

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VFEND 50 mg film-coated tablets

VFEND 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 50 or 200 mg voriconazole.

Excipient with known effect

VFEND 50 mg film-coated tablets

Each tablet contains 63.42 mg lactose monohydrate.

VFEND 200 mg film-coated tablets

Each tablet contains 253.675 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

VFEND 50 mg film-coated tablets

White to off-white, round tablet, debossed “Pfizer” on one side and “VOR50” on the reverse.

VFEND 200 mg film-coated tablets

White to off-white, capsule-shaped tablet, debossed “Pfizer” on one side and “VOR200” on the reverse.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VFEND, is a broad-spectrum, triazole antifungal agent and is indicated in adults and children aged 2 years and above as follows:

Treatment of invasive aspergillosis.

Treatment of candidaemia in non-neutropenic patients.

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

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

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

Prophylaxis of invasive fungal infections in high risk allogeneic hematopoietic stem cell transplant (HSCT) recipients.

4.2 Posology and method of administration

Posology

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

VFEND is also available as 200 mg powder for solution for infusion, 200 mg powder and solvent for solution for infusion and 40 mg/ml powder for oral suspension.

Treatment

Adults

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

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

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

* This also applies to patients aged 15 years and older

Duration of treatment

Treatment duration should be as short as possible depending on the patient's clinical and mycological response. Long term exposure to voriconazole greater than 180 days (6 months) requires careful assessment of the benefit-risk balance (see sections 4.4 and 5.1).

Dosage adjustment (Adults)

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

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

In case of use as prophylaxis, refer below.

Children (2 to <12 years) and young adolescents with low body weight (12 to 14 years and <50 kg)

Voriconazole should be dosed as children as these young adolescents may metabolize voriconazole more similarly to children than to adults.

The recommended dosing regimen is as follows:

	Intravenous	Oral
Loading Dose Regimen (first 24 hours)	9 mg/kg every 12 hours	Not recommended
Maintenance Dose (after first 24 hours)	8 mg/kg twice daily	9 mg/kg twice daily (a maximum dose of 350 mg twice daily)

Note: Based on a population pharmacokinetic analysis in 112 immunocompromised paediatric patients aged 2 to <12 years and 26 immunocompromised adolescents aged 12 to <17 years.

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

These oral dose recommendations for children are based on studies in which voriconazole was administered as the powder for oral suspension. Bioequivalence between the powder for oral suspension and tablets has not been investigated in a paediatric population. Considering the assumed limited gastro-enteric transit time in paediatric patients, the absorption of tablets may be different in paediatric compared to adult patients. It is therefore recommended to use the oral suspension formulation in children aged 2 to <12.

All other adolescents (12 to 14 years and ≥ 50 kg; 15 to 17 years regardless of body weight)
Voriconazole should be dosed as adults.

Dosage adjustment (Children [2 to <12 years] and young adolescents with low body weight [12 to 14 years and <50 kg])

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

Use in paediatric patients aged 2 to <12 years with hepatic or renal insufficiency has not been studied (see sections 4.8 and 5.2).

Prophylaxis in Adults and Children

Prophylaxis should be initiated on the day of transplant and may be administered for up to 100 days. Prophylaxis should be as short as possible depending on the risk for developing invasive fungal infection (IFI) as defined by neutropenia or immunosuppression. 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 voriconazole use for longer than 180 days has not been adequately studied in clinical trials.

Use of voriconazole in prophylaxis for greater than 180 days (6 months) requires careful assessment of the benefit-risk balance (see sections 4.4 and 5.1).

The following instructions apply to both Treatment and Prophylaxis

Dosage adjustment

For prophylaxis use, dose adjustments are not recommended in the case of lack of efficacy or treatment-related adverse events. In the case of treatment-related adverse events, discontinuation of voriconazole and use of alternative antifungal agents must be considered (see section 4.4 and 4.8)

Dosage adjustments in case of co-administration

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

The combination of voriconazole with rifabutin should, if possible be avoided. However, if the combination is strictly needed, the maintenance dose of voriconazole may be increased from 200 mg to 350 mg orally, twice daily (100 mg to 200 mg orally, twice daily in patients less than 40 kg), see sections 4.4 and 4.5.

Efavirenz may be coadministered with voriconazole if the maintenance dose of voriconazole is increased to 400 mg every 12 hours and the efavirenz dose is reduced by 50%, i.e. to 300 mg once daily. When treatment with voriconazole is stopped, the initial dosage of efavirenz should be restored (see sections 4.4 and 4.5).

Elderly

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

Renal impairment

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

Voriconazole is haemodialysed with a clearance of 121 ml/min. A 4-hour haemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment.

Hepatic impairment

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

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

There is limited data on the safety of VFEND in patients with abnormal liver function tests (aspartate transaminase [AST], alanine transaminase [ALT], alkaline phosphatase [ALP], or total bilirubin >5 times the upper limit of normal).

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

Paediatric population

The safety and efficacy of VFEND in children below 2 years has not been established. Currently available data are described in sections 4.8 and 5.1 but no recommendation on a posology can be made.

Method of administration

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

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

Coadministration of standard doses of voriconazole with efavirenz doses of 400 mg once daily or higher is contraindicated, because efavirenz significantly decreases plasma voriconazole concentrations in healthy subjects at these doses. Voriconazole also significantly increases efavirenz plasma concentrations (see section 4.5, for lower doses see section 4.4).

Coadministration with high-dose ritonavir (400 mg and above twice daily) because ritonavir significantly decreases plasma voriconazole concentrations in healthy subjects at this dose (see section 4.5, for lower doses see section 4.4).

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

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

Coadministration with St. John's Wort (see section 4.5).

4.4 Special warnings and precautions for use

Hypersensitivity

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

Cardiovascular

Voriconazole has been associated with QTc interval prolongation. There have been rare cases of torsades de pointes in patients taking voriconazole who had risk factors, such as history of cardiotoxic chemotherapy, cardiomyopathy, hypokalaemia and concomitant medicinal products that may have been contributory.

Voriconazole should be administered with caution to patients with potentially proarrhythmic conditions, such as:

- Congenital or acquired QTc-prolongation.
- Cardiomyopathy, in particular when heart failure is present.
- Sinus bradycardia.
- Existing symptomatic arrhythmias.
- Concomitant medicinal product that is known to prolong QTc interval. Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy (see section 4.2). A study has been conducted in healthy volunteers which examined the effect on QTc interval of single doses of voriconazole up to 4 times the usual daily dose. No subject experienced an interval exceeding the potentially clinically-relevant threshold of 500 msec (see section 5.1).

Hepatic toxicity

In clinical trials, there have been cases of serious hepatic reactions during treatment with voriconazole (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. Treatment duration should be as short as possible; however, if based on the benefit-risk assessment the treatment is continued (see section 4.2), 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.

Monitoring of hepatic function should be carried out in both children and adults.

Serious dermatological adverse reactions

- Phototoxicity
In addition VFEND has been associated with phototoxicity including reactions such as ephelides, lentigo, actinic keratosis and pseudoporphyria. It is recommended that all patients, including children, avoid exposure to direct sunlight during VFEND treatment and use measures such as protective clothing and sunscreen with high sun protection factor (SPF).

- Squamous cell carcinoma of the skin (SCC)
Squamous cell carcinoma of the skin has been reported in patients, some of whom have reported prior phototoxic reactions. If phototoxic reactions occur multidisciplinary advice should be sought, VFEND discontinuation and use of alternative antifungal agents 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. VFEND should be discontinued if premalignant skin lesions or squamous cell carcinoma are identified (see below the section under Long-term treatment).
- Exfoliative cutaneous reactions
Reactions such as Stevens-Johnson syndrome developed during treatment with VFEND. If a patient develops a rash he should be monitored closely and VFEND discontinued if lesions progress.

Long-term treatment

Long term exposure (treatment or prophylaxis) greater than 180 days (6 months) requires careful assessment of the benefit-risk balance and physicians should therefore consider the need to limit the exposure to VFEND (see sections 4.2 and 5.1).

Squamous cell carcinoma of the skin (SCC) has been reported in relation with long-term VFEND treatment.

Non-infectious periostitis with elevated fluoride and alkaline phosphatase levels has been reported in transplant patients. If a patient develops skeletal pain and radiologic findings compatible with periostitis VFEND discontinuation should be considered after multidisciplinary advice.

Visual adverse reactions

There have been reports of prolonged visual adverse reactions, including blurred vision, optic neuritis and papilloedema (see section 4.8).

Renal adverse reactions

Acute renal failure has been observed in severely ill patients undergoing treatment with VFEND. Patients being treated with voriconazole are likely to be treated concomitantly with nephrotoxic medicinal products 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

Patients, especially children, with risk factors for acute pancreatitis (e.g., recent chemotherapy, haematopoietic stem cell transplantation [HSCT]), should be monitored closely during VFEND treatment. Monitoring of serum amylase or lipase may be considered in this clinical situation.

Paediatric population

Safety and effectiveness in paediatric subjects below the age of two years has not been established (see sections 4.8 and 5.1). Voriconazole 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 voriconazole 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.

Prophylaxis

In case of treatment-related adverse events (hepatotoxicity, severe skin reactions including phototoxicity and SCC, severe or prolonged visual disorders and periostitis), discontinuation of voriconazole and use of alternative antifungal agents must be considered.

Phenytoin (CYP2C9 substrate and potent CYP450 inducer)

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

Efavirenz (CYP450 inducer; CYP3A4 inhibitor and substrate)

When voriconazole is coadministered with efavirenz the dose of voriconazole should be increased to 400 mg every 12 hours and the dose of efavirenz should be decreased to 300 mg every 24 hours (see sections 4.2, 4.3 and 4.5).

Rifabutin (Potent CYP450 inducer)

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

Ritonavir (potent CYP450 inducer; CYP3A4 inhibitor and substrate)

Coadministration of voriconazole 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 voriconazole (see sections 4.3 and 4.5).

Everolimus (CYP3A4 substrate, P-gp substrate)

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

Methadone (CYP3A4 substrate)

Frequent monitoring for adverse reactions and toxicity related to methadone, including QTc prolongation, is recommended when coadministered with voriconazole since methadone levels increased following coadministration of voriconazole. 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 coadministered with voriconazole (see section 4.5). As the half-life of alfentanil is prolonged in a 4-fold manner when alfentanil is coadministered with voriconazole, and in an independent published study concomitant use of voriconazole with fentanyl resulted in an increase in the mean $AUC_{0-\infty}$ of fentanyl, frequent monitoring for opiate-associated adverse reactions (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 metabolized by CYP3A4 (e.g., hydrocodone) should be considered when coadministered with voriconazole. Frequent monitoring for opiate-associated adverse reactions may be necessary (see section 4.5).

Fluconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor)

Coadministration of oral voriconazole and oral fluconazole resulted in a significant increase in C_{max} and AUC_{τ} of voriconazole in healthy subjects. The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole-associated adverse reactions is recommended if voriconazole is used sequentially after fluconazole (see section 4.5).

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

4.5 Interaction with other medicinal products and other forms of interaction

Voriconazole is metabolised by, and inhibits the activity of, cytochrome P450 isoenzymes, CYP2C19, CYP2C9, and CYP3A4. Inhibitors or inducers of these isoenzymes may increase or decrease voriconazole plasma concentrations, respectively, and there is potential for voriconazole to increase the plasma concentrations of substances metabolised by these CYP450 isoenzymes.

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

Voriconazole should be administered with caution in patients with concomitant medication that is known to prolong QTc interval. When there is also a potential for voriconazole to increase the plasma concentrations of substances metabolised by CYP3A4 isoenzymes (certain antihistamines, quinidine, cisapride, pimozide), coadministration is contraindicated (see below and section 4.3).

Interaction table

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

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

Medicinal product <i>[Mechanism of interaction]</i>	Interaction Geometric mean changes (%)	Recommendations concerning coadministration
Astemizole, cisapride, pimozide, quinidine and terfenadine <i>[CYP3A4 substrates]</i>	Although not studied, increased plasma concentrations of these medicinal products can lead to QTc prolongation and rare occurrences of torsades de pointes.	Contraindicated (see section 4.3)
Carbamazepine and long-acting barbiturates (e.g., phenobarbital, mephobarbital) <i>[potent CYP450 inducers]</i>	Although not studied, carbamazepine and long-acting barbiturates are likely to significantly decrease plasma voriconazole concentrations.	Contraindicated (see section 4.3)

Medicinal product [Mechanism of interaction]	Interaction Geometric mean changes (%)	Recommendations concerning coadministration
<p>Efavirenz (a non-nucleoside reverse transcriptase inhibitor) [CYP450 inducer; CYP3A4 inhibitor and substrate]</p> <p>Efavirenz 400 mg QD, coadministered with voriconazole 200 mg BID*</p> <p>Efavirenz 300 mg QD, coadministered with voriconazole 400 mg BID*</p>	<p>Efavirenz C_{max} ↑ 38% Efavirenz AUC_{τ} ↑ 44% Voriconazole C_{max} ↓ 61% Voriconazole AUC_{τ} ↓ 77%</p> <p>Compared to efavirenz 600 mg QD, Efavirenz C_{max} ↔ Efavirenz AUC_{τ} ↑ 17%</p> <p>Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 23% Voriconazole AUC_{τ} ↓ 7%</p>	<p>Use of standard doses of voriconazole with efavirenz doses of 400 mg QD or higher is contraindicated (see section 4.3).</p> <p>Voriconazole may be coadministered with efavirenz if the voriconazole maintenance dose is increased to 400 mg BID and the efavirenz dose is decreased to 300 mg QD. When voriconazole treatment is stopped, the initial dose of efavirenz should be restored (see section 4.2 and 4.4).</p>
<p>Ergot alkaloids (e.g., ergotamine and dihydroergotamine) [CYP3A4 substrates]</p>	<p>Although not studied, voriconazole is likely to increase the plasma concentrations of ergot alkaloids and lead to ergotism.</p>	<p>Contraindicated (see section 4.3)</p>
<p>Rifabutin [potent CYP450 inducer]</p> <p>300 mg QD</p> <p>300 mg QD (coadministered with voriconazole 350 mg BID)*</p> <p>300 mg QD (coadministered with voriconazole 400 mg BID)*</p>	<p>Voriconazole C_{max} ↓ 69% Voriconazole AUC_{τ} ↓ 78%</p> <p>Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↓ 4% Voriconazole AUC_{τ} ↓ 32%</p> <p>Rifabutin C_{max} ↑ 195% Rifabutin AUC_{τ} ↑ 331% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 104% Voriconazole AUC_{τ} ↑ 87%</p>	<p>Concomitant use of voriconazole and rifabutin should be avoided unless the benefit outweighs the risk. The maintenance dose of voriconazole may be increased to 5 mg/kg intravenously BID or from 200 mg to 350 mg orally BID (100 mg to 200 mg orally BID in patients less than 40 kg) (see section 4.2). Careful monitoring of full blood counts and adverse reactions to rifabutin (e.g., uveitis) is recommended when rifabutin is coadministered with voriconazole.</p>
<p>Rifampicin (600 mg QD) [potent CYP450 inducer]</p>	<p>Voriconazole C_{max} ↓ 93% Voriconazole AUC_{τ} ↓ 96%</p>	<p>Contraindicated (see section 4.3)</p>

Medicinal product [Mechanism of interaction]	Interaction Geometric mean changes (%)	Recommendations concerning coadministration
<p>Ritonavir (protease inhibitor) [potent CYP450 inducer; CYP3A4 inhibitor and substrate]</p> <p>High dose (400 mg BID)</p> <p>Low dose (100 mg BID)*</p>	<p>Ritonavir C_{max} and AUC_{τ} ↔ Voriconazole C_{max} ↓ 66% Voriconazole AUC_{τ} ↓ 82%</p> <p>Ritonavir C_{max} ↓ 25% Ritonavir AUC_{τ} ↓ 13% Voriconazole C_{max} ↓ 24% Voriconazole AUC_{τ} ↓ 39%</p>	<p>Coadministration of voriconazole and high doses of ritonavir (400 mg and above BID) is contraindicated (see section 4.3).</p> <p>Coadministration of voriconazole and low-dose ritonavir (100 mg BID) should be avoided unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.</p>
<p>St. John's Wort [CYP450 inducer; P- gp inducer] 300 mg TID (coadministered with voriconazole 400 mg single dose)</p>	<p>In an independent published study, Voriconazole $AUC_{0-\infty}$ ↓ 59%</p>	<p>Contraindicated (see section 4.3)</p>
<p>Everolimus [CYP3A4 substrate, P-gp substrate]</p>	<p>Although not studied, voriconazole is likely to significantly increase the plasma concentrations of everolimus.</p>	<p>Coadministration of voriconazole with everolimus is not recommended because voriconazole is expected to significantly increase everolimus concentrations (see section 4.4).</p>
<p>Fluconazole (200 mg QD) [CYP2C9, CYP2C19 and CYP3A4 inhibitor]</p>	<p>Voriconazole C_{max} ↑ 57% Voriconazole AUC_{τ} ↑ 79% Fluconazole C_{max} ND Fluconazole AUC_{τ} ND</p>	<p>The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole-associated adverse reactions is recommended if voriconazole is used sequentially after fluconazole.</p>

Medicinal product <i>[Mechanism of interaction]</i>	Interaction Geometric mean changes (%)	Recommendations concerning coadministration
<p>Phenytoin <i>[CYP2C9 substrate and potent CYP450 inducer]</i></p> <p>300 mg QD</p> <p>300 mg QD (coadministered with voriconazole 400 mg BID)*</p>	<p>Voriconazole C_{max} ↓ 49% Voriconazole AUC_τ ↓ 69%</p> <p>Phenytoin C_{max} ↑ 67% Phenytoin AUC_τ ↑ 81% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 34% Voriconazole AUC_τ ↑ 39%</p>	<p>Concomitant use of voriconazole and phenytoin should be avoided unless the benefit outweighs the risk. Careful monitoring of phenytoin plasma levels is recommended.</p> <p>Phenytoin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased to 5 mg/kg IV BID or from 200 mg to 400 mg oral BID (100 mg to 200 mg oral BID in patients less than 40 kg) (see section 4.2).</p>
<p>Anticoagulants</p> <p>Warfarin (30 mg single dose, co-administered with 300 mg BID voriconazole) <i>[CYP2C9 substrate]</i></p> <p>Other oral coumarins (e.g., phenprocoumon, acenocoumarol) <i>[CYP2C9 and CYP3A4 substrates]</i></p>	<p>Maximum increase in prothrombin time was approximately 2-fold.</p> <p>Although not studied, voriconazole may increase the plasma concentrations of coumarins that may cause an increase in prothrombin time.</p>	<p>Close monitoring of prothrombin time or other suitable anticoagulation tests is recommended, and the dose of anticoagulants should be adjusted accordingly.</p>
<p>Benzodiazepines (e.g., midazolam, triazolam, alprazolam) <i>[CYP3A4 substrates]</i></p>	<p>Although not studied clinically, voriconazole is likely to increase the plasma concentrations of benzodiazepines that are metabolised by CYP3A4 and lead to a prolonged sedative effect.</p>	<p>Dose reduction of benzodiazepines should be considered.</p>

Medicinal product [Mechanism of interaction]	Interaction Geometric mean changes (%)	Recommendations concerning coadministration
<p>Immunosuppressants [CYP3A4 substrates]</p> <p>Sirolimus (2 mg single dose)</p> <p>Ciclosporin (in stable renal transplant recipients receiving chronic ciclosporin therapy)</p> <p>Tacrolimus (0.1 mg/kg single dose)</p>	<p>In an independent published study, Sirolimus C_{max} ↑ 6.6-fold Sirolimus $AUC_{0-\infty}$ ↑ 11-fold</p> <p>Ciclosporin C_{max} ↑ 13% Ciclosporin AUC_{τ} ↑ 70%</p> <p>Tacrolimus C_{max} ↑ 117% Tacrolimus AUC_t ↑ 221%</p>	<p>Coadministration of voriconazole and sirolimus is contraindicated (see section 4.3).</p> <p>When initiating voriconazole in patients already on ciclosporin it is recommended that the ciclosporin dose be halved and ciclosporin level carefully monitored. Increased ciclosporin levels have been associated with nephrotoxicity. <u>When voriconazole is discontinued, ciclosporin levels must be carefully monitored and the dose increased as necessary.</u></p> <p>When initiating voriconazole in patients already on tacrolimus, it is recommended that the tacrolimus dose be reduced to a third of the original dose and tacrolimus level carefully monitored. Increased tacrolimus levels have been associated with nephrotoxicity. <u>When voriconazole is discontinued, tacrolimus levels must be carefully monitored and the dose increased as necessary.</u></p>
<p>Long-Acting Opiates [CYP3A4 substrates]</p> <p>Oxycodone (10 mg single dose)</p>	<p>In an independent published study, Oxycodone C_{max} ↑ 1.7-fold Oxycodone $AUC_{0-\infty}$ ↑ 3.6-fold</p>	<p>Dose reduction in oxycodone and other long-acting opiates metabolized by CYP3A4 (e.g., hydrocodone) should be considered. Frequent monitoring for opiate-associated adverse reactions may be necessary.</p>
<p>Methadone (32-100 mg QD) [CYP3A4 substrate]</p>	<p>R-methadone (active) C_{max} ↑ 31% R-methadone (active) AUC_{τ} ↑ 47% S-methadone C_{max} ↑ 65% S-methadone AUC_{τ} ↑ 103%</p>	<p>Frequent monitoring for adverse reactions and toxicity related to methadone, including QTc prolongation, is recommended. Dose reduction of methadone may be needed.</p>

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

Medicinal product <i>[Mechanism of interaction]</i>	Interaction Geometric mean changes (%)	Recommendations concerning coadministration
Other HIV Protease Inhibitors (e.g., saquinavir, amprenavir and nelfinavir)* <i>[CYP3A4 substrates and inhibitors]</i>	Not studied clinically. <i>In vitro</i> studies show that voriconazole may inhibit the metabolism of HIV protease inhibitors and the metabolism of voriconazole may also be inhibited by HIV protease inhibitors.	Careful monitoring for any occurrence of drug toxicity and/or lack of efficacy, and dose adjustment may be needed.
Other Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (e.g., delavirdine, nevirapine)* <i>[CYP3A4 substrates, inhibitors or CYP450 inducers]</i>	Not studied clinically. <i>In vitro</i> studies show that the metabolism of voriconazole may be inhibited by NNRTIs and voriconazole may inhibit the metabolism of NNRTIs. The findings of the effect of efavirenz on voriconazole suggest that the metabolism of voriconazole may be induced by an NNRTI.	Careful monitoring for any occurrence of drug toxicity and/or lack of efficacy, and dose adjustment may be needed.
Cimetidine (400 mg BID) <i>[non-specific CYP450 inhibitor and increases gastric pH]</i>	Voriconazole C_{max} ↑ 18% Voriconazole AUC_{τ} ↑ 23%	No dose adjustment
Digoxin (0.25 mg QD) <i>[P-gp substrate]</i>	Digoxin C_{max} ↔ Digoxin AUC_{τ} ↔	No dose adjustment
Indinavir (800 mg TID) <i>[CYP3A4 inhibitor and substrate]</i>	Indinavir C_{max} ↔ Indinavir AUC_{τ} ↔ Voriconazole C_{max} ↔ Voriconazole AUC_{τ} ↔	No dose adjustment
Macrolide antibiotics Erythromycin (1 g BID) <i>[CYP3A4 inhibitor]</i> Azithromycin (500 mg QD)	Voriconazole C_{max} and AUC_{τ} ↔ Voriconazole C_{max} and AUC_{τ} ↔ The effect of voriconazole on either erythromycin or azithromycin is unknown.	No dose adjustment
Mycophenolic acid (1 g single dose) <i>[UDP-glucuronyl transferase substrate]</i>	Mycophenolic acid C_{max} ↔ Mycophenolic acid AUC_t ↔	No dose adjustment
Prednisolone (60 mg single dose) <i>[CYP3A4 substrate]</i>	Prednisolone C_{max} ↑ 11% Prednisolone $AUC_{0-\infty}$ ↑ 34%	No dose adjustment
Ranitidine (150 mg BID) <i>[increases gastric pH]</i>	Voriconazole C_{max} and AUC_{τ} ↔	No dose adjustment

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data on the use of VFEND in pregnant women available.

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

VFEND must not be used during pregnancy unless the benefit to the mother clearly outweighs the

potential risk to the foetus.

Women of child-bearing potential

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

Breast-feeding

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

Fertility

In an animal study, no impairment of fertility was demonstrated in male and female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

VFEND has moderate influence on the ability to drive and use machines. It may cause transient and reversible changes to vision, including blurring, altered/enhanced visual perception and/or photophobia. Patients must avoid potentially hazardous tasks, such as driving or operating machinery while experiencing these symptoms.

4.8 Undesirable effects

Summary of safety profile

The safety profile of voriconazole in adults is based on an integrated safety database of more than 2,000 subjects (including 1,603 adult patients in therapeutic trials) and an additional 270 adults in prophylaxis 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.

The most commonly reported adverse reactions were visual impairment, pyrexia, rash, vomiting, nausea, diarrhoea, headache, peripheral oedema, liver function test abnormal, respiratory distress and abdominal pain.

The severity of the adverse reactions was generally mild to moderate. No clinically significant differences were seen when the safety data were analysed by age, race, or gender.

Tabulated list of adverse reactions

In the table below, since the majority of the studies were of an open nature, all causality adverse reactions and their frequency categories in 1,873 adults from pooled therapeutic (1,603) and prophylaxis (270) studies, by system organ class, are listed.

Frequency categories are expressed as: Very common ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1,000$); Very rare ($< 1/10,000$); Not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Undesirable effects reported in subjects receiving voriconazole:

System Organ Class	Very common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Frequency not known (cannot be estimated from available data)
Infections and infestations		sinusitis	pseudomembranous colitis		
Neoplasms benign, malignant and unspecified (including cysts and polyps)					squamous cell carcinoma*
Blood and lymphatic system disorders		agranulocytosis ¹ , pancytopenia, thrombocytopenia ² , leukopenia, anaemia	bone marrow failure, lymphadenopathy, eosinophilia	disseminated intravascular coagulation	
Immune system disorders			hypersensitivity	anaphylactoid reaction	
Endocrine disorders			adrenal insufficiency, hypothyroidism	hyperthyroidism	
Metabolism and nutrition disorders	oedema peripheral	hypoglycaemia, hypokalaemia, hyponatraemia			
Psychiatric disorders		depression, hallucination, anxiety, insomnia, agitation, confusional state			
Nervous system disorders	headache	convulsion, syncope, tremor, hypertonia ³ , paraesthesia, somnolence, dizziness	brain oedema, encephalopathy ⁴ , extrapyramidal disorder ⁵ , neuropathy peripheral, ataxia, hypoaesthesia, dysgeusia	hepatic encephalopathy, Guillain-Barre syndrome, nystagmus	
Eye disorders	visual impairment ⁶	retinal haemorrhage	optic nerve disorder ⁷ , papilloedema ⁸ , oculogyric crisis, diplopia, scleritis, blepharitis	optic atrophy, corneal opacity	
Ear and labyrinth disorders			hypoacusis, vertigo, tinnitus		

System Organ Class	Very common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Frequency not known (cannot be estimated from available data)
Cardiac disorders		arrhythmia supraventricular, tachycardia, bradycardia	ventricular fibrillation, ventricular extrasystoles, ventricular tachycardia, electrocardiogram QT prolonged, supraventricular tachycardia	torsades de pointes, atrioventricular block complete, bundle branch block, nodal rhythm	
Vascular disorders		hypotension, phlebitis	thrombophlebitis, lymphangitis		
Respiratory, thoracic and mediastinal disorders	respiratory distress ⁹	acute respiratory distress syndrome, pulmonary oedema			
Gastrointestinal disorders	diarrhoea, vomiting, abdominal pain, nausea	cheilitis, dyspepsia, constipation, gingivitis	peritonitis, pancreatitis, swollen tongue, duodenitis, gastroenteritis, glossitis		
Hepatobiliary disorders	liver function test abnormal	jaundice, jaundice cholestatic, hepatitis ¹⁰	hepatic failure, hepatomegaly, cholecystitis, cholelithiasis		
Skin and subcutaneous tissue disorders	rash	dermatitis exfoliative, alopecia, rash maculo-papular, pruritus, erythema	Stevens-Johnson syndrome, phototoxicity, purpura, urticaria, dermatitis allergic, rash papular, rash macular, eczema	toxic epidermal necrolysis, angioedema, actinic keratosis*, pseudoporphyria, erythema multiforme, psoriasis, drug eruption	cutaneous lupus erythematosus*, ephelides*, lentigo*
Musculoskeletal and connective tissue disorders		back pain	arthritis		periostitis*
Renal and urinary disorders		renal failure acute, haematuria	renal tubular necrosis, proteinuria, nephritis		
General disorders and administration	pyrexia	chest pain, face oedema ¹¹ , asthenia, chills	infusion site reaction, influenza like illness		

System Organ Class	Very common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Frequency not known (cannot be estimated from available data)
site conditions					
Investigations		blood creatinine increased	blood urea increased, blood cholesterol increased		

*ADR identified post-marketing

¹ Includes febrile neutropenia and neutropenia.

² Includes immune thrombocytopenic purpura.

³ Includes nuchal rigidity and tetany.

⁴ Includes hypoxic-ischaemic encephalopathy and metabolic encephalopathy.

⁵ Includes akathisia and parkinsonism.

⁶ See “Visual impairments” paragraph in section 4.8.

⁷ Prolonged optic neuritis has been reported post-marketing. See section 4.4.

⁸ See section 4.4.

⁹ Includes dyspnoea and dyspnoea exertional.

