AUC_{τ} was similar in subjects with moderate hepatic cirrhosis (Child-Pugh B) given a maintenance dose of 100mg twice daily and subjects with normal hepatic function given 200mg twice daily. No pharmacokinetic data are available for patients with severe hepatic cirrhosis (Child-Pugh C). See dosing and monitoring recommendations under sections 4.2 and 4.4.

5.3 Preclinical safety data

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 postnatal development study in rats at exposures lower than those obtained in humans with therapeutic doses, voriconazole prolonged the duration of gestation and labour 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 oestradiol levels, and are consistent with those observed with other azole antifungal agents.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose Monohydrate
Pregelatinised Starch
Croscarmellose Sodium
Povidone
Magnesium Stearate

Film-coat:
Hypromellose
Titanium Dioxide (E171)
Lactose Monohydrate
Glycerol Triacetate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

HDPE tablet containers of 2, 30 and 100. Not all bottle sizes may be marketed.
PVC / Aluminium blister in cartons of 2, 10, 14, 20, 28, 30, 50, 56 and 100.
Not all pack sizes may be marketed.

6.6 Instructions for use and handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ, United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/212/001-012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 March 2002

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

VFEND 200mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200mg voriconazole.
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White, capsule-shaped tablets, debossed “Pfizer” on one side and “VOR200”on the reverse.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VFEND, voriconazole, is a broad spectrum, triazole antifungal agent and is indicated as follows:

Treatment of invasive aspergillosis.

Treatment of candidemia in non-neutropenic patients

Treatment of fluconazole-resistant serious invasive *Candida* infections (including *C. krusei*).

Treatment of serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp.

VFEND should be administered primarily to patients with progressive, possibly life-threatening infections.

4.2 Posology and method of administration

VFEND film-coated tablets are to be taken at least one hour before, or one hour following, a meal.

Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy (see Section 4.4).

VFEND is also available as 50mg film-coated tablets, 200mg powder for solution for infusion and 40mg/ml powder for oral suspension.

Use in adults
Therapy must be initiated with the specified loading dose regimen of either intravenous or oral VFEND to achieve plasma concentrations on Day 1 that are close to steady state. On the basis of the high oral bioavailability (96%; see section 5.2), switching between intravenous and oral administration is appropriate when clinically indicated.

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

	Intravenous	**Oral**	
		Patients 40kg and above	Patients less than 40kg
Loading Dose Regimen (first 24 hours)	6mg/kg every 12 hours (for the first 24 hours)	400mg every 12 hours (for the first 24 hours)	200mg every 12 hours (for the first 24 hours)
Maintenance Dose (after first 24 hours)	4mg/kg twice daily	200mg twice daily	100mg twice daily

Dosage adjustment
If patient response is inadequate, the maintenance dose may be increased to 300mg twice daily for oral administration. For patients less than 40kg the oral dose may be increased to 150mg twice daily.

If patients are unable to tolerate treatment at these higher doses reduce the oral dose by 50 mg steps to the 200mg twice daily (or 100mg twice daily for patients less than 40kg) maintenance dose.

Phenytoin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased from 200 mg to 400 mg orally, twice daily (100mg to 200mg orally, twice daily in patients less than 40kg), see sections 4.4 and 4.5.

Rifabutin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased from 200mg to 350mg orally, twice daily (100mg to 200mg orally, twice daily in patients less than 40kg), see sections 4.4 and 4.5.

Treatment duration depends upon patients' clinical and mycological response.

Use in the elderly
No dose adjustment is necessary for elderly patients (see section5.2).

Use in patients with renal impairment
The pharmacokinetics of orally administered voriconazole are not affected by renal impairment. Therefore, no adjustment is necessary for oral dosing for patients with mild to severe renal impairment (see section5.2).

Voriconazole is haemodialysed with a clearance of 121ml/min. A four hour haemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment.

Use in patients with hepatic impairment
No dose adjustment is necessary in patients with acute hepatic injury, manifested by elevated liver function tests (ALAT, ASAT) (but continued monitoring of liver function tests for further elevations is recommended).

It is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B) receiving VFEND (see section5.2).

VFEND has not been studied in patients with severe chronic hepatic cirrhosis (Child-Pugh C).

VFEND has been associated with elevations in liver function tests and clinical signs of liver damage, such as jaundice, and must only be used in patients with severe hepatic impairment if the benefit outweighs the potential risk. Patients with hepatic impairment must be carefully monitored for drug toxicity (see also section 4.8).

Use in children
Safety and effectiveness in paediatric subjects below the age of 2 years has not been established (see also section 5.1). Therefore voriconazole is not recommended for children less than 2 years of age. Limited data are currently available to determine the optimal posology. However, the following regimen has been used in paediatric studies.

Children aged 2 to < 12 years:

	Intravenous	**Oral**
Loading Dose Regimen (first 24 hours)	6mg/kg every 12 hours (for the first 24 hours)	6mg/kg every 12 hours (for the first 24 hours)
Maintenance Dose (after first 24 hours)	4mg/kg twice daily	4mg/kg twice daily

If a child is able to swallow tablets, the dose should be administered to the nearest mg/kg dose possible using whole 50mg tablets.

The pharmacokinetics and tolerability of higher doses have not been characterised in paediatric populations.

Adolescents (12 to 16 years of age): should be dosed as adults.

4.3 Contraindications

VFEND is contraindicated in patients with known hypersensitivity to voriconazole or to any of the excipients.

Coadministration of the CYP3A4 substrates, terfenadine, astemizole, cisapride, pimozide or quinidine with VFEND is contraindicated since increased plasma concentrations of these medicinal products can lead to QTc prolongation and rare occurrences of *torsades de pointes* (see section 4.5).

Coadministration of VFEND with rifampicin, carbamazepine and phenobarbital is contraindicated since these medicinal products are likely to decrease plasma voriconazole concentrations significantly (see section 4.5).

Coadministration of VFEND with efavirenz is contraindicated because efavirenz significantly decreases voriconazole plasma concentrations while VFEND also significantly increases efavirenz plasma concentrations (see section 4.5)

Coadministration of VFEND with ritonavir (400mg and above twice daily) is contraindicated because ritonavir significantly decreases plasma voriconazole concentrations in healthy subjects (see section 4.5).

Coadministration of ergot alkaloids (ergotamine, dihydroergotamine), which are CYP3A4 substrates, is contraindicated since increased plasma concentrations of these medicinal products can lead to ergotism (see section 4.5).

Coadministration of voriconazole and sirolimus is contraindicated, since voriconazole is likely to increase plasma concentrations of sirolimus significantly (see section 4.5).

4.4 Special warnings and special precautions for use

Hypersensitivity: Caution should be used in prescribing VFEND to patients with hypersensitivity to other azoles (see also section 4.8).

Cardiovascular:
Some azoles, including voriconazole have been associated with QT interval prolongation. There have been rare cases of torsade de pointes in patients taking voriconazole who had risk factors, such as history of cardiotoxic chemotherapy, cardiomyopathy, hypokalaemia 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

Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy (see section 4.2). 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 experienced an interval exceeding the potentially clinically relevant threshold of 500 msec (see section 5.1).

Hepatic toxicity: In clinical trials, there have been uncommon cases of serious hepatic reactions during treatment with VFEND (including clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities). Instances of hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly haematological malignancy). Transient 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 section 4.8).

Monitoring of hepatic function: Patients at the beginning of therapy with voriconazole and patients who develop abnormal liver function tests during VFEND therapy must be routinely monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of VFEND should be considered if clinical signs and symptoms are consistent with liver disease development.

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 (see section 4.8).

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

Dermatological reactions: Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome, during treatment with VFEND. If patients develop a rash they should be monitored closely and VFEND discontinued if lesions progress. In addition VFEND has been associated with photosensitivity skin reaction especially during long term therapy. It is recommended that patients should be informed to avoid sunlight during the treatment.

Paediatric use: Safety and effectiveness in paediatric subjects below the age of two years has not been established (see also section 5.1).

Phenytoin (CYP2C9 substrate and potent CYP450 inducer): Careful monitoring of phenytoin levels is recommended when phenytoin is coadministered with voriconazole. Concomitant use of voriconazole and phenytoin should be avoided unless the benefit outweighs the risk (see section 4.5).

Rifabutin (CYP450 inducer): Careful monitoring of full blood counts and adverse events to rifabutin (e.g. uveitis) is recommended when rifabutin is coadministered with voriconazole. Concomitant use of voriconazole and rifabutin should be avoided unless the benefit outweighs the risk (see section 4.5).
Methadone (CYP3A4 substrate). Frequent monitoring for adverse events and toxicity related to methadone, including QTc prolongation, is recommended when coadministered with

voriconazole since methadone levels increased following co-administration of voriconazole. Dose reduction of methadone may be needed (see section 4.5).

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.

4.5 Interaction with other medicinal products and other forms of interaction

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

This section addresses the effects of other medicinal products on voriconazole, the effects of voriconazole on other medicinal products and two-way interactions. The interactions for the first two sections are presented in the following order: contraindications, those requiring dosage 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.

Effects of other medicinal products on voriconazole

Voriconazole is metabolised by cytochrome P450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4. Inhibitors or inducers of these isoenzymes may increase or decrease voriconazole plasma concentrations respectively.

Rifampicin (CYP450 inducer): Rifampicin (600mg once daily) decreased the C_{max} (maximum plasma concentration) and AUC_{τ} (area under the plasma concentration time curve within a dose interval) of voriconazole by 93% and 96%, respectively. Coadministration of voriconazole and rifampicin is contraindicated (see section 4.3)**.**

Ritonavir (potent CYP450 inducer; CYP3A4 inhibitor and substrate): Ritonavir (400mg twice daily) decreased the steady state C_{max} and AUC_{τ} of oral voriconazole by an average of 66% and 82%, respectively, in healthy subjects with the exception of one subject in whom a 2.5 fold increases in AUC_{τ} was observed. No extrapolation can be made for ritonavir doses lower than 400mg. Repeat oral administration of voriconazole did not have a significant effect on steady state C_{max} and AUC_{τ} of ritonavir following repeat dose administration in healthy subjects. Coadministration of voriconazole and ritonavir (400mg and above twice daily) is contraindicated (see section 4.3).

Carbamazepine and phenobarbital (potent CYP450 inducers): Although not studied, carbamazepine or phenobarbital are likely to significantly decrease plasma voriconazole concentrations. Coadministration of voriconazole with carbamazepine and phenobarbital is contraindicated (see section 4.3).

Cimetidine (non-specific CYP450 inhibitor and increases gastric pH): Cimetidine (400mg twice daily) increased voriconazole C_{max} and AUC_{τ} by 18 % and 23 %, respectively. No dosage adjustment of voriconazole is recommended.

Ranitidine (increases gastric pH): Ranitidine (150mg twice daily) had no significant effect on voriconazole C_{max} and AUC_{τ}.

Macrolide antibiotics: Erythromycin (CYP3A4 inhibitor; 1g twice daily) and azithromycin (500mg once daily) had no significant effect on voriconazole C_{max} and AUC_{τ}.

Effects of voriconazole on other medicinal products

Voriconazole inhibits the activity of cytochrome P450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4. Therefore there is potential for voriconazole to increase the plasma levels of substances metabolised by these CYP450 isoenzymes.

Terfenadine, astemizole, cisapride, pimozide and quinidine (CYP3A4 substrates): Although not studied, coadministration of voriconazole with terfenadine, astemizole, cisapride, pimozide, or quinidine is contraindicated, since increased plasma concentrations of these medicinal products can lead to QTc prolongation and rare occurrences of *torsades de pointes* (see section 4.3).

Sirolimus (CYP3A4 substrate): Voriconazole increased sirolimus (2mg single dose) C_{max} and AUC_{τ} by 556% and 1014%, respectively. Coadministration of voriconazole and sirolimus is contraindicated (see section 4.3).

Ergot alkaloids (CYP3A4 substrates): Although not studied, voriconazole may increase the plasma concentrations of ergot alkaloids (ergotamine and dihydroergotamine) and lead to ergotism. Coadministration of voriconazole with ergot alkaloids is contraindicated (see section 4.3).

Cyclosporin (CYP3A4 substrate): In stable, renal transplant recipients, voriconazole increased cyclosporin C_{max} and AUC_{τ} by at least 13 % and 70 % respectively. When initiating voriconazole in patients already receiving cyclosporin it is recommended that the cyclosporin dose be halved and cyclosporin level carefully monitored. Increased cyclosporin levels have been associated with nephrotoxicity. When voriconazole is discontinued, cyclosporin levels must be carefully monitored and the dose increased as necessary.

Methadone (CYP3A4 substrate): In subjects receiving a methadone maintenance dose (32-100mg once daily) coadministration of oral voriconazole (400mg twice daily for 1 day, then 200mg twice daily for four days) increased the C_{max} and AUC_{τ} of pharmacologically active R-methadone by 31% and 47%, respectively, whereas the C_{max} and AUC_{τ} of the S-enantiomer increased by approximately 65% and 103%, respectively. Voriconazole plasma concentrations during coadministration of methadone were comparable to voriconazole levels (historical data) in healthy subjects without any comedication. Frequent monitoring for adverse events and toxicity related to increased plasma concentrations of methadone, including QT prolongation, is recommended during coadministration. Dose reduction of methadone may be needed.

Tacrolimus (CYP3A4 substrate): Voriconazole increased tacrolimus (0.1mg/kg single dose) C_{max} and AUC_t (area under the plasma concentration time curve to the last quantifiable measurement) by 117 % and 221%, respectively. When initiating voriconazole in patients already receiving 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.

Oral anticoagulants:
Warfarin (CYP2C9 substrate): Coadministration of voriconazole (300mg twice daily) with warfarin (30mg single dose) increased maximum prothrombin time by 93%. Close monitoring of prothrombin time is recommended if warfarin and voriconazole are coadministered.
Other oral anticoagulants e.g. phenprocoumon, acenocoumarol (CYP2C9, CYP3A4 substrates): Although not studied, voriconazole may increase the plasma concentrations of coumarins and therefore may cause an increase in prothrombin time. If patients receiving coumarin preparations are treated simultaneously with voriconazole, the prothrombin time should be monitored at close intervals and the dosage of anticoagulants adjusted accordingly.

Sulphonylureas (CYP2C9 substrates): Although not studied, voriconazole may increase the plasma levels of sulphonylureas, (e.g. tolbutamide, glipizide, and glyburide) and therefore cause hypoglycaemia. Careful monitoring of blood glucose is recommended during coadministration.

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

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

Vinca Alkaloids (CYP3A4 substrates): Although not studied, voriconazole may increase the plasma levels of the vinca alkaloids (e.g. vincristine and vinblastine) and lead to neurotoxicity.

Prednisolone (CYP3A4 substrate): Voriconazole increased C_{max} and AUC_{τ} of prednisolone (60 mg single dose) by 11% and 34%, respectively. No dosage adjustment is recommended.

Digoxin (P-glycoprotein mediated transport): Voriconazole had no significant effect on C_{max} and AUC_{τ} of digoxin (0.25mg once daily).

Mycophenolic acid (UDP-glucuronyl transferase substrate): Voriconazole had no effect on the C_{max} and AUC_{t} of mycophenolic acid (1g single dose).

Two-way interactions

Phenytoin (CYP2C9 substrate and potent CYP450 inducer): Concomitant use of voricoazole and phenytoin should be avoided unless the benefit outweighs the risk.
Phenytoin (300mg once daily) decreased the C_{max} and AUC_{τ} of voriconazole by 49% and 69%, respectively. Voriconazole (400mg twice daily, see section 4.2) increased C_{max} and AUC_{τ} of phenytoin (300 mg once daily) by 67% and 81%, respectively. Careful monitoring of phenytoin plasma levels is recommended when phenytoin is coadministered with voriconazole.

Phenytoin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased to 5mg /kg intravenously twice daily or from 200mg to 400mg orally, twice daily (100mg to 200mg orally, twice daily in patients less than 40kg), see section 4.2.

Rifabutin (CYP450 inducer): Concomitant use of voriconazole and rifabutin should be avoided unless the benefit outweighs the risk.
Rifabutin (300mg once daily) decreased the C_{max} and AUC_{τ} of voriconazole at 200 mg twice daily by 69% and 78%, respectively. During coadministration with rifabutin, the C_{max} and AUC_{τ} of voriconazole at 350mg twice daily were 96% and 68% of the levels when administered alone at 200mg twice daily. At a voriconazole dose of 400mg twice daily C_{max} and AUC_{τ} were 104% and 87% higher, respectively, compared with voriconazole alone at 200mg twice daily. Voriconazole at 400mg twice daily increased C_{max} and AUC_{τ} of rifabutin by 195% and 331%, respectively.

If rifabutin coadministration with voriconazole is justified then the maintenance dose of voriconazole may be increased to 5mg/kg intravenously twice daily or from 200mg to 350mg orally, twice daily (100mg to 200mg orally, twice daily in patients less than 40kg) (see section 4.2). Careful monitoring of full blood counts and adverse events to rifabutin (e.g. uveitis) is recommended when rifabutin is coadministered with voriconazole.

Omeprazole (CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate): Omeprazole (40mg once daily) increased voriconazole C_{max} and AUC_{τ} by 15% and 41%, respectively. No dosage adjustment of voriconazole is recommended. Voriconazole increased omeprazole C_{max} and AUC_{τ} by 116% and 280%, respectively. When initiating voriconazole in patients already receiving omeprazole, it is

recommended that the omeprazole dose be halved. The metabolism of other proton pump inhibitors which are CYP2C19 substrates may also be inhibited by voriconazole.

Indinavir (CYP3A4 inhibitor and substrate): Indinavir (800mg three times daily) had no significant effect on voriconazole C_{max}, C_{min} and AUC_{τ}.
Voriconazole did not have a significant effect on C_{max} and AUC_{τ} of indinavir (800mg three times daily).

Efavirenz (a non-nucleoside reverse transcriptase inhibitor (CYP450 inducer; CYP3A4 inhibitor and substrate)): Steady-state efavirenz (400mg orally once daily) decreased the steady state Cmax and AUCτ of voriconazole by an average of 61% and 77%, respectively, in healthy subjects. In the same study voriconazole at steady state increased the steady state Cmax and AUCτ of efavirenz by an average of 38% and 44% respectively, in healthy subjects. Coadministration of voriconazole and efavirenz is contraindicated (see section 4.3).

Other HIV protease inhibitors (CYP3A4 inhibitors): *In vitro* studies suggest that voriconazole may inhibit the metabolism of HIV protease inhibitors (e.g. saquinavir, amprenavir and nelfinavir*). In vitro* studies also show that the metabolism of voriconazole may be inhibited by HIV protease inhibitors. However results of the combination of voriconazole with other HIV protease inhibitors cannot be predicted in humans only from *in vitro* studies. Patients should be carefully monitored for any occurrence of drug toxicity and/or loss of efficacy during the co-administration of voriconazole and HIV protease inhibitors.

Non-nucleoside reverse transcriptase inhibitors (NNRTI) (CYP3A4 substrates, inhibitors or CYP450 inducers): *In vitro* studies show that the metabolism of voriconazole may be inhibited by delavirdine. Although not studied, the metabolism of voriconazole may be induced by nevirapine. An in-vivo study showed that voriconazole inhibited the metabolism of efavirenz. Voriconazole may also inhibit the metabolism of NNRTIs besides efavirenz. Patients should be carefully monitored for any occurrence of drug toxicity and/or lack of efficacy during the coadministration of voriconazole and NNRTIs. Coadministration of voriconazole with efavirenz is contraindicated (see section 4.3)

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 levels of substances metabolised by CYP3A4 isoenzymes (certain antihistamines, quinidine, cisapride, pimozide) co-administration is contraindicated (see section 4.3).

4.6 Pregnancy and lactation

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

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk to humans is unknown.

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

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

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

4.7 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.

4.8 Undesirable effects

The safety profile of voriconazole is based on an integrated safety database of more than 2000 subjects (1655 patients in therapeutic trials). This represents a heterogeneous population, containing patients with haematological malignancy, HIV infected patients with oesophageal candidiasis and refractory fungal infections, non-neutropenic patients with candidaemia or aspergillosis and healthy volunteers. Five hundred and sixty one patients had a duration of voriconazole therapy of greater than 12 weeks, with 136 patients receiving voriconazole for over 6 months.

In the table below, since the majority of the studies were of an open nature all causality adverse events, by system organ class and frequency (very common >1/10, common >1/100 and <1/10, uncommon >1/1000 and <1/100 and rare, <1/1000) if possibly causally related are listed. The most commonly reported adverse events were visual disturbances, fever, rash, vomiting, nausea, diarrhoea, headache, peripheral oedema 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 analysed by age, race, or gender.

Undesirable effects reported in subjects receiving voriconazole

Body System	**Adverse Drug Reactions**
Body as a whole	
Very common	Fever, headache, abdominal pain
Common	Chills, asthenia, back pain, chest pain, injection site reaction/inflammation, face oedema, flu syndrome
Uncommon	Allergic reaction, anaphylactoid reaction, angioedema, peritonitis
Cardiovascular	
Common	Hypotension, thrombophlebitis, phlebitis
Uncommon	Atrial arrhythmia, bradycardia, syncope, tachycardia, ventricular arrhythmia, ventricular fibrillation, supraventricular tachycardia, QT interval prolongation
Rare	AV complete block, bundle branch block, nodal arrhythmia, ventricular tachycardia, torsade de pointes
Digestive	
Very common	Nausea, vomiting, diarrhoea
Common	Elevated liver function tests (includingASAT, ALAT, alkaline phosphatase, GGT, LDH, bilirubin), jaundice, cheilitis, cholestatic jaundice, gastroenteritis
Uncommon	Cholecystitis, cholelithiasis, constipation, duodenitis, dyspepsia, enlarged liver, gingivitis, glossitis, hepatitis, hepatic failure, pancreatitis, tongue oedema
Rare	Pseudomembranous colitis, hepatic coma
Endocrine	
Uncommon	Adrenal cortex insufficiency
Haemic and lymphatic	
Common	Thrombocytopenia, anaemia (including macrocytic, microcytic, normocytic, megaloblastic, aplastic), leukopenia, pancytopenia, purpura
Uncommon	Lymphadenopathy, agranulocytosis, eosinophilia, disseminated intravascular coagulation, marrow depression
Rare	Lymphangitis
Metabolic and nutritional	
Very common	Peripheral oedema
Common	Hypokalaemia, creatinine increased, hypoglycaemia
Uncommon	BUN increased, albuminuria, hypercholesterolaemia
Rare	Hyperthyroidism, hypothyroidism
Musculoskeletal	

Uncommon	Arthritis
Nervous	
Common	Dizziness, hallucinations, confusion, depression, anxiety, tremor, agitation, paraesthesia
Uncommon	Ataxia, brain oedema, diplopia, hypoaesthesia, nystagmus, vertigo
Rare	Guillain-Barre syndrome, oculogyric crisis, hypertonia, Extrapyramidal syndrome, insomnia, encephalopathy, somnolence during infusion
Respiratory	
Common	Respiratory distress syndrome, lung oedema, sinusitis
Skin and appendages	
Very common	Rash
Common	Pruritus, maculopapular rash, photosensitivity skin reaction, alopecia, exfoliative dermatitis
Uncommon	Fixed drug eruption, eczema, psoriasis, Stevens-Johnson syndrome, urticaria
Rare	Discoid lupus erythematosis, erythema multiforme, toxic epidermal necrolysis
Special senses	
Very Common	Visual disturbances (including altered/enhanced visual perception, decrease in ERG amplitude, blurred vision, colour vision change, photophobia)
Uncommon	Blepharitis, optic neuritis, papilloedema, scleritis, altered taste perception
Rare	Retinal haemorrhage, corneal opacity, optic atrophy, hypoacusis, tinnitus
Urogenital	
Common	Acute kidney failure, haematuria
Uncommon	Nephritis
Rare	Kidney tubular necrosis

Visual disturbances

Voriconazole treatment-related visual disturbances were very common. In clinical trials, short-term as well as long-term treatment, approximately 30% of subjects experienced altered/enhanced visual perception, blurred vision, colour vision change or photophobia. The visual disturbances are transient and fully reversible, with the majority spontaneously resolving within 60 minutes and no clinically significant long-term visual effects were observed. There is evidence of attenuation with repeated doses of voriconazole. The visual disturbance is generally mild, rarely results in discontinuation and has not been associated with long-term sequelae. Visual disturbances may be associated with higher plasma concentrations and/or doses.

