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SCHEDULING STATUS

S4

PROPRIETARY NAMES AND DOSAGE FORMS

VFEND® 50 mg film-coated tablets

VFEND® 200 mg film-coated tablets

VFEND® IV 200 mg powder for solution for infusion

COMPOSITION

Each VFEND 50 mg and 200 mg film-coated tablet contains voriconazole 50 mg and 200 mg respectively.

Each VFEND IV 200 mg vial contains 200 mg voriconazole. When reconstituted as directed, each ml contains 10 mg voriconazole.

VFEND film-coated tablets contain the following inactive ingredients: lactose monohydrate, pregelatinised starch, croscarmellose sodium, povidone, magnesium stearate, hypromellose, titanium dioxide, and glycerol triacetate.

VFEND IV 200 mg powder for solution for infusion contains the following inactive ingredients: sulphobutylether beta cyclodextrin sodium (SBECD) and water for injections.

PHARMACOLOGICAL CLASSIFICATION

A 20.1.7 Antimicrobial (chemotherapeutic) agents: Antifungal antibiotics

PHARMACOLOGICAL ACTION

1. Pharmacodynamic Properties

Mechanism of action:

Voriconazole is a broad spectrum triazole antifungal agent. Its mode of action is inhibition of fungal cytochrome P450-mediated 14α-sterol demethylation, an essential step in ergosterol biosynthesis.

Microbiology

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.*

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. Correlation of *in vitro* activity with clinical outcome is difficult owing to the complexity of the patients studied in clinical trials.

2. Pharmacokinetic Properties

General Pharmacokinetic Characteristics

The pharmacokinetics of voriconazole have been characterised in healthy subjects, special populations and patients. During oral administration of 200 mg or 300 mg twice daily for 14 days in patients at risk of aspergillosis (mainly patients with malignant neoplasms of lymphatic or 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 200 mg twice daily to 300 mg twice daily leads to a 2,5-fold increase in exposure (AUC_{τ}). 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 regimens, 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 %.

Detectable voriconazole concentrations are present in the cerebrospinal fluid of patients treated with voriconazole.

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 following 200 mg (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

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. However, the safety profile of voriconazole in young and elderly patients was similar and, therefore, no dosage adjustment is necessary for the elderly.

Paediatrics

VFEND IV 200 mg powder for solution for infusion

A population pharmacokinetic analysis was conducted on data from 35 immuno-compromised 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 4 mg/kg every 12 hours were similar to those in adults receiving 3 mg/kg every 12 hours, with medians of 1186 ng/ml in children and 1155 ng/ml in adults. Therefore a maintenance dose of 4 mg/kg every 12 hours is recommended for children aged between 2 to < 12 years of age.

Renal Impairment

VFEND 50 mg and 200 mg film-coated tablets

In an oral single dose (200 mg) study in subjects with normal renal function and mild (creatinine clearance 41 - 60 ml/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 ‘Dosage and directions for use’ and ‘Warnings and Special Precautions’).

VFEND IV 200 mg powder for solution for infusion

In patients with moderate to severe renal dysfunction (serum creatinine levels > 2,5 mg/dl), accumulation of the intravenous vehicle, SBECD, occurs. See dosing and monitoring recommendations under 'Dosage and directions for use' and 'Warnings and Special Precautions'.

Hepatic Impairment

After an oral single dose (200 mg), 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 100 mg twice daily and subjects with normal hepatic function given 200 mg twice daily. No pharmacokinetic data are available for patients with severe hepatic cirrhosis (Child-Pugh C). See dosing and monitoring recommendations under 'Dosage and directions for use' and 'Warnings and Special Precautions'.

INDICATIONS

Treatment of invasive aspergillosis.

Treatment of serious invasive infections caused by *Candida* spp (including *C. krusei*).

Voriconazole has been used in the treatment of serious fungal infections caused by *Scedosporium* spp and *Fusarium* spp.

Prevention of breakthrough of fungal infections in febrile high-risk patients (allogeneic bone marrow transplants, relapsed leukaemia patients) where liposomal amphotericin B cannot be used.

CONTRAINDICATIONS

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

Co-administration of the CYP3A4 substrates, 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 'Interactions').

Co-administration of VFEND with rifampicin, carbamazepine and phenobarbital is contraindicated since these medicines are likely to decrease plasma voriconazole concentrations significantly (see 'Interactions').

Co-administration of VFEND with high dose ritonavir (400 mg and above twice daily) is contraindicated because ritonavir significantly decreased plasma VFEND concentrations in healthy subjects at this dose (see 'Interactions' for lower doses).