¹⁰ Includes drug-induced liver injury, hepatitis toxic, hepatocellular injury and hepatotoxicity.

¹¹ Includes periorbital oedema, lip oedema, and oedema mouth.

Description of selected adverse reactions

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 voriconazole were very common. These visual impairments were transient and fully reversible, with the majority spontaneously resolving within 60 minutes and no clinically significant long-term visual effects were observed. There was evidence of attenuation with repeated doses of voriconazole. The visual impairments were generally mild, rarely resulted in discontinuation and were not associated with long-term sequelae. Visual impairments may be associated with higher plasma concentrations and/or doses.

The mechanism of action is unknown, although the site of action is most likely to be within the retina. In a study in healthy volunteers investigating the impact of voriconazole on retinal function, voriconazole caused a decrease in the electroretinogram (ERG) waveform amplitude. The ERG measures electrical currents in the retina. The ERG changes did not progress over 29 days of treatment and were fully reversible on withdrawal of voriconazole.

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 voriconazole in clinical trials, but these patients had serious underlying diseases and were receiving multiple concomitant medicinal products. The majority of rashes were of mild to moderate severity. Patients have developed serious cutaneous reactions, including Stevens-Johnson syndrome (uncommon), toxic epidermal necrolysis (rare) and erythema multiforme (rare) during treatment with VFEND.

If a patient develops a rash they should be monitored closely and VFEND discontinued if lesions progress. Photosensitivity reactions such as ephelides, lentigo and actinic keratosis have been reported, especially during long-term therapy (see section 4.4).

There have been reports of squamous cell carcinoma of the skin in patients treated with VFEND for long periods of time; the mechanism has not been established (see section 4.4).

Liver function tests

The overall incidence of transaminase increases $>3 \times \text{ULN}$ (not necessarily comprising an adverse event) in the voriconazole clinical programme was 18.0% (319/1,768) in adults and 25.8% (73/283) in paediatric subjects who received voriconazole 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 either resolved during treatment without dose adjustment or following dose adjustment, including discontinuation of therapy.

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

Prophylaxis

In an open-label, comparative, multicenter study comparing voriconazole and itraconazole as primary prophylaxis in adult and adolescent allogeneic HSCT recipients without prior proven or probable IFI, permanent discontinuation of voriconazole due to AEs was reported in 39.3% of subjects versus 39.6% of subjects in the itraconazole arm. Treatment-emergent hepatic AEs resulted in permanent discontinuation of study medication for 50 subjects (21.4%) treated with voriconazole and for 18 subjects (7.1%) treated with itraconazole.

Paediatric population

The safety of voriconazole was investigated in 288 paediatric patients aged 2 to <12 years (169) and 12 to <18 years (119) who received voriconazole for prophylaxis (183) and therapeutic use (105) in clinical trials. The safety of voriconazole was also investigated in 158 additional paediatric patients aged 2 to <12 years in compassionate use programs. Overall, the safety profile of voriconazole in paediatric population was similar to that in adults. However, a trend towards a higher frequency of liver enzyme elevations, reported as adverse events in clinical trials was observed in paediatric patients as compared to adults (14.2% transaminases increased in paediatrics compared to 5.3% in adults). Post-marketing data suggest there might be a higher occurrence of skin reactions (especially erythema) in the paediatric population compared to adults. In the 22 patients less than 2 years old who received voriconazole in a compassionate use programme, the following adverse reactions (for which a relationship to voriconazole could not be excluded) were reported: photosensitivity reaction (1), arrhythmia (1), pancreatitis (1), blood bilirubin increased (1), hepatic enzymes increased (1), rash (1) and papilloedema (1). There have been post-marketing reports of pancreatitis in paediatric patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

4.9 Overdose

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

There is no known antidote to voriconazole.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02A C03

Mode of Action

Voriconazole is a triazole antifungal agent. The primary mode of action of voriconazole is the inhibition of fungal cytochrome P450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of voriconazole. Voriconazole has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.

Pharmacokinetic/pharmacodynamic Relationship

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

Pharmacokinetic-Pharmacodynamic analyses of clinical trial data identified positive associations between plasma voriconazole concentrations and both liver function test abnormalities and visual disturbances. Dose adjustments in prophylaxis studies have not been explored.

Clinical efficacy and safety

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* which have limited susceptibility to existing antifungal agents.

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

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

In vitro activity against clinical isolates has been observed for *Acremonium* spp., *Alternaria* spp., *Bipolaris* spp., *Cladophialophora* spp., and *Histoplasma capsulatum*, with most strains being inhibited by concentrations of voriconazole in the range 0.05 to 2 µg/ml.

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

Breakpoints

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.

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

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

EUCAST Breakpoints

Candida species	MIC breakpoint (mg/L)	
	≤S (Susceptible)	>R (Resistant)
<i>Candida albicans</i> ¹	0.125	0.125
<i>Candida tropicalis</i> ¹	0.125	0.125
<i>Candida parapsilosis</i> ¹	0.125	0.125
<i>Candida glabrata</i> ²	Insufficient evidence	
<i>Candida krusei</i> ³	Insufficient evidence	
<i>Other Candida spp.</i> ⁴	Insufficient evidence	
¹ Strains with MIC values above the Susceptible (S) breakpoint are rare, or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. ² In clinical studies, response to voriconazole in patients with <i>C. glabrata</i> infections was 21% lower compared to <i>C. albicans</i> , <i>C. parapsilosis</i> and <i>C. tropicalis</i> . <i>In vitro</i> data showed a slight increase of resistance of <i>C. glabrata</i> to voriconazole. ³ In clinical studies, response to voriconazole in <i>C. krusei</i> infections was similar to <i>C. albicans</i> , <i>C. parapsilosis</i> and <i>C. tropicalis</i> . However, as there were only 9 cases available for EUCAST analysis, there is currently insufficient evidence to set clinical breakpoints for <i>C. krusei</i> . ⁴ EUCAST has not determined non-species related breakpoints for voriconazole.		

Clinical experience

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

Aspergillus infections – efficacy in aspergillosis patients with poor prognosis

Voriconazole has *in vitro* fungicidal activity against *Aspergillus* spp. The efficacy and survival benefit of voriconazole versus conventional amphotericin B in the primary treatment of acute invasive aspergillosis was demonstrated in an open, randomised, multicentre study in 277 immunocompromised patients treated for 12 weeks. Voriconazole was administered intravenously with a loading dose of 6 mg/kg every 12 hours for the first 24 hours followed by a maintenance dose of 4 mg/kg every 12 hours for a minimum of 7 days. Therapy could then be switched to the oral formulation at a dose of 200 mg every 12 hours. Median duration of IV voriconazole therapy was 10 days (range 2-85 days). After IV voriconazole therapy, the median duration of oral voriconazole therapy was 76 days (range 2-232 days).

A satisfactory global response (complete or partial resolution of all attributable symptoms, signs, radiographic/bronchoscopic abnormalities present at baseline) was seen in 53% of voriconazole-treated patients compared to 31% of patients treated with comparator. The 84-day survival rate for voriconazole was statistically significantly higher than that for the comparator and a clinically and statistically significant benefit was shown in favour of voriconazole for both time to death and time to discontinuation due to toxicity.

This study confirmed findings from an earlier, prospectively designed study where there was a positive outcome in subjects with risk factors for a poor prognosis, including graft versus host disease, and, in

particular, cerebral infections (normally associated with almost 100% mortality).

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

Candidaemia in non-neutropenic patients

The efficacy of voriconazole compared to the regimen of amphotericin B followed by fluconazole in the primary treatment of candidaemia was demonstrated in an open, comparative study. Three hundred and seventy non-neutropenic patients (above 12 years of age) with documented candidaemia were included in the study, of whom 248 were treated with voriconazole. Nine subjects in the voriconazole group and 5 in the amphotericin B followed by fluconazole group also had mycologically proven infection in deep tissue. Patients with renal failure were excluded from this study. The median treatment duration was 15 days in both treatment arms. In the primary analysis, successful response as assessed by a Data Review Committee (DRC) blinded to study medicinal product was defined as resolution/improvement in all clinical signs and symptoms of infection with eradication of *Candida* from blood and infected deep tissue sites 12 weeks after the end of therapy (EOT). Patients who did not have an assessment 12 weeks after EOT were counted as failures. In this analysis a successful response was seen in 41% of patients in both treatment arms.

In a secondary analysis, which utilised DRC assessments at the latest evaluable time point (EOT, or 2, 6, or 12 weeks after EOT) voriconazole and the regimen of amphotericin B followed by fluconazole had successful response rates of 65% and 71%, respectively.

The Investigator's assessment of successful outcome at each of these time points is shown in the following table.

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

Serious refractory *Candida* infections

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

Scedosporium and *Fusarium* infections

Voriconazole was shown to be effective against the following rare fungal pathogens:

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

Fusarium spp.: Seven (3 complete, 4 partial responses) of 17 patients were successfully treated with voriconazole. Of these 7 patients, 3 had eye, 1 had sinus, and 3 had disseminated infection. Four additional patients with fusariosis had an infection caused by several organisms; 2 of them had a successful outcome.

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

Primary Prophylaxis of Invasive Fungal Infections – Efficacy in HSCT recipients without prior proven or probable IFI

Voriconazole was compared to itraconazole as primary prophylaxis in an open-label, comparative, multicenter study of adult and adolescent allogeneic HSCT recipients without prior proven or probable IFI. Success was defined as the ability to continue study drug prophylaxis for 100 days after HSCT (without stopping for >14 days) and survival with no proven or probable IFI for 180 days after HSCT. The modified intent-to-treat (MITT) group included 465 allogeneic HSCT recipients with 45% of patients having AML. From all patients 58% were subject to myeloablative conditions regimens. Prophylaxis with study drug was started immediately after HSCT: 224 received voriconazole and 241 received itraconazole. The median duration of study drug prophylaxis was 96 days for voriconazole and 68 days for itraconazole in the MITT group.

Success rates and other secondary endpoints are presented in the table below:

Study Endpoints	Voriconazole N=224	Itraconazole N=241	Difference in proportions and the 95% confidence interval (CI)	P-Value
Success at day 180*	109 (48.7%)	80 (33.2%)	16.4% (7.7%, 25.1%)**	0.0002**
Success at day 100	121 (54.0%)	96 (39.8%)	15.4% (6.6%, 24.2%)**	0.0006**
Completed at least 100 days of study drug prophylaxis	120 (53.6%)	94 (39.0%)	14.6% (5.6%, 23.5%)	0.0015
Survived to day 180	184 (82.1%)	197 (81.7%)	0.4% (-6.6%, 7.4%)	0.9107
Developed proven or probable IFI to day 180	3 (1.3%)	5 (2.1%)	-0.7% (-3.1%, 1.6%)	0.5390
Developed proven or probable IFI to day 100	2 (0.9%)	4 (1.7%)	-0.8% (-2.8%, 1.3%)	0.4589
Developed proven or probable IFI while on study drug	0	3 (1.2%)	-1.2% (-2.6%, 0.2%)	0.0813

* Primary endpoint of the study

** Difference in proportions, 95% CI and p-values obtained after adjustment for randomization

The breakthrough IFI rate to Day 180 and the primary endpoint of the study, which is Success at Day 180, for patients with AML and myeloablative conditioning regimens respectively, is presented in the table below:

AML

Study endpoints	Voriconazole (N=98)	Itraconazole (N=109)	Difference in proportions and the 95% confidence interval (CI)
Breakthrough IFI – Day 180	1 (1.0%)	2 (1.8%)	-0.8% (-4.0%, 2.4%) **
Success at Day 180*	55 (56.1%)	45 (41.3%)	14.7% (1.7%, 27.7%)***

* Primary endpoint of study

** Using a margin of 5%, non inferiority is demonstrated

***Difference in proportions, 95% CI obtained after adjustment for randomization

Myeloablative conditioning regimens

Study endpoints	Voriconazole (N=125)	Itraconazole (N=143)	Difference in proportions and the 95% confidence interval (CI)
Breakthrough IFI – Day 180	2 (1.6%)	3 (2.1%)	-0.5% (-3.7%, 2.7%) **
Success at Day 180*	70 (56.0%)	53 (37.1%)	20.1% (8.5%, 31.7%)***

* Primary endpoint of study

** Using a margin of 5%, non inferiority is demonstrated

*** Difference in proportions, 95% CI obtained after adjustment for randomization

Secondary Prophylaxis of IFI – Efficacy in HSCT recipients with prior proven or probable IFI

Voriconazole was investigated as secondary prophylaxis in an open-label, non-comparative, multicenter study of adult allogeneic HSCT recipients with prior proven or probable IFI. The primary endpoint was the rate of occurrence of proven and probable IFI during the first year after HSCT. The MITT group included 40 patients with prior IFI, including 31 with aspergillosis, 5 with candidiasis, and 4 with other IFI. The median duration of study drug prophylaxis was 95.5 days in the MITT group.

Proven or probable IFIs developed in 7.5% (3/40) of patients during the first year after HSCT, including one candidemia, one scedosporiosis (both relapses of prior IFI), and one zygomycosis. The survival rate at Day 180 was 80.0% (32/40) and at 1 year was 70.0% (28/40).

Duration of treatment

In clinical trials, 705 patients received voriconazole therapy for greater than 12 weeks, with 164 patients receiving voriconazole for over 6 months.

Paediatric population

Fifty-three paediatric patients aged 2 to <18 years were treated with voriconazole in two prospective, open-label, non-comparative, multi-center clinical trials. One study enrolled 31 patients with possible, proven or probable invasive aspergillosis (IA), of whom 14 patients had proven or probable IA and were included in the MITT efficacy analyses. The second study enrolled 22 patients with invasive candidiasis including candidaemia (ICC), and esophageal candidiasis (EC) requiring either primary or salvage therapy, of whom 17 were included in the MITT efficacy analyses. For patients with IA the overall rates of global response at 6 weeks were 64.3% (9/14), the global response rate was 40% (2/5) for patients 2 to <12 years and 77.8% (7/9) for patients 12 to <18 years of age. For patients with ICC the global response rate at EOT was 85.7% (6/7) and for patients with EC the global response rate at EOT was 70% (7/10). The overall rate of response (ICC and EC combined) was 88.9% (8/9) for 2 to <12 years old and 62.5% (5/8) for 12 to <18 years old.

Clinical studies examining QTc interval

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

5.2 Pharmacokinetic properties

General pharmacokinetic characteristics

The pharmacokinetics of voriconazole have been characterised in healthy subjects, special populations and patients. During oral administration of 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}). The oral maintenance dose of 200 mg (or 100 mg for patients less than 40 kg) achieves a voriconazole exposure similar to 3 mg/kg IV. A 300 mg (or 150 mg for patients less than 40 kg) oral maintenance dose achieves an exposure similar to 4 mg/kg IV. When the recommended intravenous or oral loading dose regimens are administered, plasma concentrations close to steady state are achieved within the first 24 hours of dosing. Without the loading dose, accumulation occurs during twice daily multiple dosing with steady-state plasma voriconazole concentrations being achieved by Day 6 in the majority of subjects.

Absorption

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

Distribution

The volume of distribution at steady state for voriconazole is estimated to be 4.6 L/kg, suggesting extensive distribution into tissues. Plasma protein binding is estimated to be 58%. Cerebrospinal fluid samples from eight patients in a compassionate programme showed detectable voriconazole concentrations in all patients.

Biotransformation

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.

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 at 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.

Pharmacokinetics in special patient groups

Gender

In an oral multiple -dose study, C_{max} and AUC_{τ} for healthy young females were 83% and 113% higher, respectively, than in healthy young males (18-45 years). In the same study, no significant differences in C_{max} and AUC_{τ} were observed between healthy elderly males and healthy elderly females (≥ 65 years).

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

Elderly

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

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

Paediatric population

The recommended doses in children and adolescent patients are based on a population pharmacokinetic analysis of data obtained from 112 immunocompromised paediatric patients aged 2 to <12 years and 26 immunocompromised adolescent patients aged 12 to <17 years. Multiple intravenous doses of 3, 4, 6, 7 and 8 mg/kg twice daily and multiple oral doses (using the powder for oral suspension) of 4 mg/kg, 6 mg/kg, and 200 mg twice daily were evaluated in 3 paediatric pharmacokinetic studies. Intravenous loading doses of 6 mg/kg IV twice daily on day 1 followed by 4 mg/kg intravenous dose twice daily and 300 mg oral tablets twice daily were evaluated in one adolescent pharmacokinetic study. Larger inter-subject variability was observed in paediatric patients compared to adults.

A comparison of the paediatric and adult population pharmacokinetic data indicated that the predicted total exposure (AUC_{τ}) in children following administration of a 9 mg/kg IV loading dose was comparable to that in adults following a 6 mg/kg IV loading dose. The predicted total exposures in children following IV maintenance doses of 4 and 8 mg/kg twice daily were comparable to those in adults following 3 and 4 mg/kg IV twice daily, respectively. The predicted total exposure in children following an oral maintenance dose of 9 mg/kg (maximum of 350 mg) twice daily was comparable to that in adults following 200 mg oral twice daily. An 8 mg/kg intravenous dose will provide voriconazole exposure approximately 2-fold higher than a 9 mg/kg oral dose.

The higher intravenous maintenance dose in paediatric patients relative to adults reflects the higher elimination capacity in paediatric patients due to a greater liver mass to body mass ratio. Oral bioavailability may, however, be limited in paediatric patients with malabsorption and very low body weight for their age. In that case, intravenous voriconazole administration is recommended.

Voriconazole exposures in the majority of adolescent patients were comparable to those in adults receiving the same dosing regimens. However, lower voriconazole exposure was observed in some young adolescents with low body weight compared to adults. It is likely that these subjects may metabolize voriconazole more similarly to children than to adults. Based on the population pharmacokinetic analysis, 12- to 14-year-old adolescents weighing less than 50 kg should receive children's doses (see section 4.2).

Renal impairment

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).

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 sections 4.2 and 4.4).

5.3 Preclinical safety data

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Pregelatinised starch
Croscarmellose sodium
Povidone
Magnesium stearate

Film-coating

Hypromellose
Titanium dioxide (E171)
Lactose monohydrate
Glycerol triacetate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

HDPE tablet containers containing 2, 30 or 100 film-coated tablets.
PVC / Aluminium blister in cartons of 2, 10, 14, 20, 28, 30, 50, 56 or 100 film-coated tablets.
PVC / Aluminium/PVC/PVDC blister in cartons of 2, 10, 14, 20, 28, 30, 50, 56 or 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

VFEND 50 mg film-coated tablets

EU/1/02/212/001-012

EU/1/02/212/028-036

VFEND 200 mg film-coated tablets

EU/1/02/212/013-024

EU/1/02/212/037-045

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 March 2002

Date of latest renewal: 21 February 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency. <http://www.ema.europa.eu>

1. NAME OF THE MEDICINAL PRODUCT

VFEND 200 mg powder for solution for infusion

VFEND 200 mg powder and solvent for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VFEND 200 mg powder for solution for infusion

Each vial contains 200 mg of voriconazole.

After reconstitution each ml contains 10 mg of voriconazole. Once reconstituted further dilution is required before administration.

Excipient with known effect

Each vial contains 217.6 mg sodium.

VFEND 200 mg powder and solvent for solution for infusion

Each 50 ml polypropylene bag contains sodium chloride 0.9% in Water for Injections.

Excipient with known effect

Each bag contains 177.02 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

VFEND 200 mg powder for solution for infusion

Powder for solution for infusion: White lyophilised powder.

VFEND 200 mg powder and solvent for solution for infusion

Powder for solution for infusion: White lyophilised powder.

Solvent for solution for infusion: Clear diluent solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VFEND, is a broad-spectrum, triazole antifungal agent and is indicated in adults and children aged 2 years and above as follows:

Treatment of invasive aspergillosis.

Treatment of candidaemia in non-neutropenic patients.

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

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

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

Prophylaxis of invasive fungal infections in high risk allogeneic hematopoietic stem cell transplant (HSCT) recipients.

4.2 Posology and method of administration

Posology

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

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

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

Treatment

Adults

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

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

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

* This also applies to patients aged 15 years and older

Duration of treatment

Treatment duration should be as short as possible depending on the patient's clinical and mycological response. Long term exposure to voriconazole greater than 180 days (6 months) requires careful assessment of the benefit-risk balance (see sections 4.4 and 5.1).

Dosage adjustment (Adults)

If patient is unable to tolerate intravenous treatment at 4 mg/kg twice daily, reduce the dose to 3 mg/kg twice daily.

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

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

In case of use as prophylaxis, refer below.

Children (2 to <12 years) and young adolescents with low body weight (12 to 14 years and <50 kg)

Voriconazole should be dosed as children as these young adolescents may metabolize voriconazole more similarly to children than to adults.

The recommended dosing regimen is as follows:

	Intravenous	Oral
Loading Dose Regimen (first 24 hours)	9 mg/kg every 12 hours	Not recommended
Maintenance Dose (after first 24 hours)	8 mg/kg twice daily	9 mg/kg twice daily (a maximum dose of 350 mg twice daily)

Note: Based on a population pharmacokinetic analysis in 112 immunocompromised paediatric patients aged 2 to <12 years and 26 immunocompromised adolescents aged 12 to <17 years.

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

All other adolescents (12 to 14 years and ≥ 50 kg; 15 to 17 years regardless of body weight)
Voriconazole should be dosed as adults.

Dosage adjustment (Children [2 to <12 years] and young adolescents with low body weight [12 to 14 years and <50 kg])

If patient response to treatment is inadequate, the intravenous dose may be increased by 1 mg/kg steps. If patient is unable to tolerate treatment, reduce the intravenous dose by 1 mg/kg steps.

Use in paediatric patients aged 2 to <12 years with hepatic or renal insufficiency has not been studied (see sections 4.8 and 5.2).

Prophylaxis in Adults and Children

Prophylaxis should be initiated on the day of transplant and may be administered for up to 100 days. Prophylaxis should be as short as possible depending on the risk for developing invasive fungal infection (IFI) as defined by neutropenia or immunosuppression. 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 voriconazole use for longer than 180 days has not been adequately studied in clinical trials.

Use of voriconazole in prophylaxis for greater than 180 days (6 months) requires careful assessment of the benefit-risk balance (see sections 4.4 and 5.1).

The following instructions apply to both Treatment and Prophylaxis

Dosage adjustment

For prophylaxis use, dose adjustments are not recommended in the case of lack of efficacy or treatment-related adverse events. In the case of treatment-related adverse events, discontinuation of voriconazole and use of alternative antifungal agents must be considered (see section 4.4 and 4.8)

Dosage adjustments in case of co-administration

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

Efavirenz may be coadministered with voriconazole if the maintenance dose of voriconazole is increased to 400 mg every 12 hours and the efavirenz dose is reduced by 50%, i.e. to 300 mg once daily. When treatment with voriconazole is stopped, the initial dosage of efavirenz should be restored (see sections 4.4 and 4.5).

Elderly

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

Renal impairment

In patients with moderate to severe renal dysfunction (creatinine clearance < 50 ml/min), accumulation of the intravenous vehicle, SBECD, occurs. Oral voriconazole should be administered to these patients, unless an assessment of the risk benefit to the patient justifies the use of intravenous voriconazole. Serum creatinine levels should be closely monitored in these patients and, if increases occur, consideration should be given to changing to oral voriconazole therapy (see section 5.2).

Voriconazole is haemodialysed with a clearance of 121 ml/min. A 4-hour haemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment.

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

Hepatic impairment

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

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

There is limited data on the safety of VFEND in patients with abnormal liver function tests (aspartate transaminase [AST], alanine transaminase [ALT], alkaline phosphatase [ALP], or total bilirubin >5 times the upper limit of normal).

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

Paediatric population

The safety and efficacy of VFEND in children below 2 years has not been established. Currently available data are described in sections 4.8 and 5.1 but no recommendation on a posology can be made.

Method of administration

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

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

Coadministration of standard doses of voriconazole with efavirenz doses of 400 mg once daily or higher is contraindicated, because efavirenz significantly decreases plasma voriconazole concentrations in healthy subjects at these doses. Voriconazole also significantly increases efavirenz plasma concentrations (see section 4.5, for lower doses see section 4.4).

Coadministration with high-dose ritonavir (400 mg and above twice daily) because ritonavir significantly decreases plasma voriconazole concentrations in healthy subjects at this dose (see section 4.5, for lower doses see section 4.4).

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

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

Coadministration with St. John's Wort (see section 4.5).

4.4 Special warnings and precautions for use

Hypersensitivity

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

Duration of treatment

The duration of treatment with the intravenous formulation should be no longer than 6 months (see section 5.3).

Cardiovascular

Voriconazole has been associated with QTc interval prolongation. There have been rare cases of torsades de pointes in patients taking voriconazole who had risk factors, such as history of cardiotoxic chemotherapy, cardiomyopathy, hypokalaemia and concomitant medicinal products that may have been contributory. Voriconazole should be administered with caution to patients with potentially proarrhythmic conditions, such as:

- Congenital or acquired QTc-prolongation.
- Cardiomyopathy, in particular when heart failure is present.
- Sinus bradycardia.
- Existing symptomatic arrhythmias.
- Concomitant medicinal product that is known to prolong QTc interval. Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy (see section 4.2). A study has been conducted in healthy volunteers which examined the effect on QTc interval of single doses of voriconazole up to 4 times the usual daily dose. No subject experienced an interval exceeding the potentially clinically-relevant threshold of 500 msec (see section 5.1).

Infusion-related reactions

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

Hepatic toxicity

In clinical trials, there have been cases of serious hepatic reactions during treatment with voriconazole (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. Treatment duration should be as short as possible; however, if based on the benefit-risk assessment the treatment is continued (see section 4.2), 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.

Monitoring of hepatic function should be carried out in both children and adults.

Serious dermatological adverse reactions

- Phototoxicity
In addition VFEND has been associated with phototoxicity including reactions such as ephelides, lentigo, actinic keratosis and pseudoporphyria. It is recommended that all patients, including children, avoid exposure to direct sunlight during VFEND treatment and use measures such as protective clothing and sunscreen with high sun protection factor (SPF).
- Squamous cell carcinoma of the skin (SCC)
Squamous cell carcinoma of the skin has been reported in patients, some of whom have reported prior phototoxic reactions. If phototoxic reactions occur multidisciplinary advice should be sought, VFEND discontinuation and use of alternative antifungal agents 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. VFEND should be discontinued if premalignant skin lesions or squamous cell carcinoma are identified (see below the section under Long-term treatment).
- Exfoliative cutaneous reactions
Reactions such as Stevens-Johnson syndrome developed during treatment with VFEND. If a patient develops a rash he should be monitored closely and VFEND discontinued if lesions progress.

Long-term treatment

Long term exposure (treatment or prophylaxis) greater than 180 days (6 months) requires careful assessment of the benefit-risk balance and physicians should therefore consider the need to limit the exposure to VFEND (see sections 4.2 and 5.1).

Squamous cell carcinoma of the skin (SCC) has been reported in relation with long-term VFEND treatment.

Non-infectious periostitis with elevated fluoride and alkaline phosphatase levels has been reported in transplant patients. If a patient develops skeletal pain and radiologic findings compatible with periostitis VFEND discontinuation should be considered after multidisciplinary advice.

Visual adverse reactions

There have been reports of prolonged visual adverse reactions, including blurred vision, optic neuritis and papilloedema (see section 4.8).

Renal adverse reactions

Acute renal failure has been observed in severely ill patients undergoing treatment with VFEND. Patients being treated with voriconazole are likely to be treated concomitantly with nephrotoxic medicinal products 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

Patients, especially children, with risk factors for acute pancreatitis (e.g., recent chemotherapy, haematopoietic stem cell transplantation [HSCT]), should be monitored closely during VFEND treatment. Monitoring of serum amylase or lipase may be considered in this clinical situation.

Paediatric population

Safety and effectiveness in paediatric subjects below the age of two years has not been established (see sections 4.8 and 5.1). Voriconazole 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 voriconazole 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.

Prophylaxis

In case of treatment-related adverse events (hepatotoxicity, severe skin reactions including phototoxicity and SCC, severe or prolonged visual disorders and periostitis), discontinuation of voriconazole and use of alternative antifungal agents must be considered.

Phenytoin (CYP2C9 substrate and potent CYP450 inducer)

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

Efavirenz (CYP450 inducer; CYP3A4 inhibitor and substrate)

When voriconazole is coadministered with efavirenz the dose of voriconazole should be increased to 400 mg every 12 hours and the dose of efavirenz should be decreased to 300 mg every 24 hours (see sections 4.2, 4.3 and 4.5).

Rifabutin (Potent CYP450 inducer)

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

Ritonavir (potent CYP450 inducer; CYP3A4 inhibitor and substrate)

Coadministration of voriconazole 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 voriconazole (see sections 4.3 and 4.5).

Everolimus (CYP3A4 substrate, P-gp substrate)

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

Methadone (CYP3A4 substrate)

Frequent monitoring for adverse reactions and toxicity related to methadone, including QTc prolongation, is recommended when coadministered with voriconazole since methadone levels increased following coadministration of voriconazole. 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 coadministered with voriconazole (see section 4.5). As the half-life of alfentanil is prolonged in a 4-fold manner when alfentanil is coadministered with voriconazole, and in an independent published study concomitant use of voriconazole with fentanyl resulted in an increase in the mean AUC_{0-∞} of fentanyl, frequent monitoring for opiate-associated adverse reactions (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 metabolized by CYP3A4 (e.g., hydrocodone) should be considered when coadministered with voriconazole. Frequent monitoring for opiate-associated adverse reactions may be necessary (see section 4.5).

Fluconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor)

Coadministration of oral voriconazole and oral fluconazole resulted in a significant increase in C_{max} and AUC_T of voriconazole in healthy subjects. The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole-associated adverse reactions is recommended if voriconazole is used sequentially after fluconazole (see section 4.5).