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 treatment and were fully reversible on withdrawal of voriconazole.

Dermatological reactions

Dermatological reactions were 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 rarely developed serious cutaneous reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme during treatment with VFEND.

If patients develop a rash they should be monitored closely and VFEND discontinued if lesions progress. Photosensitivity reactions have been reported, especially during long-term therapy (see also section 4.4).

Liver Function Tests

The overall incidence of clinically significant transaminase abnormalities in the voriconazole clinical programme was 13.4% (200/1493) of subjects treated with voriconazole. Liver function test abnormalities may be associated with higher plasma concentrations and/or doses. The majority of

abnormal liver function tests either resolved during treatment without dose adjustment or following dose adjustment, including discontinuation of therapy.

Voriconazole has been infrequently associated with cases of serious hepatic toxicity in patients with other serious underlying conditions. This includes cases of jaundice, and rare cases of hepatitis and hepatic failure leading to death (see section 4.4).

4.9 Overdose

In clinical trials there were 3 cases of accidental overdose. All occurred in paediatric patients, who received up to five times the recommended intravenous dose of voriconazole. A single adverse event of photophobia of 10 minutes duration was reported.

There is no known antidote to voriconazole.

Voriconazole is haemodialysed with a clearance of 121ml/min. In an overdose, haemodialysis may assist in the removal of voriconazole from the body.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC code: J02A C03
Antimycotics for Systemic Use – Triazole derivatives

Mechanism of action

I*n 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*) and fungicidal activity against all *Aspergillus* species tested. In addition voriconazole shows *in vitro* fungicidal activity against emerging fungal pathogens, including those such as *Scedosporium* or *Fusarium* which have limited susceptibility to existing antifungal agents. Its mode of action is inhibition of fungal cytochrome P450-mediated 14α-sterol demethylation, an essential step in ergosterol biosynthesis.

In animal studies there is a correlation between minimum inhibitory concentration values and efficacy against experimental mycoses. By contrast, in clinical studies, there appears to be no correlation between minimum inhibitory concentration values and clinical outcome. Furthermore, there does not appear to be a correlation between plasma levels and clinical outcome. This is typical of azole antimycotics.

Microbiology

Clinical efficacy (with partial or complete response, see below under Clinical Experience) has been demonstrated for *Aspergillus* spp. including *A. flavus, A. fumigatus, A. terreus, A. niger, A. nidulans, Candida* spp.*,* including *C. albicans, C. glabrata, C. krusei, C. parapsilosis and C. tropicalis* and limited numbers of *C. dubliniensis, C. inconspicua,* and *C. guilliermondii, Scedosporium* spp., including *S. apiospermum, S. prolificans and Fusarium* spp.

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 2µg/ml.

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

Specimens for fungal culture and other relevant laboratory studies (serology, histopathology) should be obtained prior to therapy to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.

Clinical isolates with decreased susceptibility to voriconazole have been identified. However, elevated minimum inhibitory concentrations did not always correlate with clinical failure and clinical success has been observed in patients infected with organisms resistant to other azoles. Correlation of *in vitro* activity with clinical outcome is difficult owing to the complexity of the patients studied in clinical trials; breakpoints for voriconazole remain to be established.

Clinical Experience

Succesful outcome in this section is defined as complete or partial response.

Aspergillus infections – efficacy in aspergillosis patients with poor prognosis
Voriconazole has *in vitro* fungicidal activity against *Aspergillus* spp. The efficacy and survival benefit of voriconazole versus conventional amphotericin B in the primary treatment of acute invasive aspergillosis was demonstrated in an open, randomised, multicentre study in 277 immunocompromised patients treated for 12 weeks. A satisfactory global response (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 31% of patients treated with comparator. The 84-day survival rate for voriconazole was statistically significantly higher than that for the comparator and a clinically and statistically significant benefit was shown in favour of voriconazole for both time to death and time to discontinuation due to toxicity.

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).

The studies included cerebral, sinus, pulmonary and disseminated aspergillosis in patients with bone marrow and solid organ transplants, haematological malignancies, cancer and AIDS.

Candidaemia in non-neutropenic patients.

The efficacy of voriconazole compared to the regimen of amphotericin B followed by fluconazole in the primary treatment of candidaemia was demonstrated in an open, comparative study. Three hundred and seventy non-neutropenic patients (above 12 years of age) with documented candidaemia were included in the study, of whom 248 were treated with voriconazole. Nine subjects in the voriconazole group and five in the amphotericin B followed by fluconazole group also had mycologically proven infection in deep tissue. Patients with renal failure were excluded from this study. The median treatment duration was 15 days in both treatment arms. In the primary analysis, successful response as assessed by a Data Review Committee (DRC) blinded to study medication was defined as resolution/improvement in all clinical signs and symptoms of infection with eradication of *Candida* from blood and infected deep tissue sites at 12 weeks after the end of therapy (EOT). Patients who did not have an assessment 12 weeks after EOT were counted as failures. In this analysis a successful response was seen in 41% of patients in both treatment arms.

In a secondary analysis, which utilised *DRC* assessments at the latest evaluable time point (EOT, or 2, 6, or 12 weeks after EOT) voriconazole and the regimen of amphotericin B followed by fluconazole

had successful response rates of 65% and 71%, respectively. The Investigator's assessment of successful outcome at each of these time points is shown in the following table.

Timepoint	***Voriconazole (N=248)***	***Amphotericin B → fluconazole (N=122)***
EOT	***178 (72%)***	***88 (72%)***
2 weeks after EOT	***125 (50%)***	***62 (51%)***
6 weeks after EOT	***104 (42%)***	***55 (45%)***
12 weeks after EOT	***104 (42%)***	***51 (42%)***

There are no data in children below the age of 12 years for this indication.

Serious refractory *Candida* infections
The study comprised 55 patients with serious refractory systemic *Candida* infections (including candidaemia, 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.

Scedosporium and *Fusarium* infections
Voriconazole was shown to be effective against the following rare fungal pathogens:

Scedosporium spp.: Successful response to voriconazole therapy was seen in 16 (6 complete, 10 partial responses) of 28 patients with *S. apiospermum* and in 2 (both partial responses) of 7 patients with *S. prolificans* infection. In addition, a successful response was seen in 1 of 3 patients with infections caused by more than one organism including *Scedosporium* spp.

Fusarium spp.: Seven (3 complete, 4 partial responses) of 17 patients were successfully treated with voriconazole. Of these 7 patients, 3 had eye, 1 had sinus, and 3 had disseminated infection. Four additional patients with fusariosis had an infection caused by several organisms; two of them had a successful outcome.

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
In clinical trials, 561 patients received voriconazole therapy for greater than 12 weeks, with 136 patients receiving voriconazole for over 6 months.

Experience in paediatric patients
Sixty one paediatric patients aged 9 months up to 15 years who had definite or probable invasive fungal infections, were treated with voriconazole. This population included 34 patients 2 to < 12 years old and 20 patients 12-15 years of age.

The majority (57/61) had failed previous antifungal therapies. Therapeutic studies included 5 patients aged 12-15 years, the remaining patients received voriconazole in the compassionate use programmes. Underlying diseases in these patients included haematological malignancies and aplastic anaemia (27 patients) and chronic granulomatous disease (14 patients). The most commonly treated fungal infection was aspergillosis (43/61; 70%).

Clinical Studies Examining QT Interval

A placebo-controlled, randomized, single-dose, crossover study to evaluate the effect on the QT interval of healthy volunteers was conducted with three oral doses of voriconazole and ketoconazole.

The placebo-adjusted mean maximum increases in QTc from baseline after 800, 1200 and 1600mg of voriconazole were 5.1, 4.8, and 8.2msec, respectively and 7.0msec for ketoconazole 800mg. No subject in any group had an increase in QTc of ≥60msec from baseline. No subject experienced an interval exceeding the potentially clinically relevant threshold of 500msec.

5.2 Pharmacokinetic properties

General pharmacokinetic characteristics
The pharmacokinetics of voriconazole have been characterised in healthy subjects, special populations and patients. During oral administration of 200mg or 300mg twice daily for 14 days in patients at risk of aspergillosis (mainly patients with malignant neoplasms of lymphatic or haematopoietic tissue), the observed pharmacokinetic characteristics of rapid and consistent absorption, accumulation and non-linear pharmacokinetics were in agreement with those observed in healthy subjects.

The pharmacokinetics of voriconazole are non-linear due to saturation of its metabolism. Greater than proportional increase in exposure is observed with increasing dose. It is estimated that, on average, increasing the oral dose from 200mg twice daily to 300mg twice daily leads to a 2.5-fold increase in exposure (AUCτ). When the recommended intravenous or oral loading dose regimens are administered, 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 plasma voriconazole concentrations being achieved by day 6 in the majority of subjects.

Absorption
Voriconazole is rapidly and almost completely absorbed following oral administration, with maximum plasma concentrations (C_{max}) achieved 1-2 hours after dosing. The absolute bioavailability of voriconazole after oral administration is estimated to be 96%. When multiple doses of voriconazole are administered with high fat meals, C_{max} and AUC_{τ} are reduced by 34% and 24%, respectively. The absorption of voriconazole is not affected by changes in 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%.
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 hepatic cytochrome P450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4.

The inter-individual variability of voriconazole pharmacokinetics is high.

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. This metabolite has minimal antifungal activity and 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 radiolabelled dose of voriconazole, approximately 80% of the radioactivity is recovered in the urine after multiple intravenous dosing and 83% in the urine after multiple oral dosing. The majority (>94%) of the total radioactivity is excreted in the first 96 hours after both oral and intravenous dosing.

The terminal half-life of voriconazole depends on dose and is approximately 6 hours at 200mg (orally). Because of non-linear pharmacokinetics, the terminal half-life is not useful in the prediction of the accumulation or elimination of voriconazole.

Pharmacokinetic-Pharmacodynamic relationships
In 10 therapeutic studies, the median for the average and maximum plasma concentrations in individual subjects across the studies was 2425ng/ml (inter-quartile range 1193 to 4380 ng/ml) and 3742ng/ml (inter-quartile range 2027 to 6302ng/ml), respectively. A positive association between mean, maximum or minimum plasma voriconazole concentration and efficacy in therapeutic studies was not found.

Pharmacokinetic-Pharmacodynamic analyses of clinical trial data identified positive associations between plasma voriconazole concentrations and both liver function test abnormalities and visual disturbances.

Pharmacokinetics in special patient groups

Gender
In an oral multiple dose study, 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 C_{max} and AUC_{τ} were observed between healthy elderly males and healthy elderly females (≥ 65 years).

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

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

In the therapeutic studies no dosage adjustment was made on the basis of age. A relationship between plasma concentrations and age was observed. The safety profile of voriconazole in young and elderly patients was similar and, therefore, no dosage adjustment is necessary for the elderly (see section 4.2).

Renal impairment
In an oral single dose (200mg) study in subjects with normal renal function and mild (creatinine clearance 41-60ml/min) to severe (creatinine clearance < 20ml/min) renal impairment, the pharmacokinetics of voriconazole were not significantly affected by renal impairment. The plasma protein binding of voriconazole was similar in subjects with different degrees of renal impairment. See dosing and monitoring recommendations under sections 4.2 and 4.4.

Hepatic impairment
After an oral single dose (200mg), AUC was 233% higher in subjects with mild to moderate hepatic cirrhosis (Child-Pugh A and B) compared with subjects with normal hepatic function. Protein binding of voriconazole was not affected by impaired hepatic function.

In an oral multiple dose study, AUC_{τ} was similar in subjects with moderate hepatic cirrhosis (Child-Pugh B) given a maintenance dose of 100mg twice daily and subjects with normal hepatic function

given 200mg twice daily. No pharmacokinetic data are available for patients with severe hepatic cirrhosis (Child-Pugh C). See dosing and monitoring recommendations under sections 4.2 and 4.4.

5.3 Preclinical safety data

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 postnatal development study in rats at exposures lower than those obtained in humans with therapeutic doses, voriconazole prolonged the duration of gestation and labour 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 oestradiol levels, and are consistent with those observed with other azole antifungal agents.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose Monohydrate
Pregelatinised Starch
Croscarmellose Sodium
Povidone
Magnesium Stearate

Film-coat:
Hypromellose
Titanium Dioxide (E171)
Lactose Monohydrate
Glycerol Triacetate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

HDPE tablet containers of 2, 30 and 100. Not all bottle sizes may be marketed.
PVC / Aluminium blister in cartons of 2, 10, 14, 20, 28, 30, 50, 56 and 100.
Not all pack sizes may be marketed.

6.6 Instructions for use and handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ, United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/212/013-024

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 March 2002

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

VFEND 200mg powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Vials contain 200mg voriconazole, equivalent to a 10mg/ml solution following reconstitution (see section 6.6).
For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

VFEND powder for solution for infusion is a white lyophilised powder containing nominally 200mg voriconazole presented in a 30ml clear glass vial.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VFEND, voriconazole, is a broad spectrum, triazole antifungal agent and is indicated as follows:

Treatment of invasive aspergillosis.

Treatment of candidemia in non-neutropenic patients

Treatment of fluconazole-resistant serious invasive *Candida* infections (including *C. krusei*).

Treatment of serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp.

VFEND should be administered primarily to patients with progressive, possibly life-threatening infections.

4.2 Posology and method of administration

VFEND requires reconstitution and dilution (see section 6.6) prior to administration as an intravenous infusion. Not for bolus injection.

It is recommended that VFEND is administered at a maximum rate of 3mg/kg per hour over 1 to 2 hours.

Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy (see section 4.4).

VFEND is also available as 50mg and 200mg film-coated tablets and 40mg/ml powder for oral suspension.

<u>Use in adults</u>
Therapy must be initiated with the specified loading dose regimen of either intravenous or oral VFEND to achieve plasma concentrations on Day 1 that are close to steady state. On the basis of the high oral bioavailability (96%; see section 5.2), switching between intravenous and oral administration is appropriate when clinically indicated.

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

	Intravenous	**Oral**	
		Patients 40kg and above	Patients less than 40kg
Loading Dose Regimen (first 24 hours)	6mg/kg every 12 hours (for the first 24 hours)	400mg every 12 hours (for the first 24 hours)	200mg every 12 hours (for the first 24 hours)
Maintenance Dose (after first 24 hours)	4mg/kg twice daily	200mg twice daily	100mg twice daily

Dosage adjustment
If patients are unable to tolerate treatment at 4mg/kg twice daily, reduce the intravenous dose to 3mg/kg twice daily.

Rifabutin or phenytoin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased to 5mg/kg intravenously twice daily, see sections 4.4 and 4.5.

Treatment duration depends upon patients' clinical and mycological response. The duration of treatment with the intravenous formulation should be no longer than 6 months (see section 5.3).

Use in the elderly
No dose adjustment is necessary for elderly patients (see section 5.2).

Use in patients with renal impairment
In patients with moderate to severe renal dysfunction (creatinine clearance < 50ml/min), accumulation of the intravenous vehicle, SBECD, occurs. Oral voriconazole should be administered to these patients, unless an assessment of the risk benefit 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 5.2).

Voriconazole is haemodialysed with a clearance of 121ml/min. A four hour haemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment.

The intravenous vehicle, SBECD, is haemodialysed with a clearance of 55ml/min.

Use in patients with hepatic impairment
No dose adjustment is necessary in patients with acute hepatic injury, manifested by elevated liver function tests (ALAT, ASAT) (but continued monitoring of liver function tests for further elevations is recommended).

It is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B) receiving VFEND (see section 5.2).

VFEND has not been studied in patients with severe chronic hepatic cirrhosis (Child-Pugh C).

VFEND has been associated with elevations in liver function tests and clinical signs of liver damage, such as jaundice, and must only be used in patients with severe hepatic impairment if the benefit outweighs the potential risk. Patients with severe hepatic impairment must be carefully monitored for drug toxicity (see also section 4.8).

Use in children
Safety and effectiveness in paediatric subjects below the age of 2 years has not been established (see also section 5.1). Therefore voriconazole is not recommended for children less than 2 years of age. Limited data are currently available to determine the optimal posology. However, the following regimen has been used in paediatric studies.

Children aged 2 to < 12 years:

	Intravenous	**Oral**
Loading Dose Regimen (first 24 hours)	6mg/kg every 12 hours (for the first 24 hours)	6mg/kg every 12 hours (for the first 24 hours)
Maintenance Dose (after first 24 hours)	4mg/kg twice daily	4mg/kg twice daily

If a child is able to swallow tablets, the dose should be administered to the nearest mg/kg dose possible using whole 50mg tablets.

The pharmacokinetics and tolerability of higher doses have not been characterised in paediatric populations.

Adolescents (12 to 16 years of age): should be dosed as adults.

4.3 Contraindications

VFEND is contraindicated in patients with known hypersensitivity to voriconazole or to any of the excipients.

Coadministration of the CYP3A4 substrates, terfenadine, astemizole, cisapride, pimozide or quinidine with VFEND is contraindicated since increased plasma concentrations of these medicinal products can lead to QTc prolongation and rare occurrences of *torsades de pointes* (see section 4.5).

Coadministration of VFEND with rifampicin, carbamazepine and phenobarbital is contraindicated since these medicinal products are likely to decrease plasma voriconazole concentrations significantly (see section 4.5).

Coadministration of VFEND with efavirenz is contraindicated because efavirenz significantly decreases voriconazole plasma concentrations while VFEND also significantly increases efavirenz plasma concentrations (see section 4.5)

Coadministration of VFEND with ritonavir (400mg and above twice daily) is contraindicated because ritonavir significantly decreases plasma voriconazole concentrations in healthy subjects (see section 4.5).

Coadministration of ergot alkaloids (ergotamine, dihydroergotamine), which are CYP3A4 substrates, is contraindicated since increased plasma concentrations of these medicinal products can lead to ergotism (see section 4.5).

Coadministration of voriconazole and sirolimus is contraindicated, since voriconazole is likely to increase plasma concentrations of sirolimus significantly (see section 4.5).

4.4 Special warnings and special precautions for use

Hypersensitivity: Caution should be used in prescribing VFEND to patients with hypersensitivity to other azoles (see also section 4.8).

Cardiovascular: Some azoles, including voriconazole have been associated with QT interval prolongation. There have been rare cases of torsade de pointes in patients taking voriconazole who had risk factors, such as history of cardiotoxic chemotherapy, cardiomyopathy, hypokalaemia 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

Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy (see section 4.2). A study has been conducted in healthy volunteers which examined the effect on QT interval of single doses of voriconazole up to four times the usual daily dose. No subject experienced an interval exceeding the potentially clinically relevant threshold of 500msec (see section 5.1).

Infusion-related reactions: Infusion-related reactions, predominantly flushing and nausea, have been observed during administration of the intravenous formulation of voriconazole. Depending on the severity of symptoms, consideration should be given to stopping treatment (see section 4.8).

Hepatic toxicity: In clinical trials, there have been uncommon cases of serious hepatic reactions during treatment with VFEND (including clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities). Instances of hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly haematological malignancy). Transient 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 section 4.8).

Monitoring of hepatic function: Patients at the beginning of therapy with voriconazole and patients who develop abnormal liver function tests during VFEND therapy must be routinely monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of VFEND should be considered if clinical signs and symptoms are consistent with liver disease development.

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 (see section 4.8).

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

Dermatological reactions: Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome, during treatment with VFEND. If patients develop a rash they should be monitored closely and VFEND discontinued if lesions progress. In addition VFEND has been associated with photosensitivity skin reaction especially during long term therapy. It is recommended that patients should be informed to avoid sunlight during the treatment.

Paediatric use: Safety and effectiveness in paediatric subjects below the age of two years has not been established (see also section 5.1).

Phenytoin (CYP2C9 substrate and potent CYP450 inducer): Careful monitoring of phenytoin levels is recommended when phenytoin is coadministered with voriconazole. Concomitant use of voriconazole and phenytoin should be avoided unless the benefit outweighs the risk (see section 4.5).

Methadone (CYP3A4 substrate). Frequent monitoring for adverse events and toxicity related to methadone, including QTc prolongation, is recommended when coadministered with voriconazole since methadone levels increased following co-administration of voriconazole. Dose reduction of methadone may be needed (see section 4.5).

Rifabutin (CYP450 inducer): Careful monitoring of full blood counts and adverse events to rifabutin (e.g. uveitis) is recommended when rifabutin is coadministered with voriconazole. Concomitant use of voriconazole and rifabutin should be avoided unless the benefit outweighs the risk (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

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

This section addresses the effects of other medicinal products on voriconazole, the effects of voriconazole on other medicinal products and two-way interactions. The interactions for the first two sections are presented in the following order: contraindications, those requiring dosage 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.

Effects of other medicinal products on voriconazole

Voriconazole is metabolised by cytochrome P450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4. Inhibitors or inducers of these isoenzymes may increase or decrease voriconazole plasma concentrations respectively.

Rifampicin (CYP450 inducer): Rifampicin (600mg once daily) decreased the C_{max} (maximum plasma concentration) and AUC_{τ} (area under the plasma concentration time curve within a dose interval) of voriconazole by 93% and 96%, respectively. Coadministration of voriconazole and rifampicin is contraindicated (see section 4.3)**.**

Ritonavir (potent CYP450 inducer; CYP3A4 inhibitor and substrate): Ritonavir (400mg twice daily) decreased the steady state C_{max} and AUC_{τ} of oral voriconazole by an average of 66% and 82%, respectively, in healthy subjects with the exception of one subject in whom a 2.5 fold increases in AUC_{τ} was observed. No extrapolation can be made for ritonavir doses lower than 400mg. Repeat oral administration of voriconazole did not have a significant effect on steady state C_{max} and AUC_{τ} of ritonavir following repeat dose administration in healthy subjects. Coadministration of voriconazole and ritonavir (400mg and above twice daily) is contraindicated (see section 4.3).

