VFEND®
Voriconazole

1. NAME OF THE MEDICINAL PRODUCT

VFEND

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Film-coated tablets:
Each tablet contains 50 mg or 200 mg voriconazole.

Powder for solution for infusion:
Vials contain 200 mg voriconazole, equivalent to a 10 mg/mL solution following reconstitution (see Section 6.6).

Powder for oral suspension:
Each bottle contains 45 g powder for oral suspension providing 40 mg/mL voriconazole when constituted with water (see Section 6.6).

3. PHARMACEUTICAL FORM

Film-coated tablets:
Voriconazole 50 mg film-coated tablets are white, round tablets, debossed “Pfizer” on one side and “VOR50” on the reverse.

Voriconazole 200 mg film-coated tablets are white, capsule-shaped tablets, debossed “Pfizer” on one side and “VOR200” on the reverse.

Powder for solution for infusion:
Voriconazole powder for solution for infusion is a white lyophilised powder containing nominally 200 mg voriconazole presented in a 30 mL clear glass vial.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Voriconazole is a broad spectrum, triazole antifungal agent and is indicated 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.;
Prophylaxis in patients ≥12 years old who are at high risk of developing invasive fungal infections. The indication is based on a study which includes patients ≥12 years old undergoing allogeneic haematopoietic stem cell transplantation (see Section 5.1 on ‘Clinical experience’).

4.2 Posology and method of administration

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

Powder for oral suspension:
Voriconazole oral suspension is to be taken at least one hour before, or two hours following a meal.

Powder for solution for infusion:
Voriconazole requires reconstitution and dilution (see Section 6.6) prior to administration as an intravenous infusion.

Voriconazole powder for solution for infusion is **not** recommended for bolus injection.

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

Blood products and concentrated electrolytes

Voriconazole must not be infused concomitantly with any blood product or any short-term infusion of concentrated electrolytes, even if the two infusions are running in separate intravenous lines (or cannulas). Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be corrected prior to initiation of voriconazole therapy (see Section 4.4).

Intravenous solutions containing (non-concentrated) electrolytes

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

Total parenteral nutrition (TPN)

Voriconazole can be infused at the same time as total parenteral nutrition, but must be infused in a separate line. If infused through a multiple-lumen catheter, TPN needs to be administered using a different port from the one used for voriconazole (see Section 6.2).

Other intravenous products

Voriconazole must not be infused into the same line or cannula concomitantly with other intravenous products.

Use in adults

Therapy must be initiated with the specified loading dose regimen of either intravenous or oral voriconazole 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[a]	
		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)			
Prophylaxis of invasive fungal infections	3-4 mg/kg every 12 hours	200 mg (5 mL) every 12 hours	100 mg (2.5 mL) every 12 hours
Serious invasive *Candida*/Invasive aspergillosis/*Scedosporium* and *Fusarium* infections[b]	4 mg/kg every 12 hours	200 mg (5 mL) every 12 hours	100 mg (2.5 mL) every 12 hours
Candidaemia in non-neutropenic patients	3-4 mg/kg every 12 hours[c]	200 mg (5 mL) every 12 hours	100 mg (2.5 mL) every 12 hours

a In healthy volunteer studies, the 200 mg oral every 12 hours dose provided an exposure (AUC_τ) similar to a 3 mg/kg IV every 12 hours dose, the 300 mg oral every 12 hours dose provided an exposure (AUC_τ) similar to a 4 mg/kg IV every 12 hours dose (see Section 5.2).

b In the pivotal clinical study of invasive aspergillosis, the median duration of IV voriconazole therapy was 10 days (range 2-85 days). The median duration of oral voriconazole therapy was 76 days (range 2-232 days) (see Section 5.1).

c In clinical trials, patients with candidaemia received 3 mg/kg every 12 hours as primary therapy, while patients with other deep tissue *Candida* infections received 4 mg/kg as salvage therapy. Appropriate dose should be based on severity and nature of the infection.

Dosage adjustment

Film-coated tablets/Powder for oral suspension:
If patient response is inadequate, the maintenance dose may be increased from 200 mg (5 mL) every 12 hours (similar to 3 mg/kg IV every 12 hours) to 300 mg (7.5 mL) every 12 hours (similar to 4 mg/kg IV every 12 hours) for oral administration. For patients less than 40 kg the oral dose may be increased from 100 mg (2.5 mL) to 150 mg (3.75 mL) every 12 hours.

If patients are unable to tolerate treatment at these higher doses, reduce the oral dose by 50 mg (1.25 mL) steps to a minimum of 200 mg (5 mL) every 12 hours (or 100 mg [2.5 mL] every 12 hours for patients less than 40 kg).

Phenytoin may be co-administered with voriconazole if the maintenance dose of voriconazole is increased from 200 mg (5 mL) to 400 mg (10 mL) orally every 12 hours (from 100 mg [2.5 mL] to 200 mg [5 mL] orally, every 12 hours in patients less than 40 kg) (see Sections 4.4 and 4.5).

When voriconazole is co-administered with adjusted doses of efavirenz, voriconazole maintenance dose should be increased to 400 mg (10 mL) every 12 hours (see Sections 4.3, 4.4 and 4.5).

Treatment duration depends upon patients' clinical and mycological response.

Intravenous administration:
If patient response at 3 mg/kg every 12 hours is inadequate, the intravenous maintenance dose may be increased to 4 mg/kg every 12 hours.

If patients are unable to tolerate 4 mg/kg every 12 hours, reduce the intravenous maintenance dose to a minimum of 3 mg/kg every 12 hours.

Phenytoin may be co-administered with voriconazole if the maintenance dose of voriconazole is increased to 5 mg/kg intravenously every 12 hours (see Sections 4.4 and 4.5).

Treatment duration depends upon patients' clinical and mycological response.

Use in the elderly

No dose adjustment is necessary for elderly patients.

Use in patients with renal impairment

Film-coated tablets/Powder for oral suspension:
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.

Powder for solution for infusion:
In patients with moderate to severe renal dysfunction (creatinine clearance <50 mL/min), accumulation of the intravenous vehicle, sulphobutylether β-cyclodextrin sodium (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.

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

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

Use in patients with hepatic impairment

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

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

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

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.

Use in paediatrics

Safety and effectiveness in paediatric patients below the age of 2 years has not been established (see also Section 5.1). Therefore, voriconazole is not recommended for children less than 2 years of age.

The recommended maintenance dosing regimen in paediatric patients 2 to <12 years is as follows:

Loading Dose Regimen	No oral or intravenous loading dose is recommended	
Maintenance Dose	**Intravenous Dose***	**Oral Dose****
	7 mg/kg twice daily	200 mg twice daily

*Based on a population pharmacokinetic analysis in 82 immunocompromised patients aged 2 to <12 years.
**Based on a population pharmacokinetic analysis in 47 immunocompromised patients aged 2 to <12 years.

If paediatric patients are unable to tolerate an intravenous dose of 7 mg/kg twice daily, a dose reduction from 7 mg/kg to 4 mg/kg twice daily may be considered based on the population pharmacokinetic analysis and previous clinical experience. This provides equivalent exposure to 3 mg/kg twice daily in adults (see Section 4.2, Use in adults).

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).

The oral dose recommendation for children is based on studies in which voriconazole was administered as the powder for oral suspension formulation. Bioequivalence between the powder for oral suspension and tablets has not been investigated in a paediatric population. Considering the assumed limited gastro-enteric transit time in paediatrics, 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 years.

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

4.3 Contraindications

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

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

Co-administration of voriconazole and sirolimus is contraindicated, since voriconazole has been shown to significantly increase plasma concentrations of sirolimus in healthy subjects (see Section 4.5).

Co-administration of voriconazole with rifabutin, rifampicin, carbamazepine, long-acting barbiturates (e.g., phenobarbital) and St. John's Wort is contraindicated since these medicinal products are likely to decrease plasma voriconazole concentrations significantly (see Section 4.5).

