SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

VFEND® 50 mg film-coated tablets

VFEND® 200 mg film-coated tablets

VFEND® IV 200 mg powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Film-coated tablets

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

Contains sugar (lactose monohydrate).

Powder for solution for infusion

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

Sugar free.

Excipients with known effect

Film-coated tablets

Each VFEND 50 mg film-coated tablet contains 63,42 mg lactose monohydrate.

Each VFEND 200 mg film-coated tablet contains 253,675 mg lactose monohydrate.

Powder for solution for infusion

Each VFEND IV 200 mg vial contains 221 mg sodium.

Each VFEND IV 200 mg vial contains 3 200 mg cyclodextrin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

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.

Powder for solution for infusion

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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Treatment of invasive aspergillosis.
- Treatment of serious invasive infections caused by *Candida* spp (including *C. krusei*).
- VFEND 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.
- Prophylaxis of invasive fungal infections in high risk allogeneic haematopoietic stem cell transplant (HSCT) recipients.

4.2 Posology and method of administration

Posology

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

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) - Prophylaxis of invasive fungal infections - Prevention of breakthrough infections	3 – 4 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.

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 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.

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 sections 4.4 and 4.5).

Film-coated tablets

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 sections 4.4 and 4.5).

When VFEND is co-administered with adjusted doses of efavirenz, VFEND maintenance dose should be increased to 400 mg every 12 hours (see sections 4.4 and 4.5).

Treatment duration depends upon patients' clinical and mycological response.

Prophylaxis in adults and children

Prophylaxis should be initiated on the day of transplant and may be administered for up to 100 days. It may only be continued up to 180 days after transplantation in case of continuing immunosuppression or graft versus host disease (GvHD) (see section 5.1).

Dosage

The recommended dosing regimen for prophylaxis is the same as for treatment in the respective age groups. Please refer to the treatment tables above.

Duration of prophylaxis

The safety and efficacy of VFEND use for longer than 180 days has not been adequately studied in clinical trials.

Special populations

Elderly

No dose adjustment is necessary for elderly patients.

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 (see section 5.2).

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 (see section 5.2).

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.

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

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 medicine toxicity (see section 4.8).

Paediatric population

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.

Method of administration

Film-coated tablets

For oral use.

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

Powder for solution for infusion

VFEND requires reconstitution and dilution prior to administration as an intravenous infusion (see section 6.6).

Not for bolus injection.

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

4.3 Contraindications

- Known hypersensitivity to voriconazole or to any of the excipients of VFEND (listed in section 6.1).
- Co-administration of the CYP3A4 substrates, terfenadine, astemizole, cisapride, pimozide, quinidine or ivabradine with VFEND is contraindicated since increased plasma concentrations of these medicines can lead to QTc prolongation and rare occurrences of *Torsades de Pointes* (see section 4.5).
- Co-administration of VFEND with rifampicin, carbamazepine, phenobarbital and St John's Wort is contraindicated since these medicines are likely to decrease plasma voriconazole concentrations significantly (see section 4.5).
- Co-administration of standard doses of VFEND with efavirenz doses of 400 mg once daily or higher is contraindicated, because efavirenz significantly decreases plasma VFEND concentrations in healthy subjects at these doses. VFEND also significantly increases efavirenz plasma concentrations (see section 4.5, for lower doses see section 4.4).
- 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 section 4.5, for lower doses see section 4.4).
- Co-administration of ergot alkaloids (ergotamine, dihydroergotamine), which are CYP3A4 substrates, is contraindicated since increased plasma concentrations of these medicines can lead to ergotism (see section 4.5).
- Co-administration of VFEND and sirolimus is contraindicated, since voriconazole is likely to

increase plasma concentrations of sirolimus significantly (see section 4.5).

- Co-administration of VFEND and rifabutin is contraindicated since VFEND is likely to increase plasma concentrations of rifabutin significantly (see section 4.5).
- Co-administration of VFEND with naloxegol, a CYP3A4 substrate, is contraindicated since increased plasma concentrations of naloxegol can precipitate opioid withdrawal symptoms (see section 4.5).
- Co-administration of VFEND with tolvaptan is contraindicated since strong CYP3A4 inhibitors such as VFEND significantly increase plasma concentrations of tolvaptan (see section 4.5).
- Co-administration of VFEND with lurasidone is contraindicated since significant increases in lurasidone exposure have the potential for serious adverse reactions (see section 4.5).
- Co-administration with venetoclax at initiation and during the venetoclax dose titration phase is contraindicated since VFEND is likely to significantly increase plasma concentrations of venetoclax and increase risk of tumour lysis syndrome (see section 4.5).
- Patients with prolonged QT syndrome.
- Pregnancy and lactation.
- Severe impairment of hepatic function (Child-Pugh Class C).

4.4 Special warnings and precautions for use

Hypersensitivity

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

Infusion-related reaction

Infusion-related reactions, predominantly flushing and nausea have been observed during administration of the intravenous formulation of VFEND.

Depending on the severity of the symptoms, consideration should be given to stopping treatment (see section 4.8).