Carbamazepine and phenobarbital (potent CYP450 inducers): Although not studied, carbamazepine or phenobarbital are likely to significantly decrease plasma voriconazole concentrations. Coadministration of voriconazole with carbamazepine and phenobarbital is contraindicated (see section 4.3).

Cimetidine (non-specific CYP450 inhibitor and increases gastric pH): Cimetidine (400 mg twice daily) increased voriconazole C_{max} and AUC_{τ} by 18% and 23%, respectively. No dosage adjustment of voriconazole is recommended.

Ranitidine (increases gastric pH): Ranitidine (150mg twice daily) had no significant effect on voriconazole C_{max} and AUC_{τ}.

Macrolide antibiotics: Erythromycin (CYP3A4 inhibitor; 1g twice daily) and azithromycin (500mg once daily) had no significant effect on voriconazole C_{max} and AUC_{τ}.

Effects of voriconazole on other medicinal products

Voriconazole inhibits the activity of cytochrome P450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4. Therefore there is potential for voriconazole to increase the plasma levels of substances metabolised by these CYP450 isoenzymes.

Terfenadine, astemizole, cisapride, pimozide and quinidine (CYP3A4 substrates): Although not studied, coadministration of voriconazole with terfenadine, astemizole, cisapride, pimozide, or quinidine is contraindicated, since increased plasma concentrations of these medicinal products can lead to QTc prolongation and rare occurrences of *torsades de pointes* (see section 4.3).

Sirolimus (CYP3A4 substrate): Voriconazole increased sirolimus (2mg single dose) C_{max} and AUC_{τ} by 556% and 1014%, respectively. Coadministration of voriconazole and sirolimus is contraindicated (see section 4.3).

Ergot alkaloids (CYP3A4 substrates): Although not studied, voriconazole may increase the plasma concentrations of ergot alkaloids (ergotamine and dihydroergotamine) and lead to ergotism. Coadministration of voriconazole with ergot alkaloids is contraindicated (see section 4.3).

Cyclosporin (CYP3A4 substrate): In stable, renal transplant recipients, voriconazole increased cyclosporin C_{max} and AUC_{τ} by at least 13% and 70% , respectively. When initiating voriconazole in patients already receiving cyclosporin it is recommended that the cyclosporin dose be halved and cyclosporin level carefully monitored. Increased cyclosporin levels have been associated with nephrotoxicity. When voriconazole is discontinued, cyclosporin levels must be carefully monitored and the dose increased as necessary.

Methadone (CYP3A4 substrate): In subjects receiving a methadone maintenance dose (32-100mg once daily) coadministration of oral voriconazole (400mg twice daily for 1 day, then 200mg twice daily for four days) increased the C_{max} and AUC_{τ} of pharmacologically active R-methadone by 31% and 47%, respectively, whereas the C_{max} and AUC_{τ} of the S-enantiomer increased by approximately 65% and 103%, respectively. Voriconazole plasma concentrations during coadministration of methadone were comparable to voriconazole levels (historical data) in healthy subjects without any comedication. Frequent monitoring for adverse events and toxicity related to increased plasma concentrations of methadone, including QT prolongation, is recommended during coadministration. Dose reduction of methadone may be needed.

Tacrolimus (CYP3A4 substrate): Voriconazole increased tacrolimus (0.1 mg/kg single dose) C_{max} and AUC_t (area under the plasma concentration time curve to the last quantifiable measurement) by 117 % and 221 %, respectively. When initiating voriconazole in patients already receiving 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.

Oral anticoagulants:
Warfarin (CYP2C9 substrate): Coadministration of voriconazole (300mg twice daily) with warfarin (30mg single dose) increased maximum prothrombin time by 93%. Close monitoring of prothrombin time is recommended if warfarin and voriconazole are coadministered.
Other oral anticoagulants e.g. phenprocoumon, acenocoumarol (CYP2C9, CYP3A4 substrates): Although not studied, voriconazole may increase the plasma concentrations of coumarins and therefore may cause an increase in prothrombin time. If patients receiving coumarin preparations are treated simultaneously with voriconazole, the prothrombin time should be monitored at close intervals and the dosage of anticoagulants adjusted accordingly.

Sulphonylureas (CYP2C9 substrates): Although not studied, voriconazole may increase the plasma levels of sulphonylureas, (e.g. tolbutamide, glipizide, and glyburide) and therefore cause hypoglycaemia. Careful monitoring of blood glucose is recommended during coadministration.

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

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

Vinca Alkaloids (CYP3A4 substrates): Although not studied, voriconazole may increase the plasma levels of the vinca alkaloids (e.g. vincristine and vinblastine) and lead to neurotoxicity.

Prednisolone (CYP3A4 substrate): Voriconazole increased C_{max} and AUC_{τ} of prednisolone (60mg single dose) by 11% and 34%, respectively. No dosage adjustment is recommended.

Digoxin (P-glycoprotein mediated transport): Voriconazole had no significant effect on C_{max} and AUC_{τ} of digoxin (0.25mg once daily).

Mycophenolic acid (UDP-glucuronyl transferase substrate): Voriconazole had no effect on the C_{max} and AUC_{t} of mycophenolic acid (1g single dose).

Two-way interactions

Phenytoin (CYP2C9 substrate and potent CYP450 inducer): Concomitant use of voriconazole and phenytoin should be avoided unless the benefit outweighs the risk. Phenytoin (300mg once daily) decreased the C_{max} and AUC_{τ} of voriconazole by 49% and 69%, respectively. Voriconazole (400mg twice daily, see section 4.2) increased C_{max} and AUC_{τ} of phenytoin (300mg once daily) by 67% and 81%, respectively. Careful monitoring of phenytoin plasma levels is recommended when phenytoin is coadministered with voriconazole.

Phenytoin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased to 5mg /kg intravenously twice daily or from 200mg to 400mg orally, twice daily (100mg to 200mg orally, twice daily in patients less than 40kg), see section 4.2.

Rifabutin (CYP450 inducer): Concomitant use of voriconazole and rifabutin should be avoided unless the benefit outweighs the risk.Rifabutin (300mg once daily) decreased the C_{max} and AUC_{τ} of voriconazole at 200mg twice daily by 69% and 78%, respectively. During coadministration with rifabutin, the C_{max} and AUC_{τ} of voriconazole at 350mg twice daily were 96% and 68% of the levels when administered alone at 200mg twice daily. At a voriconazole dose of 400mg twice daily C_{max} and AUC_{τ} were 104% and 87% higher, respectively, compared with voriconazole alone at 200mg twice daily. Voriconazole at
400mg twice daily increased C_{max} and AUC_{τ} of rifabutin by 195% and 331%, respectively.

If rifabutin coadministration with voriconazole is justified then the maintenance dose of voriconazole may be increased to 5mg/kg intravenously twice daily or from 200mg to 350mg orally, twice daily (100mg to 200mg orally, twice daily in patients less than 40kg) (see section 4.2). Careful monitoring of full blood counts and adverse events to rifabutin (e.g. uveitis) is recommended when rifabutin is coadministered with voriconazole.

Omeprazole (CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate): Omeprazole (40mg once daily) increased voriconazole C_{max} and AUC_{τ} by 15% and 41%, respectively. No dosage adjustment of voriconazole is recommended. Voriconazole increased omeprazole C_{max} and AUC_{τ} by 116% and 280%, respectively. When initiating voriconazole in patients already receiving omeprazole, it is

recommended that the omeprazole dose be halved. The metabolism of other proton pump inhibitors which are CYP2C19 substrates may also be inhibited by voriconazole.

Indinavir (CYP3A4 inhibitor and substrate): Indinavir (800mg three times daily) had no significant effect on voriconazole C_{max} , C_{min} and AUC_{τ}.
Voriconazole did not have a significant effect on C_{max} and AUC_{τ} of indinavir (800mg three times daily).

Efavirenz (a non-nucleoside reverse transcriptase inhibitor (CYP450 inducer; CYP3A4 inhibitor and substrate)): Steady-state efavirenz (400mg orally once daily) decreased the steady state Cmax and AUCτ of voriconazole by an average of 61% and 77%, respectively, in healthy subjects. In the same study voriconazole at steady state increased the steady state Cmax and AUCτ of efavirenz by an average of 38% and 44% respectively, in healthy subjects. Coadministration of voriconazole and efavirenz is contraindicated (see section 4.3).

Other HIV protease inhibitors (CYP3A4 inhibitors): *In vitro* studies suggest that voriconazole may inhibit the metabolism of HIV protease inhibitors (e.g. saquinavir, amprenavir and nelfinavir). *In vitro* studies also show that the metabolism of voriconazole may be inhibited by HIV protease inhibitors. However results of the combination of voriconazole with other HIV protease inhibitors cannot be predicted in humans only from *in vitro* studies. Patients should be carefully monitored for any occurrence of drug toxicity and/or loss of efficacy during the co-administration of voriconazole and HIV protease inhibitors.

Non-nucleoside reverse transcriptase inhibitors (NNRTI) (CYP3A4 substrates, inhibitors or CYP450 inducers): *In vitro* studies show that the metabolism of voriconazole may be inhibited by delavirdine. Although not studied, the metabolism of voriconazole may be induced by nevirapine. An in-vivo study showed that voriconazole inhibited the metabolism of efavirenz. Voriconazole may also inhibit the metabolism of NNRTIs besides efavirenz. Patients should be carefully monitored for any occurrence of drug toxicity and/or lack of efficacy during the coadministration of voriconazole and NNRTIs. Coadministration of voriconazole with efavirenz is contraindicated (see section 4.3)

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 levels of substances metabolised by CYP3A4 isoenzymes (certain antihistamines, quinidine, cisapride, pimozide) co-administration is contraindicated (see section 4.3).

4.6 Pregnancy and lactation

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

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk to humans is unknown.

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

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

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

4.7 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.

4.8 Undesirable effects

The safety profile of voriconazole is based on an integrated safety database of more than 2000 subjects (1655 patients in therapeutic trials). This represents a heterogeneous population, containing patients with haematological malignancy, HIV infected patients with oesophageal candidiasis and refractory fungal infections, non-neutropenic patients with candidaemia or aspergillosis and healthy volunteers. Five hundred and sixty one patients had a duration of voriconazole therapy of greater than 12 weeks, with 136 patients receiving voriconazole for over 6 months.

In the table below, since the majority of the studies were of an open nature, all causality adverse events, by system organ class and frequency (very common >1/10, common >1/100 and <1/10, uncommon >1/1000 and <1/100 and rare, <1/1000) if possibly causally related are listed. The most commonly reported adverse events were visual disturbances, fever, rash, vomiting, nausea, diarrhoea, headache, peripheral oedema 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 analysed by age, race, or gender.

Undesirable effects reported in subjects receiving voriconazole

Body System	**Adverse Drug Reactions**
Body as a whole	
Very common	Fever, headache, abdominal pain
Common	Chills, asthenia, back pain, chest pain, injection site reaction/inflammation, face oedema, flu syndrome
Uncommon	Allergic reaction, anaphylactoid reaction, angioedema, peritonitis
Cardiovascular	
Common	Hypotension, thrombophlebitis, phlebitis
Uncommon	Atrial arrhythmia, bradycardia, syncope, tachycardia, ventricular arrhythmia, ventricular fibrillation, supraventricular tachycardia, QT interval prolongation
Rare	AV complete block, bundle branch block, nodal arrhytmia, ventricular tachycardia, torsade de pointes
Digestive	
Very common	Nausea, vomiting, diarrhoea
Common	Elevated liver function tests (including ASAT, ALAT, alkaline phosphatase, GGT, LDH, bilirubin), jaundice, cheilitis, cholestatic jaundice, gastroenteritis
Uncommon	Cholecystitis, cholelithiasis, constipation, duodenitis, dyspepsia, enlarged liver, gingivitis, glossitis, hepatitis, hepatic failure, pancreatitis, tongue oedema
Rare	Pseudomembranous colitis, hepatic coma
Endocrine	
Uncommon	Adrenal cortex insufficiency
Haemic and lymphatic	
Common	Thrombocytopenia, anaemia (including macrocytic, microcytic, normocytic, megaloblastic, aplastic), leukopenia, pancytopenia, purpura
Uncommon	Lymphadenopathy, agranulocytosis, eosinophilia, disseminated intravascular coagulation, marrow depression
Rare	Lymphangitis
Metabolic and nutritional	
Very common	Peripheral oedema
Common	Hypokalaemia, creatinine increased, hypoglycaemia
Uncommon	BUN increased, albuminuria, hypercholesterolaemia
Rare	Hyperthyroidism, hypothyroidism
Musculoskeletal	
Uncommon	Arthritis
Nervous	

Common	Dizziness, hallucinations, confusion, depression, anxiety, tremor, agitation, paraesthesia
Uncommon	Ataxia, brain oedema, diplopia, hypoaesthesia, nystagmus, vertigo
Rare	Guillain-Barre syndrome, oculogyric crisis, hypertonia, Extrapyramidal syndrome, insomnia, encephalopathy, somnolence during infusion
Respiratory	
Common	Respiratory distress syndrome, lung oedema, sinusitis
Skin and appendages	
Very common	Rash
Common	Pruritus, maculopapular rash, photosensitivity skin reaction, alopecia, exfoliative dermatitis
Uncommon	Fixed drug eruption, eczema, psoriasis, Stevens-Johnson syndrome, urticaria
Rare	Discoid lupus erythematosis, erythema multiforme, toxic epidermal necrolysis
Special senses	
Very Common	Visual disturbances (including altered/enhanced visual perception, decrease in ERG amplitude, blurred vision, colour vision change, photophobia)
Uncommon	Blepharitis, optic neuritis, papilloedema, scleritis, altered taste perception
Rare	Retinal haemorrhage, corneal opacity, optic atrophy, hypoacusis, tinnitus
Urogenital	
Common	Acute kidney failure, haematuria
Uncommon	Nephritis
Rare	Kidney tubular necrosis

Visual disturbances

Voriconazole treatment-related visual disturbances were very common. In clinical trials, short-term as well as long-term treatment, approximately 30% of subjects experienced altered/enhanced visual perception, blurred vision, colour vision change or photophobia. The visual disturbances are transient and fully reversible, with the majority spontaneously resolving within 60 minutes and no clinically significant long-term visual effects were observed. There is evidence of attenuation with repeated doses of voriconazole. The visual disturbance is generally mild, rarely results in discontinuation and has not been associated with long-term sequelae. Visual disturbances may be associated with higher plasma concentrations and/or doses.

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 treatment and were fully reversible on withdrawal of voriconazole.

Dermatological reactions

Dermatological reactions were 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 rarely developed serious cutaneous reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme during treatment with VFEND.

If patients develop a rash they should be monitored closely and VFEND-discontinued if lesions progress.Photosensitivity reactions have been reported, especially during long-term therapy (see also section 4.4).

Liver Function Tests

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

Voriconazole has been infrequently associated with cases of serious hepatic toxicity in patients with other serious underlying conditions. This includes cases of jaundice, and rare cases of hepatitis and hepatic failure leading to death (see section 4.4).

Infusion-Related Reactions
During infusion of the intravenous formulation of voriconazole in healthy subjects, anaphylactoid-type reactions, including flushing, fever, sweating, tachycardia, chest tightness, dyspnoea, faintness, nausea, pruritus and rash have occurred. Symptoms appeared immediately upon initiating the infusion (see also section 4.4).

4.9 Overdose

In clinical trials there were 3 cases of accidental overdose. All occurred in paediatric patients, who received up to five times the recommended intravenous dose of voriconazole. A single adverse event of photophobia of 10 minutes duration was reported.

There is no known antidote to voriconazole.

Voriconazole is haemodialysed with a clearance of 121ml/min. The intravenous vehicle, SBECD, is haemodialysed with a clearance of 55ml/min. In an overdose, haemodialysis may assist in the removal of voriconazole and SBECD from the body.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC code: J02A C03
Antimycotics for Systemic Use – Triazole derivatives

Mechanism of action

I*n 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*) and fungicidal activity against all *Aspergillus* species tested. In addition voriconazole shows *in vitro* fungicidal activity against emerging fungal pathogens, including those such as *Scedosporium* or *Fusarium* which have limited susceptibility to existing antifungal agents. Its mode of action is inhibition of fungal cytochrome P450-mediated 14α-sterol demethylation, an essential step in ergosterol biosynthesis.

In animal studies there is a correlation between minimum inhibitory concentration values and efficacy against experimental mycoses. By contrast, in clinical studies, there appears to be no correlation between minimum inhibitory concentration values and clinical outcome. Furthermore, there does not appear to be a correlation between plasma levels and clinical outcome. This is typical of azole antimycotics.

Microbiology

Clinical efficacy (with partial or complete response, see below under Clinical Experience) has been demonstrated for *Aspergillus* spp. including *A. flavus, A. fumigatus, A. terreus, A. niger, A. nidulans, Candida* spp.*,* including *C. albicans , C. glabrata, C. krusei, C. parapsilosis and C. tropicalis* and limited numbers of *C. dubliniensis,C. inconspicua,* and *C. guilliermondii, Scedosporium* spp., including *S. apiospermum, S. prolificans* and *Fusarium* spp.

Other treated fungal infections (with often partial or complete response, see below under Clinical Experience) 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 2μg/ml.

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

Specimens for fungal culture and other relevant laboratory studies (serology, histopathology) should be obtained prior to therapy to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.

Clinical isolates with decreased susceptibility to voriconazole have been identified. However, elevated minimum inhibitory concentrations did not always correlate with clinical failure and clinical success has been observed in patients infected with organisms resistant to other azoles. Correlation of *in vitro* activity with clinical outcome is difficult owing to the complexity of the patients studied in clinical trials; breakpoints for voriconazole remain to be established.

Clinical Experience

Succesful outcome in this section is defined as complete or partial response.

Aspergillus infections – efficacy in aspergillosis patients with poor prognosis
Voriconazole has *in vitro* fungicidal activity against *Aspergillus* spp. The efficacy and survival benefit of voriconazole versus conventional amphotericin B in the primary treatment of acute invasive aspergillosis was demonstrated in an open, randomised, multicentre study in 277 immunocompromised patients treated for 12 weeks. A satisfactory global response (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 31 % of patients treated with comparator. The 84-day survival rate for voriconazole was statistically significantly higher than that for the comparator and a clinically and statistically significant benefit was shown in favour of voriconazole for both time to death and time to discontinuation due to toxicity.

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).

The studies included cerebral, sinus, pulmonary and disseminated aspergillosis in patients with bone marrow and solid organ transplants, haematological malignancies, cancer and AIDS.

Candidaemia in non-neutropenic patients.

The efficacy of voriconazole compared to the regimen of amphotericin B followed by fluconazole in the primary treatment of candidaemia was demonstrated in an open, comparative study. Three hundred and seventy non-neutropenic patients (above 12 years of age) with documented candidaemia were included in the study, of whom 248 were treated with voriconazole. Nine subjects in the voriconazole group and five in the amphotericin B followed by fluconazole group also had mycologically proven infection in deep tissue. Patients with renal failure were excluded from this study. The median treatment duration was 15 days in both treatment arms. In the primary analysis, successful response as assessed by a Data Review Committee (DRC) blinded to study medication was defined as resolution/improvement in all clinical signs and symptoms of infection with eradication of *Candida* from blood and infected deep tissue sites at 12 weeks after the end of therapy (EOT). Patients who did not have an assessment 12 weeks after EOT were counted as failures. In this analysis a successful response was seen in 41% of patients in both treatment arms.

In a secondary analysis, which utilised *DRC* assessments at the latest evaluable time point (EOT, or 2, 6, or 12 weeks after EOT) voriconazole and the regimen of amphotericin B followed by fluconazole had successful response rates of 65% and 71%, respectively. The Investigator's assessment of successful outcome at each of these time points is shown in the following table.

Timepoint	***Voriconazole (N=248)***	***Amphotericin B → fluconazole (N=122)***
EOT	***178 (72%)***	***88 (72%)***
2 weeks after EOT	***125 (50%)***	***62 (51%)***
6 weeks after EOT	***104 (42%)***	***55 (45%)***
12 weeks after EOT	***104 (42%)***	***51 (42%)***

There are no data in children below the age of 12 years for this indication.

Serious refractory *Candida* infections
The study comprised 55 patients with serious refractory systemic *Candida* infections (including candidaemia, 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.

Scedosporium and *Fusarium* infections
Voriconazole was shown to be effective against the following rare fungal pathogens:

Scedosporium spp.: Successful response to voriconazole therapy was seen in 16 (6 complete, 10 partial responses) of 28 patients with *S. apiospermum* and in 2 (both partial response) of 7 patients with *S. prolificans* infection. In addition, a successful response was seen in 1 of 3 patients with infections caused by more than one organism including *Scedosporium* spp.

Fusarium spp.: Seven (3 complete, 4 partial responses) of 17 patients were successfully treated with voriconazole. Of these 7 patients, 3 had eye, 1 had sinus, and 3 had disseminated infection. Four additional patients with fusariosis had an infection caused by several organisms; two of them had a successful outcome.

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

In clinical trials, 561 patients received voriconazole therapy for greater than 12 weeks, with 136 patients receiving voriconazole for over 6 months.

Experience in paediatric patients

Sixty one paediatric patients aged 9 months up to 15 years who had definite or probable invasive fungal infections, were treated with voriconazole. This population included 34 patients 2 to < 12 years old and 20 patients 12-15 years of age.

The majority (57/61) had failed previous antifungal therapies. Therapeutic studies included 5 patients aged 12-15 years, the remaining patients received voriconazole in the compassionate use programmes. Underlying diseases in these patients included haematological malignancies and aplastic anaemia (27 patients) and chronic granulomatous disease (14 patients). The most commonly treated fungal infection was aspergillosis (43/61; 70 %).

Clinical Studies Examining QT Interval

A placebo-controlled, randomized, single-dose, crossover study to evaluate the effect on the QT interval of healthy volunteers was conducted with three oral doses of voriconazole and ketoconazole. The placebo-adjusted mean maximum increases in QTc from baseline after 800, 1200 and 1600 mg of voriconazole were 5.1, 4.8, and 8.2 msec, respectively and 7.0 msec for ketoconazole 800 mg. 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.

5.2 Pharmacokinetic properties

General pharmacokinetic characteristics
The pharmacokinetics of voriconazole have been characterised in healthy subjects, special populations and patients. During oral administration of 200mg or 300mg twice daily for 14 days in patients at risk of aspergillosis (mainly patients with malignant neoplasms of lymphatic or haematopoietic tissue), the observed pharmacokinetic characteristics of rapid and consistent absorption, accumulation and non-linear pharmacokinetics were in agreement with those observed in healthy subjects.