Co-administration of ergot alkaloids (ergotamine, dihydroergotamine), which are CYP3A4 substrates, is contraindicated since increased plasma concentrations of these drugs can lead to ergotism (see 'Interactions').

Co-administration of VFEND and sirolimus is contraindicated, since voriconazole is likely to increase plasma concentrations of sirolimus significantly (see 'Interactions').

Co-administration of VFEND and rifabutin is contraindicated since VFEND is likely to increase plasma concentrations of rifabutin significantly (see 'Interactions').

Co-administration of VFEND with St John's Wort is contraindicated (see 'Interactions').

Patients with prolonged QT syndrome.

Pregnancy and lactation.

Severe impairment of hepatic function.

WARNINGS AND SPECIAL PRECAUTIONS

Women of child-bearing potential

Women of childbearing potential must always use effective contraception during treatment.

Hypersensitivity

Caution should be used in prescribing VFEND to patients with hypersensitivity to other azoles (see also ‘Side effects ’).

Infusion-related reaction

During infusion of the intravenous formulation of VFEND 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. Depending on the severity of the symptoms, consideration should be given to stopping treatment.

Liver function tests

The overall incidence of clinically significant transaminase abnormalities in the VFEND clinical programme was 13,4 % of subjects treated with VFEND. Liver function test abnormalities may be associated with higher plasma concentrations and/or doses. The majority of abnormal liver function tests are either resolved during treatment without dose adjustment or following dose adjustment, including discontinuation of therapy.

VFEND 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.

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 'Side effects').

Monitoring of hepatic function

Patients at the beginning of therapy with VFEND 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.

Visual adverse events

There have been post-marketing reports of irreversible visual adverse events, including optic neuritis and papilloedema. These events occurred primarily in severely ill patients who had underlying conditions and/or concomitant medications which may have caused or contributed to these events (see 'Side effects').

In clinical trials, VFEND treatment-related visual disturbances were very common. In these studies, approximately 21 % of subjects experienced altered/enhanced visual perception, blurred vision, colour vision change or photophobia. These visual disturbances were transient and fully reversible, with the majority spontaneously resolving within 60 minutes. There was evidence of attenuation with repeated doses of VFEND. The visual disturbance were generally mild, rarely resulted in discontinuation and were not associated with long-term sequelae. Visual disturbances may be associated with higher plasma concentrations and/or doses.

There have been post-marketing reports of irreversible visual adverse events.

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 VFEND on retinal function, VFEND 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 VFEND.

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

Patients with renal adverse events

Acute renal failure has been observed in severely ill patients undergoing treatment with VFEND. Patients being treated with VFEND are likely to be treated concomitantly with nephrotoxic medications and have concurrent conditions that may result in decreased renal function (see ‘Side effects’).

Monitoring of renal function

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

Monitoring of pancreatic function

Adults and children with risk factors for acute pancreatitis (e.g. recent chemotherapy, haematopoietic stem cell transplantation [HSCT]), should be monitored for development of pancreatitis during VFEND treatment.

Dermatological adverse events

Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome, during treatment with VFEND. If a patient develops an exfoliative cutaneous reaction VFEND should be discontinued.

In addition VFEND has been associated with photosensitivity skin reaction. It is recommended that patients avoid intense or prolonged exposure to direct sunlight during VFEND treatment. In patients with photosensitivity skin reactions and additional risk factors, squamous cell carcinoma of the skin and melanoma have been

reported during long-term therapy. If a patient develops a skin lesion consistent with squamous cell carcinoma or melanoma, VFEND discontinuation should be considered.

Dermatological reactions were common in patients treated with VFEND 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.

Paediatric use

Safety and effectiveness in paediatric subjects below the age of two years has not been established.

The safety of VFEND was investigated in 245 paediatric patients aged 2 to < 12 years who were treated with VFEND in pharmacokinetic studies (87 paediatric patients) and in compassionate use programs (158 paediatric patients). The adverse event profile of these 245 paediatric patients was similar to adults. Post-marketing data show a higher occurrence of skin reactions in the paediatric population compared to adults.

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

Methadone (CYP3A4 substrate)

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

Short Acting Opiates (CYP3A4 substrate)

Reduction in the dose of alfentanil and other short acting opiates similar in structure to alfentanil and metabolised by CYP3A4 should be considered when co-administered with VFEND (see ‘Interactions’). As the half-life of alfentanil is prolonged in a 4-fold manner when alfentanil is co-administered with VFEND, frequent monitoring for opiate-associated adverse events (including a longer respiratory monitoring period) may be necessary.