Sodium content

Each vial of VFEND contains 217.6 mg of sodium. This should be taken into consideration for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Voriconazole is metabolised by, and inhibits the activity of, cytochrome P450 isoenzymes, CYP2C19, CYP2C9, and CYP3A4. Inhibitors or inducers of these isoenzymes may increase or decrease voriconazole plasma concentrations, respectively, and there is potential for voriconazole to increase the plasma concentrations of substances metabolised by these CYP450 isoenzymes.

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

Voriconazole should be administered with caution in patients with concomitant medication that is known to prolong QTc interval. When there is also a potential for voriconazole to increase the plasma concentrations of substances metabolised by CYP3A4 isoenzymes (certain antihistamines, quinidine, cisapride, pimozide), coadministration is contraindicated (see below and section 4.3).

Interaction table

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

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

Medicinal product <i>[Mechanism of interaction]</i>	Interaction Geometric mean changes (%)	Recommendations concerning coadministration
Astemizole, cisapride, pimozide, quinidine and terfenadine <i>[CYP3A4 substrates]</i>	Although not studied, increased plasma concentrations of these medicinal products can lead to QTc prolongation and rare occurrences of torsades de pointes.	Contraindicated (see section 4.3)
Carbamazepine and long-acting barbiturates (e.g., phenobarbital, mephobarbital) <i>[potent CYP450 inducers]</i>	Although not studied, carbamazepine and long-acting barbiturates are likely to significantly decrease plasma voriconazole concentrations.	Contraindicated (see section 4.3)

Medicinal product [Mechanism of interaction]	Interaction Geometric mean changes (%)	Recommendations concerning coadministration
<p>Efavirenz (a non-nucleoside reverse transcriptase inhibitor) [CYP450 inducer; CYP3A4 inhibitor and substrate]</p> <p>Efavirenz 400 mg QD, coadministered with voriconazole 200 mg BID*</p> <p>Efavirenz 300 mg QD, coadministered with voriconazole 400 mg BID*</p>	<p>Efavirenz C_{max} ↑ 38% Efavirenz AUC_{τ} ↑ 44% Voriconazole C_{max} ↓ 61% Voriconazole AUC_{τ} ↓ 77%</p> <p>Compared to efavirenz 600 mg QD, Efavirenz C_{max} ↔ Efavirenz AUC_{τ} ↑ 17%</p> <p>Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 23% Voriconazole AUC_{τ} ↓ 7%</p>	<p>Use of standard doses of voriconazole with efavirenz doses of 400 mg QD or higher is contraindicated (see section 4.3).</p> <p>Voriconazole may be coadministered with efavirenz if the voriconazole maintenance dose is increased to 400 mg BID and the efavirenz dose is decreased to 300 mg QD. When voriconazole treatment is stopped, the initial dose of efavirenz should be restored (see section 4.2 and 4.4).</p>
<p>Ergot alkaloids (e.g., ergotamine and dihydroergotamine) [CYP3A4 substrates]</p>	<p>Although not studied, voriconazole is likely to increase the plasma concentrations of ergot alkaloids and lead to ergotism.</p>	<p>Contraindicated (see section 4.3)</p>
<p>Rifabutin [potent CYP450 inducer]</p> <p>300 mg QD</p> <p>300 mg QD (coadministered with voriconazole 350 mg BID)*</p> <p>300 mg QD (coadministered with voriconazole 400 mg BID)*</p>	<p>Voriconazole C_{max} ↓ 69% Voriconazole AUC_{τ} ↓ 78%</p> <p>Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↓ 4% Voriconazole AUC_{τ} ↓ 32%</p> <p>Rifabutin C_{max} ↑ 195% Rifabutin AUC_{τ} ↑ 331% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 104% Voriconazole AUC_{τ} ↑ 87%</p>	<p>Concomitant use of voriconazole and rifabutin should be avoided unless the benefit outweighs the risk. The maintenance dose of voriconazole may be increased to 5 mg/kg intravenously BID or from 200 mg to 350 mg orally BID (100 mg to 200 mg orally BID in patients less than 40 kg) (see section 4.2). Careful monitoring of full blood counts and adverse reactions to rifabutin (e.g., uveitis) is recommended when rifabutin is coadministered with voriconazole.</p>
<p>Rifampicin (600 mg QD) [potent CYP450 inducer]</p>	<p>Voriconazole C_{max} ↓ 93% Voriconazole AUC_{τ} ↓ 96%</p>	<p>Contraindicated (see section 4.3)</p>

Medicinal product [Mechanism of interaction]	Interaction Geometric mean changes (%)	Recommendations concerning coadministration
<p>Ritonavir (protease inhibitor) [potent CYP450 inducer; CYP3A4 inhibitor and substrate]</p> <p>High dose (400 mg BID)</p> <p>Low dose (100 mg BID)*</p>	<p>Ritonavir C_{max} and AUC_{τ} ↔ Voriconazole C_{max} ↓ 66% Voriconazole AUC_{τ} ↓ 82%</p> <p>Ritonavir C_{max} ↓ 25% Ritonavir AUC_{τ} ↓ 13% Voriconazole C_{max} ↓ 24% Voriconazole AUC_{τ} ↓ 39%</p>	<p>Coadministration of voriconazole and high doses of ritonavir (400 mg and above BID) is contraindicated (see section 4.3).</p> <p>Coadministration of voriconazole and low-dose ritonavir (100 mg BID) should be avoided unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.</p>
<p>St. John's Wort [CYP450 inducer; P- gp inducer] 300 mg TID (coadministered with voriconazole 400 mg single dose)</p>	<p>In an independent published study, Voriconazole $AUC_{0-\infty}$ ↓ 59%</p>	<p>Contraindicated (see section 4.3)</p>
<p>Everolimus [CYP3A4 substrate, P-gp substrate]</p>	<p>Although not studied, voriconazole is likely to significantly increase the plasma concentrations of everolimus.</p>	<p>Coadministration of voriconazole with everolimus is not recommended because voriconazole is expected to significantly increase everolimus concentrations (see section 4.4).</p>
<p>Fluconazole (200 mg QD) [CYP2C9, CYP2C19 and CYP3A4 inhibitor]</p>	<p>Voriconazole C_{max} ↑ 57% Voriconazole AUC_{τ} ↑ 79% Fluconazole C_{max} ND Fluconazole AUC_{τ} ND</p>	<p>The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole-associated adverse reactions is recommended if voriconazole is used sequentially after fluconazole.</p>

Medicinal product <i>[Mechanism of interaction]</i>	Interaction Geometric mean changes (%)	Recommendations concerning coadministration
<p>Phenytoin <i>[CYP2C9 substrate and potent CYP450 inducer]</i></p> <p>300 mg QD</p> <p>300 mg QD (coadministered with voriconazole 400 mg BID)*</p>	<p>Voriconazole C_{max} ↓ 49% Voriconazole AUC_τ ↓ 69%</p> <p>Phenytoin C_{max} ↑ 67% Phenytoin AUC_τ ↑ 81% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 34% Voriconazole AUC_τ ↑ 39%</p>	<p>Concomitant use of voriconazole and phenytoin should be avoided unless the benefit outweighs the risk. Careful monitoring of phenytoin plasma levels is recommended.</p> <p>Phenytoin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased to 5 mg/kg IV BID or from 200 mg to 400 mg oral BID (100 mg to 200 mg oral BID in patients less than 40 kg) (see section 4.2).</p>
<p>Anticoagulants</p> <p>Warfarin (30 mg single dose, co-administered with 300 mg BID voriconazole) <i>[CYP2C9 substrate]</i></p> <p>Other oral coumarins (e.g., phenprocoumon, acenocoumarol) <i>[CYP2C9 and CYP3A4 substrates]</i></p>	<p>Maximum increase in prothrombin time was approximately 2-fold.</p> <p>Although not studied, voriconazole may increase the plasma concentrations of coumarins that may cause an increase in prothrombin time.</p>	<p>Close monitoring of prothrombin time or other suitable anticoagulation tests is recommended, and the dose of anticoagulants should be adjusted accordingly.</p>
<p>Benzodiazepines (e.g., midazolam, triazolam, alprazolam) <i>[CYP3A4 substrates]</i></p>	<p>Although not studied clinically, voriconazole is likely to increase the plasma concentrations of benzodiazepines that are metabolised by CYP3A4 and lead to a prolonged sedative effect.</p>	<p>Dose reduction of benzodiazepines should be considered.</p>

Medicinal product [Mechanism of interaction]	Interaction Geometric mean changes (%)	Recommendations concerning coadministration
<p>Immunosuppressants [CYP3A4 substrates]</p> <p>Sirolimus (2 mg single dose)</p> <p>Ciclosporin (in stable renal transplant recipients receiving chronic ciclosporin therapy)</p> <p>Tacrolimus (0.1 mg/kg single dose)</p>	<p>In an independent published study, Sirolimus C_{max} ↑ 6.6-fold Sirolimus $AUC_{0-\infty}$ ↑ 11-fold</p> <p>Ciclosporin C_{max} ↑ 13% Ciclosporin AUC_{τ} ↑ 70%</p> <p>Tacrolimus C_{max} ↑ 117% Tacrolimus AUC_t ↑ 221%</p>	<p>Coadministration of voriconazole and sirolimus is contraindicated (see section 4.3).</p> <p>When initiating voriconazole in patients already on ciclosporin it is recommended that the ciclosporin dose be halved and ciclosporin level carefully monitored. Increased ciclosporin levels have been associated with nephrotoxicity. <u>When voriconazole is discontinued, ciclosporin levels must be carefully monitored and the dose increased as necessary.</u></p> <p>When initiating voriconazole in patients already on tacrolimus, it is recommended that the tacrolimus dose be reduced to a third of the original dose and tacrolimus level carefully monitored. Increased tacrolimus levels have been associated with nephrotoxicity. <u>When voriconazole is discontinued, tacrolimus levels must be carefully monitored and the dose increased as necessary.</u></p>
<p>Long-Acting Opiates [CYP3A4 substrates]</p> <p>Oxycodone (10 mg single dose)</p>	<p>In an independent published study, Oxycodone C_{max} ↑ 1.7-fold Oxycodone $AUC_{0-\infty}$ ↑ 3.6-fold</p>	<p>Dose reduction in oxycodone and other long-acting opiates metabolized by CYP3A4 (e.g., hydrocodone) should be considered. Frequent monitoring for opiate-associated adverse reactions may be necessary.</p>
<p>Methadone (32-100 mg QD) [CYP3A4 substrate]</p>	<p>R-methadone (active) C_{max} ↑ 31% R-methadone (active) AUC_{τ} ↑ 47% S-methadone C_{max} ↑ 65% S-methadone AUC_{τ} ↑ 103%</p>	<p>Frequent monitoring for adverse reactions and toxicity related to methadone, including QTc prolongation, is recommended. Dose reduction of methadone may be needed.</p>

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

Medicinal product <i>[Mechanism of interaction]</i>	Interaction Geometric mean changes (%)	Recommendations concerning coadministration
Other HIV Protease Inhibitors (e.g., saquinavir, amprenavir and nelfinavir)* <i>[CYP3A4 substrates and inhibitors]</i>	Not studied clinically. <i>In vitro</i> studies show that voriconazole may inhibit the metabolism of HIV protease inhibitors and the metabolism of voriconazole may also be inhibited by HIV protease inhibitors.	Careful monitoring for any occurrence of drug toxicity and/or lack of efficacy, and dose adjustment may be needed.
Other Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (e.g., delavirdine, nevirapine)* <i>[CYP3A4 substrates, inhibitors or CYP450 inducers]</i>	Not studied clinically. <i>In vitro</i> studies show that the metabolism of voriconazole may be inhibited by NNRTIs and voriconazole may inhibit the metabolism of NNRTIs. The findings of the effect of efavirenz on voriconazole suggest that the metabolism of voriconazole may be induced by an NNRTI.	Careful monitoring for any occurrence of drug toxicity and/or lack of efficacy, and dose adjustment may be needed.
Cimetidine (400 mg BID) <i>[non-specific CYP450 inhibitor and increases gastric pH]</i>	Voriconazole C_{max} ↑ 18% Voriconazole AUC_{τ} ↑ 23%	No dose adjustment
Digoxin (0.25 mg QD) <i>[P-gp substrate]</i>	Digoxin C_{max} ↔ Digoxin AUC_{τ} ↔	No dose adjustment
Indinavir (800 mg TID) <i>[CYP3A4 inhibitor and substrate]</i>	Indinavir C_{max} ↔ Indinavir AUC_{τ} ↔ Voriconazole C_{max} ↔ Voriconazole AUC_{τ} ↔	No dose adjustment
Macrolide antibiotics Erythromycin (1 g BID) <i>[CYP3A4 inhibitor]</i> Azithromycin (500 mg QD)	Voriconazole C_{max} and AUC_{τ} ↔ Voriconazole C_{max} and AUC_{τ} ↔ The effect of voriconazole on either erythromycin or azithromycin is unknown.	No dose adjustment
Mycophenolic acid (1 g single dose) <i>[UDP-glucuronyl transferase substrate]</i>	Mycophenolic acid C_{max} ↔ Mycophenolic acid AUC_t ↔	No dose adjustment
Prednisolone (60 mg single dose) <i>[CYP3A4 substrate]</i>	Prednisolone C_{max} ↑ 11% Prednisolone $AUC_{0-\infty}$ ↑ 34%	No dose adjustment
Ranitidine (150 mg BID) <i>[increases gastric pH]</i>	Voriconazole C_{max} and AUC_{τ} ↔	No dose adjustment

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data on the use of VFEND in pregnant women available.

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

VFEND must not be used during pregnancy unless the benefit to the mother clearly outweighs the

potential risk to the foetus.

Women of child-bearing potential

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

Breast-feeding

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

Fertility

In an animal study, no impairment of fertility was demonstrated in male and female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

VFEND has moderate influence on the ability to drive and use machines. It may cause transient and reversible changes to vision, including blurring, altered/enhanced visual perception and/or photophobia. Patients must avoid potentially hazardous tasks, such as driving or operating machinery while experiencing these symptoms.

4.8 Undesirable effects

Summary of safety profile

The safety profile of voriconazole in adults is based on an integrated safety database of more than 2,000 subjects (including 1,603 adult patients in therapeutic trials) and an additional 270 adults in prophylaxis 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.

The most commonly reported adverse reactions were visual impairment, pyrexia, rash, vomiting, nausea, diarrhoea, headache, peripheral oedema, liver function test abnormal, respiratory distress and abdominal pain.

The severity of the adverse reactions was generally mild to moderate. No clinically significant differences were seen when the safety data were analysed by age, race, or gender.

Tabulated list of adverse reactions

In the table below, since the majority of the studies were of an open nature, all causality adverse reactions and their frequency categories in 1,873 adults from pooled therapeutic (1,603) and prophylaxis (270) studies, by system organ class, are listed.

Frequency categories are expressed as: Very common ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1,000$); Very rare ($< 1/10,000$); Not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Undesirable effects reported in subjects receiving voriconazole:

System Organ Class	Very common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Frequency not known (cannot be estimated from available data)
Infections and infestations		sinusitis	pseudomembranous colitis		
Neoplasms benign, malignant and unspecified (including cysts and polyps)					squamous cell carcinoma*
Blood and lymphatic system disorders		agranulocytosis ¹ , pancytopenia, thrombocytopenia ² , leukopenia, anaemia	bone marrow failure, lymphadenopathy, eosinophilia	disseminated intravascular coagulation	
Immune system disorders			hypersensitivity	anaphylactoid reaction	
Endocrine disorders			adrenal insufficiency, hypothyroidism	hyperthyroidism	
Metabolism and nutrition disorders	oedema peripheral	hypoglycaemia, hypokalaemia, hyponatraemia			
Psychiatric disorders		depression, hallucination, anxiety, insomnia, agitation, confusional state			
Nervous system disorders	headache	convulsion, syncope, tremor, hypertonia ³ , paraesthesia, somnolence, dizziness	brain oedema, encephalopathy ⁴ , extrapyramidal disorder ⁵ , neuropathy peripheral, ataxia, hypoaesthesia, dysgeusia	hepatic encephalopathy, Guillain-Barre syndrome, nystagmus	
Eye disorders	visual impairment ⁶	retinal haemorrhage	optic nerve disorder ⁷ , papilloedema ⁸ , oculogyric crisis, diplopia, scleritis, blepharitis	optic atrophy, corneal opacity	
Ear and labyrinth disorders			hypoacusis, vertigo, tinnitus		

System Organ Class	Very common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Frequency not known (cannot be estimated from available data)
Cardiac disorders		arrhythmia supraventricular, tachycardia, bradycardia	ventricular fibrillation, ventricular extrasystoles, ventricular tachycardia, electrocardiogram QT prolonged, supraventricular tachycardia	torsades de pointes, atrioventricular block complete, bundle branch block, nodal rhythm	
Vascular disorders		hypotension, phlebitis	thrombophlebitis, lymphangitis		
Respiratory, thoracic and mediastinal disorders	respiratory distress ⁹	acute respiratory distress syndrome, pulmonary oedema			
Gastrointestinal disorders	diarrhoea, vomiting, abdominal pain, nausea	cheilitis, dyspepsia, constipation, gingivitis	peritonitis, pancreatitis, swollen tongue, duodenitis, gastroenteritis, glossitis		
Hepatobiliary disorders	liver function test abnormal	jaundice, jaundice cholestatic, hepatitis ¹⁰	hepatic failure, hepatomegaly, cholecystitis, cholelithiasis		
Skin and subcutaneous tissue disorders	rash	dermatitis exfoliative, alopecia, rash maculo-papular, pruritus, erythema	Stevens-Johnson syndrome, phototoxicity, purpura, urticaria, dermatitis allergic, rash papular, rash macular, eczema	toxic epidermal necrolysis, angioedema, actinic keratosis*, pseudoporphyria, erythema multiforme, psoriasis, drug eruption	cutaneous lupus erythematosus*, ephelides*, lentigo*
Musculoskeletal and connective tissue disorders		back pain	arthritis		periostitis*
Renal and urinary disorders		renal failure acute, haematuria	renal tubular necrosis, proteinuria, nephritis		
General disorders and administration	pyrexia	chest pain, face oedema ¹¹ , asthenia, chills	infusion site reaction, influenza like illness		

System Organ Class	Very common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Frequency not known (cannot be estimated from available data)
site conditions					
Investigations		blood creatinine increased	blood urea increased, blood cholesterol increased		

*ADR identified post-marketing

¹ Includes febrile neutropenia and neutropenia.

² Includes immune thrombocytopenic purpura.

³ Includes nuchal rigidity and tetany.

⁴ Includes hypoxic-ischaemic encephalopathy and metabolic encephalopathy.

⁵ Includes akathisia and parkinsonism.

⁶ See “Visual impairments” paragraph in section 4.8.

⁷ Prolonged optic neuritis has been reported post-marketing. See section 4.4.

⁸ See section 4.4.

⁹ Includes dyspnoea and dyspnoea exertional.

¹⁰ Includes drug-induced liver injury, hepatitis toxic, hepatocellular injury and hepatotoxicity.

¹¹ Includes periorbital oedema, lip oedema, and oedema mouth.

Description of selected adverse reactions

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 voriconazole were very common. These visual impairments were transient and fully reversible, with the majority spontaneously resolving within 60 minutes and no clinically significant long-term visual effects were observed. There was evidence of attenuation with repeated doses of voriconazole. The visual impairments were generally mild, rarely resulted in discontinuation and were not associated with long-term sequelae. Visual impairments may be associated with higher plasma concentrations and/or doses.

The mechanism of action is unknown, although the site of action is most likely to be within the retina. In a study in healthy volunteers investigating the impact of voriconazole on retinal function, voriconazole caused a decrease in the electroretinogram (ERG) waveform amplitude. The ERG measures electrical currents in the retina. The ERG changes did not progress over 29 days of treatment and were fully reversible on withdrawal of voriconazole.

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 voriconazole in clinical trials, but these patients had serious underlying diseases and were receiving multiple concomitant medicinal products. The majority of rashes were of mild to moderate severity. Patients have developed serious cutaneous reactions, including Stevens-Johnson syndrome (uncommon), toxic epidermal necrolysis (rare) and erythema multiforme (rare) during treatment with VFEND.

If a patient develops a rash they should be monitored closely and VFEND discontinued if lesions progress. Photosensitivity reactions such as ephelides, lentigo and actinic keratosis have been reported, especially during long-term therapy (see section 4.4).

There have been reports of squamous cell carcinoma of the skin in patients treated with VFEND for long periods of time; the mechanism has not been established (see section 4.4).

Liver function tests

The overall incidence of transaminase increases >3 xULN (not necessarily comprising an adverse event) in the voriconazole clinical programme was 18.0% (319/1,768) in adults and 25.8% (73/283) in paediatric subjects who received voriconazole 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 either resolved during treatment without dose adjustment or following dose adjustment, including discontinuation of therapy.

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

Infusion-related reactions

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

Prophylaxis

In an open-label, comparative, multicenter study comparing voriconazole and itraconazole as primary prophylaxis in adult and adolescent allogeneic HSCT recipients without prior proven or probable IFI, permanent discontinuation of voriconazole due to AEs was reported in 39.3% of subjects versus 39.6% of subjects in the itraconazole arm. Treatment-emergent hepatic AEs resulted in permanent discontinuation of study medication for 50 subjects (21.4%) treated with voriconazole and for 18 subjects (7.1%) treated with itraconazole.

Paediatric population

The safety of voriconazole was investigated in 288 paediatric patients aged 2 to <12 years (169) and 12 to <18 years (119) who received voriconazole for prophylaxis (183) and therapeutic use (105) in clinical trials. The safety of voriconazole was also investigated in 158 additional paediatric patients aged 2 to <12 years in compassionate use programs. Overall, the safety profile of voriconazole in paediatric population was similar to that in adults. However, a trend towards a higher frequency of liver enzyme elevations, reported as adverse events in clinical trials was observed in paediatric patients as compared to adults (14.2% transaminases increased in paediatrics compared to 5.3% in adults). Post-marketing data suggest there might be a higher occurrence of skin reactions (especially erythema) in the paediatric population compared to adults. In the 22 patients less than 2 years old who received voriconazole in a compassionate use programme, the following adverse reactions (for which a relationship to voriconazole could not be excluded) were reported: photosensitivity reaction (1), arrhythmia (1), pancreatitis (1), blood bilirubin increased (1), hepatic enzymes increased (1), rash (1) and papilloedema (1). There have been post-marketing reports of pancreatitis in paediatric patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

There is no known antidote to voriconazole.

Voriconazole is haemodialysed with a clearance of 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 voriconazole and SBECD from the body.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02A C03

Mode of Action

Voriconazole is a triazole antifungal agent. The primary mode of action of voriconazole is the inhibition of fungal cytochrome P450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of voriconazole. Voriconazole has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.

Pharmacokinetic/pharmacodynamic Relationship

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

Pharmacokinetic-Pharmacodynamic analyses of clinical trial data identified positive associations between plasma voriconazole concentrations and both liver function test abnormalities and visual disturbances. Dose adjustments in prophylaxis studies have not been explored.

Clinical efficacy and safety

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* which have limited susceptibility to existing antifungal agents.

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

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

In vitro activity against clinical isolates has been observed for *Acremonium* spp., *Alternaria* spp., *Bipolaris* spp., *Cladophialophora* spp., and *Histoplasma capsulatum*, with most strains being inhibited by concentrations of voriconazole in the range 0.05 to 2 µg/ml.

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

Breakpoints

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.

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

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

EUCAST Breakpoints

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

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

² In clinical studies, response to voriconazole in patients with *C. glabrata* infections was 21% lower compared to *C. albicans*, *C. parapsilosis* and *C. tropicalis*. *In vitro* data showed a slight increase of resistance of *C. glabrata* to voriconazole.

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

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

Clinical experience

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

Aspergillus infections – efficacy in aspergillosis patients with poor prognosis

Voriconazole has *in vitro* fungicidal activity against *Aspergillus* spp. The efficacy and survival benefit of voriconazole versus conventional amphotericin B in the primary treatment of acute invasive aspergillosis was demonstrated in an open, randomised, multicentre study in 277 immunocompromised patients treated for 12 weeks. Voriconazole was administered intravenously with a loading dose of 6 mg/kg every 12 hours for the first 24 hours followed by a maintenance dose of 4 mg/kg every 12 hours for a minimum of 7 days. Therapy could then be switched to the oral formulation at a dose of 200 mg every 12 hours. Median duration of IV voriconazole therapy was 10 days (range 2-85 days). After IV voriconazole therapy, the median duration of oral voriconazole therapy was 76 days (range 2-232 days).

A satisfactory global response (complete or partial resolution of all attributable symptoms, signs, radiographic/bronchoscopic abnormalities present at baseline) was seen in 53% of voriconazole-treated patients compared to 31% of patients treated with comparator. The 84-day survival rate for voriconazole was

statistically significantly higher than that for the comparator and a clinically and statistically significant benefit was shown in favour of voriconazole for both time to death and time to discontinuation due to toxicity.

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

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

Candidaemia in non-neutropenic patients

The efficacy of voriconazole compared to the regimen of amphotericin B followed by fluconazole in the primary treatment of candidaemia was demonstrated in an open, comparative study. Three hundred and seventy non-neutropenic patients (above 12 years of age) with documented candidaemia were included in the study, of whom 248 were treated with voriconazole. Nine subjects in the voriconazole group and 5 in the amphotericin B followed by fluconazole group also had mycologically proven infection in deep tissue. Patients with renal failure were excluded from this study. The median treatment duration was 15 days in both treatment arms. In the primary analysis, successful response as assessed by a Data Review Committee (DRC) blinded to study medicinal product was defined as resolution/improvement in all clinical signs and symptoms of infection with eradication of *Candida* from blood and infected deep tissue sites 12 weeks after the end of therapy (EOT). Patients who did not have an assessment 12 weeks after EOT were counted as failures. In this analysis a successful response was seen in 41% of patients in both treatment arms.

In a secondary analysis, which utilised DRC assessments at the latest evaluable time point (EOT, or 2, 6, or 12 weeks after EOT) voriconazole and the regimen of amphotericin B followed by fluconazole had successful response rates of 65% and 71%, respectively.

The Investigator's assessment of successful outcome at each of these time points is shown in the following table.

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

Serious refractory *Candida* infections

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

Scedosporium and *Fusarium* infections

Voriconazole was shown to be effective against the following rare fungal pathogens:

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

caused by more than one organism including *Scedosporium* spp.

Fusarium spp.: Seven (3 complete, 4 partial responses) of 17 patients were successfully treated with voriconazole. Of these 7 patients, 3 had eye, 1 had sinus, and 3 had disseminated infection. Four additional patients with fusariosis had an infection caused by several organisms; 2 of them had a successful outcome.

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

Primary Prophylaxis of Invasive Fungal Infections – Efficacy in HSCT recipients without prior proven or probable IFI

Voriconazole was compared to itraconazole as primary prophylaxis in an open-label, comparative, multicenter study of adult and adolescent allogeneic HSCT recipients without prior proven or probable IFI. Success was defined as the ability to continue study drug prophylaxis for 100 days after HSCT (without stopping for >14 days) and survival with no proven or probable IFI for 180 days after HSCT. The modified intent-to-treat (MITT) group included 465 allogeneic HSCT recipients with 45% of patients having AML. From all patients 58% were subject to myeloablative conditions regimens. Prophylaxis with study drug was started immediately after HSCT: 224 received voriconazole and 241 received itraconazole. The median duration of study drug prophylaxis was 96 days for voriconazole and 68 days for itraconazole in the MITT group.

Success rates and other secondary endpoints are presented in the table below:

Study Endpoints	Voriconazole N=224	Itraconazole N=241	Difference in proportions and the 95% confidence interval (CI)	P-Value
Success at day 180*	109 (48.7%)	80 (33.2%)	16.4% (7.7%, 25.1%)**	0.0002**
Success at day 100	121 (54.0%)	96 (39.8%)	15.4% (6.6%, 24.2%)**	0.0006**
Completed at least 100 days of study drug prophylaxis	120 (53.6%)	94 (39.0%)	14.6% (5.6%, 23.5%)	0.0015
Survived to day 180	184 (82.1%)	197 (81.7%)	0.4% (-6.6%, 7.4%)	0.9107
Developed proven or probable IFI to day 180	3 (1.3%)	5 (2.1%)	-0.7% (-3.1%, 1.6%)	0.5390
Developed proven or probable IFI to day 100	2 (0.9%)	4 (1.7%)	-0.8% (-2.8%, 1.3%)	0.4589
Developed proven or probable IFI while on study drug	0	3 (1.2%)	-1.2% (-2.6%, 0.2%)	0.0813

* Primary endpoint of the study

** Difference in proportions, 95% CI and p-values obtained after adjustment for randomization

The breakthrough IFI rate to Day 180 and the primary endpoint of the study, which is Success at Day 180, for patients with AML and myeloablative conditioning regimens respectively, is presented in the table below:

AML

Study endpoints	Voriconazole (N=98)	Itraconazole (N=109)	Difference in proportions and the 95% confidence interval (CI)
Breakthrough IFI – Day 180	1 (1.0%)	2 (1.8%)	-0.8% (-4.0%, 2.4%) **
Success at Day 180*	55 (56.1%)	45 (41.3%)	14.7% (1.7%, 27.7%)***

* Primary endpoint of study

** Using a margin of 5%, non inferiority is demonstrated

***Difference in proportions, 95% CI obtained after adjustment for randomization

Myeloablative conditioning regimens

Study endpoints	Voriconazole (N=125)	Itraconazole (N=143)	Difference in proportions and the 95% confidence interval (CI)
Breakthrough IFI – Day 180	2 (1.6%)	3 (2.1%)	-0.5% (-3.7%, 2.7%) **
Success at Day 180*	70 (56.0%)	53 (37.1%)	20.1% (8.5%, 31.7%)***

* Primary endpoint of study

** Using a margin of 5%, non inferiority is demonstrated

*** Difference in proportions, 95% CI obtained after adjustment for randomization

Secondary Prophylaxis of IFI – Efficacy in HSCT recipients with prior proven or probable IFI

Voriconazole was investigated as secondary prophylaxis in an open-label, non-comparative, multicenter study of adult allogeneic HSCT recipients with prior proven or probable IFI. The primary endpoint was the rate of occurrence of proven and probable IFI during the first year after HSCT. The MITT group included 40 patients with prior IFI, including 31 with aspergillosis, 5 with candidiasis, and 4 with other IFI. The median duration of study drug prophylaxis was 95.5 days in the MITT group.