The pharmacokinetics of voriconazole are non-linear due to saturation of its metabolism. Greater than proportional increase in exposure is observed with increasing dose. It is estimated that, on average, increasing the oral dose from 200mg twice daily to 300mg twice daily leads to a 2.5-fold increase in exposure (AUCτ). When the recommended intravenous or oral loading dose regimens are administered, 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 plasma voriconazole concentrations being achieved by day 6 in the majority of subjects.

Absorption
Voriconazole is rapidly and almost completely absorbed following oral administration, with maximum plasma concentrations (C_{max}) achieved 1-2 hours after dosing. The absolute bioavailability of voriconazole after oral administration is estimated to be 96%. When multiple doses of voriconazole are administered with high fat meals, C_{max} and AUC_{τ} are reduced by 34% and 24%, respectively. The absorption of voriconazole is not affected by changes in 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%.
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 hepatic cytochrome P450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4.

The inter-individual variability of voriconazole pharmacokinetics is high.

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. This metabolite has minimal antifungal activity and 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 radiolabelled dose of voriconazole, approximately 80 % of the radioactivity is recovered in the urine after multiple intravenous dosing and 83 % in the urine after multiple oral dosing. The majority (> 94%) of the total radioactivity is excreted in the first 96 hours after both oral and intravenous dosing.

The terminal half-life of voriconazole depends on dose and is approximately 6 hours at 200mg (orally). Because of non-linear pharmacokinetics, the terminal half-life is not useful in the prediction of the accumulation or elimination of voriconazole.

Pharmacokinetic-Pharmacodynamic relationships

In 10 therapeutic studies, the median for the average and maximum plasma concentrations in individual subjects across the studies was 2425ng/ml (inter-quartile range 1193 to 4380ng/ml) and 3742ng/ml (inter-quartile range 2027 to 6302ng/ml), respectively. A positive association between mean, maximum or minimum plasma voriconazole concentration and efficacy in therapeutic studies was not found.

Pharmacokinetic-Pharmacodynamic analyses of clinical trial data identified positive associations between plasma voriconazole concentrations and both liver function test abnormalities and visual disturbances.

Pharmacokinetics in special patient groups

Gender
In an oral multiple dose study, 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 C_{max} and AUC_{τ} were observed between healthy elderly males and healthy elderly females (≥ 65 years).

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

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

In the therapeutic studies no dosage adjustment was made on the basis of age. A relationship between plasma concentrations and age was observed. The safety profile of voriconazole in young and elderly patients was similar and, therefore, no dosage adjustment is necessary for the elderly (see section 4.2).

Paediatrics
A population pharmacokinetic analysis was conducted on data from 35 immunocompromised subjects aged 2 to <12 years old who were included in the intravenous single or multiple dose pharmacokinetic

studies. Twenty four of these subjects received multiple doses of voriconazole. Average steady state plasma concentrations in children receiving a maintenance dose of 4mg/kg every 12 hours were similar to those in adults receiving 3 mg/kg every 12hours, with medians of 1186 ng /ml in children and 1155ng /ml in adults. Therefore a maintenance dose of 4mg/kg every 12 hours is recommended for children aged between 2 to <12 years of age.

Renal impairment
In patients with moderate to severe renal dysfunction (serum creatinine levels >2.5mg /dl), accumulation of the intravenous vehicle, SBECD, occurs. See dosing and monitoring recommendations under sections 4.2 and 4.4.

Hepatic impairment
After an oral single dose (200mg), AUC was 233% higher in subjects with mild to moderate hepatic cirrhosis (Child-Pugh A and B) compared with subjects with normal hepatic function. Protein binding of voriconazole was not affected by impaired hepatic function.

In an oral multiple dose study, AUC_{τ} was similar in subjects with moderate hepatic cirrhosis (Child-Pugh B) given a maintenance dose of 100mg twice daily and subjects with normal hepatic function given 200mg twice daily. No pharmacokinetic data are available for patients with severe hepatic cirrhosis (Child-Pugh C). See dosing and monitoring recommendations under sections 4.2 and 4.4.

5.3 Preclinical safety data

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 postnatal development study in rats at exposures lower than those obtained in humans with therapeutic doses, voriconazole prolonged the duration of gestation and labour 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 oestradiol levels, and are consistent with those observed with other azole antifungal agents.
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. As GPMT (guinea pig maximisation test) result was positive, prescribers should be aware of the hypersensitivity potential of the intravenous formulation. Standard genotoxicity and reproduction studies with the excipient SBECD reveal no special hazard for humans. Carcinogenicity studies were not performed with SBECD. An impurity, present in SBECD, has been shown to be an alkylating mutagenic agent with evidence for carcinogenicity in rodents. This impurity should be considered a substance with carcinogenic potential in humans. In the light of these data the duration of treatment of the intravenous formulation should be no longer than 6 months.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sulphobutylether beta cyclodextrin sodium (SBECD)

6.2 Incompatibilities

VFEND must not be infused into the same line or cannula concomitantly with infusions of other medicinal products including parenteral nutrition (eg Aminofusin 10% Plus). 4.2% Sodium

Bicarbonate Intravenous Infusion is not compatible with VFEND and is not recommended for use as a diluent. Compatibility with other concentrations is unknown.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Infusions of blood products must not occur simultaneously with voriconazole.

Infusion of total parenteral nutrition can occur simultaneously with voriconazole but not in the same line or cannula.

6.3 Shelf life

VFEND powder for solution for infusion: 3 years.

VFEND is a single dose unpreserved sterile lyophile. Therefore, from a microbiological point of view, once reconstituted, the product must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C.

6.4 Special precautions for storage

Reconstituted concentrate: Store at 2°C-8°C for up to 24 hours (in a refrigerator).

6.5 Nature and contents of container

Packs of 1 single use 30ml clear Type I glass vials with rubber stoppers and aluminium caps with plastic seals.

6.6 Instructions for use and handling

The powder is reconstituted with 19ml of Water for Injections to obtain an extractable volume of 20ml of clear concentrate containing 10mg/ml of voriconazole. Discard the VFEND vial if vacuum does not pull the diluent into the vial. It is recommended that a standard
20ml (non-automated) syringe be used to ensure that the exact amount (19.0ml) of Water for Injections is dispensed. This medicinal product is for single use only and any unused solution should be discarded and only clear solutions without particles should be used.

For administration, the required volume of the reconstituted concentrate is added to a recommended compatible infusion solution (detailed below) to obtain a final voriconazole solution containing 0.5-5mg/ml.

Required Volumes of 10 mg/ml VFEND Concentrate

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

Voriconazole is a single dose unpreserved sterile lyophile. Therefore, from a microbiological point of view, the reconstituted solution must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

The reconstituted solution can be diluted with:

9mg/ml (0.9%) Sodium Chloride for Infusion
Lactated Ringer's Intravenous Infusion
5% Glucose and Lactated Ringer's Intravenous Infusion
5% Glucose and 0.45% Sodium Chloride Intravenous Infusion
5% Glucose Intravenous Infusion
5% Glucose in 20mEq Potassium Chloride Intravenous Infusion
0.45% Sodium Chloride Intravenous Infusion
5% Glucose and 0.9% Sodium Chloride Intravenous Infusion

The compatibility of voriconazole with diluents other than described above or in section 6.2 is unknown.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ, United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/212/025

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 March 2002

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

VFEND 40mg/ml powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bottle contains 45g powder for oral suspension providing 40mg/ml voriconazole when constituted with water.
For excipients, see 6.1.

3. PHARMACEUTICAL FORM

White to off-white powder for oral suspension providing a white to off-white, orange flavoured suspension when constituted.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VFEND, voriconazole, is a broad spectrum, triazole antifungal agent and is indicated as follows:

Treatment of invasive aspergillosis.

Treatment of candidemia in non-neutropenic patients

Treatment of fluconazole-resistant serious invasive *Candida* infections (including *C. krusei*).

Treatment of serious fungal infections caused by *Scedosporium* spp. and *Fusarium* spp.

VFEND should be administered primarily to patients with progressive, possibly life-threatening infections.

4.2 Posology and method of administration

VFEND oral suspension is to be taken at least one hour before, or two hours following, a meal.

Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy (see Section 4.4).

VFEND is also available as 50mg and 200mg film-coated tablets and 200mg powder for solution for injection.

Use in adults
Therapy must be initiated with the specified loading dose regimen of either intravenous or oral VFEND to achieve plasma concentrations on Day 1 that are close to steady state. On the basis of the high oral bioavailability (96 %; see section 5.2), switching between intravenous and oral administration is appropriate when clinically indicated.

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

	Intravenous	**Oral Suspension**	
		Patients 40kg and above	Patients less than 40kg
Loading Dose Regimen (first 24 hours)	6mg/kg every 12 hours (for the first 24 hours)	400mg (10ml) every 12 hours (for the first 24 hours)	200mg (5ml) every 12 hours (for the first 24 hours)
Maintenance Dose (after first 24 hours)	4mg/kg twice daily	200mg (5ml) twice daily	100mg (2.5ml) twice daily

Dosage adjustment
If patient response is inadequate, the maintenance dose may be increased to 300mg twice daily for oral administration. For patients less than 40kg the oral dose may be increased to 150mg twice daily.

If patients are unable to tolerate treatment at these higher doses reduce the oral dose by 50mg steps to the 200mg twice daily (or 100mg twice daily for patients less than 40kg) maintenance dose.

Phenytoin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased from 200mg to 400mg orally, twice daily (100mg to 200mg orally, twice daily in patients less than 40kg), see sections 4.4 and 4.5.

Rifabutin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased from 200mg to 350mg orally, twice daily (100mg to 200mg orally, twice daily in patients less than 40kg), see sections 4.4 and 4.5.

Treatment duration depends upon patients' clinical and mycological response.

Use in the elderly
No dose adjustment is necessary for elderly patients (See section 5.2).

Use in patients with renal impairment
The pharmacokinetics of orally administered voriconazole are not affected by renal impairment. Therefore, no adjustment is necessary for oral dosing for patients with mild to severe renal impairment (See Section 5.2).

Voriconazole is haemodialysed with a clearance of 121ml/min. A four hour haemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment.

Use in patients with hepatic impairment
No dose adjustment is necessary in patients with acute hepatic injury, manifested by elevated liver function tests (ALAT, ASAT) (but continued monitoring of liver function tests for further elevations is recommended).

It is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B) receiving VFEND (See section 5.2).

VFEND has not been studied in patients with severe chronic hepatic cirrhosis (Child-Pugh C).

VFEND has been associated with elevations in liver function tests and clinical signs of liver damage, such as jaundice, and must only be used in patients with severe hepatic impairment if the benefit

outweighs the potential risk. Patients with hepatic impairment must be carefully monitored for drug toxicity (see also section 4.8).

Use in children
Safety and effectiveness in paediatric subjects below the age of 2 years has not been established (see also section 5.1). Therefore voriconazole is not recommended for children less than 2 years of age. Limited data are currently available to determine the optimal posology (See section 5.2). However, the following regimen has been used in paediatric studies.

Children aged 2 to < 12 years:

	Intravenous	**Oral Suspension**
Loading Dose Regimen (first 24 hours)	6mg/kg every 12 hours (for the first 24 hours)	6mg/kg every 12 hours (for the first 24 hours)
Maintenance Dose (after first 24 hours)	4mg/kg twice daily	4mg/kg twice daily

The dose should be administered to the nearest 20mg (0.5ml) as the oral syringe is graduated in increments of 0.5ml.

The pharmacokinetics and tolerability of higher doses have not been characterised in paediatric populations.

Adolescents (12 to 16 years of age): should be dosed as adults.

4.3 Contraindications

VFEND is contraindicated in patients with known hypersensitivity to voriconazole or to any of the excipients.

Coadministration of the CYP3A4 substrates, terfenadine, astemizole, cisapride, pimozide or quinidine with VFEND is contraindicated since increased plasma concentrations of these medicinal products can lead to QTc prolongation and rare occurrences of *torsades de pointes* (see section 4.5).

Coadministration of VFEND with rifampicin, carbamazepine and phenobarbital is contraindicated since these medicinal products are likely to decrease plasma voriconazole concentrations significantly (see section 4.5).

Coadministration of VFEND with efavirenz is contraindicated because efavirenz significantly decreases voriconazole plasma concentrations while VFEND also significantly increases efavirenz plasma concentrations (see section 4.5).

Coadministration of VFEND with ritonavir (400mg and above twice daily) is contraindicated because ritonavir significantly decreases plasma voriconazole concentrations in healthy subjects (see section 4.5).

Coadministration of ergot alkaloids (ergotamine, dihydroergotamine), which are CYP3A4 substrates, is contraindicated since increased plasma concentrations of these medicinal products can lead to ergotism (see section 4.5).

Coadministration of voriconazole and sirolimus is contraindicated, since voriconazole is likely to increase plasma concentrations of sirolimus significantly (see section 4.5).

4.4 Special warnings and special precautions for use

Hypersensitivity: Caution should be used in prescribing VFEND to patients with hypersensitivity to other azoles (see also section 4.8).

Cardiovascular:
Some azoles, including voriconazole have been associated with QT interval prolongation. There have been rare cases of torsade de pointes in patients taking voriconazole who had risk factors, such as history of cardiotoxic chemotherapy, cardiomyopathy, hypokalaemia 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

Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy (see section 4.2). 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 experienced an interval exceeding the potentially clinically relevant threshold of 500msec (see section 5.1).

Hepatic toxicity: In clinical trials, there have been uncommon cases of serious hepatic reactions during treatment with VFEND (including clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities). Instances of hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly haematological malignancy). Transient 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 section 4.8).

Monitoring of hepatic function: Patients at the beginning of therapy with voriconazole and patients who develop abnormal liver function tests during VFEND therapy must be routinely monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of VFEND should be considered if clinical signs and symptoms are consistent with liver disease development.

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 (see section 4.8).

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

Dermatological reactions: Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome, during treatment with VFEND. If patients develop a rash they should be monitored closely and VFEND discontinued if lesions progress. In addition VFEND has been associated with photosensitivity skin reaction especially during long-term therapy. It is recommended that patients should be informed to avoid sunlight during the treatment.

Paediatric use: Safety and effectiveness in paediatric subjects below the age of two years has not been established (see also section 5.1).

Phenytoin (CYP2C9 substrate and potent CYP450 inducer): Careful monitoring of phenytoin levels is recommended when phenytoin is coadministered with voriconazole. Concomitant use of voriconazole and phenytoin should be avoided unless the benefit outweighs the risk (see section 4.5).

Methadone (CYP3A4 substrate). Frequent monitoring for adverse events and toxicity related to methadone, including QTc prolongation, is recommended when coadministered with

voriconazole since methadone levels increased following co-administration of voriconazole. Dose reduction of methadone may be needed (see section 4.5).

Rifabutin (CYP450 inducer): Careful monitoring of full blood counts and adverse reactions to rifabutin (e.g. uveitis) is recommended when rifabutin is coadministered with voriconazole. Concomitant use of voriconazole and rifabutin should be avoided unless the benefit outweighs the risk (see section 4.5).

VFEND oral suspension contains sucrose and should not be given to patients with rare hereditary problems of fructose intolerance, sucrase-isomaltase deficiency or glucose-galactose malabsorption.

4.5 Interaction with other medicinal products and other forms of interaction

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

This section addresses the effects of other medicinal products on voriconazole, the effects of voriconazole on other medicinal products and two-way interactions. The interactions for the first two sections are presented in the following order: contraindications, those requiring dosage 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.

Effects of other medicinal products on voriconazole

Voriconazole is metabolised by cytochrome P450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4. Inhibitors or inducers of these isoenzymes may increase or decrease voriconazole plasma concentrations respectively.

Rifampicin (CYP450 inducer): Rifampicin (600 mg once daily) decreased the C_{max} (maximum plasma concentration) and AUC_{τ} (area under the plasma concentration time curve within a dose interval) of voriconazole by 93% and 96%, respectively. Coadministration of voriconazole and rifampicin is contraindicated (see section 4.3)**.**

Ritonavir (potent CYP450 inducer; CYP3A4 inhibitor and substrate): Ritonavir (400mg twice daily) decreased the steady state C_{max} and AUC_{τ} of oral voriconazole by an average of 66% and 82%, respectively, in healthy subjects with the exception of one subject in whom a 2.5 fold increases in AUC_{τ} was observed. No extrapolation can be made for ritonavir doses lower than 400mg. Repeat oral administration of voriconazole did not have a significant effect on steady state C_{max} and AUC_{τ} of ritonavir following repeat dose administration in healthy subjects. Coadministration of voriconazole and ritonavir (400mg and above twice daily) is contraindicated (see section 4.3).

Carbamazepine and phenobarbital (potent CYP450 inducers): Although not studied, carbamazepine or phenobarbital are likely to significantly decrease plasma voriconazole concentrations. Coadministration of voriconazole with carbamazepine and phenobarbital is contraindicated (see section 4.3).

Cimetidine (non-specific CYP450 inhibitor and increases gastric pH): Cimetidine (400mg twice daily) increased voriconazole C_{max} and AUC_{τ} by 18% and 23%, respectively. No dosage adjustment of voriconazole is recommended.

Ranitidine (increases gastric pH): Ranitidine (150mg twice daily) had no significant effect on voriconazole C_{max} and AUC_{τ}.

Macrolide antibiotics: Erythromycin (CYP3A4 inhibitor; 1g twice daily) and azithromycin (500mg once daily) had no significant effect on voriconazole C_{max} and AUC_{τ}.

Effects of voriconazole on other medicinal products

Voriconazole inhibits the activity of cytochrome P450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4. Therefore there is potential for voriconazole to increase the plasma levels of substances metabolised by these CYP450 isoenzymes.

Terfenadine, astemizole, cisapride, pimozide and quinidine (CYP3A4 substrates): Although not studied, coadministration of voriconazole with terfenadine, astemizole, cisapride, pimozide, or quinidine is contraindicated, since increased plasma concentrations of these medicinal products can lead to QTc prolongation and rare occurrences of *torsades de pointes* (see section 4.3).

Sirolimus (CYP3A4 substrate): Voriconazole increased sirolimus (2mg single dose) C_{max} and AUC_{τ} by 556% and 1014%, respectively. Coadministration of voriconazole and sirolimus is contraindicated (see section 4.3).

Ergot alkaloids (CYP3A4 substrates): Although not studied, voriconazole may increase the plasma concentrations of ergot alkaloids (ergotamine and dihydroergotamine) and lead to ergotism. Coadministration of voriconazole with ergot alkaloids is contraindicated (see section 4.3).

Cyclosporin (CYP3A4 substrate): In stable, renal transplant recipients, voriconazole increased cyclosporin C_{max} and AUC_{τ} by at least 13% and 70% respectively. When initiating voriconazole in patients already receiving cyclosporin it is recommended that the cyclosporin dose be halved and cyclosporin level carefully monitored. Increased cyclosporin levels have been associated with nephrotoxicity. When voriconazole is discontinued, cyclosporin levels must be carefully monitored and the dose increased as necessary.

Tacrolimus (CYP3A4 substrate): Voriconazole increased tacrolimus (0.1mg/kg single dose) C_{max} and AUC_t (area under the plasma concentration time curve to the last quantifiable measurement) by 117% and 221%, respectively. When initiating voriconazole in patients already receiving 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.

Methadone (CYP3A4 substrate): In subjects receiving a methadone maintenance dose (32-100mg once daily) coadministration of oral voriconazole (400mg twice daily for 1 day, then 200mg twice daily for four days) increased the C_{max} and AUC_{τ} of pharmacologically active R-methadone by 31% and 47%, respectively, whereas the C_{max} and AUC_{τ} of the S-enantiomer increased by approximately 65% and 103%, respectively. Voriconazole plasma concentrations during coadministration of methadone were comparable to voriconazole levels (historical data) in healthy subjects without any comedication. Frequent monitoring for adverse events and toxicity related to increased plasma concentrations of methadone, including QT prolongation, is recommended during coadministration. Dose reduction of methadone may be needed.

Oral anticoagulants:
Warfarin (CYP2C9 substrate): Coadministration of voriconazole (300mg twice daily) with warfarin (30mg single dose) increased maximum prothrombin time by 93%. Close monitoring of prothrombin time is recommended if warfarin and voriconazole are coadministered.
Other oral anticoagulants e.g. phenprocoumon, acenocoumarol (CYP2C9, CYP3A4 substrates): Although not studied, voriconazole may increase the plasma concentrations of coumarins and therefore may cause an increase in prothrombin time. If patients receiving coumarin preparations are treated simultaneously with voriconazole, the prothrombin time should be monitored at close intervals and the dosage of anticoagulants adjusted accordingly.

Sulphonylureas (CYP2C9 substrates): Although not studied, voriconazole may increase the plasma levels of sulphonylureas, (e.g. tolbutamide, glipizide, and glyburide) and therefore cause hypoglycaemia. Careful monitoring of blood glucose is recommended during coadministration.

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

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

Vinca Alkaloids (CYP3A4 substrates): Although not studied, voriconazole may increase the plasma levels of the vinca alkaloids (e.g. vincristine and vinblastine) and lead to neurotoxicity.

Prednisolone (CYP3A4 substrate): Voriconazole increased C_{max} and AUC_{τ} of prednisolone (60 mg single dose) by 11% and 34%, respectively. No dosage adjustment is recommended.

Digoxin (P-glycoprotein mediated transport): Voriconazole had no significant effect on C_{max} and AUC_{τ} of digoxin (0.25mg once daily).

Mycophenolic acid (UDP-glucuronyl transferase substrate): Voriconazole had no effect on the C_{max} and AUC_t of mycophenolic acid (1g single dose).

Two-way interactions

Phenytoin (CYP2C9 substrate and potent CYP450 inducer): Concomitant use of voricoazole and phenytoin should be avoided unless the benefit outweighs the risk.
Phenytoin (300mg once daily) decreased the C_{max} and AUC_{τ} of voriconazole by 49% and 69%, respectively. Voriconazole (400mg twice daily, see section 4.2) increased C_{max} and AUC_{τ} of phenytoin (300 mg once daily) by 67% and 81%, respectively. Careful monitoring of phenytoin plasma levels is recommended when phenytoin is coadministered with voriconazole.

Phenytoin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased to 5mg /kg intravenously twice daily or from 200mg to 400mg orally, twice daily (100mg to 200mg orally, twice daily in patients less than 40kg), see section 4.2.

Rifabutin (CYP450 inducer): Concomitant use of voriconazole and rifabutin should be avoided unless the benefit outweighs the risk.
Rifabutin (300mg once daily) decreased the C_{max} and AUC_{τ} of voriconazole at 200mg twice daily by 69 % and 78 %, respectively. During coadministration with rifabutin, the C_{max} and AUC_{τ} of voriconazole at 350mg twice daily were 96% and 68% of the levels when administered alone at 200mg twice daily. At a voriconazole dose of 400mg twice daily C_{max} and AUC_{τ} were 104 % and 87 % higher, respectively, compared with voriconazole alone at 200mg twice daily. Voriconazole at 400mg twice daily increased C_{max} and AUC_{τ} of rifabutin by 195% and 331%, respectively.

