1. NAME OF THE MEDICINAL PRODUCT

Voriconazole ADVAGEN powder for solution for infusion 200mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 200 mg of voriconazole.

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

Excipient with known effect
Each vial contains 88.74 mg sodium.
Each vial contains 2,400 mg hydroxypropylbetadex.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion.
White to off-white lyophilised powder.
pH: 5.0 – 7.0
Osmolality: 530 mOsm/Kg ± 10%
The reconstituted solution is not significantly less clear than purified water. Clear colorless solution after dilution.

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

Treatment of serious Candida infections including esophageal candidiasis;

Treatment of candidemia in non-neutropenic patients and the following Candida infections: disseminated infection in skin and infections in abdomen, kidney, bladder wall and wounds;

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

Prevention of breakthrough of fungal infections in febrile high-risk neutropenic patients.

Prophylaxis in patients ≥12 years old who are at high risk of developing invasive fungal infections. The indication is based on a study which includes patients ≥12 years old undergoing haematopoietic stem cell transplantation.

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

4.2 Posology and method of administration

Method of administration

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

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

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

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

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

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

Use in adults
Therapy must be initiated with the specified intravenous loading dose regimen of voriconazole 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%), switching between intravenous and oral administration is appropriate when clinically indicated (see Section 5.2).

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

	Intravenous
Loading dose regimen for all indications (first 24 hours)	6 mg/kg every 12 hours
Maintenance dose (after first 24 hours)	
Prevention of breakthrough infections	3 mg/kg every 12 hours
Fluconazole-resistant serious invasive *Candida*/Invasive aspergillosis/ *Scedosporium* and *Fusarium* infections[a] /Prophylaxis of invasive fungal infections	4 mg/kg every 12 hours

Candidemia in non-neutropenic patients and other deep tissue *Candida* infections	3-4 mg/kg every 12 hours[b]
Esophageal candidiasis	Not evaluated

a. 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 (2-232 days).
b. 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.

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

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

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

Treatment duration depends upon patients' clinical and mycological response.

Use in the elderly
No dose adjustment is necessary for elderly patients.

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

Voriconazole is hemodialyzed with a clearance of 121 mL/min. A four-hour hemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment. The intravenous vehicle, SBECD, is hemodialyzed with a clearance of 55 mL/min.

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

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

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

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

Use in pediatrics
Use in children (2 to <12 years) and young adolescents (12 to 14 years and <50 kg)
The recommended dosing regimen is as follows:

	Intravenous
Loading Dose Regimen (first 24 hours)	9 mg/kg every 12 hours
Maintenance Dose (after first 24 hours)	8 mg/kg twice daily

Note: Based on a population pharmacokinetic analysis in 112 immunocompromised pediatric 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.

Safety and effectiveness in pediatric patients below the age of 2 years has not been established. Therefore, voriconazole is not recommended for children less than 2 years of age. Use in pediatric patients aged 2 to <12 years with hepatic or renal insufficiency has not been studied (see Sections 4.8 and 5.2).

Use in all other adolescents (12 to 14 years and ≥50 kg; 15 to 16 years regardless of body weight)
Voriconazole should be dosed as adults.

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

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

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.

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

Coadministration of standard doses of voriconazole with efavirenz doses of 400 mg once daily or higher is contraindicated, because efavirenz significantly decreases plasma voriconazole concentrations 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 at this dose (see section 4.5, for lower doses see section 4.4).

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

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

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

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 voriconazole to patients with hypersensitivity to other azoles (see also section 4.8).

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

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

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

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

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

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
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. 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 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 such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, 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

Adrenal insufficiency has been reported in patients receiving other azoles (e.g., ketoconazole).

Reversible cases of adrenal insufficiency have been reported in patients receiving voriconazole. Patients on long-term treatment with voriconazole and corticosteroids (including inhaled corticosteroids e.g., budesonideand intranasal corticosteroids) should be carefully monitored for adrenal cortex dysfunction both during treatment and when voriconazole is discontinued

(see section 4.5).

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

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

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

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

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

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

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

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

Naloxegol (CYP3A4 substrate)
Coadministration of voriconazole and naloxegol is not recommended because voriconazole is expected to significantly increase naloxegol concentrations. Currently there are insufficient data to allow dosing recommendations of naloxegol 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 co-administered 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, 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. The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established.
Monitoring for voriconazole-associated adverse reactions is recommended if voriconazole is used sequentially after fluconazole (see section 4.5).