Proven or probable IFIs developed in 7.5% (3/40) of patients during the first year after HSCT, including one candidemia, one scedosporiosis (both relapses of prior IFI), and one zygomycosis. The survival rate at Day 180 was 80.0% (32/40) and at 1 year was 70.0% (28/40).

Duration of treatment

In clinical trials, 705 patients received voriconazole therapy for greater than 12 weeks, with 164 patients receiving voriconazole for over 6 months.

Paediatric population

Fifty-three paediatric patients aged 2 to <18 years were treated with voriconazole in two prospective, open-label, non-comparative, multi-center clinical trials. One study enrolled 31 patients with possible, proven or probable invasive aspergillosis (IA), of whom 14 patients had proven or probable IA and were included in the MITT efficacy analyses. The second study enrolled 22 patients with invasive candidiasis including candidaemia (ICC), and esophageal candidiasis (EC) requiring either primary or salvage therapy, of whom 17 were included in the MITT efficacy analyses. For patients with IA the overall rates of global response at 6 weeks were 64.3% (9/14), the global response rate was 40% (2/5) for patients 2 to <12 years and 77.8% (7/9) for patients 12 to <18 years of age. For patients with ICC the global response rate at EOT was 85.7% (6/7) and for patients with EC the global response rate at EOT was 70% (7/10). The overall rate of response (ICC and EC combined) was 88.9% (8/9) for 2 to <12 years old and 62.5% (5/8) for 12 to <18 years old.

Clinical studies examining QTc interval

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

5.2 Pharmacokinetic properties

General pharmacokinetic characteristics

The pharmacokinetics of voriconazole have been characterised in healthy subjects, special populations and patients. During oral administration of 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). The oral maintenance dose of 200 mg (or 100 mg for patients less than 40 kg) achieves a voriconazole exposure similar to 3 mg/kg IV. A 300 mg (or 150 mg for patients less than 40 kg) oral maintenance dose achieves an exposure similar to 4 mg/kg IV. When the recommended intravenous or oral loading dose regimens are administered, plasma concentrations close to steady state are achieved within the first 24 hours of dosing. Without the loading dose, accumulation occurs during twice daily multiple dosing with steady-state plasma voriconazole concentrations being achieved by Day 6 in the majority of subjects.

Absorption

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

Distribution

The volume of distribution at steady state for voriconazole is estimated to be 4.6 L/kg, suggesting extensive distribution into tissues. Plasma protein binding is estimated to be 58%.

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

Biotransformation

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.

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 at 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.

Pharmacokinetics in special patient groups

Gender

In an oral multiple-dose study, C_{max} and AUC_{τ} for healthy young females were 83% and 113% higher, respectively, than in healthy young males (18-45 years). In the same study, no significant differences in C_{max} and AUC_{τ} were observed between healthy elderly males and healthy elderly females (≥ 65 years).

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

Elderly

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

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

Paediatric population

The recommended doses in children and adolescent patients are based on a population pharmacokinetic analysis of data obtained from 112 immunocompromised paediatric patients aged 2 to <12 years and 26 immunocompromised adolescent patients aged 12 to <17 years. Multiple intravenous doses of 3, 4, 6, 7 and 8 mg/kg twice daily and multiple oral doses (using the powder for oral suspension) of 4 mg/kg, 6 mg/kg, and 200 mg twice daily were evaluated in 3 paediatric pharmacokinetic studies. Intravenous loading doses of 6 mg/kg IV twice daily on day 1 followed by 4 mg/kg intravenous dose twice daily and 300 mg oral tablets twice daily were evaluated in one adolescent pharmacokinetic study. Larger inter-subject variability was observed in paediatric patients compared to adults.

A comparison of the paediatric and adult population pharmacokinetic data indicated that the predicted total exposure (AUC_{τ}) in children following administration of a 9 mg/kg IV loading dose was comparable to that in adults following a 6 mg/kg IV loading dose. The predicted total exposures in children following IV maintenance doses of 4 and 8 mg/kg twice daily were comparable to those in adults following 3 and 4 mg/kg IV twice daily, respectively. The predicted total exposure in children following an oral maintenance dose of 9 mg/kg (maximum of 350 mg) twice daily was comparable to that in adults following 200 mg oral twice daily. An 8 mg/kg intravenous dose will provide voriconazole exposure approximately 2-fold higher than a 9 mg/kg oral dose.

The higher intravenous maintenance dose in paediatric patients relative to adults reflects the higher elimination capacity in paediatric patients due to a greater liver mass to body mass ratio. Oral bioavailability may, however, be limited in paediatric patients with malabsorption and very low body weight for their age. In that case, intravenous voriconazole administration is recommended.

Voriconazole exposures in the majority of adolescent patients were comparable to those in adults receiving the same dosing regimens. However, lower voriconazole exposure was observed in some young adolescents with low body weight compared to adults. It is likely that these subjects may metabolize voriconazole more similarly to children than to adolescents/adults. Based on the population pharmacokinetic analysis, 12- to 14-year-old adolescents weighing less than 50 kg should receive children's doses (see section 4.2).

Renal impairment

In patients with moderate to severe renal dysfunction (serum creatinine levels > 2.5 mg/dl), accumulation of the intravenous vehicle, SBECD, occurs (see sections 4.2 and 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_t 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 sections 4.2 and 4.4).

5.3 Preclinical safety data

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

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

Preclinical data on the intravenous vehicle SBECD indicated that the main effects were vacuolation of urinary tract epithelium and activation of macrophages in the liver and lungs in the repeated-dose toxicity studies. As GPMT (guinea pig maximisation test) result was positive, prescribers should be aware of the hypersensitivity potential of the intravenous formulation. Standard genotoxicity and reproduction studies with the excipient SBECD reveal no special hazard for humans. Carcinogenicity studies were not performed with SBECD. An impurity present in SBECD has been shown to be an alkylating mutagenic agent with evidence for carcinogenicity in rodents. This impurity should be considered a substance with carcinogenic potential in humans. In light of these data the duration of treatment with the intravenous formulation should be no longer than 6 months.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for infusion:

Sulfobutylether beta cyclodextrin sodium (SBECD)

Solvent for solution for infusion:

Sodium chloride 0.9% in Water for Injections

6.2 Incompatibilities

VFEND must not be infused into the same line or cannula concomitantly with other intravenous products. The bag should be checked to ensure that the infusion is complete. When the VFEND infusion is complete, the line may be used for administration of other intravenous products.

Blood products and short-term infusion of concentrated solutions of electrolytes: Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be corrected prior to initiation of voriconazole therapy (see sections 4.2 and 4.4). VFEND must not be administered simultaneously with any blood product or any short-term infusion of concentrated solutions of electrolytes, even if the two infusions are running in separate lines.

Total parenteral nutrition: Total parenteral nutrition (TPN) need *not* be discontinued when prescribed with VFEND, but does need to be infused through 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 diluted with 4.2% Sodium Bicarbonate Infusion. Compatibility with other concentrations is unknown.

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

6.3 Shelf life

VFEND 200 mg powder for solution for infusion and VFEND 200 mg powder and solvent for solution for infusion:

3 years.

From a microbiological point of view, once reconstituted, the product must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C (in a refrigerator), unless reconstitution has taken place in controlled and validated aseptic conditions.

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

Solvent for solution for infusion:

VFEND solvent for solution for infusion is a sterile, single use polypropylene infusion bag. Therefore, from a microbiological point of view, once solvent has been removed from the bag to reconstitute the VFEND powder for solution for infusion and then reintroduced into the bag, the product must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

VFEND 200 mg powder for solution for infusion:

30 ml clear Type I glass vial with rubber stopper and aluminium cap with plastic seal.

VFEND 200 mg powder and solvent for solution for infusion:

VFEND powder and solvent for solution for infusion is available in a box containing:

1 single use 30 ml clear Type I glass vial with rubber stopper and aluminium cap with plastic seal of VFEND 200 mg, powder for solution.

1 sterile, single use, foil overwrapped, polypropylene bag containing VFEND solvent for solution for infusion in one compartment (50 ml).

1 sterile, single use vial adapter.

1 sterile, single use syringe.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

VFEND 200 mg powder for solution for infusion:

The powder is reconstituted with either 19 ml of water for injections or 19 ml of 9 mg/ml (0.9%) Sodium Chloride for Infusion to obtain an extractable volume of 20 ml of clear concentrate containing 10 mg/ml of voriconazole. Discard the VFEND vial if vacuum does not pull the diluent into the vial. It is recommended that a standard 20 ml (non-automated) syringe be used to ensure that the exact amount (19.0 ml) of water for injections or (9 mg/ml [0.9%]) Sodium Chloride for Infusion is dispensed. This medicinal product is for single use only and any unused solution should be discarded. Only clear solutions without particles should be used.

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

The reconstituted solution can be diluted with:

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

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

VFEND 200 mg powder and solvent for solution for infusion:

Use only items provided in the box with VFEND powder and solvent for solution for infusion in the preparation of the infusion.

Instructions for reconstitution and use:

- This medicinal product is for single use only and any unused solution should be discarded.
- To prepare the VFEND vial for reconstitution, remove the plastic cap from the vial and wipe the top with an antiseptic swab. Hold the vial adapter over the vial and press down firmly, until the vial locks into place. The spike in the vial adapter will penetrate the vial seal.
- Remove the bag of VFEND solvent for solution for infusion from the foil overwrap (do not use scissors or any other sharp tool). Snap open the blue port of the infusion bag.
- The VFEND powder is reconstituted by using the specially marked syringe provided to remove 19 ml of VFEND solvent for solution for infusion (Sodium Chloride (0.9%)) from the blue port of the infusion bag.
- The VFEND solvent for solution for infusion is then added to the vial by unscrewing the syringe from the bag, connecting it to the vial adapter and then emptying the contents from the syringe into the vial.
- This will provide an extractable volume of 20 ml of clear concentrate containing 10 mg/ml of voriconazole. The connected syringe and vial are then gently swirled to ensure that the VFEND powder has completely dissolved and no particulates are visible (do not shake).
- For dilution, gently invert the vial, vial adapter and syringe assembly and withdraw the required volume of the reconstituted concentrate into the syringe (see table below). Only clear solutions without particulates should be used. Do not administer to the patient as a bolus injection.
- Once the syringe is reconnected to the blue port of the infusion bag, the contents are then emptied into the infusion bag from the syringe to provide a final voriconazole solution containing 0.5-5 mg/ml.
- The syringe may then be removed and the contents of the infusion bag mixed gently by inverting the bag several times. The bag should be carefully inspected to ensure that there are no particulates. The syringe, vial and vial adapter can then be discarded.

If the required volume of VFEND concentrate as described in the table below requires the use of multiple

vials in order to provide the appropriate dose for a given body weight, then multiple infusion kits should be used. The instructions should be followed for reconstitution, dilution and administration of each kit. Each kit is for single use only.

If multiple vials are required, each individual vial used must be administered using a separate sterile sodium chloride bag.

For administration, the twist-off port at the bottom of the infusion bag should be opened and the infusion line connected and primed. The contents of the infusion bag are now ready for infusion to the patient.

The infusion bag should be checked to ensure that the entire contents of the bag have been infused, especially if the same intravenous line is to be used for sequential infusion of other drugs. Other additives should not be introduced into the infusion bag.

Required Volumes of 10 mg/ml VFEND Concentrate

Body Weight (kg)	Volume of VFEND Concentrate (10 mg/ml) required for:				
	3 mg/kg dose (number of vials)	4 mg/kg dose (number of vials)	6 mg/kg dose (number of vials)	8 mg/kg dose (number of vials)	9 mg/kg dose (number of vials)
10	-	4.0 ml (1)	-	8.0 ml (1)	9.0 ml (1)
15	-	6.0 ml (1)	-	12.0 ml (1)	13.5 ml (1)
20	-	8.0 ml (1)	-	16.0 ml (1)	18.0 ml (1)
25	-	10.0 ml (1)	-	20.0 ml (1)	22.5 ml (2)
30	9.0 ml (1)	12.0 ml (1)	18.0 ml (1)	24.0 ml (2)	27.0 ml (2)
35	10.5 ml (1)	14.0 ml (1)	21.0 ml (2)	28.0 ml (2)	31.5 ml (2)
40	12.0 ml (1)	16.0 ml (1)	24.0 ml (2)	32.0 ml (2)	36.0 ml (2)
45	13.5 ml (1)	18.0 ml (1)	27.0 ml (2)	36.0 ml (2)	40.5 ml (3)
50	15.0 ml (1)	20.0 ml (1)	30.0 ml (2)	40.0 ml (2)	45.0 ml (3)
55	16.5 ml (1)	22.0 ml (2)	33.0 ml (2)	44.0 ml (3)	49.5 ml (3)
60	18.0 ml (1)	24.0 ml (2)	36.0 ml (2)	48.0 ml (3)	54.0 ml (3)
65	19.5 ml (1)	26.0 ml (2)	39.0 ml (2)	52.0 ml (3)	58.5 ml (3)
70	21.0 ml (2)	28.0 ml (2)	42.0 ml (3)	-	-
75	22.5 ml (2)	30.0 ml (2)	45.0 ml (3)	-	-
80	24.0 ml (2)	32.0 ml (2)	48.0 ml (3)	-	-
85	25.5 ml (2)	34.0 ml (2)	51.0 ml (3)	-	-
90	27.0 ml (2)	36.0 ml (2)	54.0 ml (3)	-	-
95	28.5 ml (2)	38.0 ml (2)	57.0 ml (3)	-	-
100	30.0 ml (2)	40.0 ml (2)	60.0 ml (3)	-	-

Further information is provided for medical or healthcare professionals at the end of the Package Leaflet.

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

VFEND 200 mg powder for solution for infusion
EU/1/02/212/025

VFEND 200 mg powder and solvent for solution for infusion
EU/1/02/212/027

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 March 2002

Date of latest renewal: 21 February 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency. <http://www.ema.europa.eu>

1. NAME OF THE MEDICINAL PRODUCT

VFEND 40 mg/ml powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral suspension contains 40 mg of voriconazole when reconstituted with water.

Each bottle contains 3 g of voriconazole.

Excipient with known effect

Each ml of suspension contains 0.54 g sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension

White to off-white powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

VFEND, is a broad-spectrum, triazole antifungal agent and is indicated in adults and children aged 2 years and above as follows:

Treatment of invasive aspergillosis

Treatment of candidaemia in non-neutropenic patients.

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

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

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

Prophylaxis of invasive fungal infections in high risk allogeneic hematopoietic stem cell transplant (HSCT) recipients.

4.2 Posology and method of administration

Posology

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

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

Treatment

Adults

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

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

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

* This also applies to patients aged 15 years and older

Duration of treatment

Treatment duration should be as short as possible depending on the patient's clinical and mycological response. Long term exposure to voriconazole greater than 180 days (6 months) requires careful assessment of the benefit-risk balance (see sections 4.4 and 5.1).

Dosage adjustment (Adults)

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

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

In case of use as prophylaxis, refer below.

Children (2 to <12 years) and young adolescents with low body weight (12 to 14 years and <50 kg)
Voriconazole should be dosed as children as these young adolescents may metabolize voriconazole more similarly to children than to adults.

The recommended dosing regimen is as follows:

	Intravenous	Oral
Loading Dose Regimen (first 24 hours)	9 mg/kg every 12 hours	Not recommended
Maintenance Dose (after first 24 hours)	8 mg/kg twice daily	9 mg/kg twice daily (a maximum dose of 350 mg twice daily)

Note: Based on a population pharmacokinetic analysis in 112 immunocompromised paediatric patients aged 2 to <12 years and 26 immunocompromised adolescents aged 12 to <17 years.

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

These oral dose recommendations for children are based on studies in which voriconazole was administered as the powder for oral suspension. Bioequivalence between the powder for oral suspension and tablets has not been investigated in a paediatric population. Considering the assumed limited gastro-enteric transit time in paediatric patients, the absorption of tablets may be different in paediatric compared to adult patients. It is therefore recommended to use the oral suspension formulation in children aged 2 to <12.

All other adolescents (12 to 14 years and ≥ 50 kg; 15 to 17 years regardless of body weight)
Voriconazole should be dosed as adults.

Dosage adjustment (Children [2 to <12 years] and young adolescents with low body weight [12 to 14 years and <50 kg])

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

Use in paediatric patients aged 2 to <12 years with hepatic or renal insufficiency has not been studied (see sections 4.8 and 5.2).

Prophylaxis in Adults and Children

Prophylaxis should be initiated on the day of transplant and may be administered for up to 100 days. Prophylaxis should be as short as possible depending on the risk for developing invasive fungal infection (IFI) as defined by neutropenia or immunosuppression. 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 voriconazole use for longer than 180 days has not been adequately studied in clinical trials.

Use of voriconazole in prophylaxis for greater than 180 days (6 months) requires careful assessment of the benefit-risk balance (see sections 4.4 and 5.1).

The following instructions apply to both Treatment and Prophylaxis

Dosage adjustment

For prophylaxis use, dose adjustments are not recommended in the case of lack of efficacy or treatment-related adverse events. In the case of treatment-related adverse events, discontinuation of voriconazole and use of alternative antifungal agents must be considered (see section 4.4 and 4.8)

Dosage adjustments in case of co-administration

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

The combination of voriconazole with rifabutin should, if possible be avoided. However, if the combination is strictly needed, the maintenance dose of voriconazole may be increased from 200 mg to 350 mg orally, twice daily (100 mg to 200 mg orally, twice daily in patients less than 40 kg), see sections 4.4 and 4.5.

Efavirenz may be coadministered with voriconazole if the maintenance dose of voriconazole is increased to 400 mg every 12 hours and the efavirenz dose is reduced by 50%, i.e. to 300 mg once daily. When treatment with voriconazole is stopped, the initial dosage of efavirenz should be restored (see sections 4.4 and 4.5).

Elderly

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

Renal impairment

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

Voriconazole is haemodialysed with a clearance of 121 ml/min. A 4-hour haemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment.

Hepatic impairment

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

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

There is limited data on the safety of VFEND in patients with abnormal liver function tests (aspartate transaminase [AST], alanine transaminase [ALT], alkaline phosphatase [ALP], or total bilirubin >5 times the upper limit of normal).

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

Paediatric population

The safety and efficacy of VFEND in children below 2 years has not been established. Currently available data are described in sections 4.8 and 5.1 but no recommendation on a posology can be made.

Method of administration

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

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

Coadministration of standard doses of voriconazole with efavirenz doses of 400 mg once daily or higher is contraindicated, because efavirenz significantly decreases plasma voriconazole concentrations in healthy subjects at these doses. Voriconazole also significantly increases efavirenz plasma concentrations (see section 4.5, for lower doses see section 4.4).

Coadministration with high-dose ritonavir (400 mg and above twice daily) because ritonavir significantly decreases plasma voriconazole concentrations in healthy subjects at this dose (see section 4.5, for lower doses see section 4.4).

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

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

Coadministration with St. John's Wort (see section 4.5).

4.4 Special warnings and precautions for use

Hypersensitivity

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

Cardiovascular

Voriconazole has been associated with QTc interval prolongation. There have been rare cases of torsades de pointes in patients taking voriconazole who had risk factors, such as history of cardiotoxic chemotherapy, cardiomyopathy, hypokalaemia and concomitant medicinal products that may have been contributory. Voriconazole should be administered with caution to patients with potentially proarrhythmic conditions, such as:

- Congenital or acquired QTc-prolongation.
- Cardiomyopathy, in particular when heart failure is present.
- Sinus bradycardia.
- Existing symptomatic arrhythmias.
- Concomitant medicinal product that is known to prolong QTc interval. Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy (see section 4.2). A study has been conducted in healthy volunteers which examined the effect on QTc interval of single doses of voriconazole up to 4 times the usual daily dose. No subject experienced an interval exceeding the potentially clinically-relevant threshold of 500 msec (see section 5.1).

Hepatic toxicity

In clinical trials, there have been cases of serious hepatic reactions during treatment with voriconazole (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. Treatment duration should be as short as possible; however, if based on the benefit-risk assessment the treatment is continued (see section 4.2), 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.

Monitoring of hepatic function should be carried out in both children and adults.

Serious dermatological adverse reactions

- Phototoxicity
In addition VFEND has been associated with phototoxicity including reactions such as ephelides, lentigo, actinic keratosis and pseudoporphyria. It is recommended that all patients, including children, avoid exposure to direct sunlight during VFEND treatment and use measures such as protective clothing and sunscreen with high sun protection factor (SPF).
- Squamous cell carcinoma of the skin (SCC)
Squamous cell carcinoma of the skin has been reported in patients, some of whom have reported prior phototoxic reactions. If phototoxic reactions occur multidisciplinary advice should be sought, VFEND discontinuation and use of alternative antifungal agents 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. VFEND should be discontinued if premalignant skin lesions or squamous cell carcinoma are identified (see below the section under Long-term treatment).

- Exfoliative cutaneous reactions

Reactions such as Stevens-Johnson syndrome developed during treatment with VFEND. If a patient develops a rash he should be monitored closely and VFEND discontinued if lesions progress.

Long-term treatment

Long term exposure (treatment or prophylaxis) greater than 180 days (6 months) requires careful assessment of the benefit-risk balance and physicians should therefore consider the need to limit the exposure to VFEND (see sections 4.2 and 5.1).

Squamous cell carcinoma of the skin (SCC) has been reported in relation with long-term VFEND treatment.

Non-infectious periostitis with elevated fluoride and alkaline phosphatase levels has been reported in transplant patients. If a patient develops skeletal pain and radiologic findings compatible with periostitis VFEND discontinuation should be considered after multidisciplinary advice.

Visual adverse reactions

There have been reports of prolonged visual adverse reactions, including blurred vision, optic neuritis and papilloedema (see section 4.8).

Renal adverse reactions

Acute renal failure has been observed in severely ill patients undergoing treatment with VFEND. Patients being treated with voriconazole are likely to be treated concomitantly with nephrotoxic medicinal products 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

Patients, especially children, with risk factors for acute pancreatitis (e.g., recent chemotherapy, haematopoietic stem cell transplantation [HSCT]), should be monitored closely during VFEND treatment. Monitoring of serum amylase or lipase may be considered in this clinical situation.

Paediatric population

Safety and effectiveness in paediatric subjects below the age of two years has not been established (see sections 4.8 and 5.1). Voriconazole 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 voriconazole 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.

Prophylaxis

In case of treatment-related adverse events (hepatotoxicity, severe skin reactions including phototoxicity and SCC, severe or prolonged visual disorders and periostitis), discontinuation of voriconazole and use of alternative antifungal agents must be considered.

Phenytoin (CYP2C9 substrate and potent CYP450 inducer)

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

Efavirenz (CYP450 inducer; CYP3A4 inhibitor and substrate)

When voriconazole is coadministered with efavirenz the dose of voriconazole should be increased to 400 mg every 12 hours and the dose of efavirenz should be decreased to 300 mg every 24 hours (see sections 4.2, 4.3 and 4.5).

Rifabutin (Potent CYP450 inducer)

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

Ritonavir (potent CYP450 inducer; CYP3A4 inhibitor and substrate)

Coadministration of voriconazole 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 voriconazole (see sections 4.3 and 4.5).

Everolimus (CYP3A4 substrate, P-gp substrate)

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

Methadone (CYP3A4 substrate)

Frequent monitoring for adverse reactions and toxicity related to methadone, including QTc prolongation, is recommended when coadministered with voriconazole since methadone levels increased following coadministration of voriconazole. 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 coadministered with voriconazole (see section 4.5). As the half-life of alfentanil is prolonged in a 4-fold manner when alfentanil is coadministered with voriconazole, and in an independent published study concomitant use of voriconazole with fentanyl resulted in an increase in the mean $AUC_{0-\infty}$ of fentanyl, frequent monitoring for opiate-associated adverse reactions (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 metabolized by CYP3A4 (e.g., hydrocodone) should be considered when coadministered with voriconazole. Frequent monitoring for opiate-associated adverse reactions may be necessary (see section 4.5).

Fluconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor)

Coadministration of oral voriconazole and oral fluconazole resulted in a significant increase in C_{max} and AUC_{τ} of voriconazole in healthy subjects. The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole-associated adverse reactions is recommended if voriconazole is used sequentially after fluconazole (see section 4.5).

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

4.5 Interaction with other medicinal products and other forms of interaction

Voriconazole is metabolised by, and inhibits the activity of, cytochrome P450 isoenzymes, CYP2C19, CYP2C9, and CYP3A4. Inhibitors or inducers of these isoenzymes may increase or decrease voriconazole plasma concentrations, respectively, and there is potential for voriconazole to increase the plasma concentrations of substances metabolised by these CYP450 isoenzymes.

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

Voriconazole should be administered with caution in patients with concomitant medication that is known to prolong QTc interval. When there is also a potential for voriconazole to increase the plasma concentrations of substances metabolised by CYP3A4 isoenzymes (certain antihistamines, quinidine, cisapride, pimoziide), coadministration is contraindicated (see below and section 4.3).

Interaction table

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

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

Medicinal product [Mechanism of interaction]	Interaction Geometric mean changes (%)	Recommendations concerning coadministration
Astemizole, cisapride, pimoziide, quinidine and terfenadine [CYP3A4 substrates]	Although not studied, increased plasma concentrations of these medicinal products can lead to QTc prolongation and rare occurrences of torsades de pointes.	Contraindicated (see section 4.3)
Carbamazepine and long-acting barbiturates (e.g., phenobarbital, mephobarbital) [potent CYP450 inducers]	Although not studied, carbamazepine and long-acting barbiturates are likely to significantly decrease plasma voriconazole concentrations.	Contraindicated (see section 4.3)
Efavirenz (a non-nucleoside reverse transcriptase inhibitor) [CYP450 inducer; CYP3A4 inhibitor and substrate]	Efavirenz C_{max} \uparrow 38% Efavirenz AUC_{τ} \uparrow 44% Voriconazole C_{max} \downarrow 61% Voriconazole AUC_{τ} \downarrow 77%	Use of standard doses of voriconazole with efavirenz doses of 400 mg QD or higher is contraindicated (see section 4.3).
Efavirenz 400 mg QD, coadministered with voriconazole 200 mg BID*	Compared to efavirenz 600 mg QD, Efavirenz C_{max} \leftrightarrow Efavirenz AUC_{τ} \uparrow 17%	Voriconazole may be coadministered with efavirenz if the voriconazole maintenance dose is increased to 400 mg BID and the efavirenz dose is decreased to 300 mg QD. When voriconazole treatment is stopped, the initial dose of efavirenz should be restored (see section 4.2 and 4.4).
Efavirenz 300 mg QD, coadministered with voriconazole 400 mg BID*	Compared to voriconazole 200 mg BID, Voriconazole C_{max} \uparrow 23% Voriconazole AUC_{τ} \downarrow 7%	
Ergot alkaloids (e.g., ergotamine and dihydroergotamine) [CYP3A4 substrates]	Although not studied, voriconazole is likely to increase the plasma concentrations of ergot alkaloids and lead to ergotism.	Contraindicated (see section 4.3)

Medicinal product [Mechanism of interaction]	Interaction Geometric mean changes (%)	Recommendations concerning coadministration
<p>Rifabutin [potent CYP450 inducer]</p> <p>300 mg QD</p> <p>300 mg QD (coadministered with voriconazole 350 mg BID)*</p> <p>300 mg QD (coadministered with voriconazole 400 mg BID)*</p>	<p>Voriconazole C_{max} ↓ 69% Voriconazole AUC_τ ↓ 78%</p> <p>Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↓ 4% Voriconazole AUC_τ ↓ 32%</p> <p>Rifabutin C_{max} ↑ 195% Rifabutin AUC_τ ↑ 331% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 104% Voriconazole AUC_τ ↑ 87%</p>	<p>Concomitant use of voriconazole and rifabutin should be avoided unless the benefit outweighs the risk. The maintenance dose of voriconazole may be increased to 5 mg/kg intravenously BID or from 200 mg to 350 mg orally BID (100 mg to 200 mg orally BID in patients less than 40 kg) (see section 4.2). Careful monitoring of full blood counts and adverse reactions to rifabutin (e.g., uveitis) is recommended when rifabutin is coadministered with voriconazole.</p>
<p>Rifampicin (600 mg QD) [potent CYP450 inducer]</p>	<p>Voriconazole C_{max} ↓ 93% Voriconazole AUC_τ ↓ 96%</p>	<p>Contraindicated (see section 4.3)</p>
<p>Ritonavir (protease inhibitor) [potent CYP450 inducer; CYP3A4 inhibitor and substrate]</p> <p>High dose (400 mg BID)</p> <p>Low dose (100 mg BID)*</p>	<p>Ritonavir C_{max} and AUC_τ ↔ Voriconazole C_{max} ↓ 66% Voriconazole AUC_τ ↓ 82%</p> <p>Ritonavir C_{max} ↓ 25% Ritonavir AUC_τ ↓ 13% Voriconazole C_{max} ↓ 24% Voriconazole AUC_τ ↓ 39%</p>	<p>Coadministration of voriconazole and high doses of ritonavir (400 mg and above BID) is contraindicated (see section 4.3).</p> <p>Coadministration of voriconazole and low-dose ritonavir (100 mg BID) should be avoided unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.</p>
<p>St. John's Wort [CYP450 inducer; P-gp inducer]</p> <p>300 mg TID (coadministered with voriconazole 400 mg single dose)</p>	<p>In an independent published study, Voriconazole AUC_{0-∞} ↓ 59%</p>	<p>Contraindicated (see section 4.3)</p>
<p>Everolimus [CYP3A4 substrate, P-gp substrate]</p>	<p>Although not studied, voriconazole is likely to significantly increase the plasma concentrations of everolimus.</p>	<p>Coadministration of voriconazole with everolimus is not recommended because voriconazole is expected to significantly increase everolimus concentrations (see section 4.4).</p>

Medicinal product <i>[Mechanism of interaction]</i>	Interaction Geometric mean changes (%)	Recommendations concerning coadministration
Fluconazole (200 mg QD) <i>[CYP2C9, CYP2C19 and CYP3A4 inhibitor]</i>	Voriconazole C _{max} ↑ 57% Voriconazole AUC _τ ↑ 79% Fluconazole C _{max} ND Fluconazole AUC _τ ND	The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole-associated adverse reactions is recommended if voriconazole is used sequentially after fluconazole.
Phenytoin <i>[CYP2C9 substrate and potent CYP450 inducer]</i> 300 mg QD 300 mg QD (coadministered with voriconazole 400 mg BID)*	Voriconazole C _{max} ↓ 49% Voriconazole AUC _τ ↓ 69% Phenytoin C _{max} ↑ 67% Phenytoin AUC _τ ↑ 81% Compared to voriconazole 200 mg BID, Voriconazole C _{max} ↑ 34% Voriconazole AUC _τ ↑ 39%	Concomitant use of voriconazole and phenytoin should be avoided unless the benefit outweighs the risk. Careful monitoring of phenytoin plasma levels is recommended. Phenytoin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased to 5 mg/kg IV BID or from 200 mg to 400 mg oral BID (100 mg to 200 mg oral BID in patients less than 40 kg) (see section 4.2).
Anticoagulants Warfarin (30 mg single dose, co-administered with 300 mg BID voriconazole) <i>[CYP2C9 substrate]</i> Other oral coumarins (e.g., phenprocoumon, acenocoumarol) <i>[CYP2C9 and CYP3A4 substrates]</i>	Maximum increase in prothrombin time was approximately 2-fold. Although not studied, voriconazole may increase the plasma concentrations of coumarins that may cause an increase in prothrombin time.	Close monitoring of prothrombin time or other suitable anticoagulation tests is recommended, and the dose of anticoagulants should be adjusted accordingly.
Benzodiazepines (e.g., midazolam, triazolam, alprazolam) <i>[CYP3A4 substrates]</i>	Although not studied clinically, voriconazole is likely to increase the plasma concentrations of benzodiazepines that are metabolised by CYP3A4 and lead to a prolonged sedative effect.	Dose reduction of benzodiazepines should be considered.