Cardiovascular

VFEND has been associated with QTc interval prolongation. There have been rare cases of *Torsades de pointes* in patients taking VFEND who had risk factors, such as history of cardiotoxic chemotherapy, cardiomyopathy, hypokalaemia and concomitant medicines that may have been contributory. VFEND should be administered with caution to patients with potentially prodysrhythmic conditions, such as:

- Congenital or acquired QTc prolongation
- Cardiomyopathy, in particular when heart failure is present
- Sinus bradycardia
- Existing symptomatic dysrhythmias
- Concomitant medicines known to prolong QTc interval.

Electrolyte disturbances such as hypokalaemia, hypomagnesemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation of and during VFEND therapy (see section 4.2).

Hepatic toxicity

In clinical trials, there have been cases of serious hepatic reactions during treatment with VFEND (including clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities). Instances of hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly 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 receiving VFEND must be carefully monitored for hepatic toxicity. Clinical management should include laboratory evaluation of hepatic function (specifically AST and ALT) at the initiation of treatment with VFEND and at least weekly for the first month of treatment. If treatment is continued, monitoring frequency can be reduced to monthly if there are no changes in the liver function tests.

If the liver function tests become markedly elevated, VFEND should be discontinued, unless the medical

judgment of the risk-benefit of the treatment for the patient justifies continued use (see section 4.2).

Visual adverse events

There have been post-marketing reports of prolonged visual adverse events, including optic neuritis and papilloedema. These events occurred primarily in severely ill patients who had underlying conditions and/or concomitant medicines which may have caused or contributed to these events (see section 4.8).

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 medicines 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.

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

During treatment with VFEND, patients have developed severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) which can be life-threatening or fatal (see section 4.8). If a patient develops a severe cutaneous adverse reaction VFEND should be discontinued.

In addition, VFEND has been associated with photosensitivity skin reaction. It is recommended that

patients, particularly children, avoid intense or prolonged exposure to direct sunlight during VFEND treatment and use measures such as protective clothing and sunscreen with high sun protection factor (SPF).

Adrenal events

Reversible cases of adrenal insufficiency have been reported in patients receiving azoles, including VFEND. Adrenal insufficiency has been reported in patients receiving azoles with or without concomitant corticosteroids. In patients receiving azoles without corticosteroids, adrenal insufficiency is related to direct inhibition of steroidogenesis by azoles. In patients taking corticosteroids, VFEND associated CYP3A4 inhibition of their metabolism may lead to corticosteroid excess and adrenal suppression (see section 4.5). Cushing's syndrome with and without subsequent adrenal insufficiency has also been reported in patients receiving VFEND concomitantly with corticosteroids.

Patients on long-term treatment with VFEND and corticosteroids (including inhaled corticosteroids e.g., budesonide and intranasal corticosteroids) should be carefully monitored for adrenal cortex dysfunction both during treatment and when VFEND is discontinued (see section 4.5). Patients should be instructed to seek immediate medical care if they develop signs and symptoms of Cushing's syndrome or adrenal insufficiency.

Long-term treatment

Squamous cell carcinoma of the skin (SCC)

In patients with photosensitivity skin reactions and additional risk factors, squamous cell carcinoma of the skin (including cutaneous SCC *in situ*, or Bowen's disease) and melanoma have been reported during long-term therapy (see section 4.8). If phototoxic reactions occur multidisciplinary advice should be sought, VFEND discontinuation and use of alternative antifungal medicines should be considered and the patient should be referred to a dermatologist. If VFEND is continued, however, dermatologic evaluation should be performed on a systematic and regular basis, to allow early detection and management of premalignant lesions.

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

Non-infectious periostitis

Periostitis has been reported in transplant patients during long-term VFEND therapy. If a patient develops skeletal pain and radiologic findings compatible with periostitis, VFEND should be discontinued (see section 4.8).

Methadone (CYP3A4 substrate)

Increased plasma concentrations of methadone have been associated with toxicity including QT prolongation. Frequent monitoring for adverse events and toxicity related to methadone is recommended during co-administration. Dose reduction of methadone may be needed (see section 4.5).

Short-acting opiates (CYP3A4 substrate)

Reduction in the dose of alfentanil, fentanyl and other short acting opiates similar in structure to alfentanil and metabolised by CYP3A4 (e.g. sufentanil) should be considered when co-administered with VFEND (see section 4.5). 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.

Long-acting opiates (CYP3A4 substrate)

Reduction in the dose of oxycodone and other long-acting opiates metabolised by CYP3A4 (e.g. hydrocodone) should be considered when co-administered with VFEND. Frequent monitoring for opiate-associated adverse events may be necessary (see section 4.5).

Fluconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor)

Co-administration of oral VFEND and oral fluconazole resulted in a significant increase in C_{max} and AUC_{τ} of voriconazole in healthy subjects. The reduced dose and/or frequency of VFEND and

fluconazole that would eliminate this effect have not been established. Monitoring for VFEND-associated adverse reactions is recommended if VFEND is used sequentially after fluconazole (see section 4.5).

Ciclosporin and tacrolimus (CYP3A4 substrates)

Clinically significant medicine interactions with VFEND may occur in patients who are receiving treatment with ciclosporin or tacrolimus (see section 4.5).

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 section 4.5).

Ritonavir (potent CYP450 inducer; CYP3A4 inhibitor and substrate)

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 section 4.5 and for higher doses see section 4.3).