Oxycodone (CYP3A4 substrate)

Reduction in the dose of oxycodone and other long-acting opiates metabolised by CYP3A4 (e.g. hydrocodone) should be considered when co-administered with VFEND. Frequent monitoring for opiate-associated adverse events may be necessary (see 'Interactions').

Ciclosporin and tacrolimus (CYP3A4 substrates)

Clinically significant drug interactions with VFEND may occur in patients who are receiving treatment with ciclosporin or tacrolimus (see 'Interactions').

Phenytoin (CYP2C9 substrate and potent CYP450 inducer)

Careful monitoring of phenytoin levels is recommended when phenytoin is co-administered with VFEND. Concomitant use of VFEND and phenytoin should be avoided unless the benefit outweighs the risk (see 'Interactions').

Ritonavir

Co-administration of VFEND and low dose ritonavir (100 mg twice daily) should be avoided unless an assessment of the benefit/risk justifies the use of VFEND. (See 'Interactions' and for higher doses see 'Contraindications').

Efavirenz (CYP450 inducer; CYP3A4 inhibitor and substrate)

When VFEND is co-administered with efavirenz the dose of VFEND should be increased to 400 mg twice daily and that of efavirenz should be decreased to 300 mg once daily (see 'Interactions').

VFEND may prolong the QT interval without a clear relationship to plasma concentration. VFEND should not be used concomitantly with other medicines which prolong the QT interval.

Lactose intolerance

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

Effects on ability to drive and use machines

VFEND 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 whilst experiencing these symptoms.

INTERACTIONS

Unless otherwise specified, drug interaction studies have been performed in healthy male subjects using multiple dosing to steady state with oral VFEND 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 VFEND, the effects of VFEND 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 that 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 VFEND plasma concentrations, respectively.

Concomitant use of the following agents with VFEND is contraindicated:

St John's Wort (CYP450 inducer; P-gp inducer): In an independent published study in healthy volunteers, St John's Wort exhibited a short initial inhibitory effect followed by induction of VFEND metabolism. Therefore, concomitant use of VFEND with St John's Wort is contraindicated (see 'Contraindications').

The exposure to VFEND is significantly reduced by the concomitant administration of the following agents:

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. Co-administration of VFEND and rifampicin is contraindicated (see 'Contraindications').

Ritonavir (potent CYP450 inducer; CYP3A4 inhibitor and substrate): The effect of the co-administration of oral VFEND (200 mg twice daily) and high dose (400 mg) and low dose (100 mg) oral ritonavir was investigated in two separate studies in healthy volunteers. High doses of ritonavir (400 mg twice daily) decreased the steady state C_{max} and AUC_{τ} of oral VFEND by an average of 66 % and 82 %, whereas low doses of ritonavir (100 mg twice daily) decreased the C_{max} and AUC_{τ} of VFEND by an average of 24 % and 39 % respectively. Administration of VFEND did not have a significant effect on mean C_{max} and AUC_{τ} of ritonavir in the high dose study, although a minor decrease in steady state C_{max} and AUC_{τ} of ritonavir with an average of 25 % and 13 % respectively was observed in the low dose ritonavir interaction study. One outlier subject with raised VFEND levels was identified in each of the ritonavir interaction studies. Co-administration of VFEND and high doses of ritonavir (400 mg and above twice daily) is contraindicated. Co-administration of VFEND and low dose ritonavir (100 mg twice daily) should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of VFEND (see 'Contraindications' & 'Warnings and Special Precautions').

Carbamazepine and phenobarbital (potent CYP450 inducers): Although not studied, carbamazepine or phenobarbital are likely to significantly decrease plasma VFEND concentrations. Co-administration of VFEND with carbamazepine and phenobarbital is contraindicated (see 'Contraindications').

Due to minor or no significant pharmacokinetic interactions, no dosage adjustment is required with the following agents:

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

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

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

Effects of VFEND on other medicinal products

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

VFEND should be administered with caution in patients receiving concomitant medication that is known to prolong QT interval. When there is also a potential for VFEND to increase the plasma levels of substances metabolized by CYP3A4 isoenzymes (e.g. certain antihistamines, quinidine, cisapride, pimozide) co-administration is contraindicated (see below and 'Contraindications').

Concomitant use of the following agents with VFEND is contraindicated:

Astemizole, cisapride, pimozide and quinidine (CYP3A4 substrates): Although not studied, co-administration of VFEND with astemizole, cisapride, pimozide, or quinidine is contraindicated, since increased plasma concentrations of these drugs can lead to QTc prolongation and rare occurrences of *Torsades de Pointes* (see 'Contraindications').

