SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VFEND® 200 mg Powder for Solution for Infusion
VFEND® 50 mg Film-Coated Tablets
VFEND® 200 mg Film-Coated Tablets
VFEND® 40 mg/mL Powder for Oral Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

VFEND Powder for solution for infusion:
Each vial contains 200 mg of voriconazole.

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

Excipients with known effect
Each vial contains 221 mg sodium.
Each vial contains 3,200 mg cyclodextrin.

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

Excipient with known effect
Each 50 or 200 mg tablet contains 62.5 or 250.0 mg lactose monohydrate respectively.

VFEND Powder for oral suspension:
Each ml of oral suspension contains 40 mg of voriconazole when reconstituted with water. Each bottle contains 3 g of voriconazole.

Excipient with known effect:
Each ml of suspension contains 0.54 g sucrose.
Each ml of suspension contains 2.40 mg sodium benzoate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

VFEND Film-coated tablets:
VFEND 50 mg film-coated tablets are white to off-white, round tablets, debossed “Pfizer” on one side and “VOR50” on the reverse.
VFEND 200 mg film-coated tablets are white to off-white, capsule-shaped tablets, debossed “Pfizer” on one side and “VOR200” on the reverse.

VFEND Powder for oral suspension:
Powder for oral suspension is a white to off-white powder providing a white to off-white opaque fluid containing undissolved solids when constituted.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Treatment of invasive aspergillosis.

Treatment of candidemia in non-neutropenic patients.

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

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

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

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

4.2 Posology and method of administration

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

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

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

Treatment

Adults
Therapy must be initiated with the specified intravenous loading dose regimen of VFEND to achieve adequate plasma concentrations on Day 1. Intravenous treatment should be continued for at least 7 days before switching to oral treatment (see section 5.1). Once the patient is clinically improved and can tolerate medication given by mouth, the oral tablet form or oral suspension form of voriconazole may be utilized. 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	----	-----
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 (2.5ml) every 12 hours
Invasive Aspergillosis/ Scedosporium and Fusarium infections/ Other serious mould infections[b]	4 mg/kg every 12 hours	200 mg (5 ml) every 12 hours	100 mg (2.5ml) every 12 hours
Candidemia in non-neutropenic patients	3-4 mg/kg every 12 hours[c]	200 mg (5 ml) every 12 hours	100 mg (2.5ml) every 12 hours

a In healthy volunteer studies, the 200 mg oral every 12 hours dose provided an exposure (AUCτ) similar to a 3 mg/kg IV every 12 hours dose, the 300 mg oral every 12 hours dose provided an exposure (AUCτ) 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 candidemia 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.

* This also applies to patients aged 15 years and older.

Duration of treatment

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

Dose adjustment (Adults)

VFEND powder for solution for infusion:

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 coadministered with voriconazole if the maintenance dose of voriconazole is increased to 5 mg/kg intravenously twice daily (see sections 4.4 and 4.5).

Efavirenz may be coadministered with voriconazole if the maintenance dose of voriconazole is increased to 400 mg every 12 hours and the efavirenz dose is reduced by 50%, i.e. to 300 mg once daily. When

treatment with voriconazole is stopped, the initial dosage of efavirenz should be restored (see sections 4.4 and 4.5).

VFEND tablets and VFEND powder for oral suspension:
If patient response is inadequate, the maintenance dose may be increased from 200 mg every 12 hours (similar to 3 mg/kg IV every 12 hours) to 300 mg 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 to 150 mg every 12 hours.

If patients are unable to tolerate treatment at these higher doses (i.e. 300 mg oral every 12 hours), reduce the oral maintenance dose by 50 mg steps to a minimum of 200 mg every 12 hours (or 100 mg every 12 hours for patients less than 40 kg).

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

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

In case of use as prophylaxis, refer below.

Use in paediatrics

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

The recommended dosing regimen is as follows:

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

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

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

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

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

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

Dosage adjustment (Children [2 to <12 years] and young adolescents with low body weight [12 to 14 years and <50 kg])
If a patient response to treatment is inadequate, the dose may be increased by 1 mg/kg steps (or by 50 mg steps if the maximum oral dose of 350 mg was used initially). If patient is unable to tolerate treatment, reduce the dose by 1 mg/kg steps (or by 50 mg steps if the maximum oral dose of 350 mg was used initially).

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

Prophylaxis in Adults and Children
Prophylaxis should be initiated on the day of transplant and may be administered for up to 100 days. Prophylaxis should be as short as possible depending on the risk for developing invasive fungal infection (IFI) as defined by neutropenia or immunosuppression. It may only be continued up to 180 days after transplantation in case of continuing immunosuppression or graft versus host disease (GvHD) (see section 5.1).