Everolimus (CYP3A4 substrate, P-gp substrate)

Co-administration of VFEND with everolimus is not recommended because VFEND is expected to significantly increase everolimus concentrations. Currently there are insufficient data to allow dosing recommendations in this situation (see section 4.5).

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 sections 4.2, 4.3 and 4.5).

Glasdegib (CYP3A4 substrate)

Co-administration of VFEND is expected to increase glasdegib plasma concentrations and increase the risk of QTc prolongation (see section 4.5). If concomitant use cannot be avoided, frequent ECG monitoring is recommended.

Tyrosine kinase inhibitors (CYP3A4 substrate)

Co-administration of VFEND with tyrosine kinase inhibitors metabolised by CYP3A4 is expected to increase tyrosine kinase inhibitor plasma concentrations and the risk of adverse reactions. If concomitant use cannot be avoided, dose reduction of the tyrosine kinase inhibitor and close clinical monitoring is recommended (see section 4.5).

Paediatric population

Safety and effectiveness in paediatric subjects below the age of two years has not been established. VFEND is indicated for paediatric patients aged two years or older. A higher frequency of liver enzyme elevations was observed in the paediatric population (see section 4.8). Hepatic function should be monitored in both children and adults. Oral bioavailability may be limited in paediatric patients aged 2 to 12 years with malabsorption and very low body weight for age. In that case, intravenous VFEND administration is recommended.

Serious dermatological adverse reactions (including SCC)

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

Excipients

Tablets

Lactose

VFEND tablets contain lactose and should not be given to patients with rare hereditary problems of

galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.

Sodium

VFEND tablets contain less than 1 mmol sodium (23 mg) per tablet. Patients on low sodium diets should be informed that this medicine is essentially 'sodium-free'.

Powder for solution for infusion

Sodium

VFEND IV powder for solution for infusion contains 221 mg of sodium per vial, equivalent to 11 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Cyclodextrins

VFEND IV powder for solution for infusion contains cyclodextrins (3 200 mg cyclodextrins in each vial which is equivalent to 160 mg/mL when reconstituted in 20 mL, see section 6.1) which can influence the properties (such as toxicity) of the active substance and other medicines. Safety aspects of cyclodextrins have been considered during the development and safety assessment of VFEND IV.

As cyclodextrins are renally excreted, in patients with moderate to severe renal dysfunction accumulation of cyclodextrin may occur.

4.5 Interaction with other medicines and other forms of interaction

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

Unless otherwise specified, medicine interaction studies have been performed in healthy adult 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.

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. When there is also a potential for VFEND to increase the plasma concentrations of substances metabolised by CYP3A4 isoenzymes (e.g. certain antihistamines, quinidine, cisapride, pimozide and ivabradine) co-administration is contraindicated (see below and section 4.3).

Interaction table

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

The interactions in the table are presented in the following order: contraindications, those requiring 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.

Medicine **[Mechanism of interaction]**	**Interaction** **geometric mean changes (%)**	**Recommendations concerning co-administration**
Astemizole, cisapride, pimozide, quinidine, terfenadine and ivabradine *[CYP3A4 substrates]*	Although not studied, increased plasma concentrations of these medicines can lead to QTc prolongation and rare occurrences of *Torsades de Pointes*.	**Contraindicated** (see section 4.3)
Carbamazepine and long-acting barbiturates (including but not limited to: phenobarbital, mephobarbital) [potent CYP450 inducers]	Although not studied, carbamazepine and long-acting barbiturates are likely to significantly decrease plasma VFEND concentrations.	**Contraindicated** (see section 4.3)
Efavirenz (a non-nucleoside reverse transcriptase inhibitor) *[CYP450 inducer; CYP3A4 inhibitor and substrate]* Efavirenz 400 mg QD, coadministered with VFEND 200 mg BID Efavirenz 300 mg QD, co-administered with VFEND 400 mg BID*	Efavirenz C_{max} ↑ 38 % Efavirenz AUCτ ↑ 44 % VFEND C_{max} ↓ 61 % VFEND AUCτ ↓ 77 % Compared to efavirenz 600 mg QD, Efavirenz C_{max} ↔ Efavirenz AUCτ ↑ 17 %	Use of standard doses of VFEND with efavirenz doses of 400 mg QD or higher is **contraindicated** (see section 4.3). VFEND may be co-administered with efavirenz if the VFEND maintenance dose is increased to 400 mg

	Compared to VFEND 200 mg BID, VFEND C_{max} ↑ 23 % VFEND AUCτ ↓ 7 %	BID and the efavirenz dose is decreased to 300 mg QD. When VFEND treatment is stopped, the initial dose of efavirenz should be restored (see section 4.2).
Ergot alkaloids (including but not limited to: ergotamine and dihydro-ergotamine) [CYP3A4 substrates]	Although not studied, VFEND is likely to increase the plasma concentrations of ergot alkaloids and lead to ergotism.	**Contraindicated** (see section 4.3)
Lurasidone *[CYP3A4 substrate]*	Although not studied, VFEND is likely to significantly increase the plasma concentrations of lurasidone	**Contraindicated** (see section 4.3)
Naloxegol *[CYP3A4 substrate]*	Although not studied, VFEND is likely to significantly increase the plasma concentrations of naloxegol	**Contraindicated** (see section 4.3)
Rifabutin *[potent CYP450 inducer]* 300 mg QD 300 mg QD (co-administered with VFEND 400 mg BID)*	 VFEND C_{max} ↓ 69 % VFEND AUCτ ↓ 78 % Rifabutin C_{max} ↑ 195 % Rifabutin AUCτ ↑ 331 % Compared to VFEND 200 mg BID,	**Contraindicated** (see section 4.3)