Sirolimus (CYP3A4 substrate): VFEND increased sirolimus (2 mg single dose) C_{max} and AUC by 556 % and 1014 % respectively. Co-administration of VFEND and sirolimus is contraindicated (see 'Contraindications').

Ergot alkaloids (CYP3A4 substrates): Although not studied, VFEND may increase the plasma concentrations of ergot alkaloids (ergotamine and dihydroergotamine) and lead to ergotism. Co-administration of VFEND with ergot alkaloids is contra-indicated (see 'Contraindications').

Interaction of VFEND with the following agents may result in increased exposure to these medicines. Therefore, careful monitoring and/or dosage adjustment should be considered.

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

Tacrolimus (CYP3A4 substrate): VFEND increased tacrolimus (0,1 mg/kg single dose) C_{max} and AUC_{τ} (area under the plasma concentration time curve to the last quantifiable measurement) by 117 % and 221 %, respectively. When initiating VFEND 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 VFEND is discontinued, tacrolimus levels must be carefully monitored and the dose increased as necessary (see 'Warnings and Special Precautions').

Methadone (CYP3A4 substrate): Repeat dose administration of oral VFEND (400 mg every 12 hours for 1 day, then 200 mg every 12 hours for 4 days) increased the C_{max} and AUC_{τ} of pharmacologically active R-methadone by 31 % (90 % CI: 22 %, 40 %) and 47 % (90 % CI: 38 %, 57 %), respectively, in subjects receiving a methadone maintenance dose (30 - 100 mg daily) (see 'Warnings and Special Precautions').

Short Acting Opiates (CYP3A4 substrate): In an independent publication, steady-state administration of oral VFEND increased the AUC_{∞} of a single dose of alfentanil by 6-fold. Reduction in the dose of alfentanil and other short acting opiates similar in structure to alfentanil and metabolised by CYP3A4, should be considered when co-administered with VFEND.

Fentanyl (CYP3A4 substrate): In an independent published study, concomitant use of VFEND (400 mg every 12 hours on Day 1, then 200 mg every 12 hours on Day 2) with a single intravenous dose of fentanyl (5 µg/kg) resulted in an increase in the mean $AUC_{0-\infty}$ of fentanyl by 1,4-fold (range 1,12 – 1,60-fold). When VFEND is co-administered with fentanyl, extended and frequent monitoring of patients for respiratory depression and other fentanyl-associated adverse events is recommended, and fentanyl dosage should be reduced if warranted.

Oxycodone (CYP3A4 substrate**):** In an independent published study, co-administration of multiple doses of oral VFEND (400 mg every 12 hours, on Day 1 followed by five doses of 200 mg every 12 hours on Days 2 to 4) with a single 10 mg oral dose of oxycodone on Day 3 resulted in an increase in the mean C_{max} and $AUC_{0-\infty}$ of oxycodone by 1,7-fold (range 1,4- to 2,2-fold) and 3,6-fold (range 2,7- to 5,6-fold), respectively. The mean elimination half-life of oxycodone was also increased by 2,0-fold (range 1,4- to 2,5-fold). A reduction in oxycodone dosage may be needed during VFEND treatment to avoid opioid related adverse effects. Extended and frequent monitoring for adverse effects associated with oxycodone and other long-acting opiates metabolised by CYP3A4 is recommended.

Oral anticoagulants:

Warfarin (CYP2C9 substrate): Co-administration of VFEND (300 mg twice daily) with warfarin (30 mg single dose) increased maximum prothrombin time / international normalised ratio (INR) by 93 %. Close monitoring of prothrombin time/INR is recommended if warfarin and VFEND are co-administered.

Sulphonylureas (CYP2C9 substrates): Although not studied, VFEND 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 co-administration.

Statins (CYP3A4 substrates): Although not studied clinically, VFEND has been shown to inhibit lovastatin metabolism *in vitro* (human liver microsomes). Therefore, VFEND 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 co-administration. Increased statin levels have been associated with rhabdomyolysis.

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

Vinca Alkaloids (CYP3A4 substrates): Although not studied, VFEND may increase the plasma levels of the vinca alkaloids (e.g. vincristine and vinblastine) and lead to neurotoxicity. It is therefore recommended that dose adjustment of the vinca alkaloid be considered.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDS): VFEND increased C_{max} and AUC of ibuprofen (400 mg single dose) by 20 % and 100 %, respectively. VFEND increased C_{max} and AUC of diclofenac (50 mg single dose) by 114 % and 78 %, respectively. Frequent monitoring for adverse events and toxicity related to NSAID's is recommended. Adjustment of dosage of NSAID's may be needed.