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

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

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

* This also applies to patients aged 15 years and older

Children
The recommended dosing regimen for prophylaxis in children is the same as mentioned in the table located under the header: *Use in paediatrics*

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

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

The following instructions apply to both treatment and prophylaxis

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

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

Renal impairment
Powder for solution for infusion:
In patients with moderate to severe renal dysfunction (creatinine clearance < 50 ml/min), accumulation of the intravenous vehicle, SBECD, occurs. Oral voriconazole should be administered to these patients, unless an assessment of the risk benefit to the patient justifies the use of intravenous voriconazole. Serum creatinine levels should be closely monitored in these patients and, if increases occur, consideration should be given to changing to oral voriconazole therapy (see section 5.2).
The intravenous vehicle, SBECD, is haemodialysed with a clearance of 55 ml/min.

Film-coated tablets or Powder for oral suspension:
The pharmacokinetics of orally administered voriconazole arenot affected by renal impairment. Therefore, no adjustment is necessary for oral dosing for patients with mild to severe renal impairment (see section 5.2).

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

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

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

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

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

Method of administration
VFEND film-coated tablets are to be taken at least one hour before, or one hour following, a meal.
VFEND oral suspension is to be taken at least one hour before, or two hours following, a meal.
VFEND powder for solution for infusion requires reconstitution and dilution (see section 6.6) prior to administration as an intravenous infusion. Not for bolus injection.

4.3 Contraindications

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

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

Coadministration with rifabutin, rifampicin, carbamazepine , phenobarbital and St John's Wort is contraindicated since these medicinal products are likely to decrease plasma voriconazole concentrations significantly (see section 4.5).

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

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

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

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

Coadministration of voriconazole with naloxegol, a CYP3A4 substrate, since increased plasma concentrations of naloxegol can precipitate opioid withdrawal symptoms (see section 4.5).

Coadministration of voriconazole with tolvaptan since strong CYP3A4 inhibitors such as voriconazole significantly increase plasma concentrations of tolvaptan (see section 4.5).

Coadministration of voriconazole with lurasidone since significant increases in lurasidone exposure have the potential for serious adverse reactions (see section 4.5).
Coadministration with venetoclax at initiation and during 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).

4.4 Special warnings and precautions for use

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

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

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

- Congenital or acquired QTc-prolongation.
- Cardiomyopathy, in particular when heart failure is present.
- Sinus bradycardia.
- Existing symptomatic arrhythmias.

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

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

Hepatic toxicity
In clinical trials, there have been cases of serious hepatic reactions during treatment with voriconazole (including clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities). Instances of hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly haematological malignancy). Transient hepatic reactions, including hepatitis and jaundice, have occurred among patients with no other identifiable risk factors. Liver dysfunction has usually been reversible on discontinuation of therapy (see section 4.8).

Monitoring of hepatic function
Patients receiving VFEND must be carefully monitored for hepatic toxicity. Clinical management should include laboratory evaluation of hepatic function (specifically AST and ALT) at the initiation of treatment with VFEND and at least weekly for the first month of treatment. Treatment duration should be as short as possible, however, if based on the benefit-risk assessment, the treatment is continued (see section 4.2), monitoring frequency can be reduced to monthly if there are no changes in the liver function tests.

If the liver function tests become markedly elevated, VFEND should be discontinued, unless the medical judgment of the risk- benefit of the treatment for the patient justifies continued use.

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

Serious dermatological adverse reactions

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

- Squamous cell carcinoma of the skin (SCC)
  Squamous cell carcinoma of the skin (including cutaneous SCC in situ, or Bowen's disease) has been reported in patients, some of whom have reported prior phototoxic reactions. If phototoxic reactions occur multidisciplinary advice should be sought, VFEND discontinuation and use of alternative antifungal agents should be considered and the patient should be referred to a dermatologist. If VFEND is continued, however, dermatologic evaluation should be performed on a systematic and regular basis, to allow early detection and management of premalignant lesions. VFEND should be discontinued if premalignant skin lesions or squamous cell carcinoma are identified (see below the section under Long-term treatment).

- Severe cutaneous adverse reactions
  Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms

(DRESS), which can be life-threatening or fatal, have been reported with the use of voriconazole. If a patient develops a rash, he should be monitored closely and VFEND discontinued if lesions progress.

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

Squamous cell carcinoma of the skin (SCC) (including cutaneous SCC in situ, or Bowen's disease) has been reported in relation with long-term VFEND treatment.

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

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

Renal adverse reactions
Acute renal failure has been observed in severely ill patients undergoing treatment with VFEND. Patients being treated with voriconazole are likely to be treated concomitantly with nephrotoxic medicinal products and have concurrent conditions that may result in decreased renal function (see section 4.8).

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

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

Paediatric population
Safety and effectiveness in paediatric subjects below the age of two years has not been established (see sections 4.8 and 5.1). Voriconazole is indicated for paediatric patients aged two years or older. A higher frequency of liver enzyme elevations was observed in the paediatric population (see section 4.8). Hepatic function should be monitored in both children and adults. Oral bioavailability may be limited in paediatric patients aged 2 to <12 years with malabsorption and very low body weight for age. In that case, intravenous voriconazole administration is recommended.

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

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

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

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

Glasdegib (CYP3A4 substrate)
Coadministration 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)
Coadministration 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).

Ritonavir (potent CYP450 inducer; CYP3A4 inhibitor and substrate)
Coadministration of voriconazole and low-dose ritonavir (100 mg twice daily) should be avoided unless an assessment of the benefit/risk to the patient justifies the use of voriconazole (see sections 4.3 and 4.5).