Co-administration of standard doses of voriconazole with efavirenz doses of 400 mg QD or higher is contraindicated because efavirenz significantly decreases plasma voriconazole concentrations in healthy subjects at these doses. Voriconazole also significantly increases efavirenz plasma concentrations (see Section 4.5, for lower doses see Section 4.4).

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

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

Co-administration of voriconazole with naloxegol is contraindicated because voriconazole may significantly increase plasma concentrations of naloxegol which may precipitate opioid withdrawal symptoms (see Section 4.5).

Co-administration of voriconazole with tolvaptan is contraindicated because voriconazole may significantly increase plasma concentrations of tolvaptan (see Section 4.5).

Co-administration of voriconazole with venetoclax is contraindicated at initiation and during the venetoclax dose titration phase since voriconazole is likely to significantly increase plasma concentrations of venetoclax and increase risk of tumour lysis syndrome (see Section 4.5).

Co-administration of voriconazole with lurasidone is contraindicated since it may result in significant increases in lurasidone exposure and the potential for serious adverse reactions (see Section 4.5).

Co-administration of voriconazole with finerenone is contraindicated since it may result in significant increases in finerenone exposure and the potential for serious adverse reactions (see Section 4.5).

4.4 Special warnings and precautions for use

Hypersensitivity: Caution should be used in prescribing voriconazole to patients with hypersensitivity to other azoles.

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).

Cardiac adverse events: Some azoles, including voriconazole, have been associated with QT interval prolongation on the electrocardiogram. During clinical development and post-marketing surveillance, 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 medications that may have been contributory. Voriconazole should be administered with caution to patients with potentially proarrhythmic conditions, such as:

- Congenital or acquired QT-prolongation
- Cardiomyopathy, in particular when heart failure is present
- Sinus bradycardia
- Existing symptomatic arrhythmias
- Concomitant medication that is known to prolong QT interval (see Section 4.5)

Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation of and during voriconazole therapy (see Section 4.2). A study has been conducted in healthy volunteers which examined the effect on QT interval of single doses of voriconazole up to 4 times the usual daily dose. No subject experienced an interval exceeding the potentially clinically relevant threshold of 500 msec (see Section 5.1).

Hepatic toxicity: In clinical trials, there have been 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.

Monitoring of hepatic function: Patients receiving voriconazole must be carefully monitored for hepatic toxicity. Clinical management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin) at the initiation of treatment with voriconazole and at least weekly for the first month of treatment. If treatment is continued, monitoring frequency can be reduced to monthly if there are no changes in the liver function tests.

If the liver function tests become markedly elevated, voriconazole should be discontinued, unless the medical judgment of the risk-benefit of the treatment for the patient justifies continued use (see Section 4.2).

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

Renal adverse events: Acute renal failure has been observed in severely ill patients undergoing treatment with voriconazole. Patients being treated with voriconazole are likely to be treated concomitantly with nephrotoxic medications and have concurrent conditions that may result in decreased renal function.

Monitoring of renal function: Patients should be monitored for the development of abnormal renal function. This should include laboratory evaluation, particularly serum creatinine (see Section 4.2).

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

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

In addition, voriconazole has been associated with photosensitivity skin reaction. An increased risk of skin toxicity with concomitant use of methotrexate, a drug associated with ultraviolet (UV) reactivation has been observed. There is a potential for this risk to be observed with other drugs associated with UV reactivation. It is recommended that patients, including children avoid exposure to direct sunlight during voriconazole treatment and use measures such as protective clothing and sunscreen with high sun protection factor (SPF).

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

Patients on long-term treatment with voriconazole and corticosteroids (including inhaled corticosteroids e.g., budesonide) should be carefully monitored for adrenal cortex dysfunction both during treatment and when voriconazole is discontinued (see Section 4.5). Patients should be instructed to seek

immediate medical care if they develop signs and symptoms of Cushing's syndrome or adrenal insufficiency.

Long-term treatment

The following severe adverse events have been reported in relation with long-term voriconazole treatment:

Squamous cell carcinoma of the skin (SCC): In patients with photosensitivity skin reactions and additional risk factors, squamous cell carcinoma of the skin (including cutaneous SCC *in situ*, or Bowen's disease) and melanoma have been reported during long-term therapy. If phototoxic reactions occur, multidisciplinary advice should be sought and the patient should be referred to a dermatologist. Voriconazole discontinuation should be considered. Dermatologic evaluation should be performed on a systematic and regular basis, whenever voriconazole is continued despite the occurrence of phototoxicity-related lesions, to allow early detection and management of premalignant lesions.

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

Non-infectious periostitis: Periostitis has been reported in transplant patients during long-term voriconazole therapy. If a patient develops skeletal pain and radiologic findings compatible with periostitis, voriconazole should be discontinued.

Paediatric use: Safety and effectiveness in paediatric subjects below the age of 2 years has not been established (see Section 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 2 to 12 years with malabsorption and very low body weight for age. In that case, intravenous voriconazole administration is recommended.

The frequency of phototoxicity reactions is higher in the 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.

Everolimus (CYP3A4 substrate, P-gp substrate): Co-administration of voriconazole with everolimus is not recommended because voriconazole is expected to significantly increase everolimus concentrations. Currently there are insufficient data to allow dosing recommendations in this situation (see Section 4.5).

Fluconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor): Co-administration of oral voriconazole and oral fluconazole resulted in a significant increase in C_{max} and AUC_{τ} of voriconazole in healthy subjects. The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole associated adverse events is recommended if voriconazole is used sequentially after fluconazole (see Section 4.5).

Efavirenz (CYP450 inducer; CYP3A4 inhibitor and substrate): When voriconazole is co-administered with efavirenz, the dose of voriconazole should be increased to 400 mg every 12 hours and that of efavirenz should be decreased to 300 mg every 24 hours (see Sections 4.2, 4.3 and 4.5).

Glasdegib (CYP3A4 substrate): Co-administration of voriconazole is expected to increase glasdegib plasma concentrations and increase the risk of QTc prolongation (see Section 4.5). If concomitant use cannot be avoided, frequent ECG monitoring is recommended.

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

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

Ritonavir (potent CYP450 inducer, CYP3A4 inhibitor and substrate): Co-administration of voriconazole and low dose ritonavir (100 mg twice daily) should be avoided unless an assessment of the benefit/risk justifies the use of voriconazole (see Section 4.5, for higher doses see Section 4.3).

Methadone (CYP3A4 substrate): Frequent monitoring for adverse events and toxicity related to methadone, including QT prolongation, is recommended when co-administered with voriconazole since methadone levels increased following co-administration 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 co-administered with voriconazole (see Section 4.5). As the half-life of alfentanil is prolonged in a 4-fold manner when alfentanil is co-administered with voriconazole and in an independent published study, concomitant use of voriconazole with fentanyl resulted in an increase in the mean $AUC_{0-\infty}$ of fentanyl by 1.4-fold, frequent monitoring for opiate-associated adverse events (including a longer respiratory monitoring period) may be necessary.

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

Visual disturbances: The effect of VFEND on visual function is not known if treatment continues beyond 28 days. If treatment continues beyond 28 days, visual function including visual acuity, visual field and colour perception should be monitored.

Cyclosporine and tacrolimus (CYP3A4 substrates): Clinically significant drug interactions with voriconazole may occur in patients who are receiving treatment with cyclosporine or tacrolimus (see Section 4.5).

Voriconazole 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, in particular for substances metabolised by CYP3A4 since voriconazole is a strong CYP3A4 inhibitor though the increase in AUC is substrate dependent (see Interaction table below).

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

Voriconazole should be administered with caution in patients with concomitant medication that is known to prolong QT interval. When there is also a potential for voriconazole to increase the plasma concentrations of substances metabolised by CYP3A4 isoenzymes (certain antihistamines, quinidine, cisapride, pimozide and ivabradine) co-administration is contraindicated (see below and Section 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 (↔), below (↓) or above (↑) the 80%-125% range. The asterisk (*) indicates a two-way interaction. AUC_{τ}, AUC_t and $AUC_{0-\infty}$ represent area under the curve over a dosing interval, from time zero to the time with detectable measurement and from time zero to infinity, respectively.