If rifabutin coadministration with voriconazole is justified then the maintenance dose of voriconazole may be increased to 5mg/kg intravenously twice daily or from 200mg to 350mg orally, twice daily (100mg to 200mg orally, twice daily in patients less than 40kg) (see section 4.2). Careful monitoring of full blood counts and adverse reactions to rifabutin (e.g. uveitis) is recommended when rifabutin is coadministered with voriconazole.

Omeprazole (CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate): Omeprazole (40mg once daily) increased voriconazole C_{max} and AUC_{τ} by 15% and 41%, respectively. No dosage adjustment of voriconazole is recommended. Voriconazole increased omeprazole C_{max} and AUC_{τ} by 116% and 280%, respectively. When initiating voriconazole in patients already receiving omeprazole, it is recommended that the omeprazole dose be halved. The metabolism of other proton pump inhibitors which are CYP2C19 substrates may also be inhibited by voriconazole.

Indinavir (CYP3A4 inhibitor and substrate): Indinavir (800mg three times daily) had no significant effect on voriconazole C_{max} , C_{min} and AUC_{τ}.
Voriconazole did not have a significant effect on C_{max} and AUC_{τ} of indinavir (800mg three times daily).

Efavirenz (a non-nucleoside reverse transcriptase inhibitor (CYP450 inducer; CYP3A4 inhibitor and substrate)): Steady-state efavirenz (400mg orally once daily) decreased the steady state C_{max} and AUC_{τ} of voriconazole by an average of 61% and 77%, respectively, in healthy subjects. In the same study voriconazole at steady state increased the steady state C_{max} and AUC_{τ} of efavirenz by an average of 38% and 44% respectively, in healthy subjects. Coadministration of voriconazole and efavirenz is contraindicated (see section 4.3).

Other HIV protease inhibitors (CYP3A4 inhibitors): In vitro studies suggest that voriconazole may inhibit the metabolism of HIV protease inhibitors (e.g. saquinavir, amprenavir and nelfinavir). In vitro studies also show that the metabolism of voriconazole may be inhibited by HIV protease inhibitors. However results of the combination of voriconazole with other HIV protease inhibitors cannot be predicted in humans only from in vitro studies. Patients should be carefully monitored for any occurrence of drug toxicity and/or loss of efficacy during the co-administration of voriconazole and HIV protease inhibitors.

Non-nucleoside reverse transcriptase inhibitors (NNRTI) (CYP3A4 substrates, inhibitors or CYP450 inducers): *In vitro* studies show that the metabolism of voriconazole may be inhibited by delavirdine. Although not studied, the metabolism of voriconazole may be induced by nevirapine. An in-vivo study showed that voriconazole inhibited the metabolism of efavirenz. Voriconazole may also inhibit the metabolism of NNRTIs besides efavirenz. Patients should be carefully monitored for any occurrence of drug toxicity and/or lack of efficacy during the coadministration of voriconazole and NNRTIs. Coadministration of voriconazole with efavirenz is contraindicated (see section 4.3)

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 levels of substances metabolised by CYP3A4 isoenzymes (certain antihistamines, quinidine, cisapride, pimozide) co-administration is contraindicated (See section 4.3).

4.6 Pregnancy and lactation

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

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk to humans is unknown.

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

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

Lactation

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

4.7 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.

4.8 Undesirable effects

The safety profile of voriconazole is based on an integrated safety database of more than 2000 subjects (1655 patients in therapeutic trials). This represents a heterogeneous population, containing patients with haematological malignancy, HIV infected patients with oesophageal candidiasis and refractory fungal infections, non-neutropenic patients with candidaemia or aspergillosis and healthy volunteers. Five hundred and sixty one patients had a duration of voriconazole therapy of greater than 12 weeks, with 136 patients receiving voriconazole for over 6 months.

In the table below, since the majority of the studies were of an open nature all causality adverse events, by system organ class and frequency (very common >1/10, common >1/100 and <1/10, uncommon >1/1000 and <1/100 and rare, <1/1000) if possibly causally related are listed. The most commonly reported adverse reactions were visual disturbances, fever, rash, vomiting, nausea, diarrhoea, headache, peripheral oedema and abdominal pain. The severity of the adverse reactions was generally mild to moderate. No clinically significant differences were seen when the safety data were analysed by age, race, or gender.

Undesirable effects reported in subjects receiving voriconazole

Body System	**Adverse Drug Reactions**
Body as a whole	
Very common	Fever, headache, abdominal pain
Common	Chills, asthenia, back pain, chest pain, injection site reaction/inflammation, face oedema, flu syndrome
Uncommon	Allergic reaction, anaphylactoid reaction, angioedema, peritonitis
Cardiovascular	
Common	Hypotension, thrombophlebitis, phlebitis
Uncommon	Atrial arrhythmia, bradycardia, syncope, tachycardia, ventricular arrhythmia, ventricular fibrillation, supraventricular tachycardia, QT interval prolongation
Rare	AV complete block, bundle branch block, nodal arrhythmia, ventricular tachycardia, torsade de pointes
Digestive	
Very common	Nausea, vomiting, diarrhoea
Common	Elevated liver function tests (includingASAT, ALAT, alkaline phosphatase, GGT, LDH, bilirubin), jaundice, cheilitis, cholestatic jaundice, gastroenteritis
Uncommon	Cholecystitis, cholelithiasis, constipation, duodenitis, dyspepsia, enlarged liver, gingivitis, glossitis, hepatitis, hepatic failure, pancreatitis, tongue oedema
Rare	Pseudomembranous colitis, hepatic coma
Endocrine	
Uncommon	Adrenal cortex insufficiency
Haemic and lymphatic	
Common	Thrombocytopenia, anaemia (including macrocytic, microcytic, normocytic, megaloblastic, aplastic), leukopenia, pancytopenia, purpura
Uncommon	Lymphadenopathy, agranulocytosis, eosinophilia, disseminated intravascular coagulation, marrow depression
Rare	Lymphangitis
Metabolic and nutritional	
Very common	Peripheral oedema
Common	Hypokalaemia, creatinine increased, hypoglycaemia

Uncommon	BUN increased, albuminuria, hypercholesterolaemia
Rare	Hyperthyroidism, hypothyroidism

Musculoskeletal	
Uncommon	Arthritis
Nervous	
Common	Dizziness, hallucinations, confusion, depression, anxiety, tremor, agitation, paraesthesia
Uncommon	Ataxia, brain oedema, diplopia, hypoaesthesia, nystagmus, vertigo
Rare	Guillain-Barre syndrome, oculogyric crisis, hypertonia, Extrapyramidal syndrome, insomnia, encephalopathy, somnolence during infusion
Respiratory	
Common	Respiratory distress syndrome, lung oedema, sinusitis
Skin and appendages	
Very common	Rash
Common	Pruritus, maculopapular rash, photosensitivity skin reaction, alopecia, exfoliative dermatitis
Uncommon	Fixed drug eruption, eczema, psoriasis, Stevens-Johnson syndrome, urticaria
Rare	Discoid lupus erythematosis, erythema multiforme, toxic epidermal necrolysis
Special senses	
Very Common	Visual disturbances (including altered/enhanced visual perception, decrease in ERG amplitude, blurred vision, colour vision change, photophobia)
Uncommon	Blepharitis, optic neuritis, papilloedema, scleritis, altered taste perception
Rare	Retinal haemorrhage, corneal opacity, optic atrophy, hypoacusis, tinnitus
Urogenital	
Common	Acute kidney failure, haematuria
Uncommon	Nephritis
Rare	Kidney tubular necrosis

Altered taste perception
In the combined data from three bioequivalence studies using the powder for oral suspension formulation, treatment related taste perversion was recorded in 12 (14%) of subjects.

Visual disturbances
Voriconazole treatment-related visual disturbances were very common. In clinical trials, short-term as well as long-term treatment, approximately 30% of subjects experienced altered/enhanced visual perception, blurred vision, colour vision change or photophobia. The visual disturbances are transient and fully reversible, with the majority spontaneously resolving within 60 minutes and no clinically significant long-term visual effects were observed. There is evidence of attenuation with repeated doses of voriconazole. The visual disturbance is generally mild, rarely results in discontinuation and has not been associated with long-term sequelae. Visual disturbances may be associated with higher plasma concentrations and/or doses.

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 treatment and were fully reversible on withdrawal of voriconazole.

Dermatological reactions
Dermatological reactions were 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 rarely developed serious cutaneous reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme during treatment with VFEND.

If patients develop a rash they should be monitored closely and VFEND discontinued if lesions progress. Photosensitivity reactions have been reported, especially during long-term therapy (see also section 4.4).

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

Voriconazole has been infrequently associated with cases of serious hepatic toxicity in patients with other serious underlying conditions. This includes cases of jaundice, and rare cases of hepatitis and hepatic failure leading to death (see section 4.4).

4.9 Overdose

In clinical trials there were 3 cases of accidental overdose. All occurred in paediatric patients, who received up to five times the recommended intravenous dose of voriconazole. A single adverse reaction of photophobia of 10 minutes duration was reported.

There is no known antidote to voriconazole.

Voriconazole is haemodialysed with a clearance of 121ml/min. In an overdose, haemodialysis may assist in the removal of voriconazole from the body.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC code: J02A C03
Antimycotics for Systemic Use – Triazole derivatives

Mechanism of action

I*n 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*) and fungicidal activity against all *Aspergillus* species tested. In addition voriconazole shows *in vitro* fungicidal activity against emerging fungal pathogens, including those such as *Scedosporium* or *Fusarium* which have limited susceptibility to existing antifungal agents. Its mode of action is inhibition of fungal cytochrome P450-mediated 14α-sterol demethylation, an essential step in ergosterol biosynthesis.

In animal studies there is a correlation between minimum inhibitory concentration values and efficacy against experimental mycoses. By contrast, in clinical studies, there appears to be no correlation between minimum inhibitory concentration values and clinical outcome. Furthermore, there does not appear to be a correlation between plasma levels and clinical outcome. This is typical of azole antimycotics.

Microbiology

Clinical efficacy (with partial or complete response, see below under Clinical Experience) has been demonstrated for *Aspergillus* spp. including *A. flavus, A. fumigatus, A. terreus, A. niger, A. nidulans, Candida* spp., including *C. albicans, C. glabrata, C. krusei, C. parapsilosis and C. tropicalis* and limited numbers of *C. dubliniensis,*

C. inconspicua, and *C. guilliermondii, Scedosporium* spp., including *S. apiospermum, S. prolificans and Fusarium* spp.

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 2µg/ml.

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

Specimens for fungal culture and other relevant laboratory studies (serology, histopathology) should be obtained prior to therapy to isolate and identify causative organisms. Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.

Clinical isolates with decreased susceptibility to voriconazole have been identified. However, elevated minimum inhibitory concentrations did not always correlate with clinical failure and clinical success has been observed in patients infected with organisms resistant to other azoles. Correlation of *in vitro* activity with clinical outcome is difficult owing to the complexity of the patients studied in clinical trials; breakpoints for voriconazole remain to be established.

Clinical Experience

Successful outcome in this section is defined as complete or partial response.

Aspergillus infections – efficacy in aspergillosis patients with poor prognosis
Voriconazole has *in vitro* fungicidal activity against *Aspergillus* spp. The efficacy and survival benefit of voriconazole versus conventional amphotericin B in the primary treatment of acute invasive aspergillosis was demonstrated in an open, randomised, multicentre study in 277 immunocompromised patients treated for 12 weeks. A satisfactory global response (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 31 % of patients treated with comparator. The 84-day survival rate for voriconazole was statistically significantly higher than that for the comparator and a clinically and statistically significant benefit was shown in favour of voriconazole for both time to death and time to discontinuation due to toxicity.

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).

The studies included cerebral, sinus, pulmonary and disseminated aspergillosis in patients with bone marrow and solid organ transplants, haematological malignancies, cancer and AIDS.

Candidaemia in non-neutropenic patients.

The efficacy of voriconazole compared to the regimen of amphotericin B followed by fluconazole in the primary treatment of candidaemia was demonstrated in an open, comparative study. Three hundred and seventy non-neutropenic patients (above 12 years of age) with documented candidaemia were included in the study, of whom 248 were treated with voriconazole. Nine subjects in the voriconazole group and five in the amphotericin B followed by fluconazole group also had mycologically proven infection in deep tissue. Patients with renal failure were excluded from this study. The median

treatment duration was 15 days in both treatment arms. In the primary analysis, successful response as assessed by a Data Review Committee (DRC) blinded to study medication was defined as resolution/improvement in all clinical signs and symptoms of infection with eradication of *Candida* from blood and infected deep tissue sites at 12 weeks after the end of therapy (EOT). Patients who did not have an assessment 12 weeks after EOT were counted as failures. In this analysis a successful response was seen in 41% of patients in both treatment arms.

In a secondary analysis, which utilised *DRC* assessments at the latest evaluable time point (EOT, or 2, 6, or 12 weeks after EOT) voriconazole and the regimen of amphotericin B followed by fluconazole had successful response rates of 65% and 71%, respectively. The Investigator's assessment of successful outcome at each of these time points is shown in the following table.

Timepoint	***Voriconazole (N=248)***	***Amphotericin B → fluconazole (N=122)***
EOT	***178 (72%)***	***88 (72%)***
2 weeks after EOT	***125 (50%)***	***62 (51%)***
6 weeks after EOT	***104 (42%)***	***55 (45%)***
12 weeks after EOT	***104 (42%)***	***51 (42%)***

There are no data in children below the age of 12 years for this indication.

Serious refractory *Candida* infections
The study comprised 55 patients with serious refractory systemic *Candida* infections (including candidaemia, 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.

Scedosporium and *Fusarium* infections
Voriconazole was shown to be effective against the following rare fungal pathogens:

Scedosporium spp.: Successful response to voriconazole therapy was seen in 16 (6 complete, 10 partial responses) of 28 patients with *S. apiospermum* and in 2 (both partial responses) of 7 patients with *S. prolificans* infection. In addition, a successful response was seen in 1 of 3 patients with infections caused by more than one organism including *Scedosporium* spp.

Fusarium spp.: Seven (3 complete, 4 partial responses) of 17 patients were successfully treated with voriconazole. Of these 7 patients, 3 had eye, 1 had sinus, and 3 had disseminated infection. Four additional patients with fusariosis had an infection caused by several organisms; two of them had a successful outcome.

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
In clinical trials, 561 patients received voriconazole therapy for greater than 12 weeks, with 136 patients receiving voriconazole for over 6 months.

Experience in paediatric patients
Sixty-one paediatric patients aged 9 months up to 15 years who had definite or probable invasive fungal infections, were treated with voriconazole. This population included 34 patients 2 to < 12 years old and 20 patients 12-15 years of age.

The majority (57/61) had failed previous antifungal therapies. Therapeutic studies included 5 patients aged 12-15 years, the remaining patients received voriconazole in the compassionate use programmes. Underlying diseases in these patients included haematological malignancies and aplastic anaemia (27 patients) and chronic granulomatous disease (14 patients). The most commonly treated fungal infection was aspergillosis (43/61; 70%).

Clinical Studies Examining QT Interval

A placebo-controlled, randomized, single-dose, crossover study to evaluate the effect on the QT interval of healthy volunteers was conducted with three oral doses of voriconazole and ketoconazole. The placebo-adjusted mean maximum increases in QTc from baseline after 800, 1200 and 1600mg of voriconazole were 5.1, 4.8, and 8.2msec, respectively and 7.0msec for ketoconazole 800mg. No subject in any group had an increase in QTc of ≥60msec from baseline. No subject experienced an interval exceeding the potentially clinically relevant threshold of 500msec.

5.2 Pharmacokinetic properties

General pharmacokinetic characteristics
The pharmacokinetics of voriconazole have been characterised in healthy subjects, special populations and patients. During oral administration of 200mg or 300mg twice daily for 14 days in patients at risk of aspergillosis (mainly patients with malignant neoplasms of lymphatic or haematopoietic tissue), the observed pharmacokinetic characteristics of rapid and consistent absorption, accumulation and non-linear pharmacokinetics were in agreement with those observed in healthy subjects.

The pharmacokinetics of voriconazole are non-linear due to saturation of its metabolism. Greater than proportional increase in exposure is observed with increasing dose. It is estimated that, on average, increasing the oral dose from 200mg twice daily to 300mg twice daily leads to a 2.5-fold increase in exposure (AUCτ). When the recommended intravenous or oral loading dose regimens are administered, 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 plasma voriconazole concentrations being achieved by day 6 in the majority of subjects.

Absorption
Voriconazole is rapidly and almost completely absorbed following oral administration, with maximum plasma concentrations (C_{max}) achieved 1-2 hours after dosing. The absolute bioavailability of voriconazole after oral administration is estimated to be 96 %. Bioequivalence was established between the 200mg tablet and the 40mg/ml oral suspension when administered as a 200mg dose. When multiple doses of voriconazole oral suspension are administered with high fat meals, C_{max} and AUC_{τ} are reduced by 58% and 37% respectively. The absorption of voriconazole is not affected by changes in gastric pH.

Distribution
The volume of distribution at steady state for voriconazole is estimated to be 4.6l/kg, suggesting extensive distribution into tissues. Plasma protein binding is estimated to be 58%.
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 hepatic cytochrome P450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4.

The inter-individual variability of voriconazole pharmacokinetics is high.

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. This metabolite has minimal antifungal activity and 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 radiolabelled dose of voriconazole, approximately 80% of the radioactivity is recovered in the urine after multiple intravenous dosing and 83% in the urine after multiple oral dosing. The majority (> 94 %) of the total radioactivity is excreted in the first 96 hours after both oral and intravenous dosing.

The terminal half-life of voriconazole depends on dose and is approximately 6 hours at 200mg (orally). Because of non-linear pharmacokinetics, the terminal half-life is not useful in the prediction of the accumulation or elimination of voriconazole.

Pharmacokinetic-Pharmacodynamic relationships

In 10 therapeutic studies, the median for the average and maximum plasma concentrations in individual subjects across the studies was 2425ng/ml (inter-quartile range 1193 to 4380ng/ml) and 3742ng/ml (inter-quartile range 2027 to 6302ng/ml), respectively. A positive association between mean, maximum or minimum plasma voriconazole concentration and efficacy in therapeutic studies was not found.

Pharmacokinetic-Pharmacodynamic analyses of clinical trial data identified positive associations between plasma voriconazole concentrations and both liver function test abnormalities and visual disturbances.

Pharmacokinetics in special patient groups

Gender

In an oral multiple dose study, 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 C_{max} and AUC_τ were observed between healthy elderly males and healthy elderly females (≥65 years).

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

Elderly

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

In the therapeutic studies no dosage adjustment was made on the basis of age. A relationship between plasma concentrations and age was observed. The safety profile of voriconazole in young and elderly patients was similar and, therefore, no dosage adjustment is necessary for the elderly (See section 4.2).

Renal impairment
In an oral single dose (200mg) study in subjects with normal renal function and mild (creatinine clearance 41-60ml/min) to severe (creatinine clearance < 20ml/min) renal impairment, the pharmacokinetics of voriconazole were not significantly affected by renal impairment. The plasma protein binding of voriconazole was similar in subjects with different degrees of renal impairment. See dosing and monitoring recommendations under sections 4.2 and 4.4.

Hepatic impairment
After an oral single dose (200mg), AUC was 233% higher in subjects with mild to moderate hepatic cirrhosis (Child-Pugh A and B) compared with subjects with normal hepatic function. Protein binding of voriconazole was not affected by impaired hepatic function.

In an oral multiple dose study, AUC_{τ} was similar in subjects with moderate hepatic cirrhosis (Child-Pugh B) given a maintenance dose of 100mg twice daily and subjects with normal hepatic function given 200mg twice daily. No pharmacokinetic data are available for patients with severe hepatic cirrhosis (Child-Pugh C). See dosing and monitoring recommendations under sections 4.2 and 4.4.

5.3 Preclinical safety data

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 postnatal development study in rats at exposures lower than those obtained in humans with therapeutic doses, voriconazole prolonged the duration of gestation and labour 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 oestradiol levels, and are consistent with those observed with other azole antifungal agents.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose (0.54g per ml of suspension)
Silica, Colloidal
Titanium Dioxide (E171)
Xanthan Gum
Sodium Citrate
Sodium Benzoate (E211)
Citric Acid
Natural Orange Flavour (containing orange oil, maltodextrin and tocopherol)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in 6.6. It is not intended that the suspension be further diluted with water or other vehicles.

6.3 Shelf life

The shelf-life of the powder for oral suspension is 18 months.

The shelf-life of the constituted suspension is 14 days.

6.4 Special precautions for storage

Powder for oral suspension: Store at 2°C - 8°C (in a refrigerator) before constitution.
Constituted suspension: Do not store above 30°C, do not refrigerate or freeze.
Keep the container tightly closed.
Any remaining suspension should be discarded 14 days after constitution.

6.5 Nature and contents of container

One 100ml high-density polyethylene (HDPE) bottle (with a polypropylene child resistant closure) contains 45g of powder for oral suspension. Following constitution, the volume of the suspension is 75ml, providing a usable volume of 70ml.
A measuring cup (graduated to indicate 23mL), 5ml oral syringe and a press-in bottle adaptor are also provided.
Pack size: 1 bottle

6.6 Instructions for use and handling and disposal

Constitution instructions:

1. Tap the bottle to release the powder.
2. Measure 23mL of water by filling the measuring cup to the top of the marked line. Add the water to the bottle. Using the cup measure another 23mL of water and add this to the bottle.
3. Shake the closed bottle vigorously for about 1 minute.
4. Remove child-resistant cap. Press bottle adaptor into the neck of the bottle.
5. Replace the cap.
6. Write the date of expiration of the constituted suspension on the bottle label (the shelf-life of the constituted suspension is 14 days).

Instructions for use:

Shake the closed bottle of constituted suspension for approximately 10 seconds before each use.

Once constituted, VFEND oral suspension should only be administered using the oral syringe supplied with each pack. Refer to the patient leaflet for more detailed instructions for use.