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

Methadone (CYP3A4 substrate)
Frequent monitoring for adverse reactions and toxicity related to methadone, including QTc prolongation, is recommended when coadministered with voriconazole since methadone levels

increased following coadministration of voriconazole. Dose reduction of methadone may be needed (see section 4.5).

Short acting opiates (CYP3A4 substrate)
Reduction in the dose of alfentanil, fentanyl and other short-acting opiates similar in structure to alfentanil and metabolised by CYP3A4 (e.g., sufentanil) should be considered when coadministered with voriconazole (see section 4.5). As the half-life of alfentanil is prolonged in a 4 -fold manner when alfentanil is coadministered with voriconazole and in an independent published study, concomitant use of voriconazole with fentanyl resulted in an increase in the mean $AUC_{0-\infty}$ of fentanyl, frequent monitoring for opiate-associated adverse reactions (including a longer respiratory monitoring period) may be necessary.

Long-acting opiates (CYP3A4 substrate)
Reduction in the dose of oxycodone and other long-acting opiates metabolized by CYP3A4 (e.g., hydrocodone) should be considered when coadministered with voriconazole. Frequent monitoring for opiate-associated adverse reactions may be necessary (see section 4.5).

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

Excipients

VFEND Powder for Solution for Infusion
Sodium
This medicinal product contains 221 mg of sodium per vial, equivalent to 11% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Cyclodextrins
The powder for solution for infusion contains cyclodextrins (3,200 mg cyclodextrins in each vial which is equivalent to 160mg/ml when reconstituted in 20ml, see section 2 and 6.1) which can influence the properties (such as toxicity) of the active substance and other medicines. Safety aspects of cyclodextrins have been considered during the development and safety assessment of the drug product.

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

VFEND Film-coated tablets
Lactose
This medicinal product contains lactose and should not be given to patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet. Patients on low sodium diets should be informed that this medicinal product is essentially ‘sodium-free’.

VFEND Powder for Oral Suspension
Sucrose
This medicinal product contains 0.54 g sucrose per ml. This should be taken into account in patients with diabetes mellitus. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine. May be harmful to the teeth.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per 5 ml of suspension. Patients on low sodium diets should be informed that this medicinal product is essentially 'sodium-free'.

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 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 QTc interval. When there is also a potential for voriconazole to increase the plasma concentrations of substances metabolised by CYP3A4 isoenzymes (certain antihistamines, quinidine, cisapride, pimozide and ivabradine), coadministration is contraindicated (see below and section 4.3).

Interaction table

Interactions between voriconazole and other medicinal products are listed in the table below (once daily as "QD", twice daily as "BID", three times daily as "TID" and not determined as "ND"). The direction of the arrow for each pharmacokinetic parameter is based on the 90% confidence interval of the geometric mean ratio being within (↔), 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 coadministration**
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 (e.g., phenobarbital, mephobarbital) [potent CYP450 inducers]	Although not studied, carbamazepine and long-acting barbiturates are likely to significantly decrease plasma voriconazole concentrations.	**Contraindicated** (see section 4.3)

Medicinal product ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration**
Efavirenz (a non-nucleoside reverse transcriptase inhibitor) [CYP450 inducer; CYP3A4 inhibitor and substrate]		
Efavirenz 400 mg QD, coadministered with voriconazole 200 mg BID*	Efavirenz Cmax ↑ 38% Efavirenz AUCτ ↑ 44% Voriconazole Cmax ↓ 61% Voriconazole AUCτ ↓ 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, coadministered with voriconazole 400 mg BID*	Compared to efavirenz 600 mg QD, Efavirenz C_{max} ↔ Efavirenz AUCτ ↑ 17% Compared to voriconazole 200 mg BID, Voriconazole Cmax ↑ 23% Voriconazole AUCτ ↓ 7%	Voriconazole may be coadministered with efavirenz if the voriconazole maintenance dose is increased to 400 mg BID and the efavirenz dose is decreased to 300 mg QD. When voriconazole treatment is stopped, the initial dose of efavirenz should be restored (see section 4.2 and 4.4).
Ergot alkaloids (e.g., ergotamine and dihydroergotamine) [CYP3A4 substrates]	Although not studied, voriconazole is likely to increase the plasma concentrations of ergot alkaloids and lead to ergotism.	**Contraindicated** (see section 4.3)
Lurasidone *[CYP3A4 substrate]*	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of lurasidone.	**Contraindicated** (see section 4.3)
Naloxegol *[CYP3A4 substrate]*	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of naloxegol.	**Contraindicated** (see section 4.3)