No significant pharmacokinetic interactions were observed when VFEND was co-administered with the following agents. Therefore, no dosage adjustment for these agents is necessary.

Prednisolone (CYP3A4 substrate): VFEND 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): VFEND had no significant effect on C_{max} and AUC_{τ} of digoxin (0,25 mg once daily).

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

Two-way interactions

Efavirenz (a non-nucleoside reverse transcriptase inhibitor [CYP450 inducer; CYP3A4 inhibitor and substrate]): Standard doses of VFEND and standard doses of efavirenz must not be co-administered. In healthy subjects steady state efavirenz (400 mg oral once daily) decreased the steady state C_{max} and AUC_t of VFEND by an average of 61 % and 77 %, respectively. In the same study, VFEND at steady state (400 mg oral every 12 hours for 1 day, then 200 mg oral every 12 hours for 8 days) increased the steady state C_{max} and AUC_t of efavirenz by an average of 38 % and 44 %, respectively, in the same subjects.

In a separate study in healthy subjects, VFEND dose of 300 mg twice daily in combination with low dose efavirenz (300 mg once daily) did not lead to sufficient VFEND exposure.

Following co-administration of VFEND 400 mg twice daily with efavirenz 300 mg orally once daily, in healthy subjects, the AUC_{τ} of VFEND was decreased by 7 % and C_{max} was increased by 23 %, compared to VFEND 200 mg twice daily alone. The AUC_{τ} of efavirenz was increased by 17 % and C_{max} was equivalent compared to efavirenz 600 mg once daily alone. These differences were not considered to be clinically significant.

When VFEND is co-administered with efavirenz, the VFEND maintenance dose should be increased to 400 mg twice daily and the efavirenz dose should be reduced by 50 %, i.e. to 300 mg once daily (see 'Dosage and directions for use'). When treatment with VFEND is stopped, the initial dosage of efavirenz should be restored.

Phenytoin (CYP2C9 substrate and potent CYP450 inducer): Concomitant use of VFEND and phenytoin should be avoided unless the benefit outweighs the risk.
Phenytoin (300 mg once daily) decreased the C_{max} and AUC_{τ} of VFEND by 49 % and 69 %, respectively. VFEND (400 mg twice daily, see 'Dosage and directions for use') increased C_{max} and AUC_{τ} of phenytoin (300 mg once daily) by 67 % and 81 %, respectively. Careful monitoring of plasma phenytoin levels is recommended when phenytoin is co-administered with VFEND.
Phenytoin may be co-administered with VFEND if the maintenance dose of VFEND is increased from 3 mg/kg to 5 mg /kg intravenously twice daily or from 200 mg to 400 mg orally, twice daily (100 mg to 200 mg orally, twice daily in patients less than 40 kg), see 'Dosage and directions for use'.

Rifabutin (CYP450 inducer): Concomitant use of VFEND and rifabutin is contraindicated. (see 'Contraindications').
Rifabutin (300 mg once daily) decreased the C_{max} and AUC_{τ} of VFEND at 200 mg twice daily by 69 % and 78 %, respectively. During co-administration with rifabutin, the C_{max} and AUC_{τ} of VFEND at 350 mg twice daily were 96 % and 68 % of the levels when administered alone at 200 mg twice daily. At a VFEND dose of 400 mg twice daily, C_{max} and AUC_{τ} were 104 % and 87 % higher, respectively, compared with VFEND alone at 200 mg twice daily, VFEND at 400 mg twice daily increased C_{max} and AUC_{τ} of rifabutin by 195 % and 331 %, respectively.

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

Oral Contraceptives (CYP3A4 substrate): Co-administration of VFEND and an oral contraceptive (1 mg norethisterone and 0,035 mg ethinylestradiol; once daily) in healthy female subjects resulted in increases in the C_{max} and AUC_{τ} of ethinylestradiol (36 % and 61 % respectively) and norethisterone (15 % and 53 % respectively). VFEND C_{max} and AUC_{τ} increased by 14 % and 46 % respectively. Oral contraceptives containing doses other than 1 mg norethisterone and 0,035 mg ethinylestradiol have not been studied. As the ratio between norethisterone and ethinylestradiol remained similar during interaction with VFEND, their contraceptive activity would probably not be affected. Monitoring for adverse events related to oral contraceptives is recommended during co-administration.

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

Other HIV protease inhibitors (CYP3A4 inhibitors)**:** *In vitro* studies suggest that VFEND may inhibit the metabolism of HIV protease inhibitors (e.g. saquinavir, amprenavir and nelfinavir). *In vitro* studies also show that the metabolism of VFEND may be inhibited by HIV protease inhibitors. However results of the combination of VFEND 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.