Sodium content
This medicinal product contains 88.74 mg sodium per vial dose, equivalent to 4.44 % of the WHO recommended maximum daily intake for sodium.

The maximum daily dose of this product is equivalent to 26.62 % of the WHO recommended maximum daily intake for sodium.

Voriconazole is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

Hydroxypropylbetadex
In children less than 2 years, the lower glomerular function may protect against renal toxicity, but can lead to higher blood levels of cyclodextrins.

In patients with moderate to severe renal dysfunction accumulation of cyclodextrins may occur.

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 CYP3A4inhibitor though the increase in AUC is substrate dependent (see Table below).

Voriconazole should be administered with caution in patients with concomitant medicinal product 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), co-administration is contraindicated (see below and section 4.3).

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

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

Medicinal product *[Mechanism of interaction]*	**Interaction Geometric mean changes (%)**	**Recommendations concerning co-administration**
Astemizole, cisapride, pimozide, quinidine, terfenadine and ivabradine *[CYP3A4 substrates]*	Although not studied, increased plasma concentrations of these medicinal products can lead to QTc prolongation and rare occurrences of torsades de pointes.	**Contraindicated** (see section 4.3)
Carbamazepine and long-acting barbiturates (e.g. phenobarbital, mephobarbital) *[potent CYP450 inducers]*	Although not studied, carbamazepine and long-acting barbiturates are likely to significantly decrease plasma voriconazole concentrations.	**Contraindicated** (see section 4.3)
Efavirenz (a non-nucleoside reverse transcriptase inhibitor) *[CYP450 inducer; CYP3A4 inhibitor and substrate]*		
Efavirenz 400 mg QD, coadministered with voriconazole 200 mg BID*	Efavirenz C_{max} ↑ 38% Efavirenz AUC_{τ} ↑ 44% Voriconazole C_{max} ↓ 61% Voriconazole AUC_{τ} ↓ 77%	Use of standard doses of voriconazole with efavirenz doses of 400 mg QD or higher is **contraindicated** (see section 4.3).
Efavirenz 300 mg QD, coadministered with voriconazole 400 mg BID*	Compared to efavirenz 600 mg QD, Efavirenz C_{max} ↔ Efavirenz AUC_{τ} ↑ 17% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 23% Voriconazole AUC_{τ} ↓ 7%	Voriconazole may be 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).
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)
Rifabutin *[potent CYP450 inducer]* 300 mg QD	Voriconazole C_{max} ↓ 69% Voriconazole AUC_{τ} ↓ 78%	Concomitant use of voriconazole and rifabutin

Medicinal product *[Mechanism of interaction]*	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
		should be avoided unless the benefit outweighs the risk.
300 mg QD (co-administered with voriconazole 350 mg BID)*	Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↓ 4% Voriconazole AUC_{τ} ↓ 32%	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).
300 mg QD (co-administered with voriconazole 400 mg BID)*	Rifabutin C_{max} ↑ 195% Rifabutin AUC_{τ} ↑ 331% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 104% Voriconazole AUC_{τ} ↑ 87%	Careful monitoring of full blood counts and adverse reactions to rifabutin (e.g. uveitis) is recommended when rifabutin is coadministered with voriconazole.
Rifampicin (600 mg QD) *[potent CYP450 inducer]*	Voriconazole C_{max} ↓ 93% Voriconazole AUC_{τ} ↓ 96%	**Contraindicated** (see section 4.3)
Ritonavir (protease inhibitor) *[potent CYP450 inducer; CYP3A4 inhibitor and substrate]*		
High dose (400 mg BID)	Ritonavir C_{max} and AUC_{τ}↔ Voriconazole C_{max} ↓ 66% Voriconazole AUC_{τ} ↓ 82%	Co-administration of voriconazole and high doses of ritonavir (400 mg and above BID) is **contraindicated** (see section 4.3).
Low dose (100 mg BID)*	Ritonavir C_{max} ↓ 25% Ritonavir AUC_{τ} ↓13% Voriconazole C_{max} ↓ 24% Voriconazole AUC_{τ} ↓ 39%	Co-administration of voriconazole and low-dose ritonavir (100 mg BID) should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.
St John's Wort *[CYP450 inducer; P-gp inducer]* 300 mg TID (coadministered with voriconazole 400 mg single dose)	In an independent published study, Voriconazole $AUC_{0-\infty}$ ↓ 59%	**Contraindicated** (see section 4.3)