Medicinal product ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration**
Rifabutin [potent CYP450 inducer] 300 mg QD 300 mg QD (coadministered with voriconazole 350 mg BID)* 300 mg QD (coadministered with voriconazole 400 mg BID)*	 Voriconazole C_{max} ↓ 69% Voriconazole AUCτ ↓ 78% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↓ 4% Voriconazole AUCτ ↓ 32% Rifabutin C_{max} ↑ 195% Rifabutin AUCτ ↑ 331% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 104% Voriconazole AUCτ ↑ 87%	**Contraindicated** (see Section 4.3)
Rifampicin (600 mg QD) [potent CYP450 inducer]	Voriconazole C_{max} ↓ 93% Voriconazole AUCτ ↓ 96%	**Contraindicated** (see section 4.3)
Ritonavir (protease inhibitor) [potent CYP450 inducer; CYP3A4 inhibitor and substrate] High dose (400 mg BID) Low dose (100 mg BID)*	 Ritonavir C_{max} and AUCτ ↔ Voriconazole C_{max} ↓ 66% Voriconazole AUCτ ↓ 82% Ritonavir C_{max} ↓ 25% Ritonavir AUCτ ↓13% Voriconazole C_{max} ↓ 24% Voriconazole AUCτ ↓ 39%	Coadministration of voriconazole and high doses of ritonavir (400 mg and above BID) is **contraindicated** (see section 4.3). Coadministration of voriconazole and low dose ritonavir (100 mg BID) should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.
St. John's Wort [CYP450 inducer; P-gp inducer] 300 mg TID (coadministered 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 coadministration**
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 AUCτ ↑ 79% Fluconazole C_{max} ND Fluconazole AUCτ ND	The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole-associated adverse reactions is recommended if voriconazole is used sequentially after fluconazole.
Phenytoin [CYP2C9 substrate and potent CYP450 inducer]		Concomitant use of voriconazole and phenytoin should be avoided unless the benefit outweighs the risk.
300 mg QD	Voriconazole C_{max} ↓ 49% Voriconazole AUCτ ↓ 69%	Careful monitoring of phenytoin plasma levels is recommended.
300 mg QD (coadministered with voriconazole 400 mg BID)*	Phenytoin C_{max} ↑ 67% Phenytoin AUCτ ↑ 81% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 34% Voriconazole AUCτ ↑ 39%	Phenytoin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased to 5 mg/kg IV BID or from 200 mg to 400 mg oral BID (100 mg to 200 mg oral BID in patients less than 40 kg) (see section 4.2).
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.
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.
Tyrosine kinase inhibitors (e.g., 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 metabolized by CYP3A4.	If concomitant use cannot be avoided, dose reduction of the tyrosine kinase inhibitor is recommended.

Medicinal product ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration**
Anticoagulants Warfarin (30 mg single dose, co administered with 300 mg BID voriconazole) [CYP2C9 substrate] Other oral coumarins (e.g., 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 effects.	Dose reduction of ivacaftor is recommended.
Benzodiazepines [CYP3A4 substrates] Midazolam (0.05 mg/kg IV single dose) Midazolam (7.5 mg oral single dose) Other benzodiazepines (e.g., 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.

Medicinal product ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration**
Immunosuppressants [CYP3A4 substrates]		
Sirolimus (2 mg single dose)	In an independent published study, Sirolimus C_{max} ↑ 6.6-fold Sirolimus $AUC_{0-\infty}$ ↑ 11-fold	Coadministration of voriconazole and sirolimus is **contraindicated** (see section 4.3).
Everolimus *[also P-gP substrate]*	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of everolimus.	Coadministration of voriconazole and everolimus is not recommended because voriconazole is expected to significantly increase everolimus concentrations (see section 4.4).
Ciclosporin (in stable renal transplant recipients receiving chronic ciclosporin therapy)	Ciclosporin C_{max} ↑ 13% Ciclosporin AUCτ ↑ 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 AUCτ ↑ 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 metabolized by CYP3A4 (e.g., hydrocodone) should be considered. Frequent monitoring for opiate-associated adverse reactions may be necessary.

Medicinal product ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration**
Methadone (32-100 mg QD) [CYP3A4 substrate]	R-methadone (active) C_{max} ↑ 31% R-methadone (active) AUCτ ↑ 47% S-methadone C_{max} ↑ 65% S-methadone AUCτ ↑ 103%	Frequent monitoring for adverse reactions and toxicity related to methadone, including QTc 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 reactions and toxicity related to NSAIDs is recommended. Dose reduction of NSAIDs may be needed.
Omeprazole (40 mg QD) * [CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate]	Omeprazole C_{max} ↑ 116% Omeprazole AUCτ ↑ 280% Voriconazole C_{max} ↑ 15% Voriconazole AUCτ ↑ 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 AUCτ ↑ 61% Norethisterone C_{max} ↑ 15% Norethisterone AUCτ ↑ 53% Voriconazole C_{max} ↑ 14% Voriconazole AUCτ ↑ 46%	Monitoring for adverse reactions 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 reactions 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.
Sulfonylureas (e.g., tolbutamide, glipizide, glyburide) [CYP2C9 substrates]	Although not studied, voriconazole is likely to increase the plasma concentrations of sulfonylureas and cause hypoglycaemia.	Careful monitoring of blood glucose is recommended. Dose reduction of sulfonylureas should be considered.