	VFEND C_{max} ↑ 104 % VFEND AUCτ ↑ 87 %	
Rifampicin (600 mg QD) *[potent CYP450 inducer]*	VFEND C_{max} ↓ 93 % VFEND AUCτ ↓ 96 %	**Contraindicated** (see section 4.3)
Ritonavir (protease inhibitor) *[potent CYP450 inducer; CYP3A4 inhibitor and substrate]* High dose (400 mg BID) Low dose (100 mg BID)*	 Ritonavir C_{max} and AUCτ ↔ VFEND C_{max} ↓ 66 % VFEND AUCτ ↓ 82 % Ritonavir C_{max} ↓ 25 % Ritonavir AUCτ ↓13 % VFEND C_{max} ↓ 24 % VFEND AUCτ ↓ 39 %	 Co-administration of VFEND and high doses of ritonavir (400 mg and above BID) is **contraindicated** (see sections 4.3 and 4.4). Co-administration of VFEND and low dose ritonavir (100 mg BID) should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of VFEND.
St John's Wort *[CYP450 inducer; P-gp inducer]* 300 mg TID (co-administered with VFEND 400 mg single dose)	In an independent published study, VFEND $AUC_{0-\infty}$ ↓ 59 %	**Contraindicated** (see section 4.3)

Tolvaptan *[CYP3A substrate]*	Although not studied, VFEND is likely to significantly increase the plasma concentrations of tolvaptan.	**Contraindicated** (see section 4.3)
Venetoclax *[CYP3A substrate]*	Although not studied, VFEND is likely to significantly increase the plasma concentrations of venetoclax.	Concomitant administration of VFEND is **contraindicated** at initiation and during venetoclax dose titration phase (see section 4.3). Dose reduction of venetoclax is required as instructed in venetoclax prescribing information during steady daily dosing; close monitoring for signs of toxicity is recommended.
Fluconazole (200 mg QD) *[CYP2C9, CYP2C19 and CYP3A4 inhibitor]*	VFEND C_{max} ↑ 57 % VFEND AUC_{τ} ↑ 79 % Fluconazole C_{max} ND Fluconazole AUC_{τ} ND	The reduced dose and/or frequency of VFEND and fluconazole that would eliminate this effect have not been established. Monitoring for VFEND-associated adverse events is recommended if VFEND is used sequentially after fluconazole.

Phenytoin *[CYP2C9 substrate and potent CYP450 inducer]* 300 mg QD	 VFEND C_{max} ↓ 49 % VFEND AUCτ ↓ 69 %	Concomitant use of VFEND and phenytoin should be avoided unless the benefit outweighs the risk. Careful monitoring of phenytoin plasma levels is recommended.
300 mg QD (co-administered with VFEND 400 mg BID)*	Phenytoin C_{max} ↑ 67 % Phenytoin AUCτ ↑ 81 % Compared to VFEND 200 mg BID, VFEND C_{max} ↑ 34 % VFEND AUCτ ↑ 39 %	Phenytoin may be co-administered with VFEND if the maintenance dose of VFEND is increased to 5 mg/kg IV BID or from 200 mg to 400 mg oral BID, (100 mg to 200 mg oral BID in patients less than 40 kg) (see section 4.2).
Letermovir *[CYP2C9 and CYP2C19 inducer]*	VFEND C_{max} ↓ 39 % VFEND AUC_{0-12} ↓ 44 % VFEND C_{12} ↓ 51 %	If concomitant administration of VFEND with letermovir cannot be avoided, monitor for loss of VFEND effectiveness.
Flucloxacillin *[CYP450 inducer]*	Significantly decreased plasma VFEND concentrations have been reported.	If concomitant administration of VFEND with flucloxacillin cannot be avoided, monitor for potential loss of VFEND effectiveness (e.g., by therapeutic medicine monitoring); increasing the dose of VFEND may be

		needed.
Glasdegib *[CYP3A4 substrate]*	Although not studied, VFEND is likely to increase the plasma concentrations of glasdegib and increase risk of QTc prolongation.	If concomitant use cannot be avoided, frequent ECG monitoring is recommended (see section 4.4).
Tyrosine kinase inhibitors (including but not limited to: axitinib, bosutinib, cabozantinib, ceritinib, cobimetinib, dabrafenib, dasatinib, nilotinib, sunitinib, ibrutinib, ribociclib) *[CYP3A4 substrates]*	Although not studied, VFEND may increase plasma concentrations of tyrosine kinase inhibitors metabolised by CYP3A4.	If concomitant use cannot be avoided, dose reduction of the tyrosine kinase inhibitor and close clinical monitoring is recommended (see section 4.4).
Anticoagulants Warfarin (30 mg single dose, co-administered with 300 mg BID VFEND) [CYP2C9 substrate] Other oral coumarins (including but not limited to: phen-procoumon, acenocoumarol) *[CYP2C9 and CYP3A4 substrates]*	 Maximum increase in prothrombin time was approximately 2-fold Although not studied, VFEND may increase the plasma concentrations of coumarins that may cause an increase in prothrombin time.	 Close monitoring of prothrombin time or other suitable anticoagulation tests is recommended, and the dose of anticoagulants should be adjusted accordingly.