Medicinal product ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
Venetoclax *[CYP3A substrate]*	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of venetoclax.	Concomitant administration of voriconazole is contraindicated at initiation and during venetoclax dose titration phase (see section 4.3). Dose reduction of venetoclax is required as instructed in venetoclax prescribing information during steady daily dosing; close monitoring for signs of toxicity is recommended.
Everolimus *[CYP3A4 substrate, P-gp substrate]*	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of everolimus.	Co-administration of voriconazole with everolimus is not recommended because voriconazole is expected to significantly increase everolimus concentrations (see section 4.4).
Naloxegol *[CYP3A4 substrate]*	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of naloxegol.	Co-administration of voriconazole and naloxegol is not recommended, as there is insufficient data to allow dosing recommendations of naloxegol in this situation (see section 4.4).
Fluconazole (200 mg QD) *[CYP2C9, CYP2C19 and CYP3A4 inhibitor]*	Voriconazole C_{max} ↑ 57% Voriconazole AUC_{τ} ↑ 79% Fluconazole C_{max} ND Fluconazole AUC_{τ} ND	The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole-associated adverse reactions is recommended if voriconazole is used sequentially after fluconazole.

Medicinal product *[Mechanism of interaction]*	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
Phenytoin *[CYP2C9 substrate and potent CYP450 inducer]* 300 mg QD 300 mg QD (co-administered with voriconazole 400 mg BID)*	 Voriconazole C_{max} ↓ 49% Voriconazole AUC_{τ}↓69% Phenytoin C_{max} ↑ 67% Phenytoin AUC_{τ} ↑ 81% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 34% Voriconazole AUC_{τ} ↑ 39%	Concomitant use of voriconazole and phenytoin should be avoided unless the benefit outweighs the risk. Careful monitoring of phenytoin plasma levels is recommended. Phenytoin may be co-administered with voriconazole if the maintenance dose of voriconazole is increased to 5 mg/kg IV BID or from 200 mg to 400 mg oral BID (100 mg to 200 mg oral BID in patients less than 40 kg) (see section 4.2).
Letermovir *[CYP2C9 and CYP2C19 inducer]*	Voriconazole C_{max}↓39% Voriconazole AUC_{0-12} ↓ 44% Voriconazole C_{12} ↓ 51%	If concomitant administration of voriconazole with letermovir cannot be avoided, monitor for loss of voriconazole effectiveness.
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.

Medicinal product *[Mechanism of interaction]*	**Interaction Geometric mean changes (%)**	**Recommendations concerning co-administration**
Benzodiazepines (e.g. midazolam, triazolam, alprazolam) *[CYP3A4 substrates]*	Although not studied clinically, voriconazole is likely to increase the plasma concentrations of benzodiazepines that are metabolised by CYP3A4 and lead to a prolonged sedative effect.	Dose reduction of benzodiazepines should be considered.
Tolvaptan *[CYP3A4 substrate]*	Although not studied clinically, voriconazole is likely to significantly increase the plasma concentrations of tolvaptan.	If concomitant administration of voriconazole with tolvaptan cannot be avoided, dose reduction of tolvaptan is recommended
Immunosuppressants *[CYP3A4 substrates]*		
Sirolimus (2 mg single dose)	Sirolimus C_{max} ↑ 6.6-fold Sirolimus $AUC_{0-\infty}$ ↑ 11-fold	Co-administration of voriconazole and sirolimus is **contraindicated** (see section 4.3).
Ciclosporin (in stable renal transplant recipients receiving chronic ciclosporin therapy)	Ciclosporin C_{max} ↑ 13% Ciclosporin AUC_{τ} ↑ 70%	When initiating voriconazole in patients already on ciclosporin it is recommended that the ciclosporin dose be halved and ciclosporin level carefully monitored. Increased ciclosporin levels have been associated with nephrotoxicity. When voriconazole is discontinued, ciclosporin levels must be carefully monitored and the dose increased as necessary.
Tacrolimus (0.1 mg/kg single dose)	Tacrolimus C_{max} ↑ 117% Tacrolimus AUC_t ↑221%	When initiating voriconazole in patients already on tacrolimus, it is recommended that the tacrolimus dose be reduced to a third of the original dose and tacrolimus level carefully monitored. Increased tