Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Voriconazole Teva 200 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg voriconazole.

Excipient with known effect
Each film-coated tablet contains 250 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
White, oblong film-coated tablet (dimensions: approx. 17.2 mm x 7.2 mm) with imprint “V” on one and “200” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Treatment of invasive aspergillosis.

Treatment of candidaemia in non-neutropenic patients.

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

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

Voriconazole Teva Film-coated Tablets should be administered primarily to patients with progressive, possibly life-threatening infections.

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

4.2 Posology and method of administration

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

Voriconazole Teva Film-coated Tablet is available as 50 mg and 200 mg film-coated tablets. Further voriconazole containing pharmaceutical forms, such as powder for solution for infusion and powder for oral suspension, are available on the market.

Treatment

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

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

	Intravenous	Oral	
		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 (afterfirst24 hours)	4 mg/kg twice daily	200 mg twice daily	100 mg twice daily

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

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

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

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

In case of use as prophylaxis, refer below.

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

The recommended dosing regimen is as follows:

	Intravenous	Oral
Loading Dose Regimen (first24 hours)	9 mg/kg every 12 hours	Not recommended
Maintenance Dose (after first 24 hours)	8 mg/kg twice daily	9 mg/kg twice daily (a maximum dose of 350 mg twice daily)

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

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

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

All other adolescents (12to 14 yearsand≥50kg;15to 17 yearsregardlessofbodyweight)
Voriconazole should be dosed as adults.

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

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

Prophylaxis in Adults and Children

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

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

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

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

The following instructions apply to both Treatment and Prophylaxis

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

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

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

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

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

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

Voriconazole is haemodialysed with a clearance of 121 ml/min. A four 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 voriconazole in patients with abnormal liver function tests (aspartate transaminase [AST], alanine transaminase [ALT], alkaline phosphatase [ALP], or total bilirubin >5 times the upper limit of normal).

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

Paediatric population

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

Method of administration
Voriconazole Teva Film-coated Tablets are to be taken at least one hour before, or one hour following, a meal.

4.3 Contraindications

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

Coadministration of voriconazole is contraindicated with medicinal products that are highly dependent on CYP3A4 for metabolism, and for which elevated plasma concentrations are associated with serious and/or life-threatening reactions (see section 4.5):

- Terfenadine, Astemizole
- Cisapride
- Pimozide, Lurasidone
- Quinidine
- Ivabradine
- Ergot alkaloids (e.g., ergotamine, dihydroergotamine)
- Sirolimus
- Naloxegol
- Tolvaptan
- Finerenone
- Venetoclax: Coadministration contraindicated at initiation and during venetoclax dose titration phase.

Coadministration of voriconazole is contraindicated with medicinal products that induce CYP3A4 and significantly reduce voriconazole plasma concentrations:

- Coadministration with rifampicin, carbamazepine, long-acting barbiturates e.g., phenobarbital, and St John`s Wort (see section 4.5).
- Efavirenz:Coadministration of standard doses of voriconazole with efavirenz doses of 400 mg once daily or higher is contraindicated (see section 4.5). For information on coadministration of voriconazole and lower doses of efavirenz see section 4.4.
- Ritonavir: Coadministration with high-dose ritonavir (400 mg and above twice daily) is contraindicated (see section 4.5). For information on coadministration with lower doses of ritonavir see section 4.4.

4.4 Special warnings and precautions for use

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

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

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

Hepatic toxicity

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

Monitoring of hepatic function

Patients receiving voriconazole 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 voriconazole 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, voriconazole 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 voriconazole has been associated with phototoxicity including reactions such as ephelides, lentigo, actinic keratosis and pseudoporphyria. There is a potential increased risk of skin reactions/toxicity with concomitant use of photosensitising agents (e.g., methotrexate, etc). It is recommended that all patients, including children, avoid exposure to direct sunlight during voriconazole treatment and use measures such as protective clothing and sunscreen with high sun protection factor (SPF).

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, voriconazole discontinuation and use of alternative antifungal agents should be considered and the patient should be referred to a dermatologist. If voriconazole is continued, however, dermatologic evaluation should be performed on a systematic and regular basis, to allow early detection and management of premalignant lesions. Voriconazole 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 voriconazole 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 voriconazole (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 voriconazole treatment (see section 4.8).