Medicinal product [Mechanism of interaction]	Interaction Geometric mean changes (%)	Recommendations concerning coadministration
<p>Immunosuppressants [CYP3A4 substrates]</p> <p>Sirolimus (2 mg single dose)</p> <p>Ciclosporin (in stable renal transplant recipients receiving chronic ciclosporin therapy)</p> <p>Tacrolimus (0.1 mg/kg single dose)</p>	<p>In an independent published study, Sirolimus C_{max} ↑ 6.6-fold Sirolimus $AUC_{0-\infty}$ ↑ 11-fold</p> <p>Ciclosporin C_{max} ↑ 13% Ciclosporin AUC_{τ} ↑ 70%</p> <p>Tacrolimus C_{max} ↑ 117% Tacrolimus AUC_t ↑ 221%</p>	<p>Coadministration of voriconazole and sirolimus is contraindicated (see section 4.3).</p> <p>When initiating voriconazole in patients already on ciclosporin it is recommended that the ciclosporin dose be halved and ciclosporin level carefully monitored. Increased ciclosporin levels have been associated with nephrotoxicity. <u>When voriconazole is discontinued, ciclosporin levels must be carefully monitored and the dose increased as necessary.</u></p> <p>When initiating voriconazole in patients already on tacrolimus, it is recommended that the tacrolimus dose be reduced to a third of the original dose and tacrolimus level carefully monitored. Increased tacrolimus levels have been associated with nephrotoxicity. <u>When voriconazole is discontinued, tacrolimus levels must be carefully monitored and the dose increased as necessary.</u></p>
<p>Long-Acting Opiates [CYP3A4 substrates]</p> <p>Oxycodone (10 mg single dose)</p>	<p>In an independent published study, Oxycodone C_{max} ↑ 1.7-fold Oxycodone $AUC_{0-\infty}$ ↑ 3.6-fold</p>	<p>Dose reduction in oxycodone and other long-acting opiates metabolized by CYP3A4 (e.g., hydrocodone) should be considered. Frequent monitoring for opiate-associated adverse reactions may be necessary.</p>
<p>Methadone (32-100 mg QD) [CYP3A4 substrate]</p>	<p>R-methadone (active) C_{max} ↑ 31% R-methadone (active) AUC_{τ} ↑ 47% S-methadone C_{max} ↑ 65% S-methadone AUC_{τ} ↑ 103%</p>	<p>Frequent monitoring for adverse reactions and toxicity related to methadone, including QTc prolongation, is recommended. Dose reduction of methadone may be needed.</p>

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

Medicinal product <i>[Mechanism of interaction]</i>	Interaction Geometric mean changes (%)	Recommendations concerning coadministration
Other HIV Protease Inhibitors (e.g., saquinavir, amprenavir and nelfinavir)* <i>[CYP3A4 substrates and inhibitors]</i>	Not studied clinically. <i>In vitro</i> studies show that voriconazole may inhibit the metabolism of HIV protease inhibitors and the metabolism of voriconazole may also be inhibited by HIV protease inhibitors.	Careful monitoring for any occurrence of drug toxicity and/or lack of efficacy, and dose adjustment may be needed.
Other Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (e.g., delavirdine, nevirapine)* <i>[CYP3A4 substrates, inhibitors or CYP450 inducers]</i>	Not studied clinically. <i>In vitro</i> studies show that the metabolism of voriconazole may be inhibited by NNRTIs and voriconazole may inhibit the metabolism of NNRTIs. The findings of the effect of efavirenz on voriconazole suggest that the metabolism of voriconazole may be induced by an NNRTI.	Careful monitoring for any occurrence of drug toxicity and/or lack of efficacy, and dose adjustment may be needed.
Cimetidine (400 mg BID) <i>[non-specific CYP450 inhibitor and increases gastric pH]</i>	Voriconazole C_{max} ↑ 18% Voriconazole AUC_{τ} ↑ 23%	No dose adjustment
Digoxin (0.25 mg QD) <i>[P-gp substrate]</i>	Digoxin C_{max} ↔ Digoxin AUC_{τ} ↔	No dose adjustment
Indinavir (800 mg TID) <i>[CYP3A4 inhibitor and substrate]</i>	Indinavir C_{max} ↔ Indinavir AUC_{τ} ↔ Voriconazole C_{max} ↔ Voriconazole AUC_{τ} ↔	No dose adjustment
Macrolide antibiotics Erythromycin (1 g BID) <i>[CYP3A4 inhibitor]</i> Azithromycin (500 mg QD)	Voriconazole C_{max} and AUC_{τ} ↔ Voriconazole C_{max} and AUC_{τ} ↔ The effect of voriconazole on either erythromycin or azithromycin is unknown.	No dose adjustment
Mycophenolic acid (1 g single dose) <i>[UDP-glucuronyl transferase substrate]</i>	Mycophenolic acid C_{max} ↔ Mycophenolic acid AUC_t ↔	No dose adjustment
Prednisolone (60 mg single dose) <i>[CYP3A4 substrate]</i>	Prednisolone C_{max} ↑ 11% Prednisolone $AUC_{0-\infty}$ ↑ 34%	No dose adjustment
Ranitidine (150 mg BID) <i>[increases gastric pH]</i>	Voriconazole C_{max} and AUC_{τ} ↔	No dose adjustment

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data on the use of VFEND in pregnant women available.

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

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

Women of child-bearing potential

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

Breast-feeding

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

Fertility

In an animal study, no impairment of fertility was demonstrated in male and female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

VFEND has moderate influence on the ability to drive and use machines. It may cause transient and reversible changes to vision, including blurring, altered/enhanced visual perception and/or photophobia. Patients must avoid potentially hazardous tasks, such as driving or operating machinery while experiencing these symptoms.

4.8 Undesirable effects

Summary of safety profile

The safety profile of voriconazole in adults is based on an integrated safety database of more than 2,000 subjects (including 1,603 adult patients in therapeutic trials) and an additional 270 adults in prophylaxis 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.

The most commonly reported adverse reactions were visual impairment, pyrexia, rash, vomiting, nausea, diarrhoea, headache, peripheral oedema, liver function test abnormal, respiratory distress and abdominal pain.

The severity of the adverse reactions was generally mild to moderate. No clinically significant differences were seen when the safety data were analysed by age, race, or gender.

Tabulated list of adverse reactions

In the table below, since the majority of the studies were of an open nature, all causality adverse reactions and their frequency categories in 1,873 adults from pooled therapeutic (1,603) and prophylaxis (270) studies, by system organ class, are listed.

Frequency categories are expressed as: Very common ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1,000$); Very rare ($< 1/10,000$); Not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Undesirable effects reported in subjects receiving voriconazole:

System Organ Class	Very common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Frequency not known (cannot be estimated from available data)
Infections and infestations		sinusitis	pseudomembranous colitis		
Neoplasms benign, malignant and unspecified (including cysts and polyps)					squamous cell carcinoma*
Blood and lymphatic system disorders		agranulocytosis ¹ , pancytopenia, thrombocytopenia ² , leukopenia, anaemia	bone marrow failure, lymphadenopathy, eosinophilia	disseminated intravascular coagulation	
Immune system disorders			hypersensitivity	anaphylactoid reaction	
Endocrine disorders			adrenal insufficiency, hypothyroidism	hyperthyroidism	
Metabolism and nutrition disorders	oedema peripheral	hypoglycaemia, hypokalaemia, hyponatraemia			
Psychiatric disorders		depression, hallucination, anxiety, insomnia, agitation, confusional state			
Nervous system disorders	headache	convulsion, syncope, tremor, hypertonia ³ , paraesthesia, somnolence, dizziness	brain oedema, encephalopathy ⁴ , extrapyramidal disorder ⁵ , neuropathy peripheral, ataxia, hypoaesthesia, dysgeusia	hepatic encephalopathy, Guillain-Barre syndrome, nystagmus	
Eye disorders	visual impairment ⁶	retinal haemorrhage	optic nerve disorder ⁷ , papilloedema ⁸ , oculogyric crisis, diplopia, scleritis, blepharitis	optic atrophy, corneal opacity	
Ear and labyrinth disorders			hypoacusis, vertigo, tinnitus		

System Organ Class	Very common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Frequency not known (cannot be estimated from available data)
Cardiac disorders		arrhythmia supraventricular, tachycardia, bradycardia	ventricular fibrillation, ventricular extrasystoles, ventricular tachycardia, electrocardiogram QT prolonged, supraventricular tachycardia	torsades de pointes, atrioventricular block complete, bundle branch block, nodal rhythm	
Vascular disorders		hypotension, phlebitis	thrombophlebitis, lymphangitis		
Respiratory, thoracic and mediastinal disorders	respiratory distress ⁹	acute respiratory distress syndrome, pulmonary oedema			
Gastrointestinal disorders	diarrhoea, vomiting, abdominal pain, nausea	cheilitis, dyspepsia, constipation, gingivitis	peritonitis, pancreatitis, swollen tongue, duodenitis, gastroenteritis, glossitis		
Hepatobiliary disorders	liver function test abnormal	jaundice, jaundice cholestatic, hepatitis ¹⁰	hepatic failure, hepatomegaly, cholecystitis, cholelithiasis		
Skin and subcutaneous tissue disorders	rash	dermatitis exfoliative, alopecia, rash maculo-papular, pruritus, erythema	Stevens-Johnson syndrome, phototoxicity, purpura, urticaria, dermatitis allergic, rash papular, rash macular, eczema	toxic epidermal necrolysis, angioedema, actinic keratosis*, pseudoporphyria, erythema multiforme, psoriasis, drug eruption	cutaneous lupus erythematosus*, ephelides*, lentigo*
Musculoskeletal and connective tissue disorders		back pain	arthritis		periostitis*
Renal and urinary disorders		renal failure acute, haematuria	renal tubular necrosis, proteinuria, nephritis		
General disorders and administration	pyrexia	chest pain, face oedema ¹¹ , asthenia, chills	infusion site reaction, influenza like illness		

System Organ Class	Very common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Frequency not known (cannot be estimated from available data)
site conditions					
Investigations		blood creatinine increased	blood urea increased, blood cholesterol increased		

*ADR identified post-marketing

¹ Includes febrile neutropenia and neutropenia.

² Includes immune thrombocytopenic purpura.

³ Includes nuchal rigidity and tetany.

⁴ Includes hypoxic-ischaemic encephalopathy and metabolic encephalopathy.

⁵ Includes akathisia and parkinsonism.

⁶ See “Visual impairments” paragraph in section 4.8.

⁷ Prolonged optic neuritis has been reported post-marketing. See section 4.4.

⁸ See section 4.4.

⁹ Includes dyspnoea and dyspnoea exertional.

¹⁰ Includes drug-induced liver injury, hepatitis toxic, hepatocellular injury and hepatotoxicity.

¹¹ Includes periorbital oedema, lip oedema, and oedema mouth.

Description of selected adverse reactions

Altered taste perception

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

Visual 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 voriconazole were very common. These visual impairments were transient and fully reversible, with the majority spontaneously resolving within 60 minutes and no clinically significant long-term visual effects were observed. There was evidence of attenuation with repeated doses of voriconazole. The visual impairments were generally mild, rarely resulted in discontinuation and were not associated with long-term sequelae. Visual impairments may be associated with higher plasma concentrations and/or doses.

The mechanism of action is unknown, although the site of action is most likely to be within the retina. In a study in healthy volunteers investigating the impact of voriconazole on retinal function, voriconazole caused a decrease in the electroretinogram (ERG) waveform amplitude. The ERG measures electrical currents in the retina. The ERG changes did not progress over 29 days of treatment and were fully reversible on withdrawal of voriconazole.

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 voriconazole in clinical trials, but these patients had serious underlying diseases and were receiving multiple concomitant medicinal products. The majority of rashes were of mild to moderate severity. Patients have developed serious cutaneous reactions, including Stevens-Johnson syndrome (uncommon), toxic epidermal necrolysis (rare) and erythema multiforme (rare) during treatment with VFEND.

If a patient develops a rash they should be monitored closely and VFEND discontinued if lesions progress. Photosensitivity reactions such as ephelides, lentigo and actinic keratosis have been reported, especially during long-term therapy (see section 4.4).

There have been reports of squamous cell carcinoma of the skin in patients treated with VFEND for long periods of time; the mechanism has not been established (see section 4.4).

Liver function tests

The overall incidence of transaminase increases $>3 \times \text{ULN}$ (not necessarily comprising an adverse event) in the voriconazole clinical programme was 18.0% (319/1,768) in adults and 25.8% (73/283) in paediatric subjects who received voriconazole 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 either resolved during treatment without dose adjustment or following dose adjustment, including discontinuation of therapy.

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

Prophylaxis

In an open-label, comparative, multicenter study comparing voriconazole and itraconazole as primary prophylaxis in adult and adolescent allogeneic HSCT recipients without prior proven or probable IFI, permanent discontinuation of voriconazole due to AEs was reported in 39.3% of subjects versus 39.6% of subjects in the itraconazole arm. Treatment-emergent hepatic AEs resulted in permanent discontinuation of study medication for 50 subjects (21.4%) treated with voriconazole and for 18 subjects (7.1%) treated with itraconazole.

Paediatric population

The safety of voriconazole was investigated in 288 paediatric patients aged 2 to <12 years (169) and 12 to <18 years (119) who received voriconazole for prophylaxis (183) and therapeutic use (105) in clinical trials. The safety of voriconazole was also investigated in 158 additional paediatric patients aged 2 to <12 years in compassionate use programs. Overall, the safety profile of voriconazole in paediatric population was similar to that in adults. However, a trend towards a higher frequency of liver enzyme elevations, reported as adverse events in clinical trials was observed in paediatric patients as compared to adults (14.2% transaminases increased in paediatrics compared to 5.3% in adults). Post-marketing data suggest there might be a higher occurrence of skin reactions (especially erythema) in the paediatric population compared to adults. In the 22 patients less than 2 years old who received voriconazole in a compassionate use programme, the following adverse reactions (for which a relationship to voriconazole could not be excluded) were reported: photosensitivity reaction (1), arrhythmia (1), pancreatitis (1), blood bilirubin increased (1), hepatic enzymes increased (1), rash (1) and papilloedema (1). There have been post-marketing reports of pancreatitis in paediatric patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system listed in [Appendix V](#)**.

4.9 Overdose

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

There is no known antidote to voriconazole.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02A C03

Mode of Action

Voriconazole is a triazole antifungal agent. The primary mode of action of voriconazole is the inhibition of fungal cytochrome P450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of voriconazole. Voriconazole has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.

Pharmacokinetic/pharmacodynamic Relationship

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

Pharmacokinetic-Pharmacodynamic analyses of clinical trial data identified positive associations between plasma voriconazole concentrations and both liver function test abnormalities and visual disturbances. Dose adjustments in prophylaxis studies have not been explored.

Clinical efficacy and safety

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* which have limited susceptibility to existing antifungal agents.

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

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

In vitro activity against clinical isolates has been observed for *Acremonium* spp., *Alternaria* spp., *Bipolaris* spp., *Cladophialophora* spp., and *Histoplasma capsulatum*, with most strains being inhibited by concentrations of voriconazole in the range 0.05 to 2 µg/ml.

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

Breakpoints

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.

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

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

EUCAST Breakpoints

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

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

² In clinical studies, response to voriconazole in patients with *C. glabrata* infections was 21% lower compared to *C. albicans*, *C. parapsilosis* and *C. tropicalis*. *In vitro* data showed a slight increase of resistance of *C. glabrata* to voriconazole.

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

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

Clinical experience

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

Aspergillus infections – efficacy in aspergillosis patients with poor prognosis

Voriconazole has *in vitro* fungicidal activity against *Aspergillus* spp. The efficacy and survival benefit of voriconazole versus conventional amphotericin B in the primary treatment of acute invasive aspergillosis was demonstrated in an open, randomised, multicentre study in 277 immunocompromised patients treated for 12 weeks. Voriconazole was administered intravenously with a loading dose of 6 mg/kg every 12 hours for the first 24 hours followed by a maintenance dose of 4 mg/kg every 12 hours for a minimum of 7 days. Therapy could then be switched to the oral formulation at a dose of 200 mg every 12 hours. Median duration of IV voriconazole therapy was 10 days (range 2-85 days). After IV voriconazole therapy, the median duration of oral voriconazole therapy was 76 days (range 2-232 days).

A satisfactory global response (complete or partial resolution of all attributable symptoms, signs, radiographic/bronchoscopic abnormalities present at baseline) was seen in 53% of voriconazole-treated patients compared to 31% of patients treated with comparator. The 84-day survival rate for voriconazole was statistically significantly higher than that for the comparator and a clinically and statistically significant benefit was shown in favour of voriconazole for both time to death and time to discontinuation due to toxicity.

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

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

Candidaemia in non-neutropenic patients

The efficacy of voriconazole compared to the regimen of amphotericin B followed by fluconazole in the primary treatment of candidaemia was demonstrated in an open, comparative study. Three hundred and seventy non-neutropenic patients (above 12 years of age) with documented candidaemia were included in the study, of whom 248 were treated with voriconazole. Nine subjects in the voriconazole group and 5 in the amphotericin B followed by fluconazole group also had mycologically proven infection in deep tissue. Patients with renal failure were excluded from this study. The median treatment duration was 15 days in both treatment arms. In the primary analysis, successful response as assessed by a Data Review Committee (DRC) blinded to study medicinal product was defined as resolution/improvement in all clinical signs and symptoms of infection with eradication of *Candida* from blood and infected deep tissue sites 12 weeks after the end of therapy (EOT). Patients who did not have an assessment 12 weeks after EOT were counted as failures. In this analysis a successful response was seen in 41% of patients in both treatment arms.

In a secondary analysis, which utilised DRC assessments at the latest evaluable time point (EOT, or 2, 6, or 12 weeks after EOT) voriconazole and the regimen of amphotericin B followed by fluconazole had successful response rates of 65% and 71%, respectively.

The Investigator's assessment of successful outcome at each of these time points is shown in the following table.

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

Serious refractory *Candida* infections

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

Scedosporium and *Fusarium* infections

Voriconazole was shown to be effective against the following rare fungal pathogens:

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

Fusarium spp.: Seven (3 complete, 4 partial responses) of 17 patients were successfully treated with

voriconazole. Of these 7 patients, 3 had eye, 1 had sinus, and 3 had disseminated infection. Four additional patients with fusariosis had an infection caused by several organisms; 2 of them had a successful outcome.

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

Primary Prophylaxis of Invasive Fungal Infections – Efficacy in HSCT recipients without prior proven or probable IFI

Voriconazole was compared to itraconazole as primary prophylaxis in an open-label, comparative, multicenter study of adult and adolescent allogeneic HSCT recipients without prior proven or probable IFI. Success was defined as the ability to continue study drug prophylaxis for 100 days after HSCT (without stopping for >14 days) and survival with no proven or probable IFI for 180 days after HSCT. The modified intent-to-treat (MITT) group included 465 allogeneic HSCT recipients with 45% of patients having AML. From all patients 58% were subject to myeloablative conditions regimens. Prophylaxis with study drug was started immediately after HSCT: 224 received voriconazole and 241 received itraconazole. The median duration of study drug prophylaxis was 96 days for voriconazole and 68 days for itraconazole in the MITT group.

Success rates and other secondary endpoints are presented in the table below:

Study Endpoints	Voriconazole N=224	Itraconazole N=241	Difference in proportions and the 95% confidence interval (CI)	P-Value
Success at day 180*	109 (48.7%)	80 (33.2%)	16.4% (7.7%, 25.1%)**	0.0002**
Success at day 100	121 (54.0%)	96 (39.8%)	15.4% (6.6%, 24.2%)**	0.0006**
Completed at least 100 days of study drug prophylaxis	120 (53.6%)	94 (39.0%)	14.6% (5.6%, 23.5%)	0.0015
Survived to day 180	184 (82.1%)	197 (81.7%)	0.4% (-6.6%, 7.4%)	0.9107
Developed proven or probable IFI to day 180	3 (1.3%)	5 (2.1%)	-0.7% (-3.1%, 1.6%)	0.5390
Developed proven or probable IFI to day 100	2 (0.9%)	4 (1.7%)	-0.8% (-2.8%, 1.3%)	0.4589
Developed proven or probable IFI while on study drug	0	3 (1.2%)	-1.2% (-2.6%, 0.2%)	0.0813

* Primary endpoint of the study

** Difference in proportions, 95% CI and p-values obtained after adjustment for randomization

The breakthrough IFI rate to Day 180 and the primary endpoint of the study, which is Success at Day 180, for patients with AML and myeloablative conditioning regimens respectively, is presented in the table below:

AML

Study endpoints	Voriconazole (N=98)	Itraconazole (N=109)	Difference in proportions and the 95% confidence interval (CI)
Breakthrough IFI – Day 180	1 (1.0%)	2 (1.8%)	-0.8% (-4.0%, 2.4%) **
Success at Day 180*	55 (56.1%)	45 (41.3%)	14.7% (1.7%, 27.7%)***

* Primary endpoint of study

** Using a margin of 5%, non inferiority is demonstrated

***Difference in proportions, 95% CI obtained after adjustment for randomization

Myeloablative conditioning regimens

Study endpoints	Voriconazole (N=125)	Itraconazole (N=143)	Difference in proportions and the 95% confidence interval (CI)
Breakthrough IFI – Day 180	2 (1.6%)	3 (2.1%)	-0.5% (-3.7%, 2.7%) **
Success at Day 180*	70 (56.0%)	53 (37.1%)	20.1% (8.5%, 31.7%)***

* Primary endpoint of study

** Using a margin of 5%, non inferiority is demonstrated

*** Difference in proportions, 95% CI obtained after adjustment for randomization

Secondary Prophylaxis of IFI – Efficacy in HSCT recipients with prior proven or probable IFI

Voriconazole was investigated as secondary prophylaxis in an open-label, non-comparative, multicenter study of adult allogeneic HSCT recipients with prior proven or probable IFI. The primary endpoint was the rate of occurrence of proven and probable IFI during the first year after HSCT. The MITT group included 40 patients with prior IFI, including 31 with aspergillosis, 5 with candidiasis, and 4 with other IFI. The median duration of study drug prophylaxis was 95.5 days in the MITT group.

Proven or probable IFIs developed in 7.5% (3/40) of patients during the first year after HSCT, including one candidemia, one scedosporiosis (both relapses of prior IFI), and one zygomycosis. The survival rate at Day 180 was 80.0% (32/40) and at 1 year was 70.0% (28/40).

Duration of treatment

In clinical trials, 705 patients received voriconazole therapy for greater than 12 weeks, with 164 patients receiving voriconazole for over 6 months.

Paediatric population

Fifty-three paediatric patients aged 2 to <18 years were treated with voriconazole in two prospective, open-label, non-comparative, multi-center clinical trials. One study enrolled 31 patients with possible, proven or probable invasive aspergillosis (IA), of whom 14 patients had proven or probable IA and were included in the MITT efficacy analyses. The second study enrolled 22 patients with invasive candidiasis including candidaemia (ICC), and esophageal candidiasis (EC) requiring either primary or salvage therapy, of whom 17 were included in the MITT efficacy analyses. For patients with IA the overall rates of global response at 6 weeks were 64.3% (9/14), the global response rate was 40% (2/5) for patients 2 to <12 years and 77.8% (7/9) for patients 12 to <18 years of age. For patients with ICC the global response rate at EOT was 85.7% (6/7) and for patients with EC the global response rate at EOT was 70% (7/10). The overall rate of response (ICC and EC combined) was 88.9% (8/9) for 2 to <12 years old and 62.5% (5/8) for 12 to <18 years old.

Clinical studies examining QTc interval

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

5.2 Pharmacokinetic properties

General pharmacokinetic characteristics

The pharmacokinetics of voriconazole have been characterised in healthy subjects, special populations and patients. During oral administration of 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). The oral maintenance dose of 200 mg (or 100 mg for patients less than 40 kg) achieves a voriconazole exposure similar to 3 mg/kg IV. A 300 mg (or 150 mg for patients less than 40 kg) oral maintenance dose achieves an exposure similar to 4 mg/kg IV. When the recommended intravenous or oral loading dose regimens are administered, plasma concentrations close to steady state are achieved within the first 24 hours of dosing. Without the loading dose, accumulation occurs during twice daily multiple dosing with steady-state plasma voriconazole concentrations being achieved by Day 6 in the majority of subjects.

Absorption

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

Distribution

The volume of distribution at steady state for voriconazole is estimated to be 4.6 L/kg, suggesting extensive distribution into tissues. Plasma protein binding is estimated to be 58%. Cerebrospinal fluid samples from eight patients in a compassionate programme showed detectable voriconazole concentrations in all patients.

Biotransformation

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.

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 at 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.

Pharmacokinetics in special patient groups

Gender

In an oral multiple-dose study, C_{max} and AUC τ for healthy young females were 83% and 113% higher, respectively, than in healthy young males (18-45 years). In the same study, no significant differences in C_{max}

and AUC_τ were observed between healthy elderly males and healthy elderly females (≥65 years).

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

Elderly

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

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

Paediatric population

The recommended doses in children and adolescent patients are based on a population pharmacokinetic analysis of data obtained from 112 immunocompromised paediatric patients aged 2 to <12 years and 26 immunocompromised adolescent patients aged 12 to <17 years. Multiple intravenous doses of 3, 4, 6, 7 and 8 mg/kg twice daily and multiple oral doses (using the powder for oral suspension) of 4 mg/kg, 6 mg/kg, and 200 mg twice daily were evaluated in 3 paediatric pharmacokinetic studies. Intravenous loading doses of 6 mg/kg IV twice daily on day 1 followed by 4 mg/kg intravenous dose twice daily and 300 mg oral tablets twice daily were evaluated in one adolescent pharmacokinetic study. Larger inter-subject variability was observed in paediatric patients compared to adults.

A comparison of the paediatric and adult population pharmacokinetic data indicated that the predicted total exposure (AUC_τ) in children following administration of a 9 mg/kg IV loading dose was comparable to that in adults following a 6 mg/kg IV loading dose. The predicted total exposures in children following IV maintenance doses of 4 and 8 mg/kg twice daily were comparable to those in adults following 3 and 4 mg/kg IV twice daily, respectively. The predicted total exposure in children following an oral maintenance dose of 9 mg/kg (maximum of 350 mg) twice daily was comparable to that in adults following 200 mg oral twice daily. An 8 mg/kg intravenous dose will provide voriconazole exposure approximately 2-fold higher than a 9 mg/kg oral dose.

The higher intravenous maintenance dose in paediatric patients relative to adults reflects the higher elimination capacity in paediatric patients due to a greater liver mass to body mass ratio. Oral bioavailability may, however, be limited in paediatric patients with malabsorption and very low body weight for their age. In that case, intravenous voriconazole administration is recommended.