Ivacaftor *[CYP3A4 substrate]*	Although not studied, VFEND is likely to increase the plasma concentrations of ivacaftor with risk of increased adverse reactions.	Dose reduction of ivacaftor is recommended.
Benzodiazepines *[CYP3A4 substrates]* Midazolam (0,05 mg/kg IV single dose) Midazolam (7,5 mg oral single dose) Other benzodiazepines (including but not limited to: triazolam, alprazolam)	 In an independent published study, Midazolam $AUC_{0-\infty}$ ↑ 3,7-fold In an independent published study, Midazolam C_{max} ↑ 3,8-fold Midazolam $AUC_{0-\infty}$ ↑ 10,3-fold Although not studied, VFEND is likely to increase the plasma concentrations of other benzodiazepines that are metabolised by CYP3A4 and lead to a prolonged sedative effect.	Dose reduction of benzodiazepines should be considered.
Immuno-suppressants *[CYP3A4 substrates]* Sirolimus (2 mg single dose)	 In an independent published study, Sirolimus C_{max} ↑ 6,6-fold	 Co-administration of VFEND and sirolimus is **contraindicated** (see

	Sirolimus $AUC_{0-\infty}$ ↑ 11-fold	section 4.3).
Everolimus *[also P-gp substrate]*	Although not studied, VFEND is likely to significantly increase the plasma concentrations of everolimus.	Co-administration of VFEND and everolimus is not recommended because VFEND is expected to significantly increase everolimus concentrations (see section 4.4).
Ciclosporin (in stable renal transplant recipients receiving chronic ciclosporin therapy)	Ciclosporin C_{max} ↑ 13 % Ciclosporin AUC_{τ} ↑ 70 %	When initiating VFEND in patients already on ciclosporin it is recommended that the ciclosporin dose be halved and ciclosporin level carefully monitored. Increased ciclosporin levels have been associated with nephrotoxicity. When VFEND is discontinued, ciclosporin levels must be carefully monitored and the dose increased as necessary (see section 4.4).
Tacrolimus (0,1 mg/kg single dose)	Tacrolimus C_{max} ↑ 117 % Tacrolimus AUC_t ↑ 221 %	When initiating VFEND in patients already on tacrolimus, it is

		recommended that the tacrolimus dose be reduced to a third of the original dose and tacrolimus level carefully monitored. Increased tacrolimus levels have been associated with nephrotoxicity. When VFEND is discontinued, tacrolimus levels must be carefully monitored and the dose increased as necessary (see sections 4.2 and 4.4).
Long acting opiates *[CYP3A4 substrates]* Oxycodone (10 mg single dose)	In an independent published study, Oxycodone C_{max} ↑ 1,7-fold Oxycodone $AUC_{0-\infty}$ ↑ 3,6-fold	Dose reduction in oxycodone and other long-acting opiates metabolised by CYP3A4 (e.g., hydrocodone) should be considered. Frequent monitoring for opiate-associated adverse events may be necessary.
Methadone (32 – 100 mg QD) *[CYP3A4 substrate]*	R-methadone (active) C_{max} ↑ 31 % R-methadone (active) $AUC\tau$ ↑ 47 % S-methadone C_{max} ↑ 65 %	Frequent monitoring for adverse events and toxicity related to methadone, including QT prolongation, is recommended. Dose

	S-methadone AUCτ ↑ 103 %	reduction of methadone may be needed.
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) *[CYP2C9 substrates]* Ibuprofen (400 mg single dose) Diclofenac (50 mg single dose)	S-Ibuprofen C_{max} ↑ 20 % S-Ibuprofen $AUC_{0-\infty}$ ↑ 100 % Diclofenac C_{max} ↑ 114 % Diclofenac $AUC_{0-\infty}$ ↑ 78 %	Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Dose reduction of NSAIDs may be needed.
Omeprazole (40 mg QD)* *[CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate]*	Omeprazole C_{max} ↑ 116 % Omeprazole AUCτ ↑ 280 % VFEND C_{max} ↑ 15 % VFEND AUCτ ↑ 41 % Other proton pump inhibitors that are CYP2C19 substrates may also be inhibited by VFEND and may result in increased plasma concentrations of these medicines.	No dose adjustment of VFEND is recommended. When initiating VFEND in patients already receiving omeprazole doses of 40 mg or above, it is recommended that the omeprazole dose be halved.
Oral contraceptives* *[CYP3A4 substrate; CYP2C19 inhibitor]* Norethisterone/ ethinylestradiol (1 mg/0,035 mg QD)	Ethinylestradiol C_{max} ↑ 36 % Ethinylestradiol AUCτ ↑ 61 % Norethisterone C_{max} ↑ 15 % Norethisterone AUCτ ↑ 53 % VFEND C_{max} ↑ 14 %	Monitoring for adverse events related to oral contraceptives, in addition to those for VFEND, is recommended.