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 voriconazole discontinuation should be considered after multidisciplinary advice (see section 4.8).

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 voriconazole. 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 voriconazole 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 (includingSCC)

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).

Rifabutin (potent CYP450 inducer)
Careful monitoring of full blood counts and adverse reactions to rifabutin (e.g. uveitis) is recommended when rifabutin is coadministered with voriconazole. Concomitant use of voriconazole and rifabutin should be avoided unless the benefit outweighs the risk (see section 4.5).

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

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

Methadone (CYP3A4 substrate)
Frequent monitoring for adverse reactions and toxicity related to methadone, including QTc prolongation, is recommended when coadministered with voriconazole since methadone levels increased following coadministration of voriconazole. Dose reduction of methadone may be needed (see section 4.5).

Short-acting opiates (CYP3A4 substrate)
Reduction in the dose of alfentanil, fentanyl and other short acting opiates similar in structure to alfentanil and metabolised by CYP3A4 (e.g sufentanil) should be considered when coadministered with voriconazole (see section 4.5). As the half-life of alfentanil is prolonged in a four-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 AUC0-∞ 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 metabolised 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 Cmax and AUCτ 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

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per film-coated tablet, that is to say 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") ordered by therapeutic class. 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. AUCτ, AUCt and AUC0-∞ 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.

Medicinal product	**Interaction geometric mean changes(%)**	**Recommendations concerning coadministration**
Antacids		
Cimetidine (400 mg BID) *[non-specificCYP450 inhibitor and increasesgastricpH]*	Voriconazole Cmax ↑ 18% Voriconazole AUCτ ↑ 23%	No dose adjustment
Omeprazole (40 mg QD)* *[CYP2C19inhibitor;CYP2C19 and CYP3A4 substrate]*	Omeprazole Cmax ↑ 116% Omeprazole AUCτ ↑ 280% Voriconazole Cmax ↑ 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.
Ranitidine (150 mg BID) *[increasesgastricpH]*	Voriconazole Cmax and AUCτ ↔	No dose adjustment
Antiarrhythmics		
Digoxin (0.25 mg QD) *[P-gpsubstrate]*	Digoxin Cmax ↔ Digoxin AUCτ ↔	No dose adjustment
Quinidine	Although not	**Contraindicated**(see section 4.3)

[CYP3A4 substrates]	studied, increased plasma concentrations of quinidine can lead to QTc prolongation and rare occurrences of torsades de pointes.	
Antibacterials		
Flucloxacillin *[CYP450 inducer]*	Significantly decreased plasma voriconazole concentrations have been reported.	If concomitant administration of voriconazole with flucloxacillin cannot be avoided, monitor for potential loss of voriconazole effectiveness (e.g. by therapeutic drug monitoring); increasing the dose of voriconazole may be needed.
Macrolide antibiotics Azithromycin (500 mg QD) Erythromycin (1 g BID) *[CYP3A4 inhibitor]*	Voriconazole Cmax and AUCτ ↔ Voriconazole Cmax and AUCτ ↔ The effect of voriconazole on either erythromycin or azithromycin is unknown.	No dose adjustment
Rifabutin *[potentCYP450 inducer]* 300 mg QD 300 mg QD (coadministered with voriconazole 350 mg BID)* 300 mg QD (coadministered with voriconazole 400 mg BID)*	Voriconazole Cmax ↓ 69% Voriconazole AUCτ ↓ 78% Compared to voriconazole 200 mg BID, Voriconazole Cmax ↓ 4% Voriconazole AUCτ ↓ 32% Rifabutin Cmax ↑ 195% Rifabutin AUCτ ↑ 331% Compared to voriconazole 200 mg BID,	Concomitant use of voriconazole and rifabutin should be avoided unless the benefit outweighs the risk. The maintenance dose of voriconazole may be increased to 5 mg/kg intravenously BID or from 200 mg to 350 mg orally BID (100 mg to 200 mg orally BID in patients less than 40 kg) (see section 4.2). Careful monitoring of full blood counts and adverse reactions to rifabutin (e.g., uveitis) is recommended when rifabutin is coadministered with voriconazole.