7. MARKETING AUTHORISATION HOLDER

Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ, United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/212/026

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 February 2004

10. DATE OF REVISION OF THE TEXT

ANNEX II

A. MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

A MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Tablets
Heinrich Mack Nachf. GmbH & Co.KG
Ein Unternehmen der Pfizer-Gruppe
Heinrich-Mack-Str. 35
D-89257 Illertissen
Germany

Powder for solution for infusion and powder for oral suspension:
Pfizer PGM
Zone Industrielle
29 Route des Industries
37530 Pocé-Sur-Cisse
France

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch

B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Blister pack for 50mg film-coated tablets – Pack of 2

1. NAME OF THE MEDICINAL PRODUCT

VFEND 50mg film-coated tablets
Voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50mg voriconazole

3. LIST OF EXCIPIENTS

Includes lactose monohydrate - see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

2 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read enclosed leaflet before use

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/001

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Blister pack for 50mg film-coated tablets – Pack of 10

1. NAME OF THE MEDICINAL PRODUCT

VFEND 50mg film-coated tablets
Voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50mg voriconazole

3. LIST OF EXCIPIENTS

Includes lactose monohydrate - see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

10 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read enclosed leaflet before use

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/002

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Blister pack for 50mg film-coated tablets – Pack of 14

1. NAME OF THE MEDICINAL PRODUCT

VFEND 50mg film-coated tablets
Voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50mg voriconazole

3. LIST OF EXCIPIENTS

Includes lactose monohydrate - see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read enclosed leaflet before use

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/003

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Blister pack for 50mg film-coated tablets – Pack of 20

1. NAME OF THE MEDICINAL PRODUCT

VFEND 50mg film-coated tablets
Voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50mg voriconazole

3. LIST OF EXCIPIENTS

Includes lactose monohydrate - see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

20 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read enclosed leaflet before use

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/004

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Blister pack for 50mg film-coated tablets – Pack of 28

1. NAME OF THE MEDICINAL PRODUCT

VFEND 50mg film-coated tablets
Voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50mg voriconazole

3. LIST OF EXCIPIENTS

Includes lactose monohydrate - see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read enclosed leaflet before use

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/005

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Blister pack for 50mg film-coated tablets – Pack of 30

1. NAME OF THE MEDICINAL PRODUCT

VFEND 50mg film-coated tablets
Voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50mg voriconazole

3. LIST OF EXCIPIENTS

Includes lactose monohydrate - see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read enclosed leaflet before use

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/006

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Blister pack for 50mg film-coated tablets – Pack of 50

1. NAME OF THE MEDICINAL PRODUCT

VFEND 50mg film-coated tablets
Voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50mg voriconazole

3. LIST OF EXCIPIENTS

Includes lactose monohydrate - see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

50 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read enclosed leaflet before use

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/007

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Blister pack for 50mg film-coated tablets – Pack of 56

1. NAME OF THE MEDICINAL PRODUCT

VFEND 50mg film-coated tablets
Voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50mg voriconazole

3. LIST OF EXCIPIENTS

Includes lactose monohydrate - see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

56 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read enclosed leaflet before use

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/008

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Blister pack for 50mg film-coated tablets – Pack of 100

1. NAME OF THE MEDICINAL PRODUCT

VFEND 50mg film-coated tablets
Voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50mg voriconazole

3. LIST OF EXCIPIENTS

Includes lactose monohydrate - see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read enclosed leaflet before use

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/009

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister foil for 50mg film-coated tablets (all blister packs)

1. NAME OF THE MEDICINAL PRODUCT

VFEND 50mg film-coated tablets
Voriconazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd (as MA Holder logo)

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Bottle outer pack for 50mg film-coated tablets – Pack of 2

1. NAME OF THE MEDICINAL PRODUCT

VFEND 50mg film-coated tablets
Voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50mg voriconazole

3. LIST OF EXCIPIENTS

Includes lactose monohydrate - see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

2 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read enclosed leaflet before use

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/010

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Bottle label for 50mg film-coated tablets – Pack of 2

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

VFEND 50mg film-coated tablets
Voriconazole
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 film-coated tablets
Each tablet contains 50mg voriconazole

Medicinal product subject to medical prescription.
Keep out of the reach and sight of children.
Read enclosed leaflet before use.

Pfizer Limited
Sandwich
Kent, CT13 9NJ, UK

EU/I/02/212/010

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Bottle outer pack for 50mg film-coated tablets – Pack of 30

1. NAME OF THE MEDICINAL PRODUCT

VFEND 50mg film-coated tablets
Voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50mg voriconazole

3. LIST OF EXCIPIENTS

Includes lactose monohydrate - see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read enclosed leaflet before use

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/011

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Bottle label for 50mg film-coated tablets – Pack of 30

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

VFEND 50mg film-coated tablets
Voriconazole
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

30 film-coated tablets
Each tablet contains 50 mg voriconazole

Medicinal product subject to medical prescription.
Keep out of the reach and sight of children.
Read enclosed leaflet before use.

Pfizer Limited
Sandwich
Kent, CT13 9NJ, UK

EU/I/02/212/011

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Bottle outer pack for 50mg film-coated tablets – Pack of 100

1. NAME OF THE MEDICINAL PRODUCT

VFEND 50mg film-coated tablets
Voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50mg voriconazole

3. LIST OF EXCIPIENTS

Includes lactose monohydrate - see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read enclosed leaflet before use

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/012

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Bottle label for 50mg film-coated tablets – Pack of 100

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

VFEND 50mg film-coated tablets
Voriconazole
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 film-coated tablets
Each tablet contains 50mg voriconazole

Medicinal product subject to medical prescription.
Keep out of the reach and sight of children.
Read enclosed leaflet before use.

Pfizer Limited
Sandwich
Kent, CT13 9NJ, UK

EU/I/02/212/012

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Blister pack for 200mg film-coated tablets – Pack of 2

1. NAME OF THE MEDICINAL PRODUCT

VFEND 200mg film-coated tablets
Voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200mg voriconazole

3. LIST OF EXCIPIENTS

Includes lactose monohydrate - see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

2 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read enclosed leaflet before use

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/013

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Blister pack for 200mg film-coated tablets - Pack of 10

1. NAME OF THE MEDICINAL PRODUCT

VFEND 200mg film-coated tablets
Voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200mg voriconazole

3. LIST OF EXCIPIENTS

Includes lactose monohydrate - see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

10 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read enclosed leaflet before use

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/014

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Blister pack for 200mg film-coated tablets – Pack of 14

1. NAME OF THE MEDICINAL PRODUCT

VFEND 200mg film-coated tablets
Voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200mg voriconazole

3. LIST OF EXCIPIENTS

Includes lactose monohydrate - see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read enclosed leaflet before use

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/015

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Blister pack for 200mg film-coated tablets – Pack of 20

1. NAME OF THE MEDICINAL PRODUCT

VFEND 200mg film-coated tablets
Voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200mg voriconazole

3. LIST OF EXCIPIENTS

Includes lactose monohydrate - see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

20 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read enclosed leaflet before use

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/016

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Blister pack for 200mg film-coated tablets – Pack of 28

1. NAME OF THE MEDICINAL PRODUCT

VFEND 200mg film-coated tablets
Voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200mg voriconazole

3. LIST OF EXCIPIENTS

Includes lactose monohydrate - see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read enclosed leaflet before use

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/017

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Blister pack for 200mg film-coated tablets - Pack of 30

1. NAME OF THE MEDICINAL PRODUCT

VFEND 200mg film-coated tablets
Voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200mg voriconazole

3. LIST OF EXCIPIENTS

Includes lactose monohydrate - see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read enclosed leaflet before use

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/018

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Blister pack for 200mg film-coated tablets – Pack of 50

1. NAME OF THE MEDICINAL PRODUCT

VFEND 200mg film-coated tablets
Voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200mg voriconazole

3. LIST OF EXCIPIENTS

Includes lactose monohydrate - see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

50 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read enclosed leaflet before use

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/019

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Blister pack for 200mg film-coated tablets – Pack of 56

1. NAME OF THE MEDICINAL PRODUCT

VFEND 200mg film-coated tablets
Voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200mg voriconazole

3. LIST OF EXCIPIENTS

Includes lactose monohydrate - see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

56 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read enclosed leaflet before use

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/020

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Blister pack for 200mg film-coated tablets – Pack of 100

1. NAME OF THE MEDICINAL PRODUCT

VFEND 200mg film-coated tablets
Voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200mg voriconazole

3. LIST OF EXCIPIENTS

Includes lactose monohydrate - see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read enclosed leaflet before use

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/021

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister foil for 200mg film-coated tablets (all blister packs)

1. NAME OF THE MEDICINAL PRODUCT

VFEND 200mg film-coated tablets
Voriconazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ltd (as MA Holder logo)

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Bottle outer pack for 200mg film-coated tablets – Pack of 2

1. NAME OF THE MEDICINAL PRODUCT

VFEND 200mg film-coated tablets
Voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200mg voriconazole

3. LIST OF EXCIPIENTS

Includes lactose monohydrate - see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

2 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read enclosed leaflet before use

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/022

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Bottle label for 200mg film-coated tablets – Pack of 2

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

VFEND 200mg film-coated tablets
Voriconazole
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 film-coated tablets
Each tablet contains 200mg voriconazole

Medicinal product subject to medical prescription.
Keep out of the reach and sight of children.
Read enclosed leaflet before use.

Pfizer Limited
Sandwich
Kent, CT13 9NJ, UK

EU/I/02/212/022

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Bottle outer pack for 200mg film-coated tablets – Pack of 30

1. NAME OF THE MEDICINAL PRODUCT

VFEND 200mg film-coated tablets
Voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200mg voriconazole

3. LIST OF EXCIPIENTS

Includes lactose monohydrate - see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read enclosed leaflet before use

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/023

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Bottle label for 200mg film-coated tablets – Pack of 30

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

VFEND 200mg film-coated tablets
Voriconazole
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

30 film-coated tablets
Each tablet contains 200mg voriconazole

Medicinal product subject to medical prescription.
Keep out of the reach and sight of children.
Read enclosed leaflet before use.

Pfizer Limited
Sandwich
Kent, CT13 9NJ, UK

EU/I/02/212/023

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Bottle outer pack for 200mg film-coated tablets – Pack of 100

1. NAME OF THE MEDICINAL PRODUCT

VFEND 200mg film-coated tablets
Voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200mg voriconazole

3. LIST OF EXCIPIENTS

Includes lactose monohydrate - see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read enclosed leaflet before use

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/024

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Bottle label for 200mg film-coated tablets – Pack of 100

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

VFEND 200mg film-coated tablets
Voriconazole
Oral use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 film-coated tablets
Each tablet contains 200mg voriconazole

Medicinal product subject to medical prescription.
Keep out of the reach and sight of children.
Read enclosed leaflet before use.

Pfizer Limited
Sandwich
Kent, CT13 9NJ, UK

EU/I/02/212/024

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

VFEND 200mg powder for solution for infusion
Voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Equivalent to 10mg/ml voriconazole when reconstituted as recommended

3. LIST OF EXCIPIENTS

Excipient: sulphobutylether beta cyclodextrin sodium

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder for solution for infusion
Single use vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Reconstitute and dilute before use
Intravenous use only
Not for bolus injection

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Read enclosed leaflet before use
Infuse at a maximum rate of 3mg/kg per hour

8. EXPIRY DATE

EXP:
Shelf life after reconstitution: 24 hours when stored at 2°C - 8°C

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/025

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label on the vial

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

VFEND 200mg powder for solution for infusion
Voriconazole
Intravenous use only
Single use vial

2. METHOD OF ADMINISTRATION

Reconstitute and dilute before use – see leaflet

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Batch:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

200mg per vial (10 mg/ml)
1 vial

PARTICULARS TO APPEAR ON THE OUTER PACKAGING OR, WHERE THERE IS NO OUTER PACKAGING, ON THE IMMEDIATE PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

VFEND 40mg/ml powder for oral suspension
Voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of the constituted suspension contains 40mg voriconazole

3. LIST OF EXCIPIENTS

Also contains sucrose – see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Each bottle contains 45g powder for oral suspension providing 70ml of suspension when constituted

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use after constitution
Shake bottle for approximately 10 seconds before use
Use the oral syringe provided in the pack to measure the correct dose

Read the package leaflet before use

Constitution instructions:
Tap the bottle to release the powder
Add 46ml of water and shake vigorously for about 1 minute
Further dilution is not appropriate

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

–

8. EXPIRY DATE

EXP:

Any remaining suspension should be discarded 14 days after constitution

9. SPECIAL STORAGE CONDITIONS

Powder for oral suspension: store at 2°C - 8°C (in a refrigerator) before constitution

For the constituted oral suspension:
Do not store above 30°C
Do not refrigerate or freeze

Keep the container tightly closed

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

–

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ, United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/026

13. MANUFACTURER'S BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

–

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Bottle

1. NAME OF THE MEDICINAL PRODUCT

VFEND 40mg/ml powder for oral suspension
Voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of the constituted suspension contains 40mg voriconazole

3. LIST OF EXCIPIENTS

Also contains sucrose – see leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

Each bottle contains 45g powder for oral suspension providing 70ml of suspension when constituted

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use after constitution
Shake bottle for approximately 10 seconds before use
Use the oral syringe provided in the pack to measure the correct dose

Read enclosed leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. EXPIRY DATE

EXP:

Any remaining suspension should be discarded 14 days after constitution

Expiry date of the constituted suspension:

8. SPECIAL STORAGE CONDITIONS

Powder for oral suspension: store at 2°C - 8°C (in a refrigerator) before constitution

For the constituted oral suspension:
Do not store above 30°C
Do not refrigerate or freeze

Keep the container tightly closed

9. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Sandwich
Kent, CT13 9NJ, United Kingdom

10. MANUFACTURER'S BATCH NUMBER

Batch:

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

B. PACKAGE LEAFLET

PACKAGE LEAFLET

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet we explain:

VFEND 50 mg film-coated tablets
voriconazole

- The active substance is voriconazole. Each tablet contains 50mg voriconazole.
- The other ingredients are lactose monohydrate, pregelatinised starch, croscarmellose sodium, povidone and magnesium stearate which make up the tablet core and hypromellose, titanium dioxide (E171), lactose monohydrate and glycerol triacetate which make up the film-coat.

The marketing authorisation for VFEND is held by:
Pfizer Limited, Sandwich, Kent, CT13 9NJ, United Kingdom.

VFEND is made by:
Heinrich Mack Nachf. GmbH & Co. KG
Heinrich-Mack-Str. 35 D-89257 Illertissen Germany (which is wholly owned by Pfizer Inc.)

1. WHAT VFEND IS AND WHAT IT IS USED FOR

VFEND is supplied as white round film-coated tablets with Pfizer marked on one side and VOR50 on the reverse.

VFEND belongs to a group of medicines called triazole antifungal agents. These medicines are used to treat a wide variety of fungal infections. VFEND works by killing or stopping the growth of the fungi that cause infections.

What fungal infections are treated with VFEND?
VFEND is used to treat serious fungal infections caused by *Aspergillus*, *Scedosporium*, *Fusarium* and *Candida*.

The information in this leaflet is about VFEND 50mg tablets only.For further information on VFEND 200mg tablets, VFEND powder for solution for infusion or VFEND powder for oral suspension, please see the User Package Leaflets for these products.

VFEND has been prescribed for you. Do not allow anyone else to take it.
This product should only be taken under the supervision of a doctor. VFEND is mainly for use in seriously ill patients.

2. WHAT YOU SHOULD KNOW BEFORE YOU TAKE VFEND

Do not take VFEND:
- if you are allergic to voriconazole or any of the other ingredients of VFEND.

It is very important that you inform your doctor or pharmacist if you are taking or have taken any other medicines, even those that are obtained without a prescription. Some medicines affect the way VFEND works, or VFEND may affect the way they work.

A list of the medicines that may affect VFEND is shown in the section 'Taking other medicines with VFEND'. However, the medicines in the following list must not be taken during your course of VFEND treatment:

- Terfenadine (used for allergy)
- Astemizole (used for allergy)
- Cisapride (used for stomach problems)
- Pimozide (used for treating mental illness)
- Quinidine (used for irregular heart beat)
- Rifampicin (used for treating tuberculosis)
- Carbamazepine (used to treat seizures)
- Phenobarbital (used for severe insomnia and seizures)
- Ergot alkaloids (e.g. ergotamine, dihydroergotamine; used for migraine)
- Sirolimus (used in transplant patients)
- Efavirenz (used for treating HIV)
- Ritonavir (used for treating HIV) in doses of 400mg and more twice daily

Take special care with VFEND:

- if you are known to have an abnormality of electrocardiogram (ECG) called 'long QT syndrome'.

Before being treated with VFEND, tell your doctor if:

- you have had an allergic reaction to other azoles.

- you are suffering from, or have ever suffered from liver disease. If you have liver disease, your doctor may prescribe a lower dose of VFEND. Your doctor should also monitor your liver function while you are being treated with VFEND by doing blood tests.

- you are already being treated with phenytoin (used to treat epilepsy). Your blood concentration of phenytoin will need to be monitored during your treatment with VFEND and your dose may be adjusted.

- you are already being treated with rifabutin (used for treating tuberculosis). Your blood counts and side effects to rifabutin will need to be monitored.

While being treated with VFEND:

- tell your doctor immediately if you develop a severe skin rash or blisters.

- avoid sunlight while being treated with VFEND, as an increased sensitivity of skin to the sun's UV rays can occur.

- your doctor should monitor the function of your liver and kidney by doing blood tests.

Taking VFEND with food and drink:
VFEND tablets must be taken at least one hour before or one hour after a meal.

Pregnancy
VFEND must not be taken during pregnancy, unless indicated by your doctor. Effective contraception must be used in women of childbearing potential. Contact your doctor immediately if you become pregnant while taking VFEND.

Breast-feeding
VFEND must not be taken during breast-feeding. Ask your doctor or pharmacist for advice before taking any medicine whilst breast-feeding.

Driving and using machines:
VFEND may cause blurring of vision or uncomfortable sensitivity to light. While affected, do not drive or operate any tools or machines. Contact your doctor if you experience this.

Important information about some of the ingredients of VFEND:
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.

Taking other medicines with VFEND:
Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including those that are obtained without a prescription.

Some medicines, when taken at the same time as VFEND, may affect the way VFEND works or VFEND may affect the way they work. Tell your doctor if you are taking any of the following medicines, as VFEND must not be taken if you are already taking any of these medicines (See also Section 2 above 'Do not take VFEND'):

- Terfenadine (used for allergy)
- Astemizole (used for allergy)
- Carbamazepine (used to treat seizures)
- Cisapride (used for stomach problems)
- Pimozide (used for treating mental illness)
- Quinidine (used for irregular heart beat)
- Rifampicin (used for treating tuberculosis)
- Phenobarbital (used for severe insomnia and seizures)
- Ergot alkaloids (e.g. ergotamine, dihydroergotamine; used for migraine)
- Sirolimus (used in transplant patients)
- Efavirenz (used for treating HIV)
- Ritonavir (used for treating HIV) in doses of 400mg and more twice daily

Tell your doctor if you are taking either of the following medicines, as treatment with VFEND at the same time should be avoided if possible, and a dose adjustment of voriconazole may be required:
- Rifabutin (used for treating tuberculosis)
- Phenytoin (used to treat epilepsy)

Tell your doctor if you are taking any of the following medicines, as a dose adjustment or monitoring may be required to check that they are still having the desired effect:
- Warfarin and other anticoagulants (e.g. phenprocoumon, acenocoumarol; used to slow down clotting of the blood)
- Cyclosporin (used in transplant patients)
- Tacrolimus (used in transplant patients)
- Sulphonylureas (used for diabetes)
- Statins (used for lowering cholesterol)
- Benzodiazepines (used for severe insomnia and stress)
- Omeprazole (used for treating ulcers)
- Vinca alkaloids (used in treating cancer)

- Indinavir and other HIV protease inhibitors (used for treating HIV)
- Non-nucleoside reverse transcriptase inhibitors (used for treating HIV)
- Methadone (used to treat heroin addiction)

3. HOW TO TAKE VFEND

Always take VFEND exactly as directed by your doctor. You should check with your doctor or pharmacist if you are unsure.

Your doctor will determine your dose depending on your weight and the type of infection you have.

- The usual dose for adults (including elderly patients) is as follows:

	Tablets	
	Patients 40kg and above	Patients less than 40kg
Dose for the first 24 hours (Loading Dose)	400mg every 12 hours for the first 24 hours	200mg every 12 hours for the first 24 hours
Dose after the first 24 hours (Maintenance Dose)	200mg twice a day	100mg twice a day

- The usual dose for children aged 2 to less than 12 years:

	Tablets
Dose for the first 24 hours (Loading Dose)	6mg/kg every 12 hours for the first 24 hours
Dose after the first 24 hours (Maintenance Dose)	4mg/kg twice a day

Tablets must only be given if the child is able to swallow tablets and the dose will be given to the nearest mg/kg dose possible using whole 50 mg tablets.

VFEND should not be given to children younger than 2 years of age.

- Teenagers (aged 12 to 16 years) should be dosed as for adults.

Take your tablet at least one hour before, or one hour after a meal. Swallow the tablet whole with some water.

Continue taking VFEND until your doctor tells you to stop. Do not stop treatment early because your infection may not be cured. Patients with a weakened immune system or those with difficult infections may require long term treatment to prevent the infection from returning.

If you take more VFEND than you should:
If you take more tablets than prescribed (or if someone else takes your tablets) you must seek medical advice or go to the nearest hospital casualty department immediately. Take your box of VFEND tablets with you.

If you forget to take VFEND:

It is important to take your VFEND tablets regularly at the same time each day. If you forget to take one dose, take your next dose when it is due. Do not take a double dose to make up for the forgotten dose.

Effects when treatment with VFEND is stopped:
It has been shown that taking all doses at the appropriate times may greatly increase the effectiveness of your medicine. Therefore unless your doctor instructs you to stop treatment, it is important to keep taking VFEND correctly, as described above.

When VFEND treatment is stopped by your doctor you should not experience any effects. However if you were taking medicines containing cyclosporin or tacrolimus you must mention this to your doctor, as the dose will need to be adjusted.

4. POSSIBLE SIDE EFFECTS

Like all medicines, VFEND can have side effects. If any side effects occur, most are likely to be minor and temporary. However, some may be serious and need medical attention.

The most commonly reported side effects (occurring in more than one out of 10 patients in clinical trials) are visual disturbances, fever, rash, nausea, vomiting, diarrhoea, headache, swelling of the extremities and stomach pains.

As VFEND has been known to affect the liver and the kidney, your doctor should monitor the function of your liver and kidney by doing blood tests. Please advise your doctor if you have any stomach pains or if your stools have a different consistency.

Other reported side effects include: changes in heart rate or rhythm, changes in blood pressure, blood cell changes, blood chemistry changes, dizziness, itchiness, weakness, back pain, chest pain, flu-like symptoms, facial swelling, hallucinations and other nervous symptoms, tingling, cough, breathing difficulty, hair loss, pain and irritation of the eyes, hearing difficulties, joint pain disruption of brain function, inability to sleep, feeling sleepy during infusion.

If any of these side effects persist or are troublesome, please tell your doctor.

If you notice any side effects not mentioned in this leaflet, please tell your doctor or pharmacist.

5. STORING VFEND

Keep out of the reach and sight of children.

There are no special storage instructions.

Do not use after the expiry date stated on the label.