Medicinal product ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration**
Vinca Alkaloids (e.g., 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 (e.g., 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) (e.g., 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 an NNRTI.	Careful monitoring for any occurrence of drug toxicity and/or lack of efficacy, and dose adjustment may be needed.
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 AUCτ ↑ 23%	No dose adjustment
Digoxin (0.25 mg QD) [P-gp substrate]	Digoxin C_{max} ↔ Digoxin AUCτ ↔	No dose adjustment
Indinavir (800 mg TID) [CYP3A4 inhibitor and substrate]	Indinavir C_{max} ↔ Indinavir AUCτ ↔ Voriconazole C_{max} ↔ Voriconazole AUCτ ↔	No dose adjustment
Macrolide antibiotics Erythromycin (1 g BID) [CYP3A4 inhibitor] Azithromycin (500 mg QD)	 Voriconazole C_{max} and AUCτ ↔ Voriconazole C_{max} and AUCτ ↔ 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 AUCτ ↔	No dose adjustment

Medicinal product *[Mechanism of interaction]*	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning coadministration**
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 and intranasal corticosteroids) 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 AUCτ ↔	No dose adjustment

4.6 Fertility, pregnancy and lactation

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

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

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

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile
The safety profile of voriconazole in adults is based on an integrated safety database of more than 2,000 subjects (including 1,603 adult patients in therapeutic trials) and an additional 270 adults in prophylaxis trials. This represents a heterogeneous population, containing patients with haematological malignancy, HIV - infected patients with oesophageal candidiasis and refractory fungal infections, non-neutropenic

patients with candidaemia or aspergillosis and healthy volunteers.

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

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

Tabulated list of adverse reactions

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

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

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

Undesirable effects reported in subjects receiving voriconazole:

System Organ Class	**Very common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1,000 to < 1/100**	**Rare ≥ 1/10,000 to < 1/1,000**	**Frequency not known (cannot be estimated from available data)**
Infections and infestations		sinusitis	pseudomembranous colitis		
Neoplasms benign, malignant and unspecified (including cysts and polyps)					squamous cell carcinoma (including cutaneous SCC in situ, or Bowen's disease)*
Blood and lymphatic system disorders		agranulocytosis[1], pancytopenia, thrombocytopenia[2], leukopenia, anaemia	bone marrow failure, lymphadenopathy, eosinophilia	disseminated intravascular coagulation	
Immune system disorders			hypersensitivity	anaphylactoid reaction	
Endocrine disorders			adrenal insufficiency, hypothyroidism	hyperthyroidism	

System Organ Class	Very common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Frequency not known (cannot be estimated from available data)
Metabolism and nutrition disorders	oedema peripheral	hypoglycaemia, hypokalaemia, hyponatraemia			
Psychiatric disorders		depression, hallucination, anxiety, insomnia, agitation, confusional state			
Nervous system disorders	headache	convulsion, syncope, tremor, hypertonia[3], paraesthesia, somnolence, dizziness	brain oedema, encephalopathy[4], extrapyramidal disorder[5], neuropathy peripheral, ataxia, hypoaesthesia, dysgeusia	hepatic encephalopathy, Guillain-Barre syndrome, nystagmus	
Eye disorders	visual impairment[6]	retinal haemorrhage	optic nerve disorder[7], papilloedema[8], oculogyric crisis, diplopia, scleritis, blepharitis	optic atrophy, corneal opacity	
Ear and labyrinth disorders			hypoacusis, vertigo, tinnitus		
Cardiac disorders		arrhythmia supraventricular, tachycardia, bradycardia	ventricular fibrillation, ventricular extrasystoles, ventricular tachycardia, electrocardiogram QT prolonged, supraventricular tachycardia	torsades de pointes, atrioventricular block complete, bundle branch block, nodal rhythm	
Vascular disorders		hypotension, phlebitis	thrombophlebitis, lymphangitis		
Respiratory, thoracic and mediastinal disorders	respiratory distress[9]	acute respiratory distress syndrome, pulmonary oedema			
Gastrointestinal disorders	diarrhoea, vomiting, abdominal pain, nausea	cheilitis, dyspepsia, constipation, gingivitis	peritonitis, pancreatitis, swollen tongue, duodenitis,		

System Organ Class	Very common ≥ 1/10	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1,000 to < 1/100	Rare ≥ 1/10,000 to < 1/1,000	Frequency not known (cannot be estimated from available data)
			gastroenteritis, glossitis		
Hepatobiliary disorders	liver function test abnormal	jaundice, jaundice cholestatic, hepatitis[10]	hepatic failure, hepatomegaly, cholecystitis, cholelithiasis		
Skin and subcutaneous tissue disorders	rash	dermatitis exfoliative, alopecia, rash maculo-papular, pruritus, erythema	Stevens-Johnson syndrome[8], phototoxicity, purpura, urticaria, dermatitis allergic, rash papular, rash macular, eczema	toxic epidermal necrolysis[8], drug reaction with eosinophilia and systemic symptoms (DRESS)[8], angioedema, actinic keratosis*, pseudoporphyria, erythema multiforme, psoriasis, drug eruption	cutaneous lupus erythematosus*, ephelides*, lentigo*
Musculoskeletal and connective tissue disorders		back pain	arthritis		periostitis*
Renal and urinary disorders		renal failure acute, haematuria	renal tubular necrosis, proteinuria, nephritis		
General disorders and administration site conditions	pyrexia	chest pain, face oedema[11], asthenia, chills	infusion site reaction, influenza like illness		
Investigations		blood creatinine increased	blood urea increased, blood cholesterol increased		

*ADR identified post-marketing

[1] Includes febrile neutropenia and neutropenia.