	VFEND AUCτ ↑ 46 %	
Short acting opiates *[CYP3A4 substrates]* Alfentanil (20 µg/kg single dose, with concomitant naloxone) Fentanyl (5 µg/kg single dose)	 In an independent published study, Alfentanil $AUC_{0-\infty}$ ↑ 6-fold In an independent published study, Fentanyl $AUC_{0-\infty}$ ↑ 1,34-fold	Dose reduction of alfentanil, fentanyl and other short acting opiates similar in structure to alfentanil and metabolised by CYP3A4 (e.g., sufentanil) should be considered. Extended and frequent monitoring for respiratory depression and other opiate-associated adverse events is recommended.
Statins (e.g., lovastatin) *[CYP3A4 substrates]*	Although not studied, VFEND is likely to increase the plasma concentrations of statins that are metabolised by CYP3A4 and could lead to rhabdomyolysis.	If concomitant administration of VFEND with statins metabolised by CYP3A4 cannot be avoided, dose reduction of the statin should be considered.
Sulphonylureas (including but not limited to: tolbutamide, glipizide, glyburide) *[CYP2C9 substrates]*	Although not studied, VFEND is likely to increase the plasma concentrations of sulphonylureas and cause hypoglycaemia.	Careful monitoring of blood glucose is recommended. Dose reduction of sulfonylureas should be considered.
Vinca alkaloids (including but not limited to: vincristine and vinblastine) *[CYP3A4 substrates]*	Although not studied, VFEND is likely to increase the plasma concentrations of vinca alkaloids and lead to neurotoxicity.	Dose reduction of vinca alkaloids should be considered.
Other HIV protease inhibitors	Not studied clinically. *In vitro*	Careful monitoring for any

(including but not limited to: saquinavir, amprenavir and nelfinavir)* *[CYP3A4 substrates and inhibitors]*	studies show that VFEND may inhibit the metabolism of HIV protease inhibitors and the metabolism of VFEND may also be inhibited by HIV protease inhibitors.	occurrence of medicine toxicity and/or lack of efficacy, and dose adjustment may be needed.
Other Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (including but not limited to: delavirdine, nevirapine)* *[CYP3A4 substrates, inhibitors or CYP450 inducers]*	Not studied clinically. *In vitro* studies show that the metabolism of VFEND may be inhibited by NNRTIs and VFEND may inhibit the metabolism of NNRTIs. The findings of the effect of efavirenz on VFEND suggest that the metabolism of VFEND may be induced by a NNRTI.	Careful monitoring for any occurrence of medicine toxicity and/or lack of efficacy, and dose adjustment may be needed.
Tretinoin *[CYP3A4 substrate]*	Although not studied, VFEND may increase tretinoin concentrations and increase risk of adverse reactions (pseudotumour cerebri, hypercalcaemia).	Dose adjustment of tretinoin is recommended during treatment with VFEND and after its discontinuation.
Cimetidine (400 mg BID) *[non-specific CYP450 inhibitor and increases gastric pH]*	VFEND C_{max} ↑ 18 % VFEND AUCτ ↑ 23 %	No dose adjustment
Digoxin (0,25 mg QD) *[P-gp substrate]*	Digoxin C_{max} ↔ Digoxin AUCτ ↔	No dose adjustment

Indinavir (800 mg TID) *[CYP3A4 inhibitor and substrate]*	Indinavir C_{max} ↔ Indinavir AUCτ ↔ VFEND C_{max} ↔ VFEND AUCτ ↔	No dose adjustment
Macrolide antibiotics Erythromycin (1 g BID) *[CYP3A4 inhibitor]* Azithromycin (500 mg QD)	 VFEND C_{max} and AUCτ ↔ VFEND C_{max} and AUCτ ↔ The effect of VFEND on either erythromycin or azithromycin is unknown.	No dose adjustment
Mycophenolic acid (1 g single dose) *[UDP-glucuronyl transferase substrate]*	Mycophenolic acid C_{max} ↔ Mycophenolic acid AUC_t ↔	No dose adjustment
Corticosteroids Prednisolone (60 mg single dose) *[CYP3A4 substrate]*	 Prednisolone C_{max} ↑ 11 % Prednisolone $AUC_{0-\infty}$ ↑ 34 %	No dose adjustment Patients on long-term treatment with VFEND and corticosteroids (including inhaled corticosteroids e.g., budesonide and intranasal corticosteroids) should be carefully monitored for adrenal cortex dysfunction both during treatment and when VFEND is

		discontinued (see section 4.4).
Ranitidine (150 mg BID) *[increases gastric pH]*	VFEND C_{max} and AUCτ ↔	No dose adjustment

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential

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

Pregnancy (see section 4.3)

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.

Breastfeeding

The excretion of VFEND into breastmilk has not been investigated. Breastfeeding must be stopped on initiation of treatment with VFEND (see section 4.3).

Fertility

In an animal study, no impairment of fertility was demonstrated in male and female rats.

4.7 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.

4.8 Undesirable effects

Summary of the safety profile

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 addition, the safety of VFEND was investigated in 279 patients (including 270 adults) who were treated with VFEND in prophylaxis studies. The adverse event profile in these prophylaxis studies was similar to the established safety profile from 2000 subjects in VFEND clinical trials.

Tabulated summary of adverse reactions

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 if possibly causally related are listed as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100) and rare (≥ 1/10 000 to < 1/1 000).