Voriconazole exposures in the majority of adolescent patients were comparable to those in adults receiving the same dosing regimens. However, lower voriconazole exposure was observed in some young adolescents with low body weight compared to adults. It is likely that these subjects may metabolize voriconazole more similarly to children than to adults. Based on the population pharmacokinetic analysis, 12- to 14-year-old adolescents weighing less than 50 kg should receive children's doses (see section 4.2).

Renal impairment

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).

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 sections 4.2 and 4.4).

5.3 Preclinical safety data

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Silica Colloidal Anhydrous
Titanium Dioxide (E171)
Xanthan Gum
Sodium Citrate
Citric Acid Anhydrous
Sodium Benzoate (E211)
Natural Orange Flavour

6.2 Incompatibilities

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

6.3 Shelf life

2 years
The shelf life of the constituted suspension is 14 days.
Constituted suspension: Do not store above 30°C; do not refrigerate or freeze.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
For storage conditions after constitution, see section 6.3.
Keep the container tightly closed.

6.5 Nature and contents of container

One 100 ml high-density polyethylene (HDPE) bottle (with a polypropylene child resistant closure) contains 45 g of powder for oral suspension. A measuring cup (graduated to indicate 23 ml), 5 ml oral syringe and a press-in bottle adaptor are also provided.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Constitution instructions:

1. Tap the bottle to release the powder.
2. Add 2 measuring cups of water, providing a total volume of 46 ml.
3. Shake the closed bottle vigorously for about 1 minute.
4. Remove child-resistant cap. Press bottle adaptor into the neck of the bottle.
5. Replace the cap.
6. Write the date of expiration of the constituted suspension on the bottle label (the shelf-life of the constituted suspension is 14 days).

Following constitution, the volume of the suspension is 75 ml, providing a usable volume of 70 ml.

Instructions for use:

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

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

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/212/026

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 March 2002

Date of latest renewal: 21 February 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency. <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Tablets

R-Pharm Germany GmbH
Heinrich-Mack-Str. 35, 89257 Illertissen
Germany

Pfizer Italia S.r.l.
Località Marino del Tronto
63100 Ascoli Piceno (AP)
Italy

Powder for solution for infusion and powder for oral suspension:

Fareva Amboise
Zone Industrielle
29 route des Industries
37530 Pocé-sur-Cisse
France

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• **Risk Management Plan (RMP)**

The MAH shall perform the pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**
- Health Care Professional (HCP) Question and Answer Brochure for Phototoxicity, SCC and Hepatic toxicity;
 - Advises HCPs on the risks of phototoxicity, skin SCC and liver toxicity associated with voriconazole use.
 - Provides HCPs with the current recommendations to monitor and manage these risks.
 - Reminds HCPs of use of the HCP Checklist and the Patient Alert Card and how to obtain additional copies.
- Health Care Professional (HCP) Checklist for Phototoxicity, SCC and Hepatic toxicity:
 - Reminds HCPs of the risks of phototoxicity, skin SCC and hepatotoxicity reported with voriconazole use.
 - Provides HCPs with the current recommendations to monitor and manage these risks.
 - Reminds HCPs to discuss with the patient/care giver the risks of phototoxicity/skin SCC and hepatotoxicity, what to look for, how and when to seek immediate attention.
 - Reminds HCPs to provide a Patient Alert Card to the patient.
- Patient Alert Card for Phototoxicity and SCC:
 - Reminds patients of the risk of phototoxicity and skin SCC.
 - Reminds patients when and how to report relevant signs and symptoms of phototoxicity and skin cancer.
 - Reminds patients to take steps to minimize the risk of skin reactions and skin SCC (by avoiding exposure to direct sunlight, use of a sunscreen and protective clothing) and inform HCPs if they experience relevant skin abnormalities.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Blister pack for 50 mg film-coated tablets – Pack of 2, 10, 14, 20, 28, 30, 50, 56, 100

1. NAME OF THE MEDICINAL PRODUCT

VFEND 50 mg film-coated tablets
voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50 mg voriconazole.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

2 film-coated tablets
10 film-coated tablets
14 film-coated tablets
20 film-coated tablets
28 film-coated tablets
30 film-coated tablets
50 film-coated tablets
56 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

Sealed Pack
Do not use if box has been opened.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/001 2 film-coated tablets
EU/I/02/212/002 10 film-coated tablets
EU/I/02/212/003 14 film-coated tablets
EU/I/02/212/004 20 film-coated tablets
EU/I/02/212/005 28 film-coated tablets
EU/I/02/212/006 30 film-coated tablets
EU/I/02/212/007 50 film-coated tablets
EU/I/02/212/008 56 film-coated tablets
EU/I/02/212/009 100 film-coated tablets
EU/I/02/212/028 2 film-coated tablets
EU/I/02/212/029 10 film-coated tablets
EU/I/02/212/030 14 film-coated tablets
EU/I/02/212/031 20 film-coated tablets
EU/I/02/212/032 28 film-coated tablets
EU/I/02/212/033 30 film-coated tablets
EU/I/02/212/034 50 film-coated tablets
EU/I/02/212/035 56 film-coated tablets
EU/I/02/212/036 100 film-coated tablets

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE**

16. INFORMATION IN BRAILLE

VFEND 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER –HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

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

1. NAME OF THE MEDICINAL PRODUCT

VFEND 50 mg film-coated tablets
voriconazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MA Holder logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Bottle outer pack and bottle label for 50 mg film-coated tablets – Pack of 2, 30, 100

1. NAME OF THE MEDICINAL PRODUCT

VFEND 50 mg film-coated tablets
voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 50 mg voriconazole.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

2 film-coated tablets
30 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/010 2 film-coated tablets
EU/I/02/212/011 30 film-coated tablets
EU/I/02/212/012 100 film-coated tablets

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

VFEND 50 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Blister pack for 200 mg film-coated tablets – Pack of 2, 10, 14, 20, 28, 30, 50, 56, 100

1. NAME OF THE MEDICINAL PRODUCT

VFEND 200 mg film-coated tablets
voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg voriconazole.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

2 film-coated tablets
10 film-coated tablets
14 film-coated tablets
20 film-coated tablets
28 film-coated tablets
30 film-coated tablets
50 film-coated tablets
56 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read enclosed leaflet before use.
Oral use

Sealed Pack
Do not use if box has been opened.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/013 2 film-coated tablets
EU/I/02/212/014 10 film-coated tablets
EU/I/02/212/015 14 film-coated tablets
EU/I/02/212/016 20 film-coated tablets
EU/I/02/212/017 28 film-coated tablets
EU/I/02/212/018 30 film-coated tablets
EU/I/02/212/019 50 film-coated tablets
EU/I/02/212/020 56 film-coated tablets
EU/I/02/212/021 100 film-coated tablets
EU/I/02/212/037 2 film-coated tablets
EU/I/02/212/038 10 film-coated tablets
EU/I/02/212/039 14 film-coated tablets
EU/I/02/212/040 20 film-coated tablets
EU/I/02/212/041 28 film-coated tablets
EU/I/02/212/042 30 film-coated tablets
EU/I/02/212/043 50 film-coated tablets
EU/I/02/212/044 56 film-coated tablets
EU/I/02/212/045 100 film-coated tablets

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE**

16. INFORMATION IN BRAILLE

VFEND 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:

SN:

NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

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

1. NAME OF THE MEDICINAL PRODUCT

VFEND 200 mg film-coated tablets
voriconazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MA Holder logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

Bottle outer pack and bottle label for 200 mg film-coated tablets – Pack of 2, 30, 100

1. NAME OF THE MEDICINAL PRODUCT

VFEND 200 mg film-coated tablets
voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg voriconazole.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

2 tablets
30 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read enclosed leaflet before use.
Oral use

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/022 2 film-coated tablets
EU/I/02/212/023 30 film-coated tablets
EU/I/02/212/024 100 film-coated tablets

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

VFEND 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

VFEND 200 mg powder for solution for infusion
voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 200 mg of voriconazole.
After reconstitution each ml contains 10 mg of voriconazole.

3. LIST OF EXCIPIENTS

Excipient: sulfobutylether beta cyclodextrin sodium. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Reconstitute and dilute before use.
Intravenous use only
Not for bolus injection

Single use vial
Infuse at a maximum rate of 3 mg/kg per hour.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

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

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/025

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

VFEND 200 mg powder and solvent for solution for infusion
voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Vial contains 200 mg of voriconazole.
After reconstitution each ml contains 10 mg of voriconazole.

3. LIST OF EXCIPIENTS

50 ml infusion bag containing 0.9% of sodium chloride.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for infusion
Each pack contains:
1 vial of VFEND powder for solution for infusion (single use vial)
1 overwrap
1 vial adaptor
1 syringe

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Please refer to Patient Information Leaflet for detailed instructions.
Reconstitute and dilute before use.
For intravenous use
Not for bolus injection
Not for use with other products

Infuse at a maximum rate of 3 mg/kg per hour.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

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

9. SPECIAL STORAGE CONDITIONS

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/212/027

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

Instructions for Use – please be guided by the pictograms to understand how to use this product.

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label on the vial

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

VFEND 200 mg powder for solution for infusion
voriconazole
Intravenous use

2. METHOD OF ADMINISTRATION

Reconstitute and dilute before use – see leaflet.
Infuse at a maximum rate of 3 mg/kg per hour.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

200 mg (10 mg/ml)

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label on the overwrap

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

Solvent for VFEND powder for solution for infusion
Sodium Chloride 0.9% in Water for Injections
Intravenous use

2. METHOD OF ADMINISTRATION

Not for bolus injection

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Batch

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

50 ml

6. OTHER

Keep out of the sight and reach of children.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Outer carton

1. NAME OF THE MEDICINAL PRODUCT

VFEND 40 mg/ml powder for oral suspension
voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of the constituted suspension contains 40 mg voriconazole.

3. LIST OF EXCIPIENTS

Also contains sucrose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral suspension
1 bottle of 45 g
A measuring cup (graduated to indicate 23 ml), 5 ml oral syringe and a press-in bottle adaptor

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

Constitution instructions:
Tap the bottle to release the powder.
Add 46 ml of water and shake vigorously for about 1 minute.

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Any remaining suspension should be discarded 14 days after constitution.

9. SPECIAL STORAGE CONDITIONS

Powder: store at in a refrigerator before constitution.

For the constituted oral suspension:

Do not store above 30°C.

Do not refrigerate or freeze.

Keep the container tightly closed.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Pfizer Europe MA EEIG

Boulevard de la Plaine 17

1050 Bruxelles

Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/212/026

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

VFEND 40 mg/ml

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:

SN:

NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

Bottle

1. NAME OF THE MEDICINAL PRODUCT

VFEND 40 mg/ml powder for oral suspension
voriconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of the constituted suspension contains 40 mg voriconazole.

3. LIST OF EXCIPIENTS

Also contains sucrose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral suspension
45 g

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Any remaining suspension should be discarded 14 days after constitution.
Expiry date of the constituted suspension:

9. SPECIAL STORAGE CONDITIONS

Powder: store at in a refrigerator before constitution.

For the constituted oral suspension:

Do not store above 30°C.

Do not refrigerate or freeze.

Keep the container tightly closed.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/I/02/212/026

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

B. PACKAGE LEAFLET

Package Leaflet: Information for the user

VFEND 50 mg film-coated tablets

VFEND 200 mg film-coated tablets

Voriconazole

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What VFEND is and what it is used for
2. What you need to know before you take VFEND
3. How to take VFEND
4. Possible side effects
5. How to store VFEND
6. Content of the pack and other information

1. What VFEND is and what it is used for

VFEND contains the active substance voriconazole. VFEND is an antifungal medicine. It works by killing or stopping the growth of the fungi that cause infections.

It is used for the treatment of patients (adults and children over the age of 2) with:

- invasive aspergillosis (a type of fungal infection due to *Aspergillus sp*),
- candidaemia (another type of fungal infection due to *Candida sp*) in non-neutropenic patients (patients without abnormally low white blood cells count),
- serious invasive *Candida sp.* infections when the fungus is resistant to fluconazole (another antifungal medicine),
- serious fungal infections caused by *Scedosporium sp.* or *Fusarium sp.* (two different species of fungi).

VFEND is intended for patients with worsening, possibly life-threatening, fungal infections.

Prevention of fungal infections in high risk bone marrow transplant recipients.

This product should only be taken under the supervision of a doctor.

2. What you need to know before you take VFEND

Do not take VFEND:

If you are allergic to voriconazole or any of the other ingredients of this medicine (listed in section 6).

It is very important that you inform your doctor or pharmacist if you are taking or have taken any other medicines, even those that are obtained without a prescription, or herbal medicines.

The medicines in the following list must not be taken during your course of VFEND treatment:

- Terfenadine (used for allergy)
- Astemizole (used for allergy)

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

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking VFEND if:

- you have had an allergic reaction to other azoles.
- you are suffering from, or have ever suffered from liver disease. If you have liver disease, your doctor may prescribe a lower dose of VFEND. Your doctor should also monitor your liver function while you are being treated with VFEND by doing blood tests.
- you are known to have cardiomyopathy, irregular heart beat, slow heart rate or an abnormality of electrocardiogram (ECG) called 'long QTc syndrome'.

You should avoid any sunlight and sun exposure while being treated. It is important to cover sun exposed areas of skin and use sunscreen with high sun protection factor (SPF), as an increased sensitivity of skin to the sun's UV rays can occur. These precautions are also applicable to children.

While being treated with VFEND:

- tell your doctor immediately if you develop
 - sunburn
 - severe skin rash or blisters
 - bone pain

If you develop skin disorders as described above, your doctor may refer you to a dermatologist, who after consultation may decide that it is important for you to be seen on a regular basis. There is a small chance that skin cancer could develop with long-term use of VFEND.

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

Children and adolescents

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

Other medicines and VFEND

Please tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including those that are obtained without a prescription.

Some medicines, when taken at the same time as VFEND, may affect the way VFEND works or VFEND may affect the way they work.

Tell your doctor if you are taking the following medicine, as treatment with VFEND at the same time should be avoided if possible:

- Ritonavir (used for treating HIV) in doses of 100 mg twice daily

Tell your doctor if you are taking either of the following medicines, as treatment with VFEND at the same time should be avoided if possible, and a dose adjustment of voriconazole may be required:

- Rifabutin (used for treating tuberculosis). If you are already being treated with rifabutin your blood

counts and side effects to rifabutin will need to be monitored.

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

Tell your doctor if you are taking any of the following medicines, as a dose adjustment or monitoring may be required to check that the medicines and/ or VFEND are still having the desired effect:

- Warfarin and other anticoagulants (e.g., phenprocoumon, acenocoumarol; used to slow down clotting of the blood)
- Ciclosporin (used in transplant patients)
- Tacrolimus (used in transplant patients)
- Sulfonylureas (e.g., tolbutamide, glipizide, and glyburide) (used for diabetes)
- Statins (e.g., atorvastatin, simvastatin) (used for lowering cholesterol)
- Benzodiazepines (e.g. midazolam, triazolam) (used for severe insomnia and stress)
- Omeprazole (used for treating ulcers)
- Oral contraceptives (if you take VFEND whilst using oral contraceptives, you may get side effects such as nausea and menstrual disorders)
- Vinca alkaloids (e.g., vincristine and vinblastine) (used in treating cancer)
- Indinavir and other HIV protease inhibitors (used for treating HIV)
- Non-nucleoside reverse transcriptase inhibitors (e.g., efavirenz, delavirdine, nevirapine) (used for treating HIV) (some doses of efavirenz can NOT be taken at the same time as VFEND)
- Methadone (used to treat heroin addiction)
- Alfentanil and fentanyl and other short-acting opiates such as sufentanil (painkillers used for surgical procedures)
- Oxycodone and other long-acting opiates such as hydrocodone (used for moderate to severe pain)
- Non-steroidal anti-inflammatory drugs (e.g., ibuprofen, diclofenac) (used for treating pain and inflammation)
- Fluconazole (used for fungal infections)
- Everolimus (used for treating advanced kidney cancer and in transplant patients)

Pregnancy and breast-feeding

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

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

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

VFEND contains lactose

If you have been told by your doctor that you have an intolerance to some sugars, tell your doctor before taking VFEND.

3. How to take VFEND

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

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

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

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

Depending on your response to treatment, your doctor may increase the daily dose to 300 mg twice a day.

The doctor may decide to decrease the dose if you have mild to moderate cirrhosis.

Use in children and adolescents

The recommended dose for children and teenagers is as follows:

	Tablets	
	Children aged 2 to less than 12 years and teenagers aged 12 to 14 years weighing less than 50 kg	Teenagers aged 12 to 14 years weighing 50 kg or more; and all teenagers older than 14
Dose for the first 24 hours (Loading Dose)	Your treatment will be started as an infusion	400 mg every 12 hours for the first 24 hours
Dose after the first 24 hours (Maintenance Dose)	9 mg/kg twice a day (a maximum dose of 350 mg twice daily)	200 mg twice a day

Depending on your response to treatment, your doctor may increase or decrease the daily dose.

- Tablets must only be given if the child is able to swallow tablets.

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

If you or your child are taking VFEND for prevention of fungal infections, your doctor may stop giving VFEND if you or your child develop treatment related side effects.

If you take more VFEND than you should

If you take more tablets than prescribed (or if someone else takes your tablets) you must seek medical advice or go to the nearest hospital casualty department immediately. Take your box of VFEND tablets with you. You may experience abnormal intolerance to light as a result of taking more VFEND than you should.

If you forget to take VFEND

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

If you stop taking VFEND

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

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

When VFEND treatment is stopped by your doctor you should not experience any effects.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If any side effects occur, most are likely to be minor and temporary. However, some may be serious and need medical attention.

Serious side effects – Stop taking VFEND and see a doctor immediately

- Rash
- Jaundice; Changes in blood tests of liver function
- Pancreatitis

Other side effects

Very common: may affect more than 1 in 10 people

- Visual impairment (change in vision including blurred vision, visual color alterations, abnormal intolerance to visual perception of light, colour blindness, eye disorder, halo vision, night blindness, swinging vision, seeing sparks, visual aura, visual acuity reduced, visual brightness, loss of part of the usual field of vision, spots before the eyes)
- Fever
- Rash
- Nausea, vomiting, diarrhoea
- Headache
- Swelling of the extremities
- Stomach pains
- Breathing difficulties
- Elevated liver enzymes

Common: may affect up to 1 in 10 people

- Inflammation of the sinuses, inflammation of the gums, chills, weakness
- Low numbers of some types, including severe, of red (sometimes immune-related) and/or white blood cells (sometimes with fever), low numbers of cells called platelets that help the blood to clot
- Low blood sugar, low blood potassium, low sodium in the blood
- Anxiety, depression, confusion, agitation, inability to sleep, hallucinations
- Seizures, tremors or uncontrolled muscle movements, tingling or abnormal skin sensations, increase in muscle tone, sleepiness, dizziness
- Bleeding in the eye
- Heart rhythm problems including very fast heartbeat, very slow heartbeat, fainting
- Low blood pressure, inflammation of a vein (which may be associated with the formation of a blood clot)
- Acute breathing difficulty, chest pain, swelling of the face (mouth, lips and around eyes), fluid accumulation in the lungs
- Constipation, indigestion, inflammation of the lips
- Jaundice, inflammation of the liver and liver injury
- Skin rashes which may lead to severe blistering and peeling of the skin characterized by a flat, red area on the skin that is covered with small confluent bumps, redness of the skin

- Itchiness
- Hair loss
- Back pain
- Kidney failure, blood in the urine, changes in kidney function tests

Uncommon: may affect up to 1 in 100 people

- Flu-like symptoms, irritation and inflammation of the gastrointestinal tract, inflammation of the gastrointestinal tract causing antibiotic associated diarrhoea, inflammation of the lymphatic vessels
- Inflammation of the thin tissue that lines the inner wall of the abdomen and covers the abdominal organ
- Enlarged lymph glands (sometimes painful), failure of blood marrow, increased eosinophil
- Depressed function of the adrenal gland, underactive thyroid gland
- Abnormal brain function, Parkinson-like symptoms, nerve injury resulting in numbness, pain, tingling or burning in the hands or feet
- Problems with balance or coordination
- Swelling of the brain
- Double vision, serious conditions of the eye including: pain and inflammation of the eyes and eyelids, abnormal eye movement, damage to the optic nerve resulting in vision impairment, optic disc swelling
- Decreased sensitivity to touch
- Abnormal sense of taste
- Hearing difficulties, ringing in the ears, vertigo
- Inflammation of certain internal organs- pancreas and duodenum, swelling and inflammation of the tongue
- Enlarged liver, liver failure, gallbladder disease, gallstones
- Joint inflammation, inflammation of the veins under the skin (which may be associated with the formation of a blood clot)
- Inflammation of the kidney, proteins in the urine, damage to the kidney
- Very fast heart rate or skipped heartbeats, sometimes with erratic electrical impulses
- Abnormal electrocardiogram (ECG)
- Blood cholesterol increased, blood urea increased
- Allergic skin reactions (sometimes severe), including life-threatening skin condition that causes painful blisters and sores of the skin and mucous membranes, especially in the mouth, inflammation of the skin, hives, sunburn or severe skin reaction following exposure to light or sun, skin redness and irritation, red or purple discoloration of the skin which may be caused by low platelet count, eczema
- Infusion site reaction
- Allergic reaction or exaggerated immune response

Rare: may affect up to 1 in 1000 people

- Overactive thyroid gland
- Deterioration of brain function that is a serious complication of liver disease
- Loss of most fibers in the optic nerve, clouding of the cornea, involuntary movement of the eye
- Bullous photosensitivity
- A disorder in which the body's immune system attacks part of the peripheral nervous system
- Heart rhythm or conduction problems (sometimes life threatening)
- Life threatening allergic reaction
- Disorder of blood clotting system
- Allergic skin reactions (sometimes severe), including rapid swelling (oedema) of the dermis, subcutaneous tissue, mucosa and submucosal tissues, itchy or sore patches of thick, red skin with silvery scales of skin, irritation of the skin and mucous membranes, life-threatening skin condition that causes large portions of the epidermis, the skin's outermost layer, to detach from the layers of skin below
- Small dry scaly skin patches, sometimes thick with spikes or 'horns'

Side effects with frequency not known:

- Freckles and pigmented spots

Other significant side effects whose frequency is not known, but should be reported to your doctor immediately:

- Skin cancer
- Inflammation of the tissue surrounding the bone
- Red, scaly patches or ring-shaped skin lesions that may be a symptom of an autoimmune disease called cutaneous lupus erythematosus

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

There have been reports of skin cancer in patients treated with VFEND for long periods of time.

Sunburn or severe skin reaction following exposure to light or sun was experienced more frequently in children. If you or your child develops skin disorders, your doctor may refer you to a dermatologist, who after consultation may decide that it is important for you or your child to be seen on a regular basis. Elevated liver enzymes were also observed more frequently in children.

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

Reporting of side effects

If you get any side effects, talk to your doctor or, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store VFEND

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What VFEND contains

- The active substance is voriconazole. Each tablet contains either 50 mg voriconazole (for VFEND 50 mg film-coated tablets) or 200 mg voriconazole (for VFEND 200 mg film-coated tablets).
- The other ingredients are lactose monohydrate, pregelatinised starch, croscarmellose sodium, povidone and magnesium stearate which make up the tablet core and hypromellose, titanium dioxide (E171), lactose monohydrate and glycerol triacetate which make up the film-coat.

What VFEND looks like and contents of the pack

VFEND 50 mg film-coated tablets are supplied as white to off-white round film-coated tablets with Pfizer marked on one side and VOR50 on the reverse.

VFEND 200 mg film-coated tablets are supplied as white to off-white capsule shaped film-coated tablets with Pfizer marked on one side and VOR200 on the reverse.

VFEND 50 mg film-coated tablets and 200 mg film-coated tablets are available as packs of 2, 10, 14, 20, 28, 30, 50, 56 and 100.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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This leaflet was last approved in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>

Package Leaflet: Information for the user

VFEND 200 mg powder for solution for infusion Voriconazole

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What VFEND is and what it is used for
2. What you need to know before you take VFEND
3. How to use VFEND
4. Possible side effects
5. How to store VFEND
6. Content of the pack and other information

1. What VFEND is and what it is used for

VFEND contains the active substance voriconazole. VFEND is an antifungal medicine. It works by killing or stopping the growth of the fungi that cause infections.

It is used for the treatment of patients (adults and children over the age of 2) with:

- invasive aspergillosis (a type of fungal infection due to *Aspergillus sp.*),
- candidaemia (another type of fungal infection due to *Candida sp.*) in non-neutropenic patients (patients without abnormally low white blood cells count),
- serious invasive *Candida sp.* infections when the fungus is resistant to fluconazole (another antifungal medicine),
- serious fungal infections caused by *Scedosporium sp.* or *Fusarium sp.* (two different species of fungi).

VFEND is intended for patients with worsening, possibly life-threatening, fungal infections.

Prevention of fungal infections in high risk bone marrow transplant recipients.

This product should only be used under the supervision of a doctor.

2. What you need to know before you take VFEND

Do not take VFEND:

- If you are allergic to the active ingredient voriconazole, or to sulfobutylether beta cyclodextrin sodium (listed in section 6).

It is very important that you inform your doctor or pharmacist if you are taking or have taken any other medicines, even those that are obtained without a prescription, or herbal medicines.

The medicines in the following list must not be taken during your course of VFEND treatment:

- Terfenadine (used for allergy)
- Astemizole (used for allergy)

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

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking VFEND if:

- you have had an allergic reaction to other azoles.
- you are suffering from, or have ever suffered from liver disease. If you have liver disease, your doctor may prescribe a lower dose of VFEND. Your doctor should also monitor your liver function while you are being treated with VFEND by doing blood tests.
- you are known to have cardiomyopathy, irregular heart beat, slow heart rate or an abnormality of electrocardiogram (ECG) called 'long QTc syndrome'.

You should avoid any sunlight and sun exposure while being treated. It is important to cover sun exposed areas of skin and use sunscreen with high sun protection factor (SPF), as an increased sensitivity of skin to the sun's UV rays can occur. These precautions are also applicable to children.

While being treated with VFEND:

- tell your doctor immediately if you develop
 - sunburn
 - severe skin rash or blisters
 - bone pain

If you develop skin disorders as described above, your doctor may refer you to a dermatologist, who after consultation may decide that it is important for you to be seen on a regular basis. There is a small chance that skin cancer could develop with long-term use of VFEND.

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

Children and adolescents

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

Other medicines and VFEND

Please tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including those that are obtained without a prescription.

Some medicines, when taken at the same time as VFEND, may affect the way VFEND works or VFEND may affect the way they work.

Tell your doctor if you are taking the following medicine, as treatment with VFEND at the same time should be avoided if possible:

- Ritonavir (used for treating HIV) in doses of 100 mg twice daily

Tell your doctor if you are taking either of the following medicines, as treatment with VFEND at the same time should be avoided if possible, and a dose adjustment of voriconazole may be required:

- Rifabutin (used for treating tuberculosis). If you are already being treated with rifabutin your blood

counts and side effects to rifabutin will need to be monitored.

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

Tell your doctor if you are taking any of the following medicines, as a dose adjustment or monitoring may be required to check that the medicines and/ or VFEND are still having the desired effect:

- Warfarin and other anticoagulants (e.g., phenprocoumon, acenocoumarol; used to slow down clotting of the blood)
- Ciclosporin (used in transplant patients)
- Tacrolimus (used in transplant patients)
- Sulfonylureas (e.g., tolbutamide, glipizide, and glyburide) (used for diabetes)
- Statins (e.g., atorvastatin, simvastatin) (used for lowering cholesterol)
- Benzodiazepines (e.g. midazolam, triazolam) (used for severe insomnia and stress)
- Omeprazole (used for treating ulcers)
- Oral contraceptives (if you take VFEND whilst using oral contraceptives, you may get side effects such as nausea and menstrual disorders)
- Vinca alkaloids (e.g., vincristine and vinblastine) (used in treating cancer)
- Indinavir and other HIV protease inhibitors (used for treating HIV)
- Non-nucleoside reverse transcriptase inhibitors (e.g., efavirenz, delavirdine, nevirapine) (used for treating HIV) (some doses of efavirenz can NOT be taken at the same time as VFEND)
- Methadone (used to treat heroin addiction)
- Alfentanil and fentanyl and other short-acting opiates such as sufentanil (painkillers used for surgical procedures)
- Oxycodone and other long-acting opiates such as hydrocodone (used for moderate to severe pain)
- Non-steroidal anti-inflammatory drugs (e.g., ibuprofen, diclofenac) (used for treating pain and inflammation)
- Fluconazole (used for fungal infections)
- Everolimus (used for treating advanced kidney cancer and in transplant patients)

Pregnancy and breast-feeding

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

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

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

VFEND contains sodium

Each vial of VFEND contains 217.6 mg of sodium per vial. This should be taken into consideration if you are on a strictly controlled sodium diet.

3. How to use VFEND

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

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

Your doctor may change your dose depending on your condition.

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

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

Depending on your response to treatment, your doctor may decrease the dose to 3 mg/kg twice daily.

The doctor may decide to decrease the dose if you have mild to moderate cirrhosis.

Use in children and adolescents

The recommended dose for children and teenagers is as follows:

	Intravenous	
	Children aged 2 to less than 12 years and teenagers aged 12 to 14 years weighing less than 50 kg	Teenagers aged 12 to 14 years weighing 50 kg or more; and all teenagers older than 14
Dose for the first 24 hours (Loading Dose)	9 mg/kg every 12 hours for the first 24 hours	6 mg/kg every 12 hours for the first 24 hours
Dose after the first 24 hours (Maintenance Dose)	8 mg/kg twice a day	4 mg/kg twice a day

Depending on your response to treatment, your doctor may increase or decrease the daily dose.