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

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

Medicinal product ***[Mechanism of Interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
Naloxegol *[CYP3A4 substrate]*	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of naloxegol.	**Contraindicated** (see Section 4.3)
Finerenone *[CYP3A4 substrate]*	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of finerenone.	**Contraindicated** (see Section 4.3)
Rifabutin *[potent CYP450 inducer]* 300 mg QD 300 mg QD (co-administered with voriconazole 350 mg BID)* 300 mg QD (co-administered with voriconazole 400 mg BID)*	 Voriconazole C_{max} ↓ 69% Voriconazole AUC_{τ} ↓ 78% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↓ 4% Voriconazole AUC_{τ} ↓ 32% Rifabutin C_{max} ↑ 195% Rifabutin AUC_{τ} ↑ 331% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 104% Voriconazole AUC_{τ} ↑ 87%	**Contraindicated** (see Section 4.3).
Rifampicin (600 mg QD) *[potent CYP450 inducer]*	Voriconazole C_{max} ↓ 93% Voriconazole AUC_{τ} ↓ 96%	**Contraindicated** (see Section 4.3).
Ritonavir (protease inhibitor) *[potent CYP450 inducer; CYP3A4 inhibitor and substrate]* High dose (400 mg BID) Low dose (100 mg BID)*	 Ritonavir C_{max} and AUC_{τ} ↔ Voriconazole C_{max} ↓ 66% Voriconazole AUC_{τ} ↓ 82% Ritonavir C_{max} ↓ 25% Ritonavir AUC_{τ} ↓13% Voriconazole C_{max} ↓ 24% Voriconazole AUC_{τ} ↓ 39%	 Co-administration of voriconazole and high doses of ritonavir (400 mg and higher BID) is **contraindicated** (see Section 4.3). Co-administration of voriconazole and low dose ritonavir (100 mg BID) should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.
St. John's Wort *[CYP450 inducer; P-gp inducer]* 300 mg TID (co-administered with voriconazole 400 mg single dose)	In an independent published study, Voriconazole $AUC_{0-\infty}$ ↓ 59%	**Contraindicated** (see Section 4.3).
Tolvaptan *[CYP3A substrate]*	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of tolvaptan.	**Contraindicated** (see Section 4.3)

Medicinal product ***[Mechanism of Interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
Venetoclax *[CYP3A substrate]*	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of venetoclax.	Concomitant administration of voriconazole is **contraindicated** at initiation and during venetoclax dose titration phase (see Section 4.3). Dose reduction of venetoclax is required as instructed in venetoclax prescribing information during steady daily dosing; close monitoring for signs of toxicity is recommended.
Fluconazole (200 mg QD) *[CYP2C9, CYP2C19 and CYP3A4 inhibitor]*	Voriconazole C_{max} ↑ 57% Voriconazole AUC_{τ} ↑ 79% Fluconazole C_{max} ND Fluconazole AUC_{τ} ND	The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole-associated adverse events is recommended if voriconazole is used sequentially after fluconazole.
Phenytoin *[CYP2C9 substrate and potent CYP450 inducer]* 300 mg QD 300 mg QD (co-administered with voriconazole 400 mg BID)*	 Voriconazole C_{max} ↓ 49% Voriconazole AUC_{τ} ↓ 69% Phenytoin C_{max} ↑ 67% Phenytoin AUC_{τ} ↑ 81% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 34% Voriconazole AUC_{τ} ↑ 39%	Concomitant use of voriconazole and phenytoin should be avoided unless the benefit outweighs the risk. Careful monitoring of phenytoin plasma levels is recommended. Phenytoin may be co-administered with voriconazole if the maintenance dose of voriconazole is increased to 5 mg/kg IV BID or from 200 mg to 400 mg oral BID (100 mg to 200 mg oral BID in patients less than 40 kg) (see Section 4.2).
Letermovir *[CYP2C9 and CYP2C19 inducer]*	Voriconazole C_{max} ↓ 39% Voriconazole AUC_{0-12} ↓ 44% Voriconazole C_{12} ↓ 51%	If concomitant administration of voriconazole with letermovir cannot be avoided, monitor for loss of voriconazole effectiveness.
Flucloxacillin *[CYP450 inducer]*	Although not studied, flucloxacillin has been reported to significantly decrease plasma voriconazole concentrations.	If concomitant administration of voriconazole with flucloxacillin cannot be avoided, monitor for potential loss of voriconazole effectiveness.
Lemborexant *[CYP3A4 substrate]*	Although not studied, voriconazole is likely to increase the plasma concentrations of lemborexant.	Concomitant use of voriconazole and lemborexant should be avoided.
Glasdegib *[CYP3A4 substrate]*	Although not studied, voriconazole is likely to increase the plasma concentrations of glasdegib and increase risk of QTc prolongation.	If concomitant use cannot be avoided, frequent ECG monitoring is recommended.

Medicinal product ***[Mechanism of Interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
Tyrosine kinase inhibitors (including but not limited to: axitinib, bosutinib, cabozantinib, ceritinib, cobimetinib, dabrafenib, dasatinib, nilotinib, sunitinib, ibrutinib, ribociclib) *[CYP3A4 substrates]*	Although not studied, voriconazole may increase plasma concentrations of tyrosine kinase inhibitors metabolised by CYP3A4.	If concomitant use cannot be avoided, dose reduction of the tyrosine kinase inhibitor and close clinical monitoring is recommended.
Anticoagulants Warfarin (30 mg single dose, co-administered with 300 mg BID voriconazole) *[CYP2C9 substrate]* Other oral coumarins (including but not limited to: phenprocoumon, acenocoumarol) *[CYP2C9 and CYP3A4 substrates]*	 Maximum increase in prothrombin time was approximately 2-fold. Although not studied, voriconazole may increase the plasma concentrations of coumarins that may cause an increase in prothrombin time.	 Close monitoring of prothrombin time or other suitable anticoagulation tests is recommended, and the dose of anticoagulants should be adjusted accordingly.
Ivacaftor *[CYP3A4 substrate]*	Although not studied, voriconazole is likely to increase the plasma concentrations of ivacaftor with risk of increased adverse reactions.	Dose reduction of ivacaftor is recommended.
Eszopiclone *[CYP3A4 substrate]*	Although not studied, voriconazole is likely to increase the plasma concentrations and sedative effect of eszopiclone.	Dose reduction of eszopiclone is recommended.
Benzodiazepines *[CYP3A4 substrates]* Midazolam (0.05 mg/kg IV single dose) Midazolam (7.5 mg oral single dose) Other benzodiazepines (including but not limited to: triazolam, alprazolam)	 In an independent published study, Midazolam $AUC_{0-\infty}$ ↑ 3.7-fold In an independent published study, Midazolam C_{max} ↑ 3.8-fold Midazolam $AUC_{0-\infty}$ ↑ 10.3-fold Although not studied, voriconazole is likely to increase the plasma concentrations of other benzodiazepines that are metabolised by CYP3A4 and lead to a prolonged sedative effect.	Dose reduction of benzodiazepines should be considered.
Immunosuppressants *[CYP3A4 substrates]* Sirolimus (2 mg single dose) Everolimus *[also P-gp substrate]*	 In an independent published study, Sirolimus C_{max} ↑ 6.6-fold Sirolimus $AUC_{0-\infty}$ ↑ 11-fold Although not studied, voriconazole is likely to significantly increase the plasma concentrations of everolimus.	 Co-administration of voriconazole and sirolimus is **contraindicated** (see Section 4.3). Co-administration of voriconazole and everolimus is not recommended because voriconazole is expected to significantly increase everolimus concentrations (see Section 4.4).