6. FURTHER INFORMATION

If you have further questions, please ask your doctor or pharmacist.
For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

België /Belgique/Belgien
Pfizer S.A./N.V.
Tél/Tel: +32 (0)2 554 62 11

Luxembourg/Luxemburg
Pfizer S.A.
Tél: +32 (0)2 554 62 11

Česká republika
Pfizer s.r.o.
Tel: +420-283-004-111

Danmark
Pfizer ApS
Tlf: +45 44 20 11 00

Deutschland
Pfizer Pharma GmbH
Tel: +49 (0)721 6101 9000

Eesti
Pfizer Luxembourg SARL, Eesti filiaal
Tel: +372 6 405 328

Ελλάδα
Pfizer Hellas A.E.
Τηλ: +30 210 7517981-3

España
Pfizer S.A.
Tel: +34 91 490 99 00

France
Pfizer
Tél: +33 (0)1 58 07 34 40

Ireland
Pfizer Healthcare Ireland
Tel: +353 1800 633 363

Ísland
PharmaNor hf.,
Tel: + 354 535 7000

Italia
Pfizer Italia S.r.l.
Tel: +39 06 33 18 21

Κύπρος
GEO. PAVLIDES & ARAOUZOS LTD,
Τηλ: +35722818087

Latvija
Pfizer Luxembourg SARL
Tel: +371 70 35 775

Lietuva
Pfizer Luxembourg SARL Representation
filialas Lietuvoje
Tel. +3705 2514000

Magyarország
Pfizer Kft.
Tel. + 36 1 488 37 00

Malta
V.J. Salomone Pharma Ltd.
Tel : +356 21 22 01 74

Nederland
Pfizer bv
Tel: +31 (0)10 406 42 00

Norge
Pfizer AS
Tlf: +47 67 52 61 00

Österreich
Pfizer Corporation Austria Ges.m.b.H.
Tel: +43 (0)1 521 15-0

Polska
Pfizer Polska Sp. z o.o.,
Tel.: +48 22 549 38 00

Portugal
Laboratórios Pfizer, Lda.
Tel: +351 423 5500

Slovenija
Pfizer Luxembourg SARL, Podružnica Ljubljana
Tel: + 386/1/52 11 400

Slovenská republika
Pfizer Luxembourg SARL, organizačná zložka
Tel: +421–2–5941 8500

Suomi/Finland
Pfizer Oy
Puh/Tel: +358(0)9 43 00 40

Sverige
Pfizer AB
Tel: +46 (0)8 519 062 00

United Kingdom
Pfizer Limited
Tel: +44 (0)1737 331111

This leaflet was last approved on <<date>>.

PACKAGE LEAFLET

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet we explain:

VFEND 200mg film-coated tablets
voriconazole

- The active substance is voriconazole. Each tablet contains 200mg voriconazole.
- The other ingredients are lactose monohydrate, pregelatinised starch, croscarmellose sodium, povidone and magnesium stearate which make up the tablet core and hypromellose, titanium dioxide (E171), lactose monohydrate and glycerol triacetate which make up the film-coat.

The marketing authorisation for VFEND is held by:
Pfizer Limited, Sandwich, Kent, CT13 9NJ, United Kingdom.

VFEND is made by:
Heinrich Mack Nachf. GmbH & Co. KG
Heinrich-Mack-Str. 35 D-89257 Illertissen Germany (which is wholly owned by Pfizer Inc.)

1. WHAT VFEND IS AND WHAT IT IS USED FOR

VFEND is supplied as white capsule shaped film-coated tablets with Pfizer marked on one side and VOR200 on the reverse.

VFEND belongs to a group of medicines called triazole antifungal agents. These medicines are used to treat a wide variety of fungal infections. VFEND works by killing or stopping the growth of the fungi that cause infections.

What fungal infections are treated with VFEND?
VFEND is used to treat serious fungal infections caused by *Aspergillus*, *Scedosporium*, *Fusarium* and *Candida*.

The information in this leaflet is about VFEND 200mg tablets only. For further information on VFEND 50mg tablets, VFEND powder for solution for infusion, or VFEND powder for oral suspension, please see the User Package Leaflets for these products.

VFEND has been prescribed for you. Do not allow anyone else to take it.
This product should only be taken under the supervision of a doctor. VFEND is mainly for use in seriously ill patients.

2. WHAT YOU SHOULD KNOW BEFORE YOU TAKE VFEND

Do not take VFEND:
- if you are allergic to voriconazole or any of the other ingredients of VFEND.

It is very important that you inform your doctor or pharmacist if you are taking or have taken any other medicines, even those that are obtained without a prescription. Some medicines affect the way VFEND works, or VFEND may affect the way they work.

A list of the medicines that may affect VFEND is shown in the section 'Taking other medicines with VFEND'. However, the medicines in the following list must not be taken during your course of VFEND treatment:

- Terfenadine (used for allergy)
- Astemizole (used for allergy)
- Cisapride (used for stomach problems)
- Pimozide (used for treating mental illness)
- Quinidine (used for irregular heart beat)
- Rifampicin (used for treating tuberculosis)
- Carbamazepine (used to treat seizures)
- Phenobarbital (used for severe insomnia and seizures)
- Ergot alkaloids (e.g. ergotamine, dihydroergotamine; used for migraine)
- Sirolimus (used in transplant patients)
- Efavirenz (used for treating HIV)
- Ritonavir (used for treating HIV) in doses of 400mg and more twice daily

Take special care with VFEND:

- if you are known to have an abnormality of electrocardiogram (ECG) called 'long QT syndrome'.

Before being treated with VFEND, tell your doctor if:

- you have had an allergic reaction to other azoles.

- you are suffering from, or have ever suffered from liver disease. If you have liver disease, your doctor may prescribe a lower dose of VFEND. Your doctor should also monitor your liver function while you are being treated with VFEND by doing blood tests.

- you are already being treated with phenytoin (used to treat epilepsy). Your blood concentration of phenytoin will need to be monitored during your treatment with VFEND and your dose may be adjusted.

- you are already being treated with rifabutin (used for treating tuberculosis). Your blood counts and side effects to rifabutin will need to be monitored.

While being treated with VFEND:

- tell your doctor immediately if you develop a severe skin rash or blisters.

- avoid sunlight while being treated with VFEND, as an increased sensitivity of skin to the sun's UV rays can occur.

- your doctor should monitor the function of your liver and kidney by doing blood tests.

Taking VFEND with food and drink:
VFEND tablets must be taken at least one hour before or one hour after a meal.

Pregnancy
VFEND must not be taken during pregnancy, unless indicated by your doctor. Effective contraception must be used in women of childbearing potential. Contact your doctor immediately if you become pregnant while taking VFEND.

Breast-feeding
VFEND must not be taken during breast-feeding. Ask your doctor or pharmacist for advice before taking any medicine whilst breast-feeding.

Driving and using machines:
VFEND may cause blurring of vision or uncomfortable sensitivity to light. While affected, do not drive or operate any tools or machines. Contact your doctor if you experience this.

Important information about some of the ingredients of VFEND:
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.

Taking other medicines with VFEND:
Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including those that are obtained without a prescription.

Some medicines, when taken at the same time as VFEND, may affect the way VFEND works or VFEND may affect the way they work. Tell your doctor if you are taking any of the following medicines, as VFEND must not be taken if you are already taking any of these medicines (See also Section 2 above 'Do not take VFEND'):

- Terfenadine (used for allergy)
- Astemizole (used for allergy)
- Carbamazepine (used to treat seizures)
- Cisapride (used for stomach problems)
- Pimozide (used for treating mental illness)
- Quinidine (used for irregular heart beat)
- Rifampicin (used for treating tuberculosis)
- Phenobarbital (used for severe insomnia and seizures)
- Ergot alkaloids (e.g. ergotamine, dihydroergotamine; used for migraine)
- Sirolimus (used in transplant patients)
- Efavirenz (used for treating HIV)
- Ritonavir (used for treating HIV) in doses of 400mg and more twice daily

Tell your doctor if you are taking either of the following medicines, as treatment with VFEND at the same time should be avoided if possible, and a dose adjustment of voriconazole may be required:
- Rifabutin (used for treating tuberculosis)
- Phenytoin (used to treat epilepsy)

Tell your doctor if you are taking any of the following medicines, as a dose adjustment or monitoring may be required to check that they are still having the desired effect:
- Warfarin and other anticoagulants (e.g. phenprocoumon, acenocoumarol; used to slow down clotting of the blood)
- Cyclosporin (used in transplant patients)
- Tacrolimus (used in transplant patients)
- Sulphonylureas (used for diabetes)
- Statins (used for lowering cholesterol)
- Benzodiazepines (used for severe insomnia and stress)
- Omeprazole (used for treating ulcers)
- Vinca alkaloids (used in treating cancer)

- Indinavir and other HIV protease inhibitors (used for treating HIV)
- Non-nucleoside reverse transcriptase inhibitors (used for treating HIV)
- Methadone (used to treat heroin addiction)

3. HOW TO TAKE VFEND

Always take VFEND exactly as directed by your doctor. You should check with your doctor or pharmacist if you are unsure.

Your doctor will determine your dose depending on your weight and the type of infection you have.

- The usual dose for adults (including elderly patients) is as follows:

	Tablets	
	Patients 40kg and above	Patients less than 40kg
Dose for the first 24 hours (Loading Dose)	400mg every 12 hours for the first 24 hours	200mg every 12 hours for the first 24 hours
Dose after the first 24 hours (Maintenance Dose)	200mg twice a day	100mg twice a day

- The usual dose for children aged 2 to less than 12 years:

	Tablets
Dose for the first 24 hours (Loading Dose)	6mg/kg every 12 hours for the first 24 hours
Dose after the first 24 hours (Maintenance Dose)	4mg/kg twice a day

Tablets must only be given if the child is able to swallow tablets and the dose will be given to the nearest mg/kg dose possible using whole 50mg tablets.

VFEND should not be given to children younger than 2 years of age.

- Teenagers (aged 12 to 16 years) should be dosed as for adults.

Take your tablet at least one hour before, or one hour after a meal. Swallow the tablet whole with some water.

Continue taking VFEND until your doctor tells you to stop. Do not stop treatment early because your infection may not be cured. Patients with a weakened immune system or those with difficult infections may require long term treatment to prevent the infection from returning.

If you take more VFEND than you should:
If you take more tablets than prescribed (or if someone else takes your tablets) you must seek medical advice or go to the nearest hospital casualty department immediately. Take your box of VFEND tablets with you.

If you forget to take VFEND:

It is important to take your VFEND tablets regularly at the same time each day. If you forget to take one dose, take your next dose when it is due. Do not take a double dose to make up for the forgotten dose.

Effects when treatment with VFEND is stopped:
It has been shown that taking all doses at the appropriate times may greatly increase the effectiveness of your medicine. Therefore unless your doctor instructs you to stop treatment, it is important to keep taking VFEND correctly, as described above.

When VFEND treatment is stopped by your doctor you should not experience any effects. However if you were taking medicines containing cyclosporin or tacrolimus you must mention this to your doctor, as the dose will need to be adjusted.

4. POSSIBLE SIDE EFFECTS

Like all medicines, VFEND can have side effects. If any side effects occur, most are likely to be minor and temporary. However, some may be serious and need medical attention.

The most commonly reported side effects (occurring in more than one out of 10 patients in clinical trials) are visual disturbances, fever, rash, nausea, vomiting, diarrhoea, headache, swelling of the extremities and stomach pains.

As VFEND has been known to affect the liver and the kidney, your doctor should monitor the function of your liver and kidney by doing blood tests. Please advise your doctor if you have any stomach pains or if your stools have a different consistency.

Other reported side effects include: changes in heart rate or rhythm, changes in blood pressure, blood cell changes, blood chemistry changes, dizziness, itchiness, weakness, back pain, chest pain, flu-like symptoms, facial swelling, hallucinations and other nervous symptoms, tingling, cough, breathing difficulty, hair loss, pain and irritation of the eyes, hearing difficulties, joint pain disruption of brain function, inability to sleep, feeling sleepy during infusion.

If any of these side effects persist or are troublesome, please tell your doctor.

If you notice any side effects not mentioned in this leaflet, please tell your doctor or pharmacist.

5. STORING VFEND

Keep out of the reach and sight of children.

There are no special storage instructions.

Do not use after the expiry date stated on the label.

6. FURTHER INFORMATION

If you have further questions, please ask your doctor or pharmacist.
For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

België /Belgique/Belgien
Pfizer S.A./N.V.
Tél/Tel: +32 (0)2 554 62 11

Luxembourg/Luxemburg
Pfizer S.A.
Tél: +32 (0)2 554 62 11

Česká republika
Pfizer s.r.o.
Tel: +420-283-004-111

Danmark
Pfizer ApS
Tlf: +45 44 20 11 00

Deutschland
Pfizer Pharma GmbH
Tel: +49 (0)721 6101 9000

Eesti
Pfizer Luxembourg SARL, Eesti filiaal
Tel: +372 6 405 328

Ελλάδα
Pfizer Hellas A.E.
Τηλ: +30 210 7517981-3

España
Pfizer S.A.
Tel: +34 91 490 99 00

France
Pfizer
Tél: +33 (0)1 58 07 34 40

Ireland
Pfizer Healthcare Ireland
Tel: +353 1800 633 363

Ísland
PharmaNor hf.,
Tel: + 354 535 7000

Italia
Pfizer Italia S.r.l.
Tel: +39 06 33 18 21

Κύπρος
GEO. PAVLIDES & ARAOUZOS LTD,
Τηλ: +35722818087

Latvija
Pfizer Luxembourg SARL
Tel: +371 70 35 775

Lietuva
Pfizer Luxembourg SARL Representation
filialas Lietuvoje
Tel. +3705 2514000

Magyarország
Pfizer Kft.
Tel. + 36 1 488 37 00

Malta
V.J. Salomone Pharma Ltd.
Tel : +356 21 22 01 74

Nederland
Pfizer bv
Tel: +31 (0)10 406 42 00

Norge
Pfizer AS
Tlf: +47 67 52 61 00

Österreich
Pfizer Corporation Austria Ges.m.b.H.
Tel: +43 (0)1 521 15-0

Polska
Pfizer Polska Sp. z o.o.,
Tel.: +48 22 549 38 00

Portugal
Laboratórios Pfizer, Lda.
Tel: +351 423 5500

Slovenija
Pfizer Luxembourg SARL, Podružnica Ljubljana
Tel: + 386/1/52 11 400

Slovenská republika
Pfizer Luxembourg SARL, organizačná zložka
Tel: +421–2–5941 8500

Suomi/Finland
Pfizer Oy
Puh/Tel: +358(0)9 43 00 40

Sverige
Pfizer AB
Tel: +46 (0)8 519 062 00

United Kingdom
Pfizer Limited
Tel: +44 (0)1737 331111

This leaflet was last approved on <<date>>.

PACKAGE LEAFLET

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet we explain:

VFEND 200mg powder for solution for infusion
voriconazole

- The active substance is voriconazole. Each vial contains 200mg voriconazole, equivalent to a 10mg/ml solution when reconstituted as directed by your hospital pharmacist or nurse (see the information at the end of this leaflet).
- The other ingredient is sulphobutylether beta cyclodextrin sodium.

The marketing authorisation for VFEND is held by:
Pfizer Limited, Sandwich, Kent, CT13 9NJ, United Kingdom.

VFEND is made by:
Pfizer PGM, Zone Industrielle, 29 route des Industries, 37530 Pocé-sur-Cisse, France.

1. WHAT VFEND IS AND WHAT IT IS USED FOR

VFEND is presented in single use glass vials as a powder for solution for infusion.

VFEND belongs to a group of medicines called triazole antifungal agents. These medicines are used to treat a wide variety of fungal infections. VFEND works by killing or stopping the growth of the fungi that cause infections.

What fungal infections are treated with VFEND?
VFEND is used to treat serious fungal infections caused by *Aspergillus*, *Scedosporium*, *Fusarium* and *Candida*.

The information in this leaflet is about VFEND powder for solution for infusion only. For further information on VFEND 50mg and 200mg tablets or VFEND powder for oral suspension, please see the User Package Leaflet for these products.

VFEND has been prescribed for you. Do not allow anyone else to use it.
This product should only be used under the supervision of a doctor. VFEND is mainly for use in seriously ill patients.

2. WHAT YOU SHOULD KNOW BEFORE YOU ARE TREATED WITH VFEND

You should not be treated with VFEND:
- if you are allergic to the active ingredient voriconazole, or to sulphobutylether beta cyclodextrin sodium.

It is very important that you inform your doctor or pharmacist if you are taking or have taken any other medicines, even those that are obtained without a prescription. Some medicines affect the way VFEND works, or VFEND may affect the way they work.

A list of the medicines that may affect VFEND is shown in the section 'Taking other medicines with VFEND'. However, the medicines in the following list must not be taken during your VFEND treatment:

- Terfenadine (used for allergy)
- Astemizole (used for allergy)
- Cisapride (used for stomach problems)
- Pimozide (used for treating mental illness)
- Quinidine (used for irregular heart beat)
- Rifampicin (used for treating tuberculosis)
- Carbamazepine (used to treat seizures)
- Phenobarbital (used for severe insomnia and seizures)
- Ergot alkaloids (e.g. ergotamine, dihydroergotamine; used for migraine)
- Sirolimus (used in transplant patients)
- Efavirenz (used for treating HIV)
- Ritonavir (used for treating HIV) in doses of 400mg and more twice daily

Take special care with VFEND:

- if you are known to have an abnormality of electrocardiogram (ECG) called 'long QT syndrome'.

Before being treated with VFEND, tell your doctor if:

- you have had an allergic reaction to other azoles.

- you are suffering from, or have ever suffered from kidney disease. Dependent upon the degree of kidney disease the doctor may decide to give you VFEND tablets. Your doctor should monitor your renal function while you are being treated with VFEND by doing blood tests.

- you are suffering from, or have ever suffered from liver disease. If you have liver disease, your doctor may prescribe a lower dose of VFEND. Your doctor should also monitor your liver function while you are being treated with VFEND by doing blood tests.

- you are already being treated with phenytoin (used to treat epilepsy). Your blood concentration of phenytoin will need to be monitored during your treatment with VFEND and your dose may be adjusted.

- you are already being treated with rifabutin (used for treating tuberculosis). Your blood counts and side effects to rifabutin will need to be monitored.

While being treated with VFEND:

- tell your doctor immediately if you develop a severe skin rash or blisters.

- avoid sunlight while being treated with VFEND, as an increased sensitivity of skin to the sun's UV rays can occur.

- your doctor should monitor the function of your liver and kidney by doing blood tests.

- reactions during the infusion have occurred uncommonly with VFEND (including flushing and nausea). Your doctor may stop the infusion of VFEND if this occurs.

Pregnancy
VFEND must not be used during pregnancy, unless indicated by your doctor. Effective contraception must be used in women of childbearing potential. Contact your doctor immediately if you become pregnant while being treated with VFEND.

Breast-feeding
VFEND must not be used during breast-feeding. Ask your doctor or pharmacist for advice before taking any medicine whilst breast-feeding.

Driving and using machines:
VFEND may cause blurring of vision or uncomfortable sensitivity to light. While affected, do not drive or operate any tools or machines. Tell your doctor if you experience this.

Taking other medicines with VFEND:
Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including those that are obtained without a prescription.

Some medicines, when taken at the same time as VFEND, may affect the way VFEND works or VFEND may affect the way they work. Tell your doctor if you are taking any of the following medicines, as VFEND must not be taken if you are already taking any of these medicines (See also Section 2 above 'Do not take VFEND):

- Terfenadine (used for allergy)
- Astemizole (used for allergy)
- Carbamazepine (used to treat seizures)
- Cisapride (used for stomach problems)
- Pimozide (used for treating mental illness)
- Quinidine (used for irregular heart beat)
- Rifampicin (used for treating tuberculosis)
- Phenobarbital (used for severe insomnia and seizures)
- Ergot alkaloids (e.g. ergotamine, dihydroergotamine; used for migraine)
- Sirolimus (used in transplant patients)
- Efavirenz (used for treating HIV)
- Ritonavir (used for treating HIV) in doses of 400mg and more twice daily

Tell your doctor if you are taking either of the following medicines, as treatment with VFEND at the same time should be avoided if possible, and a dose adjustment of voriconazole may be required:
- Rifabutin (used for treating tuberculosis)
- Phenytoin (used to treat epilepsy)

Tell your doctor if you are taking any of the following medicines, as a dose adjustment or monitoring may be required to check that they are still having the desired effect:
- Warfarin and other anticoagulants (e.g. phenprocoumon, acenocoumarol; used to slow down clotting of the blood)
- Cyclosporin (used in transplant patients)
- Tacrolimus (used in transplant patients)
- Sulphonylureas (used for diabetes)
- Statins (used for lowering cholesterol)
- Benzodiazepines (used for severe insomnia and stress)
- Omeprazole (used for treating ulcers)
- Vinca alkaloids (used in treating cancer)

- Indinavir and other HIV protease inhibitors (used for treating HIV)
- Non-nucleoside reverse transcriptase inhibitors (used for treating HIV)
- Methadone (used to treat heroin addiction)

3. HOW TO USE VFEND

VFEND must only be used as directed by your doctor.

Your doctor will determine your dose depending on your weight and the type of infection you have. Your doctor may change your dose depending on your condition.

- The usual dose for adults (including elderly patients) is as follows:

	Intravenous
Dose for the first 24 hours (Loading Dose)	6 mg/kg every 12 hours for the first 24 hours
Dose after the first 24 hours (Maintenance Dose)	4 mg/kg twice a day

- The usual dose for children (aged 2 to less than 12 years) and teenagers (aged 12 to 16 years) is the same as for adults.

VFEND should not be given to children younger than 2 years of age.

VFEND powder for solution for infusion will be reconstituted and diluted to the correct concentration by your hospital pharmacist or nurse. (Please refer to the end of this leaflet for further information)

This will be given to you by intravenous infusion (into a vein) at a maximum rate of 3 mg/kg per hour over 1 to 2 hours.

VFEND treatment will continue for as long as your doctor advises, however duration of treatment with VFEND powder for solution for infusion should be no more than 6 months.

Patients with a weakened immune system or those with difficult infections may require long term treatment to prevent the infection from returning.

You may be switched from the intravenous infusion to tablets once your condition improves.

If a dose of VFEND has been forgotten:
As you will be given this medicine under closer medical supervision, it is unlikely that a dose would be missed. However tell your doctor or pharmacist if you think that a dose has been forgotten.

Effects when treatment with VFEND is stopped:
When VFEND treatment is stopped by your doctor you should not experience any effects. However if you were taking medicines containing cyclosporin or tacrolimus you must mention this to your doctor, as the dose will need to be adjusted.

4. POSSIBLE SIDE EFFECTS

Like all medicines, VFEND can have side effects. If any side effects occur, most are likely to be minor and temporary. However, some may be serious and need medical attention.

The most commonly reported side effects (occurring in more than one out of 10 patients in clinical trials) are visual disturbances, fever, rash, nausea, vomiting, diarrhoea, headache, swelling of the extremities and stomach pains. Soreness at the injection site was also reported.

Reactions during the infusion have occurred uncommonly with VFEND (including flushing, fever, sweating, increased heart rate and shortness of breath). Your doctor may stop the infusion if this occurs.

As VFEND has been known to affect the liver and the kidney, your doctor should monitor the function of your liver and kidney by doing blood tests. Please advise your doctor if you have any stomach pains or if your stools have a different consistency.

Other reported side effects include: changes in heart rate or rhythm, changes in blood pressure, blood cell changes, blood chemistry changes, dizziness, itchiness, weakness, back pain, chest pain, irritation at the injection site, flu-like symptoms, facial swelling, hallucinations and other nervous symptoms, tingling, cough, breathing difficulty, hair loss, pain and irritation of the eyes, hearing difficulties, joint pain disruption of brain function, inability to sleep, feeling sleepy during infusion.

If any of these side effects persist or are troublesome, please tell your doctor.

If you notice any side effects not mentioned in this leaflet, please tell your doctor or pharmacist.

5. STORING VFEND

Keep VFEND out of the reach and sight of children.

Once reconstituted, VFEND should be used immediately, but if necessary may be stored for up to 24 hours at 2°C - 8°C (in a refrigerator). Reconstituted VFEND needs to be diluted with a compatible infusion solution first before it is infused. (Please refer to the end of this leaflet for further information).

Do not use after the expiry date stated on the label.

6. FURTHER INFORMATION

If you have further questions, please ask your doctor or pharmacist.
For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

België /Belgique/Belgien
Pfizer S.A./N.V.
Tél/Tel: +32 (0)2 554 62 11

Česká republika
Pfizer s.r.o.
Tel: +420-283-004-111

Danmark
Pfizer ApS
Tlf: +45 44 20 11 00

Luxembourg/Luxemburg
Pfizer S.A.
Tél: +32 (0)2 554 62 11

Magyarország
Pfizer Kft.
Tel. + 36 1 488 37 00

Malta
V.J. Salmone Pharma Ltd.
Tel : +356 21 22 01 74

Deutschland
Pfizer Pharma GmbH
Tel: +49 (0)721 6101 9000

Eesti
Pfizer Luxembourg SARL, Eesti filiaal
Tel: +372 6 405 328

Ελλάδα
Pfizer Hellas A.E.
Τηλ: +30 210 7517981-3

España
Pfizer S.A.
Tel: +34 91 490 99 00

France
Pfizer
Tél: +33 (0)1 58 07 34 40

Ireland
Pfizer Healthcare Ireland
Tel: +353 1800 633 363

Ísland
PharmaNor hf.,
Tel: + 354 535 7000

Italia
Pfizer Italia S.r.l.
Tel: +39 06 33 18 21

Κύπρος
GEO. PAVLIDES & ARAOUZOS LTD,
Τηλ: +35722818087

Latvija
Pfizer Luxembourg SARL
Tel: +371 70 35 775

Lietuva
Pfizer Luxembourg SARL Representation
filialas Lietuvoje
Tel. +3705 2514000

Nederland
Pfizer bv
Tel: +31 (0)10 406 42 00

Norge
Pfizer AS
Tlf: +47 67 52 61 00

Österreich
Pfizer Corporation Austria Ges.m.b.H.
Tel: +43 (0)1 521 15-0

Polska
Pfizer Polska Sp. z o.o.,
Tel.: +48 22 549 38 00

Portugal
Laboratórios Pfizer, Lda.
Tel: +351 423 5500

Slovenija
Pfizer Luxembourg SARL, Podružnica Ljubljana
Tel: + 386/1/52 11 400

Slovenská republika
Pfizer Luxembourg SARL, organizačná zložka
Tel: +421–2–5941 8500

Suomi/Finland
Pfizer Oy
Puh/Tel: +358(0)9 43 00 40

Sverige
Pfizer AB
Tel: +46 (0)8 519 062 00

United Kingdom
Pfizer Limited
Tel: +44 (0)1737 331111

This leaflet was last approved on <<date>>.

The following information is intended for medical or healthcare professionals only:

Reconstitution and Dilution information

- VFEND powder for solution for infusion needs to first be reconstituted with 19ml of Water for Injections to obtain an extractable volume of 20ml of clear concentrate containing 10mg/ml voriconazole.
- Discard the VFEND vial if the vacuum does not pull the diluent into the vial.
- It is recommended that a standard 20ml (non-automated) syringe be used to ensure that the exact amount (19.0ml) of Water for Injections is dispensed.
- The required volume of the reconstituted concentrate is then added to a recommended compatible infusion solution listed below to obtain a final VFEND solution containing 0.5 to 5mg/ml of voriconazole.
- This medicinal product is for single use only and any unused solution should be discarded and only clear solutions without particles should be used.
- Not for administration as a bolus injection.
- For storage information, please refer to Section 5 'Storing VFEND'.

Required Volumes of 10 mg/ml VFEND Concentrate

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

VFEND is a single dose unpreserved sterile lyophile. Therefore, from a microbiological point of view, the reconstituted solution must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Compatible Infusion Solutions:

The reconstituted solution can be diluted with:

9mg/ml (0.9%) Sodium Chloride for Infusion
Lactated Ringer's Intravenous Infusion
5% Glucose andLactated Ringer's Intravenous Infusion
5% Glucose and 0.45% Sodium Chloride Intravenous Infusion
5% Glucose Intravenous Infusion
5% Glucose in 20mEq Potassium Chloride Intravenous Infusion
0.45% Sodium Chloride Intravenous Infusion

5% Glucose and 0.9% Sodium Chloride Intravenous Infusion

The compatibility of VFEND with diluents other than listed above (or listed below under 'Incompatibilities') is unknown.

Incompatibilities:

VFEND must not be infused into the same line or cannula concomitantly with other drug infusions, including parenteral nutrition (e.g., Aminofusin 10% Plus).

Infusions of blood products must not occur simultaneously with VFEND.

Infusion of total parenteral nutrition can occur simultaneously with VFEND but not in the same line or cannula.

VFEND must not be diluted with 4.2% Sodium Bicarbonate Infusion.

PACKAGE LEAFLET

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet we explain:

VFEND 40mg/ml powder for oral suspension.
voriconazole

- The active substance is voriconazole. Each bottle contains 45g of powder providing 70ml of suspension when constituted with water as recommended. One ml of the constituted suspension contains 40mg voriconazole. (See section 3 'How to take VFEND').
- The other ingredients are sucrose; silica, colloidal ; titanium dioxide; xanthan gum; sodium citrate; sodium benzoate; citric acid, ; natural orange flavour.

The marketing authorisation for VFEND is held by:
Pfizer Limited, Ramsgate Rd, Sandwich, Kent, CT13 9NJ, United Kingdom.

VFEND is made by:
Pfizer PGM, Zone Industrielle, 29 route des Industries, 37530 Pocé-sur-Cisse, France.

1. WHAT VFEND IS AND WHAT IT IS USED FOR

VFEND is supplied as a white to off-white powder for oral suspension providing a white to off-white, orange flavoured suspension when constituted with water.

VFEND belongs to a group of medicines called triazole antifungal agents. These medicines are used to treat a wide variety of fungal infections. VFEND works by killing or stopping the growth of the fungi that cause infections.

What fungal infections are treated with VFEND?
VFEND is used to treat serious fungal infections caused by *Aspergillus*, *Scedosporium*, *Fusarium* and *Candida*.

The information in this leaflet is about VFEND powder for oral suspension only. For further information on VFEND 50mg and 200mg tablets or VFEND powder for solution for infusion, please see the User Package Leaflets for these products.

VFEND has been prescribed for you. Do not allow anyone else to take it.
This product should only be taken under the supervision of a doctor. VFEND is mainly for use in seriously ill patients.

2. WHAT YOU SHOULD KNOW BEFORE YOU TAKE VFEND

Do not take VFEND:
- if you are allergic to voriconazole or any of the other ingredients of VFEND.

It is very important that you inform your doctor or pharmacist if you are taking or have taken any other medicines, even those that are obtained without a prescription. Some medicines affect the way VFEND works, or VFEND may affect the way they work.

A list of the medicines that may affect VFEND is shown in the section 'Taking other medicines with VFEND'. However, the medicines in the following list must not be taken during your course of VFEND treatment:

- Terfenadine (used for allergy)
- Astemizole (used for allergy)
- Cisapride (used for stomach problems)
- Pimozide (used for treating mental illness)
- Quinidine (used for irregular heart beat)
- Rifampicin (used for treating tuberculosis)
- Carbamazepine (used to treat seizures)
- Phenobarbital (used for severe insomnia and seizures)
- Ergot alkaloids (e.g. ergotamine, dihydroergotamine; used for migraine)
- Sirolimus (used in transplant patients)
- Efavirenz (used for treating HIV)
- Ritonavir (used for treating HIV) in doses of 400mg and more twice daily

Take special care with VFEND:

- if you are known to have an abnormality of electrocardiogram (ECG) called 'long QT syndrome'.

Before being treated with VFEND, tell your doctor if:

- you have had an allergic reaction to other azoles.

- you are suffering from, or have ever suffered from liver disease. If you have liver disease, your doctor may prescribe a lower dose of VFEND. Your doctor should also monitor your liver function while you are being treated with VFEND by doing blood tests.

- you are already being treated with phenytoin (used to treat epilepsy). Your blood concentration of phenytoin will need to be monitored during your treatment with VFEND and your dose may be adjusted.

- you are already being treated with rifabutin (used for treating tuberculosis). Your blood counts and side effects to rifabutin will need to be monitored.

While being treated with VFEND:

- tell your doctor immediately if you develop a severe skin rash or blisters.

- avoid sunlight while being treated with VFEND, as an increased sensitivity of skin to the sun's UV rays can occur.

- your doctor should monitor the function of your liver and kidney by doing blood tests.

Taking VFEND with food and drink:
VFEND suspension must be taken at least one hour before or two hours after a meal.

Pregnancy

VFEND must not be taken during pregnancy, unless indicated by your doctor. Effective contraception must be used in women of childbearing potential. Contact your doctor immediately if you become pregnant while taking VFEND.

Breast-feeding
VFEND must not be taken during breast-feeding. Ask your doctor or pharmacist for advice before taking any medicine whilst breast-feeding.

Driving and using machines:
VFEND may cause blurring of vision or uncomfortable sensitivity to light. While affected, do not drive or operate any tools or machines. Contact your doctor if you experience this.

Important information about some of the ingredients of VFEND:
VFEND suspension contains 0.54g sucrose per ml of suspension. This medicine is unsuitable if you have rare hereditary problems of fructose intolerance, sucrase-isomaltase deficiency or glucose-galactose malabsorption. Tell your doctor or pharmacist before taking this medicine.

Taking other medicines with VFEND:
Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including those that are obtained without a prescription.

Some medicines, when taken at the same time as VFEND, may affect the way VFEND works or VFEND may affect the way they work. Tell your doctor if you are taking any of the following medicines, as VFEND must not be taken if you are already taking any of these medicines (See also Section 2 above 'Do not take VFEND'):

- Terfenadine (used for allergy)
- Astemizole (used for allergy)
- Carbamazepine (used to treat seizures)
- Cisapride (used for stomach problems)
- Pimozide (used for treating mental illness)
- Quinidine (used for irregular heart beat)
- Rifampicin (used for treating tuberculosis)
- Phenobarbital (used for severe insomnia and seizures)
- Ergot alkaloids (e.g. ergotamine, dihydroergotamine; used for migraine)
- Sirolimus (used in transplant patients)
- Efavirenz (used for treating HIV)
- Ritonavir (used for treating HIV) in doses of 400mg and more twice daily

Tell your doctor if you are taking either of the following medicines, as treatment with VFEND at the same time should be avoided if possible, and a dose adjustment of voriconazole may be required:
- Rifabutin (used for treating tuberculosis)
- Phenytoin (used to treat epilepsy)

Tell your doctor if you are taking any of the following medicines, as a dose adjustment or monitoring may be required to check that they are still having the desired effect:
- Warfarin and other anticoagulants (e.g. phenprocoumon, acenocoumarol; used to slow down clotting of the blood)
- Cyclosporin (used in transplant patients)
- Tacrolimus (used in transplant patients)
- Sulphonylureas (used for diabetes)
- Statins (used for lowering cholesterol)
- Benzodiazepines (used for severe insomnia and stress)
- Omeprazole (used for treating ulcers)
- Vinca alkaloids (used in treating cancer)
- Indinavir and other HIV protease inhibitors (used for treating HIV)

- Non-nucleoside reverse transcriptase inhibitors (used for treating HIV)
- Methadone (used to treat heroin addiction)

3. HOW TO TAKE VFEND

Always take VFEND exactly as directed by your doctor. You should check with your doctor or pharmacist if you are unsure.

Your doctor will determine your dose depending on your weight and the type of infection you have.

- The usual dose for adults (including elderly patients) is as follows:

	Oral suspension	
	Patients 40kg and above	Patients less than 40kg
Dose for the first 24 hours (Loading Dose)	400mg (10ml) every 12 hours for the first 24 hours	200mg (5ml) every 12 hours for the first 24 hours
Dose after the first 24 hours (Maintenance Dose)	200mg (5ml) twice a day	100mg (2.5ml) twice a day

- The usual dose for children aged 2 to less than 12 years:

	Oral suspension
Dose for the first 24 hours (Loading Dose)	6mg/kg every 12 hours for the first 24 hours
Dose after the first 24 hours (Maintenance Dose)	4mg/kg twice a day

The dose should be administered to the nearest 20mg (0.5ml) as the oral syringe is graduated in increments of 0.5ml.

VFEND should not be given to children younger than 2 years of age.

- Teenagers (aged 12 to 16 years) should be dosed as for adults.

Take your suspension at least one hour before, or two hours after a meal.

Continue taking VFEND until your doctor tells you to stop. Do not stop treatment early because your infection may not be cured. Patients with a weakened immune system or those with difficult infections may require long-term treatment to prevent the infection from returning.

VFEND suspension should not be mixed with any other medication. The suspension should not be further diluted with water or any other liquids.

If you take more VFEND than you should:
If you take more suspension than prescribed (or if someone else takes your suspension) you must seek medical advice or go to the nearest hospital casualty department immediately. Take your bottle of VFEND suspension with you.

If you forget to take VFEND:

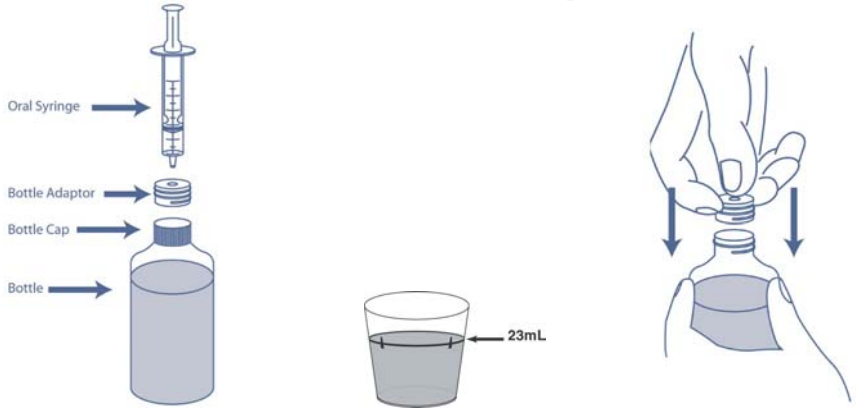
It is important to take your VFEND suspension regularly at the same time each day. If you forget to take one dose, take your next dose when it is due. Do not take a double dose to make up for the forgotten dose.

Effects when treatment with VFEND is stopped:
It has been shown that taking all doses at the appropriate times may greatly increase the effectiveness of your medicine. Therefore unless your doctor instructs you to stop treatment, it is important to keep taking VFEND correctly, as described above.

When VFEND treatment is stopped by your doctor you should not experience any effects. However if you were taking medicines containing cyclosporin or tacrolimus you must mention this to your doctor, as the dose will need to be adjusted.

Instructions to constitute the suspension:
It is recommended that your pharmacist constitutes VFEND suspension before giving it to you. VFEND suspension is constituted if it is in a liquid form. If it appears to be a dry powder you should constitute the oral suspension by following the instructions below.

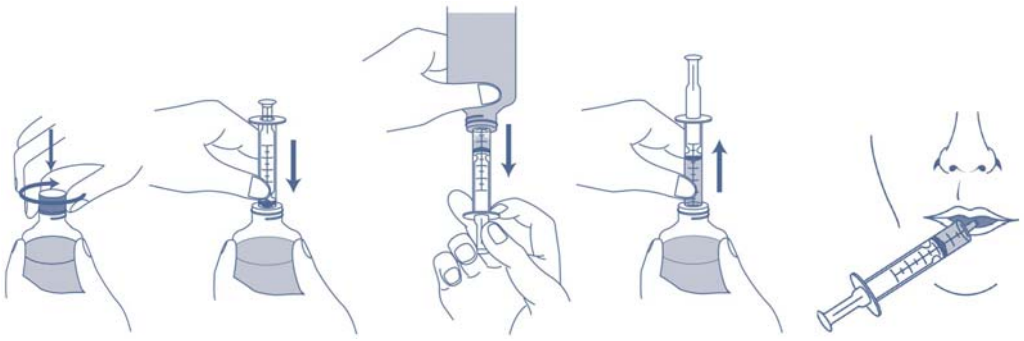
1. Tap the bottle to release the powder.
2. Remove the cap.
3. Measure 23mL of water by filling the measuring cup (included in the carton) to the top of the marked line then pour the water into the bottle. Using the cup measure another 23mL of water and add this to the bottle. You should always add a total of 46mL (2 x 23mL) of water irrespective of the dose you are taking.
4. Replace the cap and shake the bottle vigorously for about 1 minute.
5. Remove the cap. Press the bottle adaptor into the neck of the bottle (as shown on figure below). The adaptor is provided so that you can fill the oral syringe with medicine from the bottle. Replace the cap on the bottle.
6. Write the date of expiry of the constituted suspension on the bottle label (the shelf-life of the constituted suspension is 14 days). Any unused suspension should be discarded after this date.



Instructions for use:
Your pharmacist should advise you how to measure the medicine using the multi-dosing oral syringe provided in the pack. Please see instructions below before using VFEND suspension.

1. Shake the closed bottle of constituted suspension for approximately 10 seconds before use. Remove the cap.
2. While the bottle is upright, on a flat surface, insert the tip of the oral syringe into the adaptor.
3. Turn the bottle upside down while holding the oral syringe in place. Slowly pull back the plunger of the oral syringe to the graduation mark that marks the dose for you. To measure the dose accurately, the top edge of the black ring should be lined up with the graduated mark on the oral syringe.
4. If large bubbles can be seen, slowly push the plunger back into the syringe. This will force the medicine back into the bottle. Repeat step 3 again.

5. Turn the bottle back upright with the oral syringe still in place. Remove the oral syringe from the bottle.
6. Put the tip of the oral syringe into the mouth. Point the tip of the oral syringe towards the inside of the cheek. SLOWLY push down the plunger of the oral syringe. Do not squirt the medicine out quickly. If the medicine is to be given to a child, make sure the child is sitting, or is held, upright before giving the medicine.
7. Replace the cap on the bottle, leaving the bottle adaptor in place. Wash the oral syringe as instructed below.



Cleaning and storing the syringe:
1. The syringe should be washed after each dose. Pull the plunger out of the syringe and wash both parts in warm soapy water. Then rinse with water.
2. Dry the two parts. Push the plunger back in to the syringe. Keep it in a clean safe place with the medicine.

4. POSSIBLE SIDE EFFECTS

Like all medicines, VFEND can have side effects. If any side effects occur, most are likely to be minor and temporary. However, some may be serious and need medical attention.

The most commonly reported side effects (occurring in more than one out of 10 patients in clinical trials) are visual disturbances, altered taste, fever, rash, nausea, vomiting, diarrhoea, headache, swelling of the extremities and stomach pains.

As VFEND has been known to affect the liver and the kidney, your doctor should monitor the function of your liver and kidney by doing blood tests. Please advise your doctor if you have any stomach pains or if your stools have a different consistency.

Other reported side effects include: changes in heart rate or rhythm, changes in blood pressure, blood cell changes, blood chemistry changes, dizziness, itchiness, weakness, back pain, chest pain, flu-like symptoms, facial swelling, hallucinations and other nervous symptoms, tingling, cough, breathing difficulty, hair loss, pain and irritation of the eyes, hearing difficulties, joint pain disruption of brain function, inability to sleep, feeling sleepy during infusion.

If any of these side effects persist or are troublesome, please tell your doctor.

If you notice any side effects not mentioned in this leaflet, please tell your doctor or pharmacist.

5. STORING VFEND

Keep out of the reach and sight of children.

Powder for oral suspension: store at 2°C - 8°C (in a refrigerator) before constitution.
Do not use after the expiry date stated on the label.

For the constituted suspension:
Do not store above 30°C.
Do not refrigerate or freeze.
Store in the original container.
Keep the container tightly closed.
Any remaining suspension should be discarded 14 days after constitution.

6. FURTHER INFORMATION

- If you have further questions, please ask your doctor or pharmacist.
- For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder.

België /Belgique/Belgien
Pfizer S.A./N.V.
Tél/Tel: +32 (0)2 554 62 11

Česká republika
Pfizer s.r.o.
Tel: +420-283-004-111

Danmark
Pfizer ApS
Tlf: +45 44 20 11 00

Deutschland
Pfizer Pharma GmbH
Tel: +49 (0)721 6101 9000

Eesti
Pfizer Luxembourg SARL, Eesti filiaal
Tel: +372 6 405 328

Ελλάδα
Pfizer Hellas A.E.
Τηλ: +30 210 7517981-3

España
Pfizer S.A.
Tel: +34 91 490 99 00

France
Pfizer
Tél: +33 (0)1 58 07 34 40

Ireland
Pfizer Healthcare Ireland
Tel: +353 1800 633 363

Ísland
PharmaNor hf.,
Tel: + 354 535 7000

Luxembourg/Luxemburg
Pfizer S.A.
Tél: +32 (0)2 554 62 11

Magyarország
Pfizer Kft.
Tel. + 36 1 488 37 00

Malta
V.J. Salomone Pharma Ltd.
Tel : +356 21 22 01 74

Nederland
Pfizer bv
Tel: +31 (0)10 406 42 00

Norge
Pfizer AS
Tlf: +47 67 52 61 00

Österreich
Pfizer Corporation Austria Ges.m.b.H.
Tel: +43 (0)1 521 15-0

Polska
Pfizer Polska Sp. z o.o.,
Tel.: +48 22 549 38 00

Portugal
Laboratórios Pfizer, Lda.
Tel: +351 423 5500

Slovenija
Pfizer Luxembourg SARL, Podružnica Ljubljana
Tel: + 386/1/52 11 400

Slovenská republika
Pfizer Luxembourg SARL, organizačná zložka
Tel: +421–2–5941 8500

Italia
Pfizer Italia S.r.l.
Tel: +39 06 33 18 21

Κύπρος
GEO. PAVLIDES & ARAOUZOS LTD,
Τηλ: +35722818087

Latvija
Pfizer Luxembourg SARL
Tel: +371 70 35 775

Lietuva
Pfizer Luxembourg SARL
filialas Lietuvoje
Tel. +3705 2514000

Suomi/Finland
Pfizer Oy
Puh/Tel: +358(0)9 43 00 40

Sverige
Pfizer AB
Tel: +46 (0)8 519 062 00

United Kingdom
Pfizer Limited
Tel: +44 (0)1737 331111

This leaflet was last approved on