VFEND powder for solution for infusion will be reconstituted and diluted to the correct concentration by your hospital pharmacist or nurse. (Please refer to the end of this leaflet for further information)

This will be given to you by intravenous infusion (into a vein) at a maximum rate of 3 mg/kg per hour over 1 to 3 hours.

If you or your child are taking VFEND for prevention of fungal infections, your doctor may stop giving VFEND if you or your child develop treatment related side effects.

If a dose of VFEND has been forgotten

As you will be given this medicine under close medical supervision, it is unlikely that a dose would be missed. However tell your doctor or pharmacist if you think that a dose has been forgotten.

If you stop taking VFEND

VFEND treatment will continue for as long as your doctor advises, however duration of treatment with VFEND powder for solution for infusion should be no more than 6 months.

Patients with a weakened immune system or those with difficult infections may require long-term treatment to prevent the infection from returning. You may be switched from the intravenous infusion to tablets once your condition improves.

When VFEND treatment is stopped by your doctor you should not experience any effects.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If any side effects occur, most are likely to be minor and temporary. However, some may be serious and need medical attention.

Serious side effects – Stop taking VFEND and see a doctor immediately

- Rash
- Jaundice; Changes in blood tests of liver function
- Pancreatitis

Other side effects

Very common: may affect more than 1 in 10 people

- Visual impairment (change in vision including blurred vision, visual color alterations, abnormal intolerance to visual perception of light, colour blindness, eye disorder, halo vision, night blindness, swinging vision, seeing sparks, visual aura, visual acuity reduced, visual brightness, loss of part of the usual field of vision, spots before the eyes)
- Fever
- Rash
- Nausea, vomiting, diarrhoea
- Headache
- Swelling of the extremities
- Stomach pains
- Breathing difficulties
- Elevated liver enzymes

Common: may affect up to 1 in 10 people

- Inflammation of the sinuses, inflammation of the gums, chills, weakness
- Low numbers of some types, including severe, of red (sometimes immune-related) and/or white blood cells (sometimes with fever), low numbers of cells called platelets that help the blood to clot
- Low blood sugar, low blood potassium, low sodium in the blood
- Anxiety, depression, confusion, agitation, inability to sleep, hallucinations
- Seizures, tremors or uncontrolled muscle movements, tingling or abnormal skin sensations, increase in muscle tone, sleepiness, dizziness
- Bleeding in the eye
- Heart rhythm problems including very fast heartbeat, very slow heartbeat, fainting
- Low blood pressure, inflammation of a vein (which may be associated with the formation of a blood clot)
- Acute breathing difficulty, chest pain, swelling of the face (mouth, lips and around eyes), fluid accumulation in the lungs
- Constipation, indigestion, inflammation of the lips
- Jaundice, inflammation of the liver and liver injury
- Skin rashes which may lead to severe blistering and peeling of the skin characterized by a flat, red area on the skin that is covered with small confluent bumps, redness of the skin
- Itchiness
- Hair loss
- Back pain
- Kidney failure, blood in the urine, changes in kidney function tests

Uncommon: may affect up to 1 in 100 people

- Flu-like symptoms, irritation and inflammation of the gastrointestinal tract, inflammation of the gastrointestinal tract causing antibiotic associated diarrhoea, inflammation of the lymphatic vessels
- Inflammation of the thin tissue that lines the inner wall of the abdomen and covers the abdominal organ
- Enlarged lymph glands (sometimes painful), failure of blood marrow, increased eosinophil
- Depressed function of the adrenal gland, underactive thyroid gland
- Abnormal brain function, Parkinson-like symptoms, nerve injury resulting in numbness, pain, tingling or burning in the hands or feet
- Problems with balance or coordination
- Swelling of the brain
- Double vision, serious conditions of the eye including: pain and inflammation of the eyes and eyelids, abnormal eye movement, damage to the optic nerve resulting in vision impairment, optic disc swelling
- Decreased sensitivity to touch
- Abnormal sense of taste
- Hearing difficulties, ringing in the ears, vertigo
- Inflammation of certain internal organs- pancreas and duodenum, swelling and inflammation of the tongue
- Enlarged liver, liver failure, gallbladder disease, gallstones
- Joint inflammation, inflammation of the veins under the skin (which may be associated with the formation of a blood clot)
- Inflammation of the kidney, proteins in the urine, damage to the kidney
- Very fast heart rate or skipped heartbeats, sometimes with erratic electrical impulses
- Abnormal electrocardiogram (ECG)
- Blood cholesterol increased, blood urea increased
- Allergic skin reactions (sometimes severe), including life-threatening skin condition that causes painful blisters and sores of the skin and mucous membranes, especially in the mouth, inflammation of the skin, hives, sunburn or severe skin reaction following exposure to light or sun, skin redness and irritation, red or purple discoloration of the skin which may be caused by low platelet count, eczema
- Infusion site reaction
- Allergic reaction or exaggerated immune response

Rare: may affect up to 1 in 1000 people

- Overactive thyroid gland
- Deterioration of brain function that is a serious complication of liver disease
- Loss of most fibers in the optic nerve, clouding of the cornea, involuntary movement of the eye
- Bullous photosensitivity
- A disorder in which the body's immune system attacks part of the peripheral nervous system
- Heart rhythm or conduction problems (sometimes life threatening)
- Life threatening allergic reaction
- Disorder of blood clotting system
- Allergic skin reactions (sometimes severe), including rapid swelling (oedema) of the dermis, subcutaneous tissue, mucosa and submucosal tissues, itchy or sore patches of thick, red skin with silvery scales of skin, irritation of the skin and mucous membranes, life-threatening skin condition that causes large portions of the epidermis, the skin's outermost layer, to detach from the layers of skin below
- Small dry scaly skin patches, sometimes thick with spikes or 'horns'

Side effects with frequency not known:

- Freckles and pigmented spots

Other significant side effects whose frequency is not known, but should be reported to your doctor immediately:

- Skin cancer

- Inflammation of the tissue surrounding the bone
- Red, scaly patches or ring-shaped skin lesions that may be a symptom of an autoimmune disease called cutaneous lupus erythematosus

Reactions during the infusion have occurred uncommonly with VFEND (including flushing, fever, sweating, increased heart rate and shortness of breath). Your doctor may stop the infusion if this occurs.

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

There have been reports of skin cancer in patients treated with VFEND for long periods of time.

Sunburn or severe skin reaction following exposure to light or sun was experienced more frequently in children. If you or your child develops skin disorders, your doctor may refer you to a dermatologist, who after consultation may decide that it is important for you or your child to be seen on a regular basis. Elevated liver enzymes were also observed more frequently in children.

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

Reporting of side effects

If you get any side effects, talk to your doctor or, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store VFEND

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

Once reconstituted, VFEND should be used immediately, but if necessary may be stored for up to 24 hours at 2°C - 8°C (in a refrigerator). Reconstituted VFEND needs to be diluted with a compatible infusion solution first before it is infused. (Please refer to the end of this leaflet for further information).

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer required. These measures will help protect the environment.

6. Contents of the pack and other information

What VFEND contains

-The active substance is voriconazole.

-The other ingredient is sulfobutylether beta cyclodextrin sodium.

Each vial contains 200 mg voriconazole, equivalent to a 10 mg/ml solution when reconstituted as directed by your hospital pharmacist or nurse (see the information at the end of this leaflet).

What VFEND looks like and contents of the pack

VFEND is presented in single use glass vials as a powder for solution for infusion.

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This leaflet was last approved in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site:

<http://www.ema.europa.eu>

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The following information is intended for medical or healthcare professionals only:

Reconstitution and Dilution information

- VFEND powder for solution for infusion needs to first be reconstituted with either 19 ml of Water for Injections or 19 ml of 9 mg/ml (0.9%) Sodium Chloride for Infusion to obtain an extractable volume of 20 ml of clear concentrate containing 10 mg/ml voriconazole.
- Discard the VFEND vial if the vacuum does not pull the diluent into the vial.
- It is recommended that a standard 20 ml (non-automated) syringe be used to ensure that the exact amount (19.0 ml) of Water for Injections or of 9 mg/ml (0.9%) Sodium Chloride for Infusion is dispensed.
- The required volume of the reconstituted concentrate is then added to a recommended compatible infusion solution listed below to obtain a final VFEND solution containing 0.5 to 5 mg/ml of voriconazole.
- This medicinal product is for single use only and any unused solution should be discarded and only clear solutions without particles should be used.
- Not for administration as a bolus injection.
- For storage information, please refer to Section 5 'How to store VFEND'.

Required Volumes of 10 mg/ml VFEND Concentrate

Body Weight (kg)	Volume of VFEND Concentrate (10 mg/ml) required for:				
	3 mg/kg dose (number of vials)	4 mg/kg dose (number of vials)	6 mg/kg dose (number of vials)	8 mg/kg dose (number of vials)	9 mg/kg dose (number of vials)
10	-	4.0 ml (1)	-	8.0 ml (1)	9.0 ml (1)
15	-	6.0 ml (1)	-	12.0 ml (1)	13.5 ml (1)
20	-	8.0 ml (1)	-	16.0 ml (1)	18.0 ml (1)
25	-	10.0 ml (1)	-	20.0 ml (1)	22.5 ml (2)
30	9.0 ml (1)	12.0 ml (1)	18.0 ml (1)	24.0 ml (2)	27.0 ml (2)
35	10.5 ml (1)	14.0 ml (1)	21.0 ml (2)	28.0 ml (2)	31.5 ml (2)
40	12.0 ml (1)	16.0 ml (1)	24.0 ml (2)	32.0 ml (2)	36.0 ml (2)
45	13.5 ml (1)	18.0 ml (1)	27.0 ml (2)	36.0 ml (2)	40.5 ml (3)
50	15.0 ml (1)	20.0 ml (1)	30.0 ml (2)	40.0 ml (2)	45.0 ml (3)
55	16.5 ml (1)	22.0 ml (2)	33.0 ml (2)	44.0 ml (3)	49.5 ml (3)
60	18.0 ml (1)	24.0 ml (2)	36.0 ml (2)	48.0 ml (3)	54.0 ml (3)
65	19.5 ml (1)	26.0 ml (2)	39.0 ml (2)	52.0 ml (3)	58.5 ml (3)
70	21.0 ml (2)	28.0 ml (2)	42.0 ml (3)	-	-
75	22.5 ml (2)	30.0 ml (2)	45.0 ml (3)	-	-

80	24.0 ml (2)	32.0 ml (2)	48.0 ml (3)	-	-
85	25.5 ml (2)	34.0 ml (2)	51.0 ml (3)	-	-
90	27.0 ml (2)	36.0 ml (2)	54.0 ml (3)	-	-
95	28.5 ml (2)	38.0 ml (2)	57.0 ml (3)	-	-
100	30.0 ml (2)	40.0 ml (2)	60.0 ml (3)	-	-

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

Compatible Infusion Solutions:

The reconstituted solution can be diluted with:

- Sodium Chloride 9 mg/ml (0.9%) Solution for Injection
- Compound Sodium Lactate Intravenous Infusion
- 5% Glucose and Lactated Ringer’s Intravenous Infusion
- 5% Glucose and 0.45% Sodium Chloride Intravenous Infusion
- 5% Glucose Intravenous Infusion
- 5% Glucose in 20 mEq Potassium Chloride Intravenous Infusion
- 0.45% Sodium Chloride Intravenous Infusion
- 5% Glucose and 0.9% Sodium Chloride Intravenous Infusion

The compatibility of VFEND with diluents other than listed above (or listed below under ‘Incompatibilities’) is unknown.

Incompatibilities:

VFEND must not be infused into the same line or cannula concomitantly with other drug infusions, including parenteral nutrition (e.g., Aminofusin 10% Plus).

Infusions of blood products must not occur simultaneously with VFEND.

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

VFEND must not be diluted with 4.2% Sodium Bicarbonate Infusion.

Package Leaflet: Information for the user

VFEND 200 mg powder and solvent for solution for infusion Voriconazole

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What VFEND is and what it is used for
2. What you need to know before you take VFEND
3. How to use VFEND
4. Possible side effects
5. How to store VFEND
6. Content of the pack and other information

1. What VFEND is and what it is used for

VFEND contains the active substance voriconazole. VFEND is an antifungal medicine. It works by killing or stopping the growth of the fungi that cause infections.

It is used for the treatment of patients (adults and children over the age of 2) with:

- invasive aspergillosis (a type of fungal infection due to *Aspergillus sp*),
- candidaemia (another type of fungal infection due to *Candida sp*) in non-neutropenic patients (patients without abnormally low white blood cells count),
- serious invasive *Candida sp.* infections when the fungus is resistant to fluconazole (another antifungal medicine),
- serious fungal infections caused by *Scedosporium sp.* or *Fusarium sp.* (two different species of fungi).

VFEND is intended for patients with worsening, possibly life-threatening, fungal infections.

Prevention of fungal infections in high risk bone marrow transplant recipients.

This product should only be used under the supervision of a doctor.

2. What you need to know before you take VFEND

Do not take VFEND:

- If you are allergic to the active ingredient voriconazole, or to sulfobutylether beta cyclodextrin sodium (listed in section 6).

It is very important that you inform your doctor or pharmacist if you are taking or have taken any other medicines, even those that are obtained without a prescription, or herbal medicines.

The medicines in the following list must not be taken during your VFEND treatment:

- Terfenadine (used for allergy)
- Astemizole (used for allergy)

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

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking VFEND if:

- you have had an allergic reaction to other azoles.
- you are suffering from, or have ever suffered from liver disease. If you have liver disease, your doctor may prescribe a lower dose of VFEND. Your doctor should also monitor your liver function while you are being treated with VFEND by doing blood tests.
- you are known to have cardiomyopathy, irregular heart beat, slow heart rate or an abnormality of electrocardiogram (ECG) called 'long QTc syndrome'.

You should avoid any sunlight and sun exposure while being treated. It is important to cover sun exposed areas of skin and use sunscreen with high sun protection factor (SPF), as an increased sensitivity of skin to the sun's UV rays can occur. These precautions are also applicable to children.

While being treated with VFEND:

- tell your doctor immediately if you develop
 - sunburn
 - severe skin rash or blisters
 - bone pain

If you develop skin disorders as described above, your doctor may refer you to a dermatologist, who after consultation may decide that it is important for you to be seen on a regular basis. There is a small chance that skin cancer could develop with long-term use of VFEND.

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

Children and adolescents

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

Other medicines and VFEND

Please tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including those that are obtained without a prescription.

- Some medicines, when taken at the same time as VFEND, may affect the way VFEND works or VFEND may affect the way they work.

Tell your doctor if you are taking the following medicine, as treatment with VFEND at the same time should be avoided if possible:

- Ritonavir (used for treating HIV) in doses of 100 mg twice daily

Tell your doctor if you are taking either of the following medicines, as treatment with VFEND at the same time should be avoided if possible, and a dose adjustment of voriconazole may be required:

- Rifabutin (used for treating tuberculosis). If you are already being treated with rifabutin your blood

counts and side effects to rifabutin will need to be monitored.

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

Tell your doctor if you are taking any of the following medicines, as a dose adjustment or monitoring may be required to check that the medicines and/ or VFEND are still having the desired effect:

- Warfarin and other anticoagulants (e.g., phenprocoumon, acenocoumarol; used to slow down clotting of the blood)
- Ciclosporin (used in transplant patients)
- Tacrolimus (used in transplant patients)
- Sulfonylureas (e.g., tolbutamide, glipizide, and glyburide) (used for diabetes)
- Statins (e.g., atorvastatin, simvastatin) (used for lowering cholesterol)
- Benzodiazepines (e.g. midazolam, triazolam) (used for severe insomnia and stress)
- Omeprazole (used for treating ulcers)
- Oral contraceptives (if you take VFEND whilst using oral contraceptives, you may get side effects such as nausea and menstrual disorders)
- Vinca alkaloids (e.g., vincristine and vinblastine) (used in treating cancer)
- Indinavir and other HIV protease inhibitors (used for treating HIV)
- Non-nucleoside reverse transcriptase inhibitors (e.g., efavirenz, delavirdine, nevirapine) (used for treating HIV) (some doses of efavirenz can NOT be taken at the same time as VFEND)
- Methadone (used to treat heroin addiction)
- Alfentanil and fentanyl and other short-acting opiates such as sufentanil (painkillers used for surgical procedures)
- Oxycodone and other long-acting opiates such as hydrocodone (used for moderate to severe pain)
- Non-steroidal anti-inflammatory drugs (e.g., ibuprofen, diclofenac) (used for treating pain and inflammation)
- Fluconazole (used for fungal infections)
- Everolimus (used for treating advanced kidney cancer and in transplant patients)

Pregnancy and breast-feeding

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

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

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

VFEND contains sodium

Each vial of VFEND contains 217.6 mg of sodium per vial. This should be taken into consideration if you are on a strictly controlled sodium diet.

3. How to use VFEND

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

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

Your doctor may change your dose depending on your condition.

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

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

Depending on your response to treatment, your doctor may decrease the dose to 3 mg/kg twice daily.

The doctor may decide to decrease the dose if you have mild to moderate cirrhosis.

Use in children and adolescents

The recommended dose for children and teenagers is as follows:

	Intravenous	
	Children aged 2 to less than 12 years and teenagers aged 12 to 14 years weighing less than 50 kg	Teenagers aged 12 to 14 years weighing 50 kg or more; and all teenagers older than 14
Dose for the first 24 hours (Loading Dose)	9 mg/kg every 12 hours for the first 24 hours	6 mg/kg every 12 hours for the first 24 hours
Dose after the first 24 hours (Maintenance Dose)	8 mg/kg twice a day	4 mg/kg twice a day

Depending on your response to treatment, your doctor may increase or decrease the daily dose.

VFEND powder and solvent for solution for infusion will be reconstituted and diluted to the correct concentration by your hospital pharmacist or nurse. (Please refer to the end of this leaflet for further information)

This will be given to you by intravenous infusion (into a vein) at a maximum rate of 3 mg/kg per hour over 1 to 3 hours.

If you or your child are taking VFEND for prevention of fungal infections, your doctor may stop giving VFEND if you or your child develop treatment related side effects.

If a dose of VFEND has been forgotten

As you will be given this medicine under close medical supervision, it is unlikely that a dose would be missed. However tell your doctor or pharmacist if you think that a dose has been forgotten.

If you stop taking VFEND

VFEND treatment will continue for as long as your doctor advises, however duration of treatment with VFEND powder for solution for infusion should be no more than 6 months.

Patients with a weakened immune system or those with difficult infections may require long-term treatment to prevent the infection from returning. You may be switched from the intravenous infusion to tablets once your condition improves.

When VFEND treatment is stopped by your doctor you should not experience any effects.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If any side effects occur, most are likely to be minor and temporary. However, some may be serious and need medical attention.

Serious side effects – Stop taking VFEND and see a doctor immediately

- Rash
- Jaundice; Changes in blood tests of liver function
- Pancreatitis

Other side effects

Very common: may affect more than 1 in 10 people

- Visual impairment (change in vision including blurred vision, visual color alterations, abnormal intolerance to visual perception of light, colour blindness, eye disorder, halo vision, night blindness, swinging vision, seeing sparks, visual aura, visual acuity reduced, visual brightness, loss of part of the usual field of vision, spots before the eyes)
- Fever
- Rash
- Nausea, vomiting, diarrhoea
- Headache
- Swelling of the extremities
- Stomach pains
- Breathing difficulties
- Elevated liver enzymes

Common: may affect up to 1 in 10 people

- Inflammation of the sinuses, inflammation of the gums, chills, weakness
- Low numbers of some types, including severe, of red (sometimes immune-related) and/or white blood cells (sometimes with fever), low numbers of cells called platelets that help the blood to clot
- Low blood sugar, low blood potassium, low sodium in the blood
- Anxiety, depression, confusion, agitation, inability to sleep, hallucinations
- Seizures, tremors or uncontrolled muscle movements, tingling or abnormal skin sensations, increase in muscle tone, sleepiness, dizziness
- Bleeding in the eye
- Heart rhythm problems including very fast heartbeat, very slow heartbeat, fainting
- Low blood pressure, inflammation of a vein (which may be associated with the formation of a blood clot)
- Acute breathing difficulty, chest pain, swelling of the face (mouth, lips and around eyes), fluid accumulation in the lungs
- Constipation, indigestion, inflammation of the lips
- Jaundice, inflammation of the liver and liver injury
- Skin rashes which may lead to severe blistering and peeling of the skin characterized by a flat, red area on the skin that is covered with small confluent bumps, redness of the skin
- Itchiness
- Hair loss
- Back pain
- Kidney failure, blood in the urine, changes in kidney function tests

Uncommon: may affect up to 1 in 100 people

- Flu-like symptoms, irritation and inflammation of the gastrointestinal tract, inflammation of the gastrointestinal tract causing antibiotic associated diarrhoea, inflammation of the lymphatic vessels
- Inflammation of the thin tissue that lines the inner wall of the abdomen and covers the abdominal organ
- Enlarged lymph glands (sometimes painful), failure of blood marrow, increased eosinophil
- Depressed function of the adrenal gland, underactive thyroid gland
- Abnormal brain function, Parkinson-like symptoms, nerve injury resulting in numbness, pain, tingling or burning in the hands or feet
- Problems with balance or coordination
- Swelling of the brain
- Double vision, serious conditions of the eye including: pain and inflammation of the eyes and eyelids, abnormal eye movement, damage to the optic nerve resulting in vision impairment, optic disc swelling
- Decreased sensitivity to touch
- Abnormal sense of taste
- Hearing difficulties, ringing in the ears, vertigo
- Inflammation of certain internal organs- pancreas and duodenum, swelling and inflammation of the tongue
- Enlarged liver, liver failure, gallbladder disease, gallstones
- Joint inflammation, inflammation of the veins under the skin (which may be associated with the formation of a blood clot)
- Inflammation of the kidney, proteins in the urine, damage to the kidney
- Very fast heart rate or skipped heartbeats, sometimes with erratic electrical impulses
- Abnormal electrocardiogram (ECG)
- Blood cholesterol increased, blood urea increased
- Allergic skin reactions (sometimes severe), including life-threatening skin condition that causes painful blisters and sores of the skin and mucous membranes, especially in the mouth, inflammation of the skin, hives, sunburn or severe skin reaction following exposure to light or sun, skin redness and irritation, red or purple discoloration of the skin which may be caused by low platelet count, eczema
- Infusion site reaction
- Allergic reaction or exaggerated immune response

Rare: may affect up to 1 in 1000 people

- Overactive thyroid gland
- Deterioration of brain function that is a serious complication of liver disease
- Loss of most fibers in the optic nerve, clouding of the cornea, involuntary movement of the eye
- Bullous photosensitivity
- A disorder in which the body's immune system attacks part of the peripheral nervous system
- Heart rhythm or conduction problems (sometimes life threatening)
- Life threatening allergic reaction
- Disorder of blood clotting system
- Allergic skin reactions (sometimes severe), including rapid swelling (oedema) of the dermis, subcutaneous tissue, mucosa and submucosal tissues, itchy or sore patches of thick, red skin with silvery scales of skin, irritation of the skin and mucous membranes, life-threatening skin condition that causes large portions of the epidermis, the skin's outermost layer, to detach from the layers of skin below
- Small dry scaly skin patches, sometimes thick with spikes or 'horns'

Side effects with frequency not known:

- Freckles and pigmented spots

Other significant side effects whose frequency is not known, but should be reported to your doctor immediately:

- Skin cancer
- Inflammation of the tissue surrounding the bone
- Red, scaly patches or ring-shaped skin lesions that may be a symptom of an autoimmune disease called cutaneous lupus erythematosus

Reactions during the infusion have occurred uncommonly with VFEND (including flushing, fever, sweating, increased heart rate and shortness of breath). Your doctor may stop the infusion if this occurs.

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

There have been reports of skin cancer in patients treated with VFEND for long periods of time.

Sunburn or severe skin reaction following exposure to light or sun was experienced more frequently in children. If you or your child develops skin disorders, your doctor may refer you to a dermatologist, who after consultation may decide that it is important for you or your child to be seen on a regular basis. Elevated liver enzymes were also observed more frequently in children.

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

Reporting of side effects

If you get any side effects, talk to your doctor or, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store VFEND

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

Once the powder in the vial has been reconstituted, VFEND should be used immediately, but if necessary may be stored for up to 24 hours at 2°C - 8°C (in a refrigerator) with the infusion bag. Reconstituted VFEND concentrate needs to be further diluted with sodium chloride (0.9%) infusion solution within the infusion bag before it is infused. The bag containing the reconstituted and diluted VFEND should be used immediately, but if necessary may be stored for up to a total of 24 hours at 2°C - 8°C (in a refrigerator) or at room temperature. (Please refer to the end of this leaflet for further information).

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer required. These measures will help protect the environment.

6. Contents of the pack and other information

What VFEND contains

- The active substance is voriconazole.
- The other ingredient is sulfobutylether beta cyclodextrin sodium.

Each vial contains 200 mg voriconazole, equivalent to a 10 mg/ml solution when reconstituted as directed by your hospital pharmacist or nurse (see the information at the end of this leaflet).

Each bag contains 50 ml of sodium chloride 0.9% in Water for Injections.

What VFEND looks like and contents of the pack

VFEND powder and solvent for solution for infusion is presented as an administration kit containing:

- VFEND powder for solution for infusion in single use glass vial.
- VFEND solvent for solution for infusion in an overwrapped, sterile, single use, polypropylene infusion bag.
- A sterile, single use, syringe.
- A sterile, single use vial adapter.

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Body Weight (kg)	Volume of VFEND Concentrate (10 mg/ml) required for:				
	3 mg/kg dose (number of vials)	4 mg/kg dose (number of vials)	6 mg/kg dose (number of vials)	8 mg/kg dose (number of vials)	9 mg/kg dose (number of vials)
10	-	4.0 ml (1)	-	8.0 ml (1)	9.0 ml (1)
15	-	6.0 ml (1)	-	12.0 ml (1)	13.5 ml (1)
20	-	8.0 ml (1)	-	16.0 ml (1)	18.0 ml (1)
25	-	10.0 ml (1)	-	20.0 ml (1)	22.5 ml (2)
30	9.0 ml (1)	12.0 ml (1)	18.0 ml (1)	24.0 ml (2)	27.0 ml (2)
35	10.5 ml (1)	14.0 ml (1)	21.0 ml (2)	28.0 ml (2)	31.5 ml (2)
40	12.0 ml (1)	16.0 ml (1)	24.0 ml (2)	32.0 ml (2)	36.0 ml (2)
45	13.5 ml (1)	18.0 ml (1)	27.0 ml (2)	36.0 ml (2)	40.5 ml (3)
50	15.0 ml (1)	20.0 ml (1)	30.0 ml (2)	40.0 ml (2)	45.0 ml (3)
55	16.5 ml (1)	22.0 ml (2)	33.0 ml (2)	44.0 ml (3)	49.5 ml (3)
60	18.0 ml (1)	24.0 ml (2)	36.0 ml (2)	48.0 ml (3)	54.0 ml (3)
65	19.5 ml (1)	26.0 ml (2)	39.0 ml (2)	52.0 ml (3)	58.5 ml (3)
70	21.0 ml (2)	28.0 ml (2)	42.0 ml (3)	-	-
75	22.5 ml (2)	30.0 ml (2)	45.0 ml (3)	-	-
80	24.0 ml (2)	32.0 ml (2)	48.0 ml (3)	-	-
85	25.5 ml (2)	34.0 ml (2)	51.0 ml (3)	-	-
90	27.0 ml (2)	36.0 ml (2)	54.0 ml (3)	-	-
95	28.5 ml (2)	38.0 ml (2)	57.0 ml (3)	-	-

100	30.0 ml (2)	40.0 ml (2)	60.0 ml (3)	-	-
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VFEND is a single dose unpreserved sterile lyophile. Therefore, from a microbiological point of view, the reconstituted solution must be used immediately.