Medicinal product ***[Mechanism of Interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
Ciclosporin (In stable renal transplant recipients receiving chronic ciclosporin therapy)	Ciclosporin C_{max} ↑ 13% Ciclosporin AUC_{τ} ↑ 70%	When initiating voriconazole in patients already on ciclosporin it is recommended that the ciclosporin dose be halved and ciclosporin level carefully monitored. Increased ciclosporin levels have been associated with nephrotoxicity. When voriconazole is discontinued, ciclosporin levels must be carefully monitored and the dose increased as necessary.
Tacrolimus (0.1 mg/kg single dose)	Tacrolimus C_{max} ↑ 117% Tacrolimus AUC_{t} ↑ 221%	When initiating voriconazole in patients already on tacrolimus, it is recommended that the tacrolimus dose be reduced to a third of the original dose and tacrolimus level carefully monitored. Increased tacrolimus levels have been associated with nephrotoxicity. When voriconazole is discontinued, tacrolimus levels must be carefully monitored and the dose increased as necessary.
Long-acting Opiates *[CYP3A4 substrates]* Oxycodone (10 mg single dose)	In an independent published study, Oxycodone C_{max} ↑ 1.7-fold Oxycodone $AUC_{0-\infty}$ ↑ 3.6-fold	Dose reduction in oxycodone and other long-acting opiates metabolised by CYP3A4 (e.g., hydrocodone) should be considered. Frequent monitoring for opiate-associated adverse events may be necessary.
Methadone (32-100 mg QD) *[CYP3A4 substrate]*	R-methadone (active) C_{max} ↑ 31% R-methadone (active) AUC_{τ} ↑ 47% S-methadone C_{max} ↑ 65% S-methadone AUC_{τ} ↑ 103%	Frequent monitoring for adverse events and toxicity related to methadone, including QT prolongation, is recommended. Dose reduction of methadone may be needed.
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) *[CYP2C9 substrates]* Ibuprofen (400 mg single dose) Diclofenac (50 mg single dose)	S-Ibuprofen C_{max} ↑ 20% S-Ibuprofen $AUC_{0-\infty}$ ↑ 100% Diclofenac C_{max} ↑ 114% Diclofenac $AUC_{0-\infty}$ ↑ 78%	Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Dose reduction of NSAIDs may be needed.

Medicinal product ***[Mechanism of Interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
Omeprazole (40 mg QD)* *[CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate]*	Omeprazole C_{max} ↑ 116% Omeprazole AUC_{τ} ↑ 280% Voriconazole C_{max} ↑ 15% Voriconazole AUC_{τ} ↑ 41% Other proton pump inhibitors that are CYP2C19 substrates may also be inhibited by voriconazole and may result in increased plasma concentrations of these medicinal products.	No dose adjustment of voriconazole is recommended. When initiating voriconazole in patients already receiving omeprazole doses of 40 mg or above, it is recommended that the omeprazole dose be halved.
Oral Contraceptives* *[CYP3A4 substrate; CYP2C19 inhibitor]* Norethisterone/ethinylestradiol (1 mg/0.035 mg QD)	Ethinylestradiol C_{max} ↑ 36% Ethinylestradiol AUC_{τ} ↑ 61% Norethisterone C_{max} ↑ 15% Norethisterone AUC_{τ} ↑ 53% Voriconazole C_{max} ↑ 14% Voriconazole AUC_{τ} ↑ 46%	Monitoring for adverse events related to oral contraceptives, in addition to those for voriconazole, is recommended.
Short-acting Opiates *[CYP3A4 substrates]* Alfentanil (20 µg/kg single dose, with concomitant naloxone) Fentanyl (5 µg/kg single dose)	 In an independent published study, Alfentanil $AUC_{0-\infty}$ ↑ 6-fold In an independent published study, Fentanyl $AUC_{0-\infty}$ ↑ 1.34-fold	Dose reduction of alfentanil, fentanyl and other short-acting opiates similar in structure to alfentanil and metabolised by CYP3A4 (e.g., sufentanil) should be considered. Extended and frequent monitoring for respiratory depression and other opiate-associated adverse events is recommended.
Statins (e.g., lovastatin) *[CYP3A4 substrates]*	Although not studied, voriconazole is likely to increase the plasma concentrations of statins that are metabolised by CYP3A4 and could lead to rhabdomyolysis.	If concomitant administration of voriconazole with statins metabolised by CYP3A4 cannot be avoided, dose reduction of the statin should be considered.
Sulphonylureas (including but not limited to: tolbutamide, glipizide, glyburide) *[CYP2C9 substrates]*	Although not studied, voriconazole is likely to increase the plasma concentrations of sulphonylureas and cause hypoglycaemia.	Careful monitoring of blood glucose is recommended. Dose reduction of sulfonylureas should be considered.
Vinca Alkaloids (including but not limited to: vincristine and vinblastine) *[CYP3A4 substrates]*	Although not studied, voriconazole is likely to increase the plasma concentrations of vinca alkaloids and lead to neurotoxicity.	Dose reduction of vinca alkaloids should be considered.
Other HIV Protease Inhibitors (including but not limited to: saquinavir, amprenavir and nelfinavir)* *[CYP3A4 substrates and inhibitors]*	Not studied clinically. *In vitro* studies show that voriconazole may inhibit the metabolism of HIV protease inhibitors and the metabolism of voriconazole may also be inhibited by HIV protease inhibitors.	Careful monitoring for any occurrence of drug toxicity and/or lack of efficacy, and dose adjustment may be needed.
Other Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (including but not limited to: delavirdine, nevirapine)* *[CYP3A4 substrates, inhibitors or CYP450 inducers]*	Not studied clinically. *In vitro* studies show that the metabolism of voriconazole may be inhibited by NNRTIs and voriconazole may inhibit the metabolism of NNRTIs. The findings of the effect of efavirenz on voriconazole suggest that the metabolism of voriconazole may be induced by a NNRTI.	Careful monitoring for any occurrence of drug toxicity and/or lack of efficacy, and dose adjustment may be needed.

Medicinal product ***[Mechanism of Interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
Tretinoin *[CYP3A4 substrate]*	Although not studied, voriconazole may increase tretinoin concentrations and increase risk of adverse reactions (pseudotumor cerebri, hypercalcaemia).	Dose adjustment of tretinoin is recommended during treatment with voriconazole and after its discontinuation.
Cimetidine (400 mg BID) *[non-specific CYP450 inhibitor and increases gastric pH]*	Voriconazole C_{max} ↑ 18% Voriconazole AUC_{τ} ↑ 23%	No dose adjustment.
Digoxin (0.25 mg QD) *[P-gp substrate]*	Digoxin C_{max} ↔ Digoxin AUC_{τ} ↔	No dose adjustment.
Indinavir (800 mg TID) *[CYP3A4 inhibitor and substrate]*	Indinavir C_{max} ↔ Indinavir AUC_{τ} ↔ Voriconazole C_{max} ↔ Voriconazole AUC_{τ} ↔	No dose adjustment.
Macrolide antibiotics Erythromycin (1 g BID) *[CYP3A4 inhibitor]* 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) *[UDP-glucuronyl transferase substrate]*	Mycophenolic acid C_{max} ↔ Mycophenolic acid AUC_{t} ↔	No dose adjustment.
Corticosteroids Prednisolone (60 mg single dose) *[CYP3A4 substrate]*	 Prednisolone C_{max} ↑ 11% Prednisolone $AUC_{0-\infty}$ ↑ 34%	 No dose adjustment. Patients on long-term treatment with voriconazole and corticosteroids (including inhaled corticosteroids e.g., budesonide) should be carefully monitored for adrenal cortex dysfunction both during treatment and when voriconazole is discontinued (see Section 4.4).
Ranitidine (150 mg BID) *[increases gastric pH]*	Voriconazole C_{max} and AUC_{τ} ↔	No dose adjustment.