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	**Frequency**	**Adverse reaction**
Infections and infestations	Common	Sinusitis
	Uncommon	Pseudomembranous colitis
Blood and lymphatic	Common	Agranulocytosis[a], pancytopenia,

system disorders		thrombocytopenia[b], leukopenia, anaemia (including macrocytic, microcytic, normocytic, megaloblastic, aplastic)
	Uncommon	Bone marrow failure, lymphadenopathy, eosinophilia, disseminated intravascular coagulation
Immune system disorders	Uncommon	Hypersensitivity, anaphylactoid reaction
Endocrine disorders	Uncommon	Adrenal cortex insufficiency, hypothyroidism
	Rare	Hyperthyroidism
Metabolism and nutrition disorders	Very common	Peripheral oedema
	Common	Hypoglycaemia, hypokalaemia
Psychiatric disorders	Common	Depression, hallucinations, anxiety, insomnia, agitation, confusional state
Nervous system disorders	Very common	Headache
	Common	Syncope, tremor, hypertonia[e], paraesthesia, somnolence, dizziness
	Uncommon	Brain oedema, encephalopathy[c], extrapyramidal disorder[d], peripheral neuropathy, ataxia, hypoaesthesia, dysgeusia, nystagmus
	Rare	Hepatic encephalopathy, Guillain-Barre syndrome
Eye disorders	Very common	Visual impairment[h] (including altered/enhanced visual perception, blurred vision, colour vision change, photophobia)
	Common	Retinal haemorrhage
	Uncommon	Optic nerve disorder[f], papilloedema[g],

		oculogyric crisis, diplopia, scleritis, blepharitis
	Rare	Optic atrophy, corneal opacity
Ear and labyrinth disorders	Uncommon	Hypoacusis, vertigo, tinnitus
Cardiac disorders	Common	Supraventricular dysrhythmia, atrial dysrhythmia, tachycardia, bradycardia
	Uncommon	Ventricular fibrillation, ventricular extrasystoles, ventricular dysrhythmia, ventricular tachycardia, prolonged QT interval, supraventricular tachycardia
	Rare	*Torsades de Pointes*, atrioventricular (AV) complete block, bundle branch block, nodal rhythm
Vascular disorders	Common	Hypotension, phlebitis, thrombophlebitis
	Uncommon	Lymphangitis
Respiratory, thoracic and mediastinal disorders	Common	Acute respiratory distress syndrome, pulmonary oedema
Gastrointestinal disorders	Very common	Diarrhoea, vomiting, abdominal pain, nausea
	Common	Cheilitis, dyspepsia, constipation, gingivitis, gastroenteritis
	Uncommon	Peritonitis, pancreatitis, swollen tongue, duodenitis, glossitis
Hepato-biliary disorders	Very common	Abnormal liver function tests (including AST, ALT, alkaline phosphatase, GGT, LDH, bilirubin)
	Common	Jaundice, cholestatic jaundice, hepatitis[i]
	Uncommon	Hepatic failure, hepatomegaly,

		cholecystitis, cholelithiasis
Skin and subcutaneous tissue disorders	Very common	Rash
	Common	Exfoliative dermatitis, alopecia, purpura, maculo-papular rash, pruritus, photosensitivity skin reaction
	Uncommon	Stevens-Johnson syndrome, urticaria, eczema, psoriasis, drug eruption
	Rare	Toxic epidermal necrolysis, angioedema, pseudoporphyria, erythema multiforme, discoid lupus erythematosus
Musculoskeletal and connective tissue disorders	Common	Back pain
	Uncommon	Arthritis
Renal and urinary disorders	Common	Acute renal failure, haematuria
	Uncommon	Renal tubular necrosis, proteinuria, nephritis
General disorders and administration site conditions	Very common	Pyrexia
	Common	Chest pain, facial oedema[j], asthenia, chills, injection site reaction, influenza like illness
Investigations	Common	Increased creatinine
	Uncommon	Increased blood urea, hypercholesterolaemia

[a] Includes febrile neutropenia and neutropenia.

[b] Includes immune thrombocytopenic purpura.

[c] Includes hypoxic-ischaemic encephalopathy and metabolic encephalopathy.

[d] Includes akathisia and parkinsonism.

[e] Includes nuchal rigidity and tetany.

[f] Prolonged optic neuritis has been reported post-marketing. See section 4.4.

[g] See section 4.4.

[h] See "Visual impairments" paragraph in section 4.8.

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

[j] Includes periorbital oedema, lip oedema, and mouth oedema.

Post-marketing experience

MEDRA system organ class	**Adverse reaction**
Metabolism and nutrition disorders	Hyponatraemia
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Squamous cell carcinoma (including cutaneous SCC *in situ*, or Bowen's disease)
Skin and subcutaneous tissue disorders	Cutaneous lupus erythematosus, drug reaction with eosinophilia and systemic symptoms
Musculoskeletal and connective tissue disorders	Periostitis

Visual Impairments

In clinical trials, visual impairments (including blurred vision, photophobia, chloropsia, chromatopsia, colour blindness, cyanopsia, eye disorder, halo vision, night blindness, oscillopsia, photopsia, scintillating scotoma, visual acuity reduced, visual brightness, visual field defect, vitreous floaters, and xanthopsia) with VFEND were very common. These visual impairments were transient and fully reversible, with the majority spontaneously resolving within 60 minutes. There was evidence of attenuation with repeated doses of VFEND. The visual disturbances were generally mild, rarely resulted in discontinuation and were not associated with long-term sequelae. Visual impairments 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 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.