	Voriconazole Cmax ↑ 104% Voriconazole AUCτ ↑ 87%	
Rifampicin (600 mg QD) *[potentCYP450 inducer]*	Voriconazole Cmax ↓ 93% Voriconazole AUCτ ↓ 96%	**Contraindicated**(see section 4.3)
Anti-cancer agents		
Glasdegib *[CYP3A4substrate]*	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 (see section 4.4).
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.
Tyrosine kinase inhibitors (including but not limited to: axitinib, bosutinib, cabozantinib, ceritinib, cobimetinib, dabrafenib, dasatinib, nilotinib, sunitinib, ibrutinib, ribociclib) *[CYP3A4 substrates]*	Although not studied, voriconazole may increase plasma concentrations of tyrosine kinase inhibitors metabolised by CYP3A4.	If concomitant use cannot be avoided, dose reduction of the tyrosine kinase inhibitor and close clinical monitoring is recommended (see section 4.4).
Venetoclax *[CYP3Asubstrate]*	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.
Vinca Alkaloids (including but not limited to: vincristine and vinblastine) *[CYP3A4 substrates]*	Although not studied, voriconazole is likely to increase the plasma concentrations of vinca alkaloids and lead to neurotoxicity.	Dose reduction of vinca alkaloids should be considered.

Anticoagulants		
Warfarin (30 mg single dose, co- administered with 300 mg BID voriconazole) *[CYP2C9substrate]* Other oral coumarins (including but not limited to: phenprocoumon, acenocoumarol) *[CYP2C9andCYP3A4 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.
Anticonvulsants		
Carbamazepine and long-acting barbiturates (including but not limited to: phenobarbital, mephobarbital) *[potentCYP450 inducers]*	Although not studied, carbamazepine and long-acting barbiturates are likely to significantly decrease plasma voriconazole concentrations.	**Contraindicated**(see section 4.3)
Phenytoin *[CYP2C9substrateand potent CYP450inducer]* 300 mg QD 300 mg QD (coadministered with voriconazole 400 mg BID)*	Voriconazole Cmax ↓ 49% Voriconazole AUCτ ↓ 69% Phenytoin Cmax ↑ 67% Phenytoin AUCτ ↑ 81% Compared to voriconazole 200 mg BID, Voriconazole Cmax ↑ 34% Voriconazole AUCτ ↑ 39%	Concomitant use of voriconazole and phenytoin should be avoided unless the benefit outweighs the risk. Careful monitoring of phenytoin plasma levels is recommended. Phenytoin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased to 5 mg/kg IV BID or from 200 mg to 400 mg oral BID (100 mg to 200 mg oral BID in patients less than 40 kg) (see section 4.2).
Antidiabetics		
Sulfonylureas (including but not limited to: tolbutamide, glipizide, glyburide)	Although not studied, voriconazole is likely to increase	Careful monitoring of blood glucose is recommended. Dose reduction of sulfonylureas should be considered.

[CYP2C9substrates]	the plasma concentrations of sulfonylureas and cause hypoglycaemia.	
Antifungals		
Fluconazole (200 mg QD) *[CYP2C9,CYP2C19 and CYP3A4inhibitor]*	Voriconazole Cmax ↑ 57% Voriconazole AUCτ ↑ 79% Fluconazole Cmax 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.
Antihistamines		
Astemizole *[CYP3A4 substrates]*	Although not studied, increased plasma concentrations of astemizole can lead to QTc prolongation and rare occurrences of torsades de pointes.	**Contraindicated**(see section 4.3)
Terfenadine *[CYP3A4 substrates]*	Although not studied, increased plasma concentrations of terfenadine can lead to QTc prolongation and rare occurrences of torsades de pointes.	**Contraindicated**(see section 4.3)
Anti HIV agents		
Indinavir (800 mg TID) *[CYP3A4 inhibitorand substrate]*	Indinavir Cmax ↔ Indinavir AUCτ ↔ Voriconazole Cmax ↔ Voriconazole AUCτ ↔	No dose adjustment
Ritonavir (protease inhibitor) *[potentCYP450 inducer; CYP3A4inhibitorand substrate]* High dose (400 mg BID) Low dose (100 mg BID)*	Ritonavir Cmax and AUCτ ↔ Voriconazole Cmax ↓ 66% Voriconazole AUCτ ↓ 82% Ritonavir Cmax ↓	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.