[2] Includes immune thrombocytopenic purpura.

[3] Includes nuchal rigidity and tetany.

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

[5] Includes akathisia and parkinsonism.

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

[7] Prolonged optic neuritis has been reported post-marketing. See section 4.4.
[8] See section 4.4.
[9] Includes dyspnoea and dyspnoea exertional.
[10] Includes drug-induced liver injury, hepatitis toxic, hepatocellular injury and hepatotoxicity.
[11] Includes periorbital oedema, lip oedema, and oedema mouth.

Description of selected adverse reactions

Altered taste perception

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

Visual impairments

In clinical trials, visual impairments (including blurred vision, photophobia, chloropsia, chromatopsia, colour blindness, cyanopsia, eye disorder, halo vision, night blindness, oscillopsia, photopsia, scintillating scotoma, visual acuity reduced, visual brightness, visual field defect, vitreous floaters, and xanthopsia) with voriconazole were very common. These visual impairments were transient and fully reversible, with the majority spontaneously resolving within 60 minutes and no clinically significant long-term visual effects were observed. There was evidence of attenuation with repeated doses of voriconazole. The visual impairments were generally mild, rarely resulted in discontinuation and were not associated with long-term sequelae. Visual impairments may be associated with higher plasma concentrations and/or doses.

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

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

Dermatological reactions

Dermatological reactions were very common in patients treated with voriconazole in clinical trials, but these patients had serious underlying diseases and were receiving multiple concomitant medicinal products. The majority of rashes were of mild to moderate severity. Patients have developed severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS) (uncommon), toxic epidermal necrolysis (TEN) (rare), drug reaction with eosinophilia and systemic symptoms (DRESS) (rare) and erythema multiforme (rare) during treatment with VFEND (see section 4.4).

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

There have been reports of squamous cell carcinoma of the skin (including cutaneous SCC in situ, or Bowen's disease) in patients treated with VFEND for long periods of time; the mechanism has not been established (see section 4.4).

Liver function tests

The overall incidence of transaminase increases >3 xULN (not necessarily comprising an adverse event) in the voriconazole clinical programme was 18.0% (319/1,768) in adults and 25.8% (73/283) in paediatric subjects who received voriconazole for pooled therapeutic and prophylaxis use. Liver function test abnormalities may be associated with higher plasma concentrations and/or doses. The majority of abnormal liver function tests either resolved during treatment without dose adjustment or following dose adjustment, including discontinuation of therapy.

Voriconazole has been associated with cases of serious hepatic toxicity in patients with other serious

underlying conditions. This includes cases of jaundice, hepatitis and hepatic failure leading to death (see section 4.4).

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

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

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse event should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

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

There is no known antidote to voriconazole.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02 AC03

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

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

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

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

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

Other treated fungal infections (often with either partial or complete response) included isolated cases of *Alternaria* spp., *Blastomyces dermatitidis, Blastoschizomyces capitatus, Cladosporium* spp., *Coccidioides immitis, Conidiobolus coronatus, Cryptococcus neoformans, Exserohilum rostratum, Exophiala spinifera, Fonsecaea pedrosoi, Madurella mycetomatis, Paecilomyces lilacinus, Penicillium spp. including P. 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., and *Histoplasma capsulatum,* with most strains being inhibited by concentrations of voriconazole in the range 0.05 to 2 µg/ml.

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

Breakpoints
Specimens for fungal culture and other relevant laboratory studies (serology, histopathology) should be

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

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

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

EUCAST Breakpoints

Candida and Aspergillus species	**Minimal Inhibitory Concentration (MIC) breakpoint (mg/L)**	
	≤S (Susceptible)	**>R (Resistant)**
Candida albicans[1]	0.06	0.25
Candida dubliniensis[1]	0.06	0.25
Candida glabrata	Insufficient evidence (IE)	IE
Candida krusei	IE	IE
Candida parapsilosis[1]	0.125	0.25
Candida tropicalis[1]	0.125	0.25
Candida guilliermondii[2]	IE	IE
Non-species related breakpoints for *Candida*[3]	IE	IE
Aspergillus fumigatus[4]	1	1
Aspergillus nidulans[4]	1	1
Aspergillus flavus	IE[5]	IE[5]
Aspergillus niger	IE[5]	IE[5]
Aspergillus terreus	IE[5]	IE[5]
Non-species related breakpoints[6]	IE	IE