Calcium channel blockers (CYP3A4 substrates): Although not studied clinically, voriconazole has been shown to inhibit felodipine metabolism *in vitro*. Therefore, voriconazole is likely to increase the plasma concentrations of calcium channel blockers that are metabolised by CYP3A4. Frequent monitoring of adverse events and toxicity related to calcium channel blockers are recommended during co-administration. Dose adjustment of the calcium channel blocker may be needed.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Studies in animals have shown reproductive toxicity at high doses (see Section 5.3). The potential risk to humans is unknown.

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

Women of childbearing potential

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

Lactation

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

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

Voriconazole may cause transient and reversible changes to vision, including blurring, altered/enhanced visual perception, and/or photophobia. Patients must avoid potentially hazardous tasks, such as driving or operating machinery while experiencing these symptoms. Patients should not drive at night while taking voriconazole.

4.8 Undesirable effects

The safety profile of voriconazole in adults is based on an integrated safety database of more than 2,000 subjects (1,603 adult patients in therapeutic studies). This represents a heterogeneous population, containing patients with haematological malignancy, HIV infected patients with oesophageal candidiasis and refractory fungal infections, non-neutropenic patients with candidaemia or aspergillosis and healthy volunteers.

In addition, the safety of voriconazole was investigated in 279 patients (including 270 adults) who were treated with voriconazole in prophylaxis studies. The adverse event profile in these prophylaxis studies was similar to the established safety profile from 2,000 subjects in voriconazole clinical trials.

The table below includes all causality adverse reactions in 1,873 adults from pooled therapeutic (1,603) and prophylaxis (270) studies. The most commonly reported adverse events were visual impairment, liver function test abnormal, pyrexia, rash, vomiting, nausea, diarrhoea, headache, peripheral oedema and abdominal pain. The severity of the adverse events was generally mild to moderate. No clinically significant differences were seen when the safety data were analysed by age, race, or gender.

Adults in combined therapeutic and prophylaxis studies: ADRs by SOC and CIOMS frequency category listed in order of decreasing medical seriousness within each frequency category and SOC

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Frequency Not Known (Cannot be Estimated from the Available Data)
Infections and infestations		Sinusitis	pseudomembranous colitis		
Neoplasms benign, malignant and unspecified (including cysts and polyps)					squamous cell carcinoma (including cutaneous SCC *in situ*, or Bowen's disease)[*,g]
Blood and lymphatic system disorders		agranulocytosis[a], pancytopenia, thrombocytopenia[b], leukopenia, anaemia	bone marrow failure, lymphadenopathy, eosinophilia	disseminated intravascular coagulation	
Immune system disorders			hypersensitivity	anaphylactoid reaction	
Endocrine disorders			adrenal insufficiency, hypothyroidism	hyperthyroidism	
Metabolism and nutrition disorders	oedema peripheral	hypoglycaemia, hypokalaemia, hyponatraemia[*]			
Psychiatric disorders		depression, hallucination, anxiety, insomnia, agitation, confusional state			
Nervous system disorders	headache	syncope, tremor, hypertonia[e], paraesthesia, somnolence, dizziness	brain oedema, encephalopathy[c], extrapyramidal disorder[d], neuropathy peripheral, ataxia, hypoaesthesia, dysgeusia	convulsion, hepatic encephalopathy, Guillain-Barré syndrome, nystagmus	
Eye disorders	visual impairment[h]	retinal haemorrhage	optic nerve disorder[f], papilloedema[g], oculogyric crisis, diplopia, scleritis, blepharitis	optic atrophy, corneal opacity	
Ear and labyrinth disorders			hypoacusis, vertigo, tinnitus		
Cardiac disorders		arrhythmia supraventricular, tachycardia, bradycardia	ventricular fibrillation, ventricular extrasystoles, ventricular	*torsades de pointes*, atrioventricular block complete, bundle branch	

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Frequency Not Known (Cannot be Estimated from the Available Data)
			tachycardia, electrocardiogram QT prolonged, supraventricular tachycardia	block, nodal rhythm	
Vascular disorders		hypotension, phlebitis	thrombophlebitis, lymphangitis		
Respiratory, thoracic and mediastinal disorders		acute respiratory distress syndrome, pulmonary oedema			
Gastrointestinal disorders	diarrhoea, vomiting, abdominal pain, nausea	cheilitis, dyspepsia, constipation, gingivitis	peritonitis, pancreatitis, swollen tongue, duodenitis, gastroenteritis, glossitis		
Hepatobiliary disorders	liver function test abnormal	jaundice, jaundice cholestatic, hepatitis[i]	hepatic failure, hepatomegaly, cholecystitis, cholelithiasis		
Skin and subcutaneous tissue disorders	rash	dermatitis exfoliative, alopecia, rash maculo-papular, pruritus	Stevens-Johnson syndrome[g], photosensitivity reaction, purpura, urticaria, eczema	toxic epidermal necrolysis[g], angioedema, pseudoporphyria, erythema multiforme, psoriasis, drug eruption	cutaneous lupus erythematosus[*], drug reaction with eosinophilia and systemic symptoms[*,g]
Musculoskeletal and connective tissue disorders		back pain	arthritis		periostitis
Renal and urinary disorders		renal failure acute, haematuria	renal tubular necrosis, proteinuria, nephritis		
General disorders and administration site conditions	pyrexia	chest pain, face oedema[j], asthenia, chills	infusion site reaction, influenza like illness		
Investigations		blood creatinine increased	blood urea increased, blood cholesterol increased		

[*]ADR identified post-marketing
[a] Includes febrile neutropenia and neutropenia.
[b] Includes immune thrombocytopenic purpura.
[c] Includes hypoxic-ischaemic encephalopathy and metabolic encephalopathy.
[d] Includes akathisia and parkinsonism.
[e] Includes nuchal rigidity and tetany.
[f] Prolonged optic neuritis has been reported post-marketing. See Section 4.4.
[g] See Section 4.4.
[h] See "Visual impairments" paragraph in Section 4.8.
[i] Includes drug-induced liver injury, hepatitis toxic, hepatocellular injury and hepatotoxicity.

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

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. There was evidence of attenuation with repeated doses of voriconazole. The visual impairments were generally mild, rarely resulted in discontinuation and were not associated with long-term sequelae. Visual impairments may be associated with higher plasma levels and/or doses.

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

The mechanism of action is unknown, although the site of action is most likely to be within the retina.

In a study in healthy volunteers investigating the impact of voriconazole on retinal function, voriconazole caused a decrease in the electroretinogram (ERG) waveform amplitude. The ERG measures electrical currents in the retina. The ERG changes did not progress over 29 days of administration and were fully reversible on withdrawal of voriconazole.

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

Dermatological reactions

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

If patients develop a rash they should be monitored closely and voriconazole discontinued if lesions progress. Patients receiving long-term voriconazole therapy have developed photosensitive skin reactions (see Section 4.4).

Dermatological adverse reactions potentially related to phototoxicity (pseudoporphyria, cheilitis, and cutaneous lupus erythematosus) are also reported with voriconazole. Sun avoidance and photoprotection are recommended for all patients. If phototoxicity occurs, voriconazole discontinuation and dermatological evaluation should be considered (see Section 4.4).

Liver function tests

The overall incidence of transaminase increases >3 x ULN (not necessarily comprising an adverse event) in the voriconazole clinical program was 18.0% (319/1,768) in adults and 25.8% (73/283) in paediatric subjects who received voriconazole for pooled therapeutic and prophylaxis use. Liver function test abnormalities may be associated with higher plasma levels and/or doses. The majority of

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

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

Paediatric use

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). The adverse event profile in these 288 paediatric patients was similar to that in adults. A higher frequency of liver enzyme elevations reported as adverse events (14.2% transaminases increased in paediatrics compared to 5.3% in adults) was observed in paediatric patients as compared to adults. The safety of voriconazole was investigated in additional paediatric patients aged 2 to <12 years who were observed in compassionate use programs (158 paediatric patients). The adverse event profile in these paediatric patients was similar to that observed in adults.

Post-marketing data suggest there might be a higher occurrence of skin reactions 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 events (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.

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.

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).