	25% Ritonavir AUCτ ↓13% Voriconazole Cmax ↓ 24% Voriconazole AUCτ ↓ 39%	
Other HIV Protease Inhibitors (including but not limited to: saquinavir, amprenavir and nelfinavir)* *[CYP3A4 substratesand inhibitors]*	Not studied clinically. *Invitro* 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.
Efavirenz (a non-nucleoside reverse transcriptase inhibitor, (NNRTI)) *[CYP450inducer;CYP3A4 inhibitorand substrate]* Efavirenz 400 mg QD, coadministered with voriconazole 200 mg BID* Efavirenz 300 mg QD, coadministered with voriconazole 400 mg BID*	Efavirenz Cmax ↑ 38% Efavirenz AUCτ ↑ 44% Voriconazole Cmax ↓ 61% Voriconazole AUCτ ↓ 77% Compared to efavirenz 600 mg QD, Efavirenz Cmax ↔ Efavirenz AUCτ ↑ 17% Compared to voriconazole 200 mg BID, Voriconazole Cmax ↑ 23% Voriconazole AUCτ ↓ 7%	Use of standard doses of voriconazole with efavirenz doses of 400 mg QD or higher is **contraindicated** (see section 4.3). 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 sections 4.2 and 4.4).
Other Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (including but not limited to: delavirdine, nevirapine)* *[CYP3A4 substrates, inhibitors orCYP450inducers]*	Not studied clinically. *Invitro* studies show that the metabolism of voriconazole may be inhibited by NNRTIs and	Careful monitoring for any occurrence of drug toxicity and/or lack of efficacy, and dose adjustment may be needed.

	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.	
Antipsychotics		
Lurasidone *[CYP3A4 substrate]*	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of lurasidone.	**Contraindicated** (see section 4.3)
Pimozide *[CYP3A4 substrates]*	Although not studied, increased plasma concentrations of pimozide can lead to QTc prolongation and rare occurrences of torsades de pointes.	**Contraindicated**(see section 4.3)
Anti virals		
Letermovir *[CYP2C9 and CYP2C19 inducer]*	Voriconazole Cmax ↓ 39% Voriconazole AUC0-12 ↓ 44% Voriconazole C12 ↓ 51%	If concomitant administration of voriconazole with letermovir cannot be avoided, monitor for loss of voriconazole effectiveness.
Benzodiazepines		
[CYP3A4 substrates] Midazolam (0.05 mg/kg IV single dose) Midazolam (7.5 mg oral single dose) Other benzodiazepines (including but not limited to: triazolam, alprazolam)	In an independent published study, Midazolam AUC0−∞ 3.7-fold In an independent published study, Midazolam Cmax 3.8-fold Midazolam AUC0−∞ 10.3-fold	Dose reduction of benzodiazepines should be considered.

	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.	
Cardiovascular agents		
Ivabradine *[CYP3A4 substrates]*	Although not studied, increased plasma concentrations of ivabradine can lead to QTc prolongation and rare occurrences of torsades de pointes.	**Contraindicated**(see section 4.3)
Cystic fibrosis transmembrane conductance regulator potentiators		
Ivacaftor *[CYP3A4 substrate]*	Although not studied, voriconazole is likely to increase the plasma concentrations of ivacaftor with risk of increased adverse reactions.	Dose reduction of ivacaftor is recommended.
Ergot derivatives		
Ergot alkaloids (including but not limited to: ergotamine and dihydroergotamine) *[CYP3A4 substrates]*	Although not studied, voriconazole is likely to increase the plasma concentrations of ergot alkaloids and lead to ergotism.	**Contraindicated**(see section 4.3)
GI motility agents		
Cisapride *[CYP3A4 substrates]*	Although not studied, increased plasma concentrations of cisapride can lead to QTc prolongation and rare occurrences of torsades de	**Contraindicated**(see section 4.3)

	pointes.	
Herbal medicines		
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 AUC0−∞ ↓ 59%	**Contraindicated**(see section 4.3)
Immunosuppressants		
[CYP3A4 substrates] Ciclosporin (in stable renal transplant recipients receiving chronic ciclosporin therapy)	Ciclosporin Cmax ↑ 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. <u>When voriconazole is discontinued, ciclosporin levels mustbe carefully monitoredandthedose increased as necessary.</u>
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).
Sirolimus (2 mg single dose)	In an independent published study, Sirolimus Cmax ↑ 6.6-fold Sirolimus AUC0−∞ ↑ 11-fold	Coadministration of voriconazole and sirolimus is **contraindicated** (see section 4.3).
Tacrolimus (0.1 mg/kg single dose)	Tacrolimus Cmax ↑ 117% Tacrolimus AUCt ↑ 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. <u>Whenvoriconazole is discontinued, tacrolimus levels mustbecarefullymonitored andthedoseincreased as necessary</u>.
Mycophenolic acid (1 g single dose) *[UDP-glucuronyltransferase substrate]*	Mycophenolic acid Cmax ↔ Mycophenolic acid AUCt ↔	No dose adjustment
Lipid lowering		