Other Non-nucleoside reverse transcriptase inhibitors (NNRTI) (CYP3A4 substrates, inhibitors or CYP450 inducers)*: In vitro* studies show that the metabolism of VFEND may be inhibited by delavirdine. Although not studied, the metabolism of VFEND may be induced by nevirapine. VFEND may also inhibit the metabolism of NNRTIs. Due to the lack of *in vivo* studies, patients should be carefully monitored for any occurrence of drug toxicity and/or lack of efficacy during the co-administration of VFEND and NNRTIs.

PREGNANCY AND LACTATION

Pregnancy (see 'Contraindications')

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

Studies in animals have shown reproductive toxicity and teratogenicity. The potential risk to humans is unknown.

VFEND must not be used during pregnancy.

Lactation

The excretion of VFEND into breastmilk has not been investigated. Breastfeeding must be stopped on initiation of treatment with VFEND (see 'Contraindications').

DOSAGE AND DIRECTIONS FOR USE

VFEND 50 mg and 200 mg film-coated tablets:

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

VFEND IV 200 mg powder for solution for infusion:

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

VFEND requires reconstitution and dilution prior to administration as an intravenous infusion.

Not for bolus injection.

The vial contents are reconstituted with 19 ml of Water for Injections to obtain a clear solution containing 10 mg/ml of VFEND and an extractable volume of 20 ml. For administration, the required volume of the reconstituted solution is added to a recommended compatible infusion solution (tabulated below) to obtain, where appropriate, a final VFEND solution containing 0,5 - 5 mg/ml.

Required volumes of 10 mg/ml VFEND concentrate

Body Weight (kg)	**3 mg/kg dose (number of vials)**	**4 mg/kg dose (number of vials)**	**6 mg/kg dose (number of vials)**
10	-	4,0 ml (1)	-
15	-	6,0 ml (1)	-
20	-	8,0 ml (1)	-
25	-	10,0 ml (1)	-
30	9,0 ml (1)	12 ml (1)	18 ml (1)
35	10,5 ml (1)	14 ml (1)	21 ml (2)
40	12,0 ml (1)	16 ml (1)	24 ml (2)
45	13,5 ml (1)	18 ml (1)	27 ml (2)
50	15,0 ml (1)	20 ml (1)	30 ml (2)
55	16,5 ml (1)	22 ml (2)	33 ml (2)
60	18,0 ml (1)	24 ml (2)	36 ml (2)
65	19,5 ml (1)	26 ml (2)	39 ml (2)
70	21,0 ml (2)	28 ml (2)	42 ml (3)
75	22,5 ml (2)	30 ml (2)	45 ml (3)
80	24,0 ml (2)	32 ml (2)	48 ml (3)
85	25,5 ml (2)	34 ml (2)	51 ml (3)
90	27,0 ml (2)	36 ml (2)	54 ml (3)
95	28,5 ml (2)	38 ml (2)	57 ml (3)
100	30,0 ml (2)	40 ml (2)	60 ml (3)

VFEND IV does not contain an antimicrobial preservative. If the reconstituted solution is not used immediately, the reconstituted solution will remain suitable for its intended use for up to 24 hours, stored at 2 - 8 °C, if reconstitution has taken place in controlled and validated aseptic conditions.

The reconstituted solution can be diluted with:

0,9 % Sodium Chloride Intravenous Infusion

Compound Sodium Lactate Intravenous Infusion

5 % Glucose and Compound Sodium Lactate Intravenous Infusion

5 % Glucose and 0,45 % Sodium Chloride Intravenous Infusion

5 % Glucose Intravenous Infusion

5 % Glucose in 20 mmol 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 those described above is unknown (see incompatibilities below).

VFEND must not be infused into the same line or cannula concomitantly with other drug infusions, including parenteral nutrition. 4,2 % Sodium Bicarbonate Intravenous Infusion is not compatible with VFEND and must not be used as a diluent. Compatibility with other concentrations is unknown.

Blood products and concentrated electrolytes

VFEND must not be infused concomitantly with any blood product or any short-term infusion of concentrated electrolytes, even if the two infusions are running in separate intravenous lines (or cannulas). Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be corrected prior to initiation of VFEND therapy.