4.9 Overdose

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

There is no known antidote to voriconazole; it is recommended that treatment of overdose be symptomatic and supportive.

Voriconazole is haemodialysed with clearance of 121 mL/min. The intravenous vehicle, SBECD, is haemodialysed with 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

Mode of action

Voriconazole is a triazole antifungal agent. The primary mode of action of voriconazole is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell 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 2,425 ng/mL (inter-quartile range 1193 to 4,380 ng/mL) and 3,742 ng/mL (inter-quartile range 2,027 to 6,302 ng/mL), respectively. A positive association between mean, maximum or minimum plasma voriconazole concentration and efficacy in therapeutic studies was not found.

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

Microbiology

In vitro, voriconazole displays broad-spectrum antifungal activity with antifungal potency against *Candida* species (including fluconazole resistant *C. krusei* and resistant strains of *C. glabrata* and *C. albicans*) and fungicidal activity against all *Aspergillus* species tested. In addition voriconazole shows *in vitro* fungicidal activity against emerging fungal pathogens, including those such as *Scedosporium* or *Fusarium* which have limited susceptibility to existing antifungal agents.

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

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

In vitro activity against clinical isolates has been observed for *Acremonium* spp., *Alternaria* spp., *Bipolaris* spp., *Cladophialophora* spp., *Histoplasma capsulatum,* with most strains being inhibited by concentrations of voriconazole in the range 0.05 to 2 mcg/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 minimum inhibitory concentrations (MICs) of less than 1 mg/L for voriconazole.

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

Clinical and Laboratory Standards Institute (CLSI) Breakpoints

Breakpoint criteria established by CLSI

Susceptibility Testing Methods

Aspergillus species and other filamentous fungi: No interpretive criteria have been established for *Aspergillus* species and other filamentous fungi.

Candida species: The interpretive standards for voriconazole against *Candida* species are applicable only to tests performed using Clinical and Laboratory Standards Institute (CLSI) microbroth dilution reference method M27 for MIC read at 48 hours or disk diffusion reference method M44 for zone diameter read at 24 hours. *In vitro* susceptibility testing was performed according to the Clinical Laboratory and Standards Institute (CLSI) methods (M38-P for moulds and, M27-A and M44-A for yeasts). Voriconazole breakpoints (MIC and zone diameter) have been established for *Candida* species, but not the filamentous fungi, including *Aspergillus* species.

NOTE: Susceptibility testing by dilution methods requires the use of voriconazole susceptibility powder.

Broth Dilution Techniques: Quantitative methods are used to determine antifungal MICs. These MICs provide estimates of the susceptibility of *Candida* species to antifungal agents. MICs should be determined using a standardised procedure at 48 hours. Standardised procedures are based on a microdilution method (broth) with standardised inoculums concentrations and standardised concentrations of voriconazole powder. The MIC values should be interpreted according to the criteria provided in the table below.

Diffusion Techniques: Qualitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of *Candida* species to an antifungal agent. One such standardised procedure requires the use of standardised inoculum concentrations. This procedure uses paper discs impregnated with 1 microgram of voriconazole to test the susceptibility of yeasts to voriconazole. Disc diffusion interpretive criteria are also provided in the table below.

Susceptibility Interpretive Criteria for Voriconazole

	Broth Dilution at 48 hours (MIC in µg/mL)			Disc Diffusion at 24 hours (Zone diameters in mm)		
	Susceptible (S)	**Susceptible-dose dependent (S-DD)**	**Resistant (R)**	**Susceptible (S)**	**Susceptible-dose dependent (S-DD)**	**Resistant (R)**
Voriconazole	≤1.0	2.0	≥4.0	≥17	14-16	≤13

Note 1: Shown are the breakpoints (µg/mL) for voriconazole against *Candida* species. If MICs are measured using a scale that yields results falling between categories, the next higher category is implied. Thus, an isolate with a voriconazole MIC of 1.5 µg/mL would be placed in the S-DD category.

The susceptible category implies that isolates are inhibited by the usually achievable concentrations of antifungal agent tested when the recommended dosage is used for the site of infection. The susceptible-dose dependent category implies that an infection due to the isolate may be appropriately treated in body sites where the drugs are physiologically concentrated or when a high dosage of drug is used. The resistant category implies that isolates are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies.

Quality Control

Standardised susceptibility test procedures require the use of quality control organisms to control the technical aspects of the test procedures. Standard voriconazole powder and 1 µg discs should provide the following range of values noted in the table below.

NOTE: Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within fungi; the specific strains used for microbiological control are not clinically significant.

Acceptable Quality Control Ranges for Voriconazole to be used in Validation of Susceptibility Test Results

	Broth Dilution (MIC in µg/mL)		Disk Diffusion (Zone diameter in mm) @ 24-hour
	@24-hour	**@48-hour**	
QC Strain			
Candida parapsilosis ATCC 22019	0.016-0.12	0.03-0.25	28-37
Candida krusei ATCC 6258	0.06-0.5	0.12-1.0	16-25
Candida albicans ATCC 90028	*	*	31-42

* Quality control ranges have not been established for this strain/antifungal agent combination due to their extensive interlaboratory variation during initial quality control studies.

ATCC is a registered trademark of the American Type Culture Collection.

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 compared to 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 seven 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 PO 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.

Serious invasive *Candida* infections – efficacy 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 (370) non-neutropenic patients (above 12 years of age) with documented candidaemia were included in the study, of which 248 were treated with voriconazole. The patient population was seriously ill, with approximately 50% of subjects in the intensive care unit and 40% mechanically ventilated at baseline. The median treatment duration was 15 days in both treatment arms. In the primary analysis, successful response as assessed by a Data Review Committee (DRC) blinded to study medication was defined as resolution/improvement in all clinical signs and symptoms of infection with eradication of *Candida* from blood and infected deep tissue sites at 12 weeks after the end of therapy (EOT). In this analysis a successful response was seen in 41% of patients in both treatment arms 12 weeks after EOT.

Patients who did not have an assessment 12 weeks after EOT were counted as failures. 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.

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.

Other serious rare fungal pathogens

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

Scedosporium spp. - Successful response to voriconazole therapy was seen in 16 of 28 patients (55%) with *S. apiospermum* and in 2 of 7 patients (29%) with *S. prolificans* infection. In addition, a successful response was seen in 1 of 3 patients with mixed organism infections.

Fusarium spp. - Seven of 17 (41%) patients were successfully treated with voriconazole. Of these 7 patients, 3 had eye, 1 had sinus, and 3 had disseminated infection. Four additional patients with fusariosis had an infection caused by several organisms; two of them had a successful outcome.

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

Primary prophylaxis of invasive fungal infections – Efficacy in allogeneic haematopoietic stem cell transplant (HSCT) recipients without prior proven or probable invasive fungal infection (IFI)

Voriconazole was compared to itraconazole as primary prophylaxis in an open-label, comparative, multicentre 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 myeloablative (58%) or reduced-intensity (42%) conditioning 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 randomisation.

Pathogens responsible for breakthrough IFI in voriconazole & itraconazole groups	
Voriconazole*	*Aspergillus fumigatus*, *Candida krusei*, *Candida parapsilosis*
Itraconazole**	*Aspergillus fumigatus*, Aspergillus species

* Breakthrough IFIs occurred after study drug discontinuation.
** Three out of five cases occurred after study drug discontinuation.

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, multicentre 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 candidaemia, 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

Intravenous and oral voriconazole allows flexibility in patient care and the possibility of prolonged treatment where indicated. In clinical trials, 714 patients received voriconazole therapy for greater than 12 weeks, with 155 subjects receiving voriconazole for over 6 months.