agents/HMG-CoA reductase inhibitors		
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.
Non-steroidal selective mineralocorticoid receptor (MR) antagonists		
Finerenone *[CYP3A4 substrates]*	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of finerenone.	**Contraindicated** (see section 4.3)
Non-steroidal anti-inflammatory drugs (NSAIDs)		
[CYP2C9substrates] Ibuprofen (400 mg single dose) Diclofenac (50 mg single dose)	S-Ibuprofen Cmax ↑ 20% S-Ibuprofen AUC0−∞ ↑ 100% Diclofenac Cmax ↑ 114% Diclofenac AUC0−∞ ↑ 78%	Frequent monitoring for adverse reactions and toxicity related to NSAIDs is recommended. Dose reduction of NSAIDs may be needed.
Opioids		
Long Acting Opiates *[CYP3A4 substrates]* Oxycodone (10 mg single dose)	In an independent published study, Oxycodone Cmax ↑ 1.7-fold Oxycodone AUC0−∞ ↑ 3.6-fold	Dose reduction in oxycodone and other long-acting opiates metabolised by CYP3A4 (e.g., hydrocodone) should be considered. Frequent monitoring for opiate-associated adverse reactions may be necessary.
Methadone (32-100 mg QD) *[CYP3A4 substrate]*	R-methadone (active) Cmax ↑ 31% R-methadone (active) AUCτ ↑ 47% S-methadone Cmax ↑ 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.
Short-acting Opiates		Dose reduction of alfentanil, fentanyl and other short- acting opiates

[CYP3A4substrates] Alfentanil (20 µg/kg single dose, with concomitant naloxone) Fentanyl (5 µg/kg single dose)	In an independent published study, Alfentanil AUC0−∞ ↑ 6-fold In an independent published study, Fentanyl AUC0−∞ ↑ 1.34-fold	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.
Opioid receptor antagonists		
Naloxegol *[CYP3A4 substrate]*	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of naloxegol.	**Contraindicated**(see section 4.3)
Oral contraceptives		
Oral Contraceptives* *[CYP3A4 substrate;CYP2C19 inhibitor]* Norethisterone/ethinylestradiol (1 mg/0.035 mg QD)	Ethinylestradiol Cmax ↑ 36% Ethinylestradiol AUCτ ↑ 61% Norethisterone Cmax ↑ 15% Norethisterone AUCτ ↑ 53% Voriconazole Cmax ↑ 14% Voriconazole AUCτ ↑ 46%	Monitoring for adverse reactions related to oral contraceptives, in addition to those for voriconazole, is recommended.
Steroids		
Corticosteroids Prednisolone (60 mg single dose) *[CYP3A4 substrate]*	Prednisolone Cmax ↑ 11% Prednisolone AUC0−∞ ↑ 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).
Vasopressin receptor antagonists		
Tolvaptan *[CYP3A substrate]*	Although not studied, voriconazole is likely to significantly increase the plasma concentrations	**Contraindicated** (see section 4.3)

	of tolvaptan.	

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data on the use of voriconazole in pregnant women available.
Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.
Voriconazole Teva film-coated tablets 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 *Voriconazole Teva film-coated tablets*.

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

4.7 Effects on ability to drive and use machines

Voriconazole 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					squamous cell carcinoma (including cutaneous SCC

polyps)					*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	
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, gastroenteritis, glossitis		
Hepatobiliary disorders	liver function	jaundice, jaundice cholestatic,	hepatic failure, hepatomegaly,		

	test abnormal	hepatitis[10]	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	toxicepidermalnecrolysis[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	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

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 voriconazole (see section 4.4).

If a patient develops a rash they should be monitored closely and *Voriconazole Teva film-coated tablets* 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 voriconazole 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).