There have been post-marketing reports of prolonged visual adverse events (see section 4.4).

Dermatological reactions

Dermatological reactions were very common in patients treated with VFEND in clinical trials, but these patients had serious underlying diseases and were receiving multiple concomitant medicines. The majority of rashes were of mild to moderate severity. Patients have rarely developed severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) (uncommon), toxic epidermal necrolysis (TEN) (rare), drug reaction with eosinophilia and systemic symptoms (DRESS) which was reported post-marketing (frequency not known) and erythema multiforme (rare) during treatment with VFEND (see section 4.4).

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 section 4.4).

Dermatological adverse reactions potentially related to phototoxicity (pseudoporphyria, cheilitis, and

cutaneous lupus erythematosus) are also reported with VFEND. Sun avoidance and photoprotection are recommended for all patients. There is a potential increased risk of skin reactions/toxicity with concomitant use of photosensitising agents (e.g., methotrexate). If phototoxicity occurs, VFEND discontinuation and dermatological evaluation should be considered (see section 4.4).

Liver function tests

The overall incidence of transaminase increases > 3 x ULN (not necessarily comprising an adverse event) in the VFEND clinical programme was 18,0 % (319/1768) in adults and 25,8 % (73/283) in paediatric subjects who received VFEND for pooled therapeutic and prophylaxis use. 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 associated with cases of serious hepatic toxicity in patients with other serious underlying conditions. This includes cases of jaundice, hepatitis and hepatic failure leading to death.

Infusion-related reactions

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 (see section 4.4).

Paediatric population

The safety of VFEND was investigated in 288 paediatric patients aged 2 to < 12 years (169) and 12 to < 18 years (119) who received VFEND for prophylaxis (183) and therapeutic use (105). The adverse event profile in these 288 paediatric patients was similar to adults. A higher frequency of liver enzyme elevations reported as adverse events (14,2 % transaminases increased in paediatrics compared to 5,3 % in adults) was observed in paediatric patients as compared to adults. The safety of VFEND was investigated in additional paediatric patients aged 2 to < 12 years who were observed in compassionate

use programs (158 paediatric patients). 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

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

There is no known antidote to VFEND.

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.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.1.7 Antimicrobial (chemotherapeutic) agents: Antifungal antibiotics

Mechanism of action

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

Microbiology

In vitro, voriconazole displays broad-spectrum antifungal activity with antifungal potency against *Candida* species (including fluconazole resistant *C. krusei* and resistant strains of *C. glabrata* and *C. albicans*) 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.

5.2 Pharmacokinetic properties

General pharmacokinetic characteristics

The pharmacokinetics of voriconazole have been characterized 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.

Biotransformation

In vitro studies showed that voriconazole is metabolized 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 metabolizer 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.

Elimination

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.

Special populations

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.

Renal impairment

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 sections 4.2 and 4.4).

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 section 4.2 and section 4.4.

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 section 4.2 and section 4.4.

Paediatric population

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 1 186 ng/mL in children and 1 155 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Film-coated tablets

Tablet core

Lactose monohydrate

Pregelatinised starch

Croscarmellose sodium

Povidone

Magnesium stearate

Film-coating

White Opadry® which contains

Hypromellose

Titanium dioxide

Lactose monohydrate

Glycerol triacetate

Powder for solution for infusion

Sulphobutylether beta cyclodextrin sodium (SBECD)

Water for injections

6.2 Incompatibilities

Film-coated tablets

Not applicable.

Powder for solution for infusion

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.

VFEND must not be infused into the same line or cannula concomitantly with other medicine 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.

This medicine must not be mixed with other medicines except those listed in section 6.6.

6.3 Shelf life

Film-coated tablets

36 months

Powder for solution for infusion

36 months

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.

6.4 Special precautions for storage

Film-coated tablets

Store at or below 25 °C.

Powder for solution for infusion

Store at or 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 section 6.3.

6.5 Nature and contents of container

Film-coated tablets

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

Not all pack sizes may be marketed.

Powder for solution for infusion

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.

6.6 Special precautions for disposal and other handling

Film-coated tablets

No special requirements.

Powder for solution for infusion

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)

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 section 6.2).

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBERS

VFEND 50 mg film-coated tablets: 36/20.1.7/0106

VFEND 200 mg film-coated tablets: 36/20.1.7/0107

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

9. DATE OF FIRST AUTHORISATION

05 September 2003

10. DATE OF REVISION OF THE TEXT

18 April 2024

BOTSWANA: S2

VFEND 50 mg – Reg. No.: BOT1302360

VFEND 200 mg – Reg. No.: BOT1302361

VFEND IV 200 mg – Reg. No.: BOT1202201

NAMIBIA: NS2

VFEND 50 mg – Reg. No.: 06/20.1.7/0245

VFEND 200 mg – Reg. No.: 06/20.1.7/0246

VFEND IV 200 mg – Reg. No.: 06/20.1.7/0244