Clinical studies in children

Fifty-three paediatric patients aged 2 to <18 years were treated with voriconazole in two prospective, open-label, non-comparative, multicentre 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 oesophageal candidiasis (EC) requiring either primary or salvage therapy, of whom 17 were included in the MITT efficacy analyses. Of the total of 31 patients included in the MITT analyses, 14 were 2 to <12 years old (5 patients with IA and 9 with ICC or EC) and 17 were 12 to <18 years old (9 patients with IA and 8 with ICC and EC). The overall rates of global response were 64.3% (9/14) at 6 weeks for patients with IA, 85.7% (6/7) at EOT for patients with ICC and 70% (7/10) at EOT for patients with EC. In subjects with IA, the success rate was 40% (2/5) for patients 2 to <12 years and 77.8% (7/9) for patients 12 to <18 years of age.

Clinical studies examining QT interval

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

5.2 Pharmacokinetic properties

General pharmacokinetic characteristics

The pharmacokinetics of voriconazole has 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 is 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 an approximately 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 (see table below).

Voriconazole Pharmacokinetic Parameters in Adults Receiving Different Dosing Regimens

Geometric mean (CV%)[a]	**6 mg/kg IV (loading dose)**	**3 mg/kg IV Q12h**	**4 mg/kg IV Q12h**	**400 mg Oral (loading dose)**	**200 mg Oral Q12h**	**300 mg Oral Q12h**
n	35	23	40	17	48	16
AUC_{12} (µg·h/mL)	13.9 (32)	13.7 (53)	33.9 (54)	9.31 (38)	12.4 (78)	34.0 (53)
C_{max} (µg/mL)	3.13 (20)	3.03 (25)	4.77 (36)	2.30 (19)	2.31 (48)	4.74 (35)
C_{min} (µg/mL)	--	0.46 (97)	1.73 (74)	--	0.46 (120)	1.63 (79)

[a] Parameters were estimated based on non-compartmental analysis from 5 pharmacokinetic studies.
AUC_{12} = area under the curve over 12 hour dosing interval, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration.

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 (e.g., 6 mg/kg IV every 12 hours on Day 1 followed by 3 mg/kg IV every 12 hours; 400 mg oral every 12 hours on Day 1 followed by 200 mg oral every 12 hours). 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 to 2 hours after dosing. The oral bioavailability of voriconazole is estimated to be 96%. Bioequivalence was established between the 200 mg tablet and the 40 mg/mL oral suspension when administered as a 400 mg every 12 hours loading dose followed by a 200 mg every 12 hours maintenance dose. When multiple doses of voriconazole are administered with high fat meals, C_{max} and AUC_{τ} are reduced by 34% and 24%, respectively, when administered as a tablet and by 58% and 37%, respectively, when administered as the oral suspension.

The absorption of voriconazole is not affected by changes in gastric pH.

Distribution

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

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

Metabolism

In vitro studies showed that voriconazole is metabolised by the hepatic cytochrome P450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4.

The inter-individual variability of voriconazole pharmacokinetics is high.

In vivo studies indicated that CYP2C19 plays a key role in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism. For example, 15%-20% of Asian populations may be expected to be poor metabolisers. For Caucasians and Blacks, the prevalence of poor metabolisers is 3%-5%. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolisers have, on

average, 4-fold higher voriconazole exposure (AUC_τ) than their homozygous extensive metaboliser counterparts. Subjects who are heterozygous extensive metabolisers have on average 2-fold higher voriconazole exposure than their homozygous extensive metaboliser counterparts.

The major metabolite of voriconazole is the N-oxide, which accounts for 72% of the circulating radiolabelled metabolites in plasma. This metabolite has minimal antifungal activity and does not contribute to the overall efficacy of voriconazole.

Excretion

Voriconazole is eliminated via hepatic metabolism with less than 2% of the dose excreted unchanged in the urine.

After administration of a radiolabelled dose of voriconazole, approximately 80% of the radioactivity is recovered in the urine after multiple intravenous dosing and 83% in the urine after multiple oral dosing. The majority (>94%) of the total radioactivity is excreted in the first 96 hours after both oral and intravenous dosing.

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

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) after tablet dosing. 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 a similar study, after dosing with the oral suspension, the mean AUC for healthy young females was 45% higher than in healthy young males, whereas the mean C_{max} was comparable between genders. The steady-state trough voriconazole concentrations (C_{min}) seen in females were 100% and 91% higher than in males receiving the tablet and the oral suspension, respectively.

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

Elderly

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

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

Paediatrics

The recommended intravenous dose in paediatric patients is based on a population pharmacokinetic analysis of data pooled from 82 immunocompromised paediatric patients aged 2 to <12 years old who

were evaluated in three pharmacokinetic studies (examining single intravenous doses of 3 and 4 mg/kg twice daily, multiple intravenous doses of 3, 4, 6 and 8 mg/kg twice daily and multiple oral suspension doses of 4 and 6 mg/kg twice daily). The majority of patients received more than one dose level with a maximum duration of dosing of 30 days. A comparison of the paediatric and adult population pharmacokinetic data indicated that in order to obtain comparable exposures to those obtained in adults following intravenous maintenance doses of 4 mg/kg twice daily, intravenous maintenance doses of 7 mg/kg twice daily are required in paediatric patients. 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.

In order to obtain comparable exposures to those obtained in adults following intravenous maintenance doses of 3 mg/kg twice daily, intravenous maintenance doses of 4 mg/kg twice daily are required in paediatric patients. Based on the population pharmacokinetic analysis, no loading dose or dosage adjustment according to age is warranted in patients aged 2 to <12 years old.

The recommended oral dose in paediatrics is based on a population pharmacokinetic analysis data obtained from 47 immunocompromised paediatric patients aged 2 to <12 years old who were evaluated in a pharmacokinetic study examining multiple oral suspension doses of 4 to 6 mg/kg twice daily. A comparison of the paediatric and adult population pharmacokinetic data indicated that in order to obtain comparable exposures to those obtained in adults following a maintenance dose of 200 mg twice daily, the same dose of 200 mg of oral solution twice daily is required in paediatric patients, independent of body weight. In paediatric patients there is a general trend towards low bioavailability at lower body weights and high bioavailability at higher body weights (towards the extent demonstrated in adults). The estimated bioavailability in paediatric patients following oral administration (POS) was 44.6%. Based on the population pharmacokinetic analysis, no dosage adjustment according to age or weight is warranted in patients aged 2 to <12 years old at the 200 mg bid oral solution dosing regimen. A loading dose is not indicated in paediatric patients.

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.

Renal impairment

In a single oral 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 dosing and monitoring recommendations under Sections 4.2 and 4.4.

In patients with moderate to severe renal dysfunction (serum creatinine levels ≥220 micromol/L (2.5 mg/dL), accumulation of the intravenous vehicle, SBECD, occurs. See dosing and monitoring recommendations under Sections 4.2 and 4.4.

Hepatic impairment

After a single oral 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 a multiple oral dose study, AUC_{τ} was similar in subjects with moderate hepatic cirrhosis (Child-Pugh B) given maintenance doses 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). For dosing information, refer to use in patients with hepatic impairment Section 4.2.

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 peri-natal 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Film-coated tablets:
Tablet Core:
Lactose Monohydrate, Pre-gelatinised Starch, Croscarmellose Sodium, Povidone, Magnesium Stearate.

Film-Coat:
Hypromellose, Titanium Dioxide (E171), Lactose Monohydrate, Glycerol Triacetate.

Powder for oral suspension:
Sucrose (0.54 g per mL of suspension), Silica colloidal, Titanium dioxide (E171), Xanthan gum, Sodium citrate dihydrate, Sodium benzoate (E211), citric acid, natural orange flavour (containing orange oil, maltodextrin and tocopherol).

Powder for solution for infusion:
Sulphobutylether Beta Cyclodextrin Sodium.
Water for Injections.

6.2 Incompatibilities

Film-coated tablets:
Not applicable.

Powder for oral suspension:
Voriconazole powder for oral suspension and the 40 mg/mL reconstituted oral suspension must not be mixed with other medicinal products or additional flavouring agent. It is not intended that the suspension be further diluted with water or other vehicles.

Powder for solution for infusion:
Voriconazole must not be infused into the same line or cannula concomitantly with other intravenous products.