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 invasive fungal infections (IFI), permanent discontinuation of voriconazole due to AEs was reported in 39.3% of subjects versus 39.6% of subjects in the itraconazole arm. Treatment-emergent hepatic AEs resulted in permanent discontinuation of study medication for 50 subjects (21.4%) treated with voriconazole and for 18 subjects (7.1%) treated with itraconazole.

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie.

4.9 Overdose

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

There is no known antidote to voriconazole.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole and tetrazole derivatives, ATC code: J02AC03

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

Pharmacokinetic/pharmacodynamic Relationship
In 10 therapeutic studies, the median for the average and maximum plasma concentrations in individual subjects across the studies was 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*nvitro*, 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.parapsilosisand C.tropicalis*and limited numbers of *C. dubliniensis,C. inconspicua,*and *C. guilliermondii, Scedosporium*spp., including *S. apiospermum, S.prolificansand Fusarium*spp.

Other treated fungal infections (often with either partial or complete response) included isolated cases of *Alternaria* spp., *Blastomycesdermatitidis, Blastoschizomycescapitatus, Cladosporium*spp., *Coccidioidesimmitis, Conidioboluscoronatus, Cryptococcusneoformans, Exserohilumrostratum, Exophialaspinifera, Fonsecaea pedrosoi,Madurellamycetomatis, Paecilomyceslilacinus, Penicilliumspp. including P. marneffei, Phialophora richardsiae,ScopulariopsisbrevicaulisandTrichosporon* spp. including *T. beigelii*infections.

Invitro 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.

Invitro 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 *invitro* 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).

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for voriconazole and are listed here: <https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx>

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 seven days. Therapy could then be switched to the oral formulation at a dose of 200 mg every 12 hours. Median duration of IV voriconazole therapy was 10 days (range 2-85 days). After IV voriconazole therapy, the median duration of 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 five 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)***	***AmphotericinB → fluconazole (N=122)***
EOT	***178(72%)***	***88(72%)***
2weeks after EOT	***125(50%)***	***62(51%)***
6weeks after EOT	***104(42%)***	***55(45%)***
12weeksafter 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; two of them had a successful outcome.

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

Primary Prophylaxis of Invasive Fungal Infections - Efficacy in 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	0	3 (1.2%)	-1.2% (-2.6%, 0.2%)	0.0813

study drug				

* 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 (AUCτ). 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 (Cmax) 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, Cmax and AUCτ are reduced by 34 % and 24 %, respectively. The absorption of voriconazole is not affected by changes in gastric pH.

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

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

The inter-individual variability of voriconazole pharmacokinetics is high.

In vivo studies indicated that CYP2C19 is significantly involved in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism. For example, 15-20 % of Asian populations may be expected to be poor metabolisers. For Caucasians and Blacks the prevalence of poor metabolisers is 3-5 %. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolisers have, on average, 4-fold higher voriconazole exposure (AUCτ) 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, Cmax 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 Cmax 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 Cmax 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 Cmax 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 (AUCτ) 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 metabolise voriconazole more similarly to children than to adults. Based on the population pharmacokinetic analysis, 12- to 14-year-old adolescents weighing less than 50 kg should receive children's doses (see section 4.2).

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

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

In an oral multiple dose study, AUCτ 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 postnatal development study in rats at exposures lower than those obtained in humans with therapeutic doses, voriconazole prolonged the duration of gestation and labour and produced dystocia with consequent maternal mortality and reduced perinatal survival of pups. The effects on parturition are probably mediated by species-specific mechanisms, involving reduction of oestradiol levels, and are consistent with those observed with other azole antifungal agents. Voriconazole administration induced no impairment of male or female fertility in rats at exposures similar to those obtained in humans at therapeutic doses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose monohydrate
Croscarmellose-Sodium
Povidone K25
Pregelatinised maize starch
Magnesium stearate

Film-coating:
Hypropmellose 5 mPa·s
Glycerol 85 %
Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/Alu-blister in packs of 2, 10, 14, 20, 28, 30, 50, 56, 98 and 100.
PVC/Alu-blister in packs of 2x1, 10x1, 14x1, 20x1, 28x1, 30x1, 50x1, 56x1, 98x1 and 100x1.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Swansweg 5
2031GA Haarlem
Netherlands

8 MARKETING AUTHORISATION NUMBER

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10 DATE OF REVISION OF THE TEXT

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