If not used immediately, in-use storage times and conditions of the reconstituted vial prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Incompatibilities:

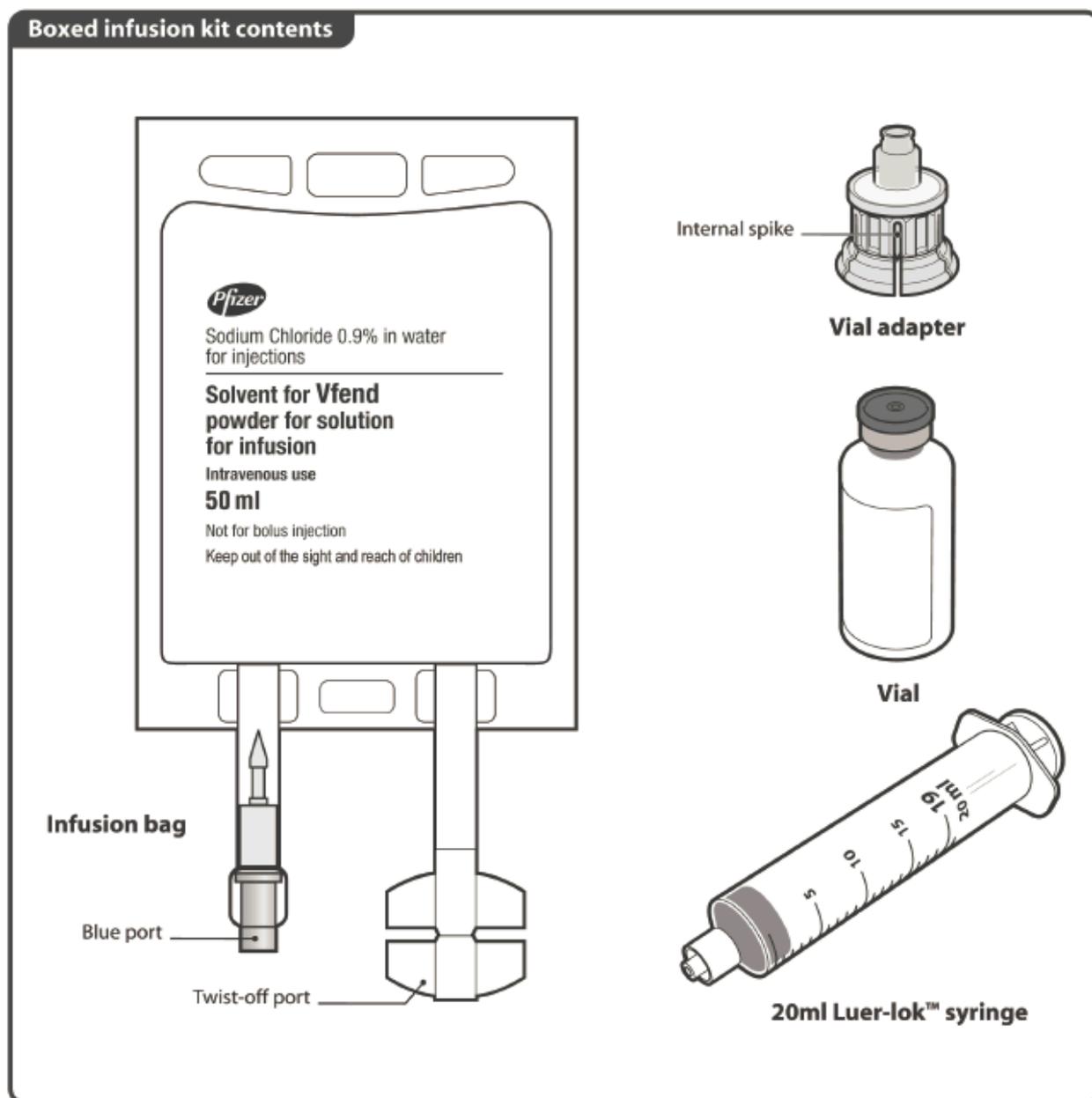
VFEND must not be infused into the same line or cannula concomitantly with other drug infusions, including parenteral nutrition (e.g., Aminofusin 10% Plus).

Infusions of blood products must not occur simultaneously with VFEND.

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

VFEND must not be diluted with 4.2% Sodium Bicarbonate Infusion.

**Kit Operating Instructions for Use:
VFEND Powder and Solvent for Solution for Infusion**

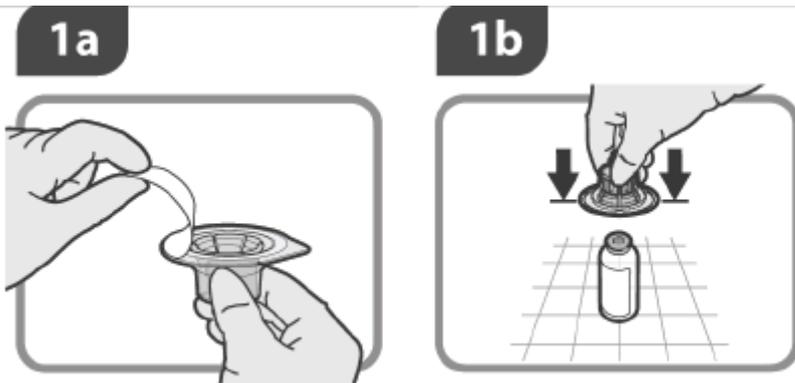


Critical Instructions for safe and effective use of infusion kit

- Aseptic procedures will be followed during kit preparation
- Bag must be inverted when the reconstituted Voriconazole is added

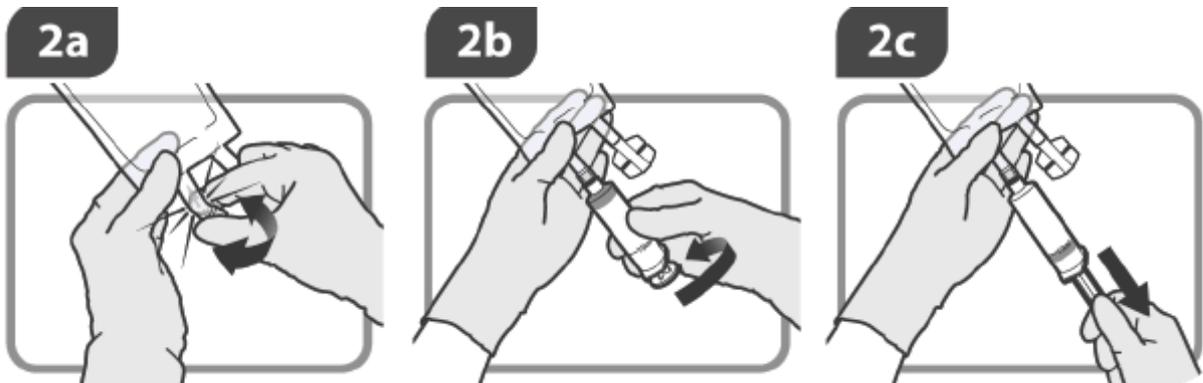
Step 1

- 1a** Peel back the seal from the vial adaptor. Do not remove casing.
- 1b** To prepare the IV vial for reconstitution, remove the plastic cap from the vial and wipe the top with an antiseptic swab. Place the vial on a flat surface. Ensure the internal spike of the vial adaptor is placed at the centre of the vial septum and push the adaptor firmly onto the vial until it snaps into place.



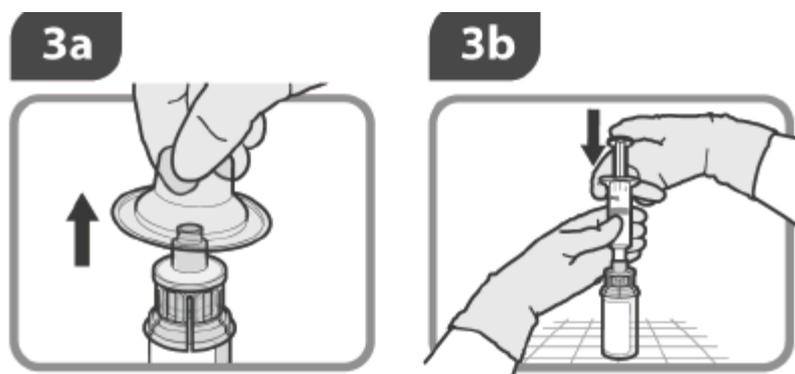
Step 2

- 2a Snap open Blue port. Bend the outer tube by 90° each way to ensure it is fully broken.
- 2b Push the syringe plunger down fully. Push and screw the syringe securely onto Blue port.
- 2c Withdraw exactly 19 mL of the solution and unscrew the syringe.



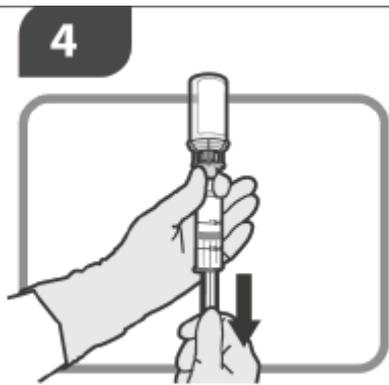
Step 3

- 3a Remove the adaptor casing from the vial adaptor and discard.
- 3b Screw the syringe onto the vial adapter. Keeping the vial upright, empty contents of the syringe into the vial.
- 3c Swirl the vial gently until all the powder is dissolved. Inspect the vial. If particles are seen, swirl again and re-inspect.



Step 4

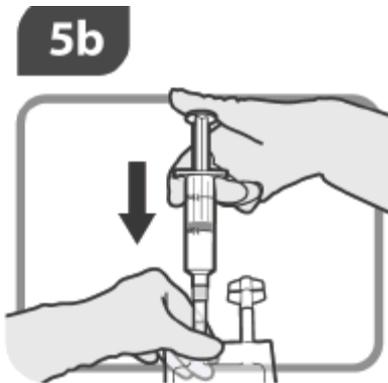
- 4 Gently invert the vial. Slowly draw off the required volume of the solution. The potential to block the venting action exists if large amounts of air or drug are injected when the vial is inverted. If this occurs, turn the vial upright and pull the piston up the syringe barrel. When cleared, proceed as directed. Unscrew the syringe and discard the vial adaptor and vial.



Step 5

5a Invert the infusion bag and screw the syringe into Blue port.

5b Empty the contents of the syringe into the bag. Remove the syringe. Gently mix the contents of the infusion bag. If any particles are seen, discard the infusion bag.

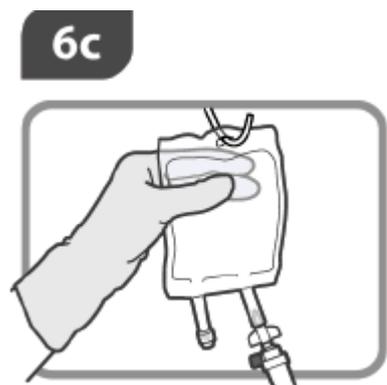
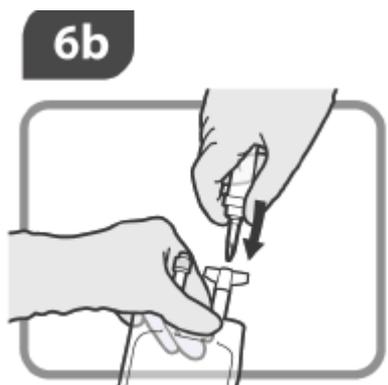
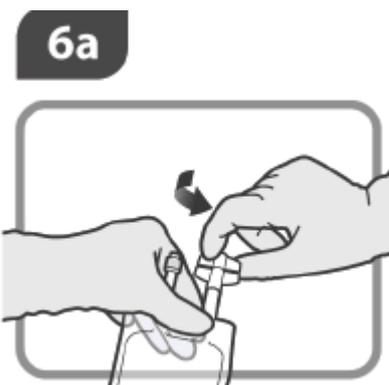


Step 6

6a Invert the infusion bag. Open the Twist-off port.

6b Keeping the infusion bag inverted, connect the infusion line.

6c Prime the IV line according to the manufacturer's guidelines. Hang the infusion bag.



Step 7

7a Attach the IV line to the patient injection site. **Set the infusion rate accurately.**

7b Once the infusion delivery to the patient starts, do not manually squeeze the bag compartment as this may interfere with the dose delivery to the patient and may cause air ingress into the IV line.

Package Leaflet: Information for the user
VFEND 40 mg/ml powder for oral suspension
Voriconazole

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What VFEND is and what it is used for
2. What you need to know before you take VFEND
3. How to take VFEND
4. Possible side effects
5. How to store VFEND
6. Content of the pack and other information

1. What VFEND is and what it is used for

VFEND contains the active substance voriconazole. VFEND is an antifungal medicine. It works by killing or stopping the growth of the fungi that cause infections.

It is used for the treatment of patients (adults and children over the age of 2) with:

- invasive aspergillosis (a type of fungal infection due to *Aspergillus sp*),
- candidaemia (another type of fungal infection due to *Candida sp*) in non-neutropenic patients (patients without abnormally low white blood cells count),
- serious invasive *Candida sp.* infections when the fungus is resistant to fluconazole (another antifungal medicine),
- serious fungal infections caused by *Scedosporium sp.* or *Fusarium sp.* (two different species of fungi).

VFEND is intended for patients with worsening, possibly life-threatening, fungal infections.

Prevention of fungal infections in high risk bone marrow transplant recipients.

This product should only be taken under the supervision of a doctor.

2. What you need to know before you take VFEND

Do not take VFEND:

If you are allergic to voriconazole or any of the other ingredients of this medicine (listed in section 6).

It is very important that you inform your doctor or pharmacist if you are taking or have taken any other medicines, even those that are obtained without a prescription, or herbal medicines.

The medicines in the following list must not be taken during your course of VFEND treatment:

- Terfenadine (used for allergy)
- Astemizole (used for allergy)
- Cisapride (used for stomach problems)

- Pimozide (used for treating mental illness)
- Quinidine (used for irregular heart beat)
- Rifampicin (used for treating tuberculosis)
- Efavirenz (used for treating HIV) in doses of 400 mg and above once daily
- Carbamazepine (used to treat seizures)
- Phenobarbital (used for severe insomnia and seizures)
- Ergot alkaloids (e.g., ergotamine, dihydroergotamine; used for migraine)
- Sirolimus (used in transplant patients)
- Ritonavir (used for treating HIV) in doses of 400mg and more twice daily
- St. John's Wort (herbal supplement)

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking VFEND if:

- you have had an allergic reaction to other azoles.
- you are suffering from, or have ever suffered from liver disease. If you have liver disease, your doctor may prescribe a lower dose of VFEND. Your doctor should also monitor your liver function while you are being treated with VFEND by doing blood tests.
- you are known to have cardiomyopathy, irregular heart beat, slow heart rate or an abnormality of electrocardiogram (ECG) called 'long QTc syndrome'.

You should avoid any sunlight and sun exposure while being treated. It is important to cover sun exposed areas of skin and use sunscreen with high sun protection factor (SPF), as an increased sensitivity of skin to the sun's UV rays can occur. These precautions are also applicable to children.

While being treated with VFEND:

- tell your doctor immediately if you develop
 - sunburn
 - severe skin rash or blisters
 - bone pain

If you develop skin disorders as described above, your doctor may refer you to a dermatologist, who after consultation may decide that it is important for you to be seen on a regular basis. There is a small chance that skin cancer could develop with long-term use of VFEND.

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

Children and adolescents

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

Other medicines and VFEND

Please tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including those that are obtained without a prescription.

Some medicines, when taken at the same time as VFEND, may affect the way VFEND works or VFEND may affect the way they work.

Tell your doctor if you are taking the following medicine, as treatment with VFEND at the same time should be avoided if possible:

- Ritonavir (used for treating HIV) in doses of 100 mg twice daily

Tell your doctor if you are taking either of the following medicines, as treatment with VFEND at the same time should be avoided if possible, and a dose adjustment of voriconazole may be required:

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

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

Tell your doctor if you are taking any of the following medicines, as a dose adjustment or monitoring may be required to check that the medicines and/ or VFEND are still having the desired effect:

- Warfarin and other anticoagulants (e.g., phenprocoumon, acenocoumarol; used to slow down clotting of the blood)
- Ciclosporin (used in transplant patients)
- Tacrolimus (used in transplant patients)
- Sulfonylureas (e.g., tolbutamide, glipizide, and glyburide) (used for diabetes)
- Statins (e.g., atorvastatin, simvastatin) (used for lowering cholesterol)
- Benzodiazepines (e.g. midazolam, triazolam) (used for severe insomnia and stress)
- Omeprazole (used for treating ulcers)
- Oral contraceptives (if you take VFEND whilst using oral contraceptives, you may get side effects such as nausea and menstrual disorders)
- Vinca alkaloids (e.g., vincristine and vinblastine) (used in treating cancer)
- Indinavir and other HIV protease inhibitors (used for treating HIV)
- Non-nucleoside reverse transcriptase inhibitors (e.g., efavirenz, delavirdine, nevirapine) (used for treating HIV) (some doses of efavirenz can NOT be taken at the same time as VFEND)
- Methadone (used to treat heroin addiction)
- Alfentanil and fentanyl-and other short-acting opiates such as sufentanil (painkillers used for surgical procedures)
- Oxycodone and other long-acting opiates such as hydrocodone (used for moderate to severe pain)
- Non-steroidal anti-inflammatory drugs (e.g., ibuprofen, diclofenac) (used for treating pain and inflammation)
- Fluconazole (used for fungal infections)
- Everolimus (used for treating advanced kidney cancer and in transplant patients)

Pregnancy and breast-feeding

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

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines

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

VFEND contains sucrose

VFEND suspension contains 0.54g sucrose per ml of suspension. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking VFEND.

3. How to take VFEND

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

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

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

	Oral suspension	
	Patients 40 kg and above	Patients less than 40 kg
Dose for the first 24 hours (Loading Dose)	400 mg (10 ml) every 12 hours for the first 24 hours	200 mg (5 ml) every 12 hours for the first 24 hours
Dose after the first 24 hours (Maintenance Dose)	200 mg (5 ml) twice a day	100 mg (2.5 ml) twice a day

Depending on your response to treatment, your doctor may increase the daily dose to 300 mg twice a day.

The doctor may decide to decrease the dose if you have mild to moderate cirrhosis.

Use in children and adolescents

The recommended dose for children and teenagers is as follows:

	Oral suspension	
	Children aged 2 to less than 12 years and teenagers aged 12 to 14 years weighing less than 50 kg	Teenagers aged 12 to 14 years weighing 50 kg or more; and all teenagers older than 14
Dose for the first 24 hours (Loading Dose)	Your treatment will be started as an infusion	400 mg every 12 hours for the first 24 hours
Dose after the first 24 hours (Maintenance Dose)	9 mg/kg twice a day (a maximum dose of 350 mg twice daily)	200 mg twice a day

Depending on your response to treatment, your doctor may increase or decrease the daily dose.

Take your suspension at least one hour before, or two hours after a meal.

If you or your child are taking VFEND for prevention of fungal infections, your doctor may stop giving VFEND if you or your child develop treatment related side effects.

VFEND suspension should not be mixed with any other medicine. The suspension should not be further diluted with water or any other liquids.

Instructions to constitute the suspension:

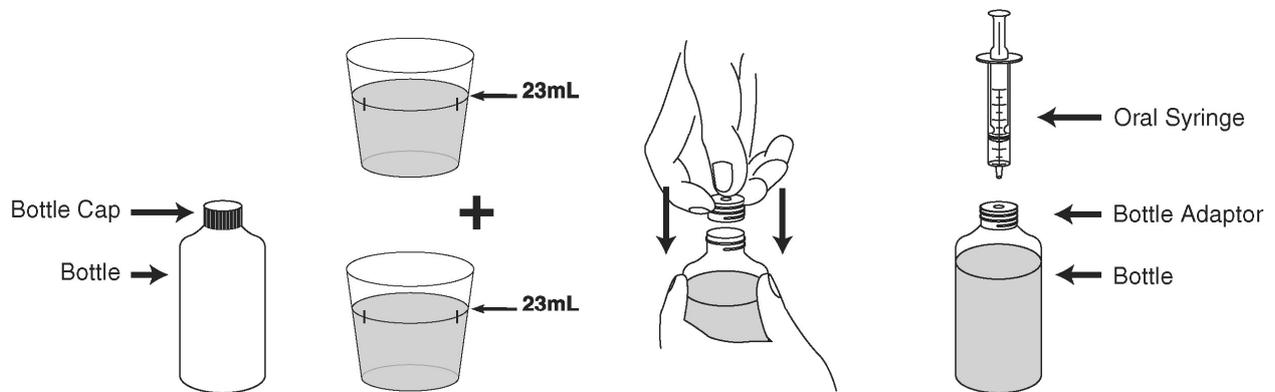
It is recommended that your pharmacist constitutes VFEND suspension before giving it to you.

VFEND suspension is constituted if it is in a liquid form. If it appears to be a dry powder you should constitute the oral suspension by following the instructions below.

1. Tap the bottle to release the powder.
2. Remove the cap.
3. Add 2 measuring cups (measure cup included in the carton) of water (total of 46 ml) to the bottle. Fill the measuring cup to the top of the marked line then pour the water into the bottle. You should always add a total of 46 ml of water irrespective of the dose you are taking.
4. Replace the cap and shake the bottle vigorously for about 1 minute. Following constitution, the total volume of the suspension must be 75 ml.
5. Remove the cap. Press the bottle adaptor into the neck of the bottle (as shown on figure below). The

adaptor is provided so that you can fill the oral syringe with medicine from the bottle. Replace the cap on the bottle.

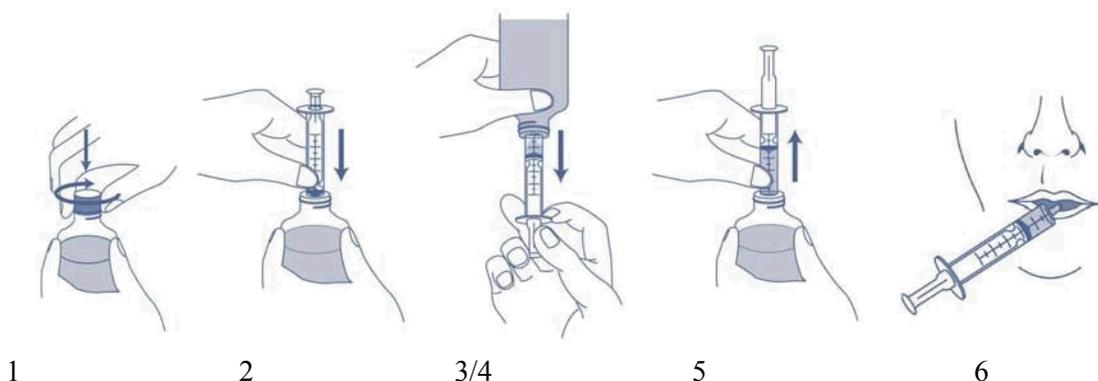
6. Write the date of expiry of the constituted suspension on the bottle label (the shelf-life of the constituted suspension is 14 days). Any unused suspension should be discarded after this date.



Instructions for use:

Your pharmacist should advise you how to measure the medicine using the multi-dosing oral syringe provided in the pack. Please see instructions below before using VFEND suspension.

1. Shake the closed bottle of constituted suspension for approximately 10 seconds before use. Remove the cap.
2. While the bottle is upright, on a flat surface, insert the tip of the oral syringe into the adaptor.
3. Turn the bottle upside down while holding the oral syringe in place. Slowly pull back the plunger of the oral syringe to the graduation mark that marks the dose for you. To measure the dose accurately, the top edge of the black ring should be lined up with the graduated mark on the oral syringe.
4. If large bubbles can be seen, slowly push the plunger back into the syringe. This will force the medicine back into the bottle. Repeat step 3 again.
5. Turn the bottle back upright with the oral syringe still in place. Remove the oral syringe from the bottle.
6. Put the tip of the oral syringe into the mouth. Point the tip of the oral syringe towards the inside of the cheek. SLOWLY push down the plunger of the oral syringe. Do not squirt the medicine out quickly. If the medicine is to be given to a child, make sure the child is sitting, or is held, upright before giving the medicine.
7. Replace the cap on the bottle, leaving the bottle adaptor in place. Wash the oral syringe as instructed below.



Cleaning and storing the syringe:

1. The syringe should be washed after each dose. Pull the plunger out of the syringe and wash both parts in warm soapy water. Then rinse with water.
2. Dry the two parts. Push the plunger back in to the syringe. Keep it in a clean safe place with the

medicine.

If you take more VFEND than you should

If you take more suspension than prescribed (or if someone else takes your suspension) you must seek medical advice or go to the nearest hospital casualty department immediately. Take your bottle of VFEND suspension with you. You may experience abnormal intolerance to light as a result of taking more VFEND than you should.

If you forget to take VFEND

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

If you stop taking VFEND

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

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

When VFEND treatment is stopped by your doctor you should not experience any effects.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If any side effects occur, most are likely to be minor and temporary. However, some may be serious and need medical attention.

Serious side effects – Stop taking VFEND and see a doctor immediately

- Rash
- Jaundice; Changes in blood tests of liver function
- Pancreatitis

Other side effects

Very common: may affect more than 1 in 10 people

- Visual impairment (change in vision including blurred vision, visual color alterations, abnormal intolerance to visual perception of light, colour blindness, eye disorder, halo vision, night blindness, swinging vision, seeing sparks, visual aura, visual acuity reduced, visual brightness, loss of part of the usual field of vision, spots before the eyes)
- Fever
- Rash
- Nausea, vomiting, diarrhoea
- Headache
- Swelling of the extremities
- Stomach pains
- Breathing difficulties
- Elevated liver enzymes

Common: may affect up to 1 in 10 people

- Inflammation of the sinuses, inflammation of the gums, chills, weakness
- Low numbers of some types, including severe, of red (sometimes immune-related) and/or white blood cells (sometimes with fever), low numbers of cells called platelets that help the blood to clot
- Low blood sugar, low blood potassium, low sodium in the blood
- Anxiety, depression, confusion, agitation, inability to sleep, hallucinations
- Seizures, tremors or uncontrolled muscle movements, tingling or abnormal skin sensations, increase in muscle tone, sleepiness, dizziness
- Bleeding in the eye
- Heart rhythm problems including very fast heartbeat, very slow heartbeat, fainting
- Low blood pressure, inflammation of a vein (which may be associated with the formation of a blood clot)
- Acute breathing difficulty, chest pain, swelling of the face (mouth, lips and around eyes), fluid accumulation in the lungs
- Constipation, indigestion, inflammation of the lips
- Jaundice, inflammation of the liver and liver injury
- Skin rashes which may lead to severe blistering and peeling of the skin characterized by a flat, red area on the skin that is covered with small confluent bumps, redness of the skin
- Itchiness
- Hair loss
- Back pain
- Kidney failure, blood in the urine, changes in kidney function tests

Uncommon: may affect up to 1 in 100 people

- Flu-like symptoms, irritation and inflammation of the gastrointestinal tract, inflammation of the gastrointestinal tract causing antibiotic associated diarrhoea, inflammation of the lymphatic vessels
- Inflammation of the thin tissue that lines the inner wall of the abdomen and covers the abdominal organ
- Enlarged lymph glands (sometimes painful), failure of blood marrow, increased eosinophil
- Depressed function of the adrenal gland, underactive thyroid gland
- Abnormal brain function, Parkinson-like symptoms, nerve injury resulting in numbness, pain, tingling or burning in the hands or feet
- Problems with balance or coordination
- Swelling of the brain
- Double vision, serious conditions of the eye including: pain and inflammation of the eyes and eyelids, abnormal eye movement, damage to the optic nerve resulting in vision impairment, optic disc swelling
- Decreased sensitivity to touch
- Abnormal sense of taste
- Hearing difficulties, ringing in the ears, vertigo
- Inflammation of certain internal organs- pancreas and duodenum, swelling and inflammation of the tongue
- Enlarged liver, liver failure, gallbladder disease, gallstones
- Joint inflammation, inflammation of the veins under the skin (which may be associated with the formation of a blood clot)
- Inflammation of the kidney, proteins in the urine, damage to the kidney
- Very fast heart rate or skipped heartbeats, sometimes with erratic electrical impulses
- Abnormal electrocardiogram (ECG)
- Blood cholesterol increased, blood urea increased
- Allergic skin reactions (sometimes severe), including life-threatening skin condition that causes painful blisters and sores of the skin and mucous membranes, especially in the mouth, inflammation of the skin, hives, sunburn or severe skin reaction following exposure to light or sun, skin redness and irritation, red or purple discoloration of the skin which may be caused by low platelet count, eczema
- Infusion site reaction
- Allergic reaction or exaggerated immune response

Rare: may affect up to 1 in 1000 people

- Overactive thyroid gland
- Deterioration of brain function that is a serious complication of liver disease
- Loss of most fibers in the optic nerve, clouding of the cornea, involuntary movement of the eye
- Bullous photosensitivity
- A disorder in which the body's immune system attacks part of the peripheral nervous system
- Heart rhythm or conduction problems (sometimes life threatening)
- Life threatening allergic reaction
- Disorder of blood clotting system
- Allergic skin reactions (sometimes severe), including rapid swelling (oedema) of the dermis, subcutaneous tissue, mucosa and submucosal tissues, itchy or sore patches of thick, red skin with silvery scales of skin, irritation of the skin and mucous membranes, life-threatening skin condition that causes large portions of the epidermis, the skin's outermost layer, to detach from the layers of skin below
- Small dry scaly skin patches, sometimes thick with spikes or 'horns'

Side effects with frequency not known:

- Freckles and pigmented spots

Other significant side effects whose frequency is not known, but should be reported to your doctor immediately:

- Skin cancer
- Inflammation of the tissue surrounding the bone
- Red, scaly patches or ring-shaped skin lesions that may be a symptom of an autoimmune disease called cutaneous lupus erythematosus

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

There have been reports of skin cancer in patients treated with VFEND for long periods of time.

Sunburn or severe skin reaction following exposure to light or sun was experienced more frequently in children. If you or your child develops skin disorders, your doctor may refer you to a dermatologist, who after consultation may decide that it is important for you or your child to be seen on a regular basis. Elevated liver enzymes were also observed more frequently in children.

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

Reporting of side effects

If you get any side effects, talk to your doctor or, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store VFEND

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

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

For the constituted suspension:

Do not store above 30°C.

Do not refrigerate or freeze.
Store in the original container
Keep the container tightly closed.
Any remaining suspension should be discarded 14 days after constitution.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer required. These measures will help protect the environment.

6. Contents of the pack and other information

What VFEND contains:

- The active substance is voriconazole. Each bottle contains 45 g of powder providing 70 ml of suspension when constituted with water as recommended. One ml of the constituted suspension contains 40 mg voriconazole. (See section 3 'How to take VFEND').
- The other ingredients are sucrose; silica colloidal; titanium dioxide; xanthan gum; sodium citrate; sodium benzoate; citric acid; natural orange flavour.

What VFEND looks like and contents of the pack

VFEND is supplied as a white to off-white powder for oral suspension providing a white to off-white, orange flavoured suspension when constituted with water.

Marketing Authorisation Holder

Pfizer Europe MA EEIG, Boulevard de la Plaine 17, 1050 Bruxelles, Belgium.

Manufacturer

Fareva Amboise, Zone Industrielle, 29 route des Industries, 37530 Pocé-sur-Cisse, France.

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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