[1] Strains with MIC values above the Susceptible/Intermediate (S/I) breakpoint are rare or not yet reported. The identification and antifungal susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint they should be reported resistant. A clinical response of 76% was achieved in infections caused by the species listed below when MICs were lower than or equal to the epidemiological cut-offs. Therefore, wild type populations of *C. albicans, C. dubliniensis, C. parapsilosis* and *C. tropicalis* are considered susceptible.
[2] The epidemiological cut-off values (ECOFFs) for these species are in general higher than for *C. albicans.*
[3] Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific *Candida* species. They are for use only for organisms that do not have specific breakpoints.
[4] Area of technical uncertainty (ATU) is 2. Report as R with the following comment: "In some clinical

situations (non-invasive infections forms) voriconazole can be used provided sufficient exposure is ensured".
[5] The ECOFFs for these species are in general one two-fold dilution higher than for *A. fumigatus*.
[6] Non-species related breakpoints have not been determined.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Study Endpoints	**Voriconazole N=224**	**Itraconazole N=241**	**Difference in proportions and the 95% confidence interval (CI)**	**P-Value**
Success at day 180*	109 (48.7%)	80 (33.2%)	16.4% (7.7%, 25.1%)**	0.0002**
Success at day 100	121 (54.0%)	96 (39.8%)	15.4% (6.6%, 24.2%)**	0.0006**
Completed at least 100 days of study drug prophylaxis	120 (53.6%)	94 (39.0%)	14.6% (5.6%, 23.5%)	0.0015
Survived to day 180	184 (82.1%)	197 (81.7%)	0.4% (-6.6%, 7.4%)	0.9107

Developed proven or probable IFI to day 180	3 (1.3%)	5 (2.1%)	-0.7% (-3.1%, 1.6%)	0.5390
Developed proven or probable IFI to day 100	2 (0.9%)	4 (1.7%)	-0.8% (-2.8%, 1.3%)	0.4589
Developed proven or probable IFI while on study drug	0	3 (1.2%)	-1.2% (-2.6%, 0.2%)	0.0813

* Primary endpoint of the study
** Difference in proportions, 95% CI and p-values obtained after adjustment for randomization

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

AML

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

* Primary endpoint of study
** Using a margin of 5%, non inferiority is demonstrated
***Difference in proportions, 95% CI obtained after adjustment for randomization

Myeloablative conditioning regimens

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

* Primary endpoint of study
** Using a margin of 5%, non inferiority is demonstrated
*** Difference in proportions, 95% CI obtained after adjustment for randomization

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

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

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

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

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

5.2 Pharmacokinetic properties

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

The pharmacokinetics of voriconazole are non-linear due to saturation of its metabolism. Greater than proportional increase in exposure is observed with increasing dose. It is estimated that, on average, increasing the oral dose from 200 mg twice daily to 300 mg twice daily leads to a 2.5-fold increase in exposure (AUC_τ). The oral maintenance dose of 200 mg (or 100 mg for patients less than 40 kg) achieves a voriconazole exposure similar to 3 mg/kg IV. A 300 mg (or 150 mg for patients less than 40 kg) oral maintenance dose achieves an exposure similar to 4 mg/kg IV. When the recommended intravenous or oral loading dose regimens are administered, plasma concentrations close to steady state are achieved within the first 24 hours of dosing. Without the loading dose, accumulation occurs during twice daily multiple dosing with steady-state plasma voriconazole concentrations being achieved by Day 6 in the majority of subjects.

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

Powder for oral suspension
Voriconazole is rapidly and almost completely absorbed following oral administration, with maximum plasma concentrations (C_{max}) achieved 1-2 hours after dosing. The absolute bioavailability of voriconazole after oral administration is estimated to be 96%.
Bioequivalence was established between the 200 mg tablet and the 40mg/ml oral suspension when administered as a 200 mg dose. When multiple doses of voriconazole are administered with high fat

meals, C_{max} and AUCτ are reduced by 58% and 37%, respectively. The absorption of voriconazole is not affected by changes in gastric pH.

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

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

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

The inter-individual variability of voriconazole pharmacokinetics is high.

In vivo studies indicated that CYP2C19 is significantly involved in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism. For example, 15-20% of Asian populations may be expected to be poor metabolisers. For Caucasians and Blacks the prevalence of poor metabolisers is 3-5%. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolisers have, on average, 4-fold higher voriconazole exposure (AUC_{τ}) than their homozygous extensive metaboliser counterparts. Subjects who are heterozygous extensive metabolisers have on average 2-fold higher voriconazole exposure than their homozygous extensive metaboliser counterparts.

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

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

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

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

Pharmacokinetics in special patient groups

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

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

Elderly
In an oral multiple dose study C_{max} and AUCτ 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

AUCτ were observed between healthy elderly females (≥ 65 years) and healthy young females (18- 45 years).