Blood products and concentrated electrolytes

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

Intravenous solutions containing (non-concentrated) electrolytes

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

Total parenteral nutrition (TPN)

Voriconazole can be infused at the same time as total parenteral nutrition but must 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 voriconazole.

Voriconazole 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

Film-coated tablets:
Please refer to outer carton for shelf-life.

Powder for oral suspension:
Please refer to outer carton for shelf-life. The shelf-life of the constituted suspension is 14 days.

Powder for solution for infusion:
Voriconazole Powder for Solution for Infusion: Please refer to outer carton for shelf-life.
Reconstituted concentrate: 24 hours at 2°C-8°C.

6.4 Special precautions for storage

Film-coated tablets:
Refer to outer carton.

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

Powder for solution for infusion:
The unreconstituted vial: Do not store above 30°C.
Reconstituted concentrate: Store at 2°C-8°C for up to 24 hours (in a refrigerator).

6.5 Nature and contents of container

Film-coated tablets:
PVC/Aluminium blister in cartons of 10's and 20's.

Powder for oral suspension:
One 100 mL high-density polyethylene (HDPE) bottle (with a polypropylene child resistant closure) contains 45 g of powder for oral suspension. Following constitution, the volume of the suspension is 75 mL, providing a usable volume of 70 mL.

A measuring cup (graduated to indicate 23 mL), 5 mL oral syringe and a press-in bottle adaptor are also provided.

Pack size:
1 bottle

Powder for solution for infusion:
Voriconazole is supplied as a sterile lyophilised powder in individually boxed, single use 30 mL clear Type I glass vials with rubber stoppers and aluminium caps with plastic seals.

6.6 Instructions for use and handling

Film-coated tablets:
Not applicable.

Powder for solution for infusion:
Voriconazole is supplied in single use vials. The vial contents are reconstituted with 19 mL of Water for Injections to obtain a clear solution containing 10 mg/mL of voriconazole and an extractable volume of 20 mL. Discard the vial if vacuum does not pull the diluent into the vial. For administration, the required volume of the reconstituted solution (table below) is added to a recommended compatible infusion solution (detailed below) to obtain, where appropriate, a final voriconazole solution containing 0.5-5 mg/mL.

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)	7 mg/kg dose (number of vials)
10	-	4.0 mL (1)	-	7.0 mL (1)
15	-	6.0 mL (1)	-	10.5 mL (1)
20	-	8.0 mL (1)	-	14.0 mL (1)
25	-	10.0 mL (1)	-	17.5 mL (1)
30	9.0 mL (1)	12 mL (1)	18 mL (1)	21.0 mL (2)
35	10.5 mL (1)	14 mL (1)	21 mL (2)	24.5 mL (2)
40	12.0 mL (1)	16 mL (1)	24 mL (2)	28.0 mL (2)

45	13.5 mL (1)	18 mL (1)	27 mL (2)	31.5 mL (2)
50	15.0 mL (1)	20 mL (1)	30 mL (2)	35.0 mL (2)
55	16.5 mL (1)	22 mL (2)	33 mL (2)	-
60	18.0 mL (1)	24 mL (2)	36 mL (2)	-
65	19.5 mL (1)	26 mL (2)	39 mL (2)	-
70	21.0 mL (2)	28 mL (2)	42 mL (3)	-
75	22.5 mL (2)	30 mL (2)	45 mL (3)	-
80	24.0 mL (2)	32 mL (2)	48 mL (3)	-
85	25.5 mL (2)	34 mL (2)	51 mL (3)	-
90	27.0 mL (2)	36 mL (2)	54 mL (3)	-
95	28.5 mL (2)	38 mL (2)	57 mL (3)	-
100	30.0 mL (2)	40 mL (2)	60 mL (3)	-

Voriconazole is a single dose unpreserved sterile lyophile. Therefore, from a microbiological point of view, 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.

The reconstituted solution can be diluted with:

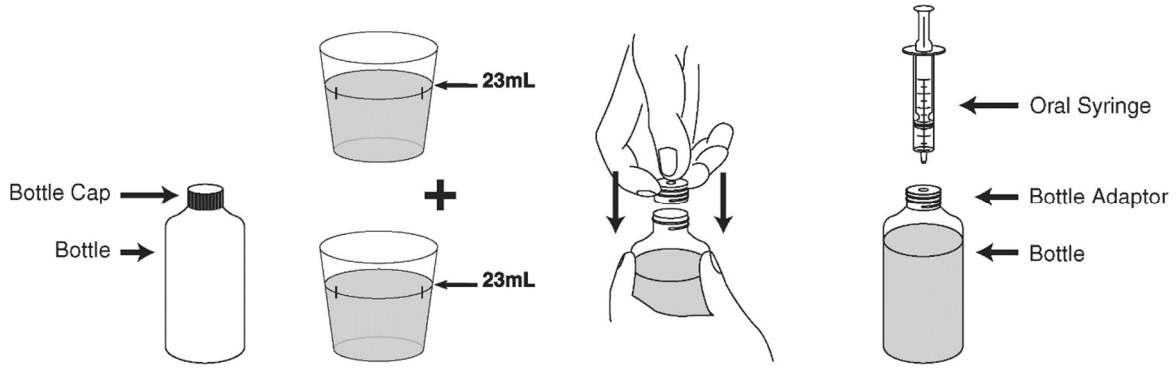
0.9% Sodium Chloride Intravenous Infusion
Compound Sodium Lactate Intravenous Infusion
5% Glucose and Compound Sodium Lactate Intravenous Infusion
5% Glucose and 0.45% Sodium Chloride Intravenous Infusion
5% Glucose Intravenous Infusion
5% Glucose in 20 mEq Potassium Chloride Intravenous Infusion
0.45% 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.

Powder for oral suspension:

Constitution instructions:

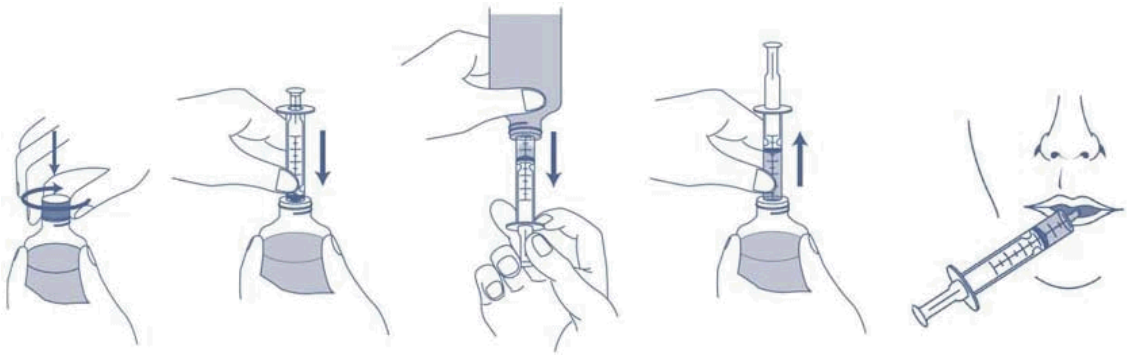
1. Tap the bottle to release the powder.
2. Remove the child-resistant cap.
3. A total of 46 mL of water should be added to the bottle: measure 23 mL of water by filling the measuring cup to the top of the marked line. Add the water to the bottle. Using the cup, measure another 23 mL of water and add this to the bottle.
4. Replace the cap and shake the closed bottle vigorously for about 1 minute.
5. Remove the cap. Press bottle adaptor into the neck of the bottle (as shown in picture below). The adaptor is provided so that you can fill the oral syringe with medicine from the bottle.
6. Replace the cap.
7. Write the date of expiration 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: (see pictures below)

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

1. Shake the closed bottle of constituted suspension for approximately 10 seconds before each 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.
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.
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 into the syringe. Keep it in a clean safe place with the medicine.

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7. PRODUCT OWNER

Pfizer Inc.
New York,
United States

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