Intravenous solutions containing (non-concentrated) electrolytes

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

Total parenteral nutrition (TPN)

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

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 %), 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 40 kg and above	Patients less than 40 kg
Loading Dose Regimen for all Indications (first 24 hours)	6 mg/kg every 12 hours (for the first 24 hours)	400 mg every 12 hours (for the first 24 hours)	200 mg every 12 hours (for the first 24 hours)
Maintenance Dose (after first 24 hours)			
Prevention of breakthrough infections	3 mg/kg every 12 hours	200 mg every 12 hours	100 mg every 12 hours
Invasive aspergillosis, serious *Candida* infections, *Scedosporium/ Fusarium* infections	4 mg/kg every 12 hours	200 mg every 12 hours	100 mg every 12 hours

Dosage adjustment

Powder for solution for infusion:

If patient response is inadequate, the maintenance dose may be increased to 4 mg/kg every 12 hours for intravenous administration.

Film-coated tablets:

If patient response is inadequate, the maintenance dose may be increased to 300 mg every 12 hours for oral administration. For patients less than 40 kg the oral dose may be increased to 150 mg twice daily.

Powder for solution for infusion:

If patients are unable to tolerate treatment at these higher doses, reduce the intravenous dose to the original maintenance dose, 3 mg/kg every 12 hours.

Film-coated tablets:

If patients are unable to tolerate treatment at these higher doses, reduce the oral dose by 50 mg steps to the 200 mg every 12 hours (or 100 mg every 12 hours for patients less than 40 kg) maintenance dose.

Powder for solution for infusion:

Phenytoin may be co-administered with VFEND if the maintenance dose of VFEND is increased to 5 mg/kg intravenously every 12 hours (see ‘Side effects ’).

Phenytoin may be co-administered with VFEND if the maintenance dose of VFEND is increased from 200 mg to 400 mg orally, every 12 hours (100 mg to 200 mg orally, every 12 hours in patients less than 40 kg), see ‘Side effects’.

When VFEND is co-administered with adjusted doses of efavirenz, VFEND maintenance dose should be increased to 400 mg every 12 hours. (see ‘Warnings and Special Precautions’ & ‘Interactions’).

Treatment duration depends upon patients’ clinical and mycological response.

Use in the elderly

No dose adjustment is necessary for elderly patients.

Use in patients with renal impairment

Film-coated tablets:

The pharmacokinetics of orally administered VFEND are not affected by renal impairment. Therefore, no adjustment is necessary for oral dosing for patients with mild to severe renal impairment.

Powder for solution for infusion:

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

Film-coated tablets and Powder for solution for infusion

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

Powder for solution for infusion

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

Use in patients with hepatic impairment

No dose adjustment is necessary in patients with acute hepatic injury, manifested by elevated liver function tests (ALT, AST), but continued monitoring of liver function tests for future elevations is recommended.

It is recommended that the standard loading dose regimens of 400 mg every 12 hours (orally) and a maintenance dose of 100 mg every 12 hours (orally) be used in patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B) receiving VFEND.

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. Patients with hepatic impairment must be carefully monitored for drug toxicity (see also 'Side effects').

Use in children

Safety and effectiveness in paediatric subjects below the age of 2 years has not been established. Therefore, VFEND 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)	6 mg/kg every 12 hours (for the first 24 hours)	6 mg/kg every 12 hours (for the first 24 hours)
Maintenance Dose (after first 24 hours)	4 mg/kg every 12 hours	4 mg/kg every 12 hours

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

Duration of Treatment

Treatment duration depends on the patient's clinical and mycological response. The duration of oral and intravenous VFEND treatment in the clinical studies ranged from 12 weeks to more than 6 months.

SIDE EFFECTS

The safety profile of VFEND is based on an integrated safety database of patients who participated in clinical 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. Duration of treatment ranged from 12 weeks to more than 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, ≥ 1/10 000 and < 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.

Side effects reported in subjects receiving VFEND.

MedDRA System Organ Class	**Side effects**
Infections and infestations	
Common	Sinusitis
Blood and lymphatic system disorders	
Common	Thrombocytopenia, anaemia (including macrocytic, microcytic, normocytic, megaloblastic, aplastic), leukopenia, pancytopenia
Uncommon	Lymphadenopathy, agranulocytosis, eosinophilia, disseminated intravascular coagulation, bone marrow depression
Immune system disorders	
Uncommon	Allergic reaction, anaphylactoid reaction
Endocrine disorders	
Uncommon	Adrenal cortex insufficiency
Rare	Hyperthyroidism, hypothyroidism
Metabolism and nutrition disorders	
Common	Hypokalaemia, hypoglycaemia
Uncommon	Hypercholesterolaemia
Psychiatric disorders	
Common	Hallucinations, confusion, depression, anxiety, agitation
Nervous system disorders	
Very common	Headache
Common	Dizziness, tremor, paraesthesia
Uncommon	Ataxia, brain oedema, hypertonia, hypoaesthesia, nystagmus, syncope, altered taste perception