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

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

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

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

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

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

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

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

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

5.3 Preclinical safety data

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

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

VFEND powder for solution for infusion:
Sulphobutylether Beta Cyclodextrin Sodium (SBECD)
Water for Injections

VFEND film coated tablets:
Tablet Core:
Lactose Monohydrate
Pregelatinised Starch
Croscarmellose Sodium
Povidone
Magnesium Stearate
Film Coat:
Hypromellose
Titanium Dioxide
Lactose Monohydrate
Glycerol Triacetate

VFEND powder for oral suspension:
Sucrose
Citric Acid Anhydrous
Natural Orange Flavour
Sodium Citrate Dihydrate
Sodium Benzoate
Xanthan Gum
Silica Colloidal anhydrous
Titanium Dioxide

6.2 Incompatibilities

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

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

Total parenteral nutrition: Total parenteral nutrition (TPN) need *not* be discontinued when prescribed with VFEND but does need to be infused through a separate line. If infused through a multiple-lumen catheter, TPN needs to be administered using a different port from the one used for VFEND. VFEND must not be diluted with 4.2% Sodium Bicarbonate Infusion. Compatibility with other concentrations is unknown.

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

VFEND film-coated tablets:
Not applicable

VFEND Powder for oral suspension:
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

VFEND powder for solution for infusion:
The expiry date of the product is indicated on the packaging materials.
From a microbiological point of view, once reconstituted, the product must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C (in a refrigerator), unless reconstitution has taken place in controlled and validated aseptic conditions.

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

VFEND film-coated tablets:
The expiry date of the product is indicated on the packaging materials.

VFEND powder for oral suspension:
The expiry date of the product is indicated on the packaging materials.

The shelf life of the constituted oral suspension is 14 days at a temperature below 30°C, do not refrigerate or freeze.

6.4 Special precautions for storage

VFEND powder for solution for infusion:
The unreconstituted vial should be stored below 30ºC.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

VFEND film-coated tablets:
In a cool place.

VFEND powder for oral suspension:
Store at 2°C- 8°C (in a refrigerator) before constitution.
For storage conditions after constitution, see section 6.3.
Keep the container tightly closed.

6.5 Nature and contents of container

VFEND powder for solution for infusion:
Sterile lyophilised powder in single use 30 mL clear Type I glass vial.

Film-coated tablets:
PVC / Aluminium blister in cartons of 2, 10, 14, 20, 28, 30, 50, 56 and 100.
Not all pack sizes may be marketed.

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

6.6 Special precautions for disposal and other handling

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

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

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)**	**8mg/kg dose (number of vials)**	9 mg/kg dose (number of vials)
10	-	4.0mL (1)	-	8.0 mL (1)	9.0 mL (1)

15	-	6.0mL (1)	-	12.0 mL (1)	13.5 mL (1)
20	-	8.0mL (1)	-	16.0 mL (1)	18.0 mL (1)
25	-	10.0mL (1)	-	20.0 mL (1)	22.5 mL (2)
30	9.0 mL (1)	12 mL (1)	18 mL (1)	24.0 mL (2)	27.0 mL (2)
35	10.5 mL (1)	14 mL (1)	21 mL (2)	28.0 mL (2)	31.5 mL (2)
40	12.0 mL (1)	16 mL (1)	24 mL (2)	32.0 mL (2)	36.0 mL (2)
45	13.5 mL (1)	18 mL (1)	27 mL (2)	36.0 mL (2)	40.5 mL (3)
50	15.0 mL (1)	20 mL (1)	30 mL (2)	40.0 mL (2)	45.0 mL (3)
55	16.5 mL (1)	22 mL (2)	33 mL (2)	44.0 mL (3)	49.5 mL (3)
60	18.0 mL (1)	24 mL (2)	36 mL (2)	48.0 mL (3)	54.0 mL (3)
65	19.5 mL (1)	26 mL (2)	39 mL (2)	52.0 mL (3)	58.5 mL (3)
70	21.0 mL (2)	28 mL (2)	42 mL (3)	-	-
75	22.5 mL (2)	30 mL (2)	45 mL (3)	-	-
80	24.0 mL (2)	32 mL (2)	48 mL (3)	-	-
85	25.5 mL (2)	34 mL (2)	51 mL (3)	-	-
90	27.0 mL (2)	36 mL (2)	54 mL (3)	-	-
95	28.5 mL (2)	38 mL (2)	57 mL (3)	-	-
100	30.0 mL (2)	40 mL (2)	60 mL (3)	-	-

The reconstituted solution can be diluted with:

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

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

VFEND film-coated tablets:
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

VFEND powder for oral suspension:
Constitution instructions:

1. Tap the bottle to release the powder.
2. Add 2 measuring cups of water, providing a total volume of 46 ml.
3. Shake the closed bottle vigorously for about 1 minute.
4. Remove child-resistant cap. Press bottle adaptor into the neck of the bottle.
5. Replace the cap.

6. Write the date of expiration of the constituted suspension on the bottle label (the shelf life of the constituted oral suspension is 14 days).

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

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

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

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

7. LICENSE HOLDER

Pfizer PFE Pharmaceuticals Israel Ltd., 9 Shenkar St., Herzliya Pituach 46725

8. LICENSE NUMBER

VFEND® Powder for Solution for Infusion
126-71-30598

VFEND® Film-coated tablets
VFEND® 50 mg Film-Coated Tablets
126-69-30596
VFEND® 200 mg Film-Coated Tablets
126-70-30597

VFEND® Powder for Oral Suspension
134-48-31157

Revised in 04/2022 according to MoH guidelines