Rare	Guillain-Barre syndrome, oculogyric crisis, extrapyramidal syndrome, hepatic coma, insomnia, encephalopathy, somnolence during infusion
Eye disorders	
Very Common	Visual disturbances (including altered/enhanced visual perception, blurred vision, colour vision change, photophobia)
Uncommon	Blepharitis, optic neuritis, papilloedema, scleritis, diplopia
Rare	Retinal haemorrhage, corneal opacity, optic atrophy
Ear and labyrinth disorders	
Uncommon	Vertigo
Rare	Hypoacusis, tinnitus
Cardiac disorders	
Common	Lung oedema
Uncommon	Atrial dysrhythmia, bradycardia, tachycardia, ventricular dysrhythmia, ventricular fibrillation, supraventricular tachycardia, prolonged QT interval
Rare	Atrioventricular (AV) complete block, bundle branch block, nodal dysrhythmia, ventricular tachycardia (including *Torsades de Pointes*)
Vascular disorders	
Common	Hypotension, thrombophlebitis, phlebitis
Rare	Lymphangitis
Respiratory, thoracic and mediastinal disorders	
Common	Respiratory distress syndrome
Gastrointestinal disorders	
Very common	Nausea, vomiting, diarrhoea, abdominal pain
Common	Cheilitis, gastroenteritis

Uncommon	Constipation, duodenitis, dyspepsia, gingivitis, glossitis, pancreatitis, tongue oedema, peritonitis
Rare	Pseudomembranous colitis
Hepatobiliary disorders	
Common	Elevated liver function tests (including AST, ALT, alkaline phosphatase, GGT, LDH, bilirubin), jaundice, cholestatic jaundice
Uncommon	Cholecystitis, cholelithiasis, enlarged liver, hepatitis, hepatic failure
Skin and subcutaneous tissue disorders	
Very common	Rash
Common	Facial oedema, pruritus, maculopapular rash, photosensitivity, skin reaction, alopecia, exfoliative dermatitis, purpura
Uncommon	Fixed drug eruption, eczema, psoriasis, Stevens-Johnson syndrome, urticaria
Rare	Angioedema, discoid lupus erythematosis, erythema multiforme, toxic epidermal necrolysis, pseudoporphyria
Musculoskeletal, connective tissue and bone disorders	
Common	Back pain
Uncommon	Arthritis
Renal and urinary disorders	
Common	Increased creatinine, acute kidney failure, haematuria
Uncommon	Increased blood urea, albuminuria, nephritis
Rare	Kidney tubular necrosis
General disorders and administration site conditions	
Very common	Fever, peripheral oedema

Common	Chills, asthenia, chest pain, injection site reaction/inflammation, flu syndrome

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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 VFEND. A single adverse event of photophobia of 10 minutes duration was reported.

There is no known antidote to VFEND.

VFEND 50 mg and 200 mg film-coated tablets

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

VFEND IV 200 mg powder for solution for infusion

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

IDENTIFICATION

VFEND 50 mg film-coated tablets are white to off-white, standard round convex tablets, debossed with “Pfizer” on one side and “VOR50” on the other.

VFEND 200 mg film-coated tablets are white to off-white, capsule-shaped tablets, debossed with “Pfizer” on one side and “VOR200” on the other.

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

PRESENTATION

VFEND film-coated tablets are available in the following containers:

Opaque plastic bottles containing 2, 30 or 100 tablets.

Transparent PVC/ Aluminium blisters with foil backing composed of hard tempered aluminium with vinylacrylate-based heat coating on the bright side of the foil, and polyester-based lacquer on the matt side. The blisters are contained in cartons of 2, 10, 14, 20, 28, 30, 50, 56 or 100 tablets.

VFEND IV 200 mg powder for solution for infusion is available as a sterile lyophilised powder in individually boxed, single use 30 ml clear Type I glass vials with rubber stoppers and aluminium caps with plastic seals.

STORAGE INSTRUCTIONS

VFEND 50 mg film-coated tablets and VFEND 200 mg film-coated tablets: Store below 25 °C.

VFEND IV 200 mg powder for solution for infusion: Store below 25 °C.

Reconstituted concentrate: Store at 2 °C - 8 °C for up to 24 hours (in a refrigerator). (For storage instructions after reconstitution, see ‘Dosage and directions for use’).

Keep out of reach of children.

REGISTRATION NUMBERS

VFEND 50 mg tablets: 36/20.1.7/0106

VFEND 200 mg tablets: 36/20.1.7/0107

VFEND IV 200 mg powder for solution for infusion: 36/20.1.7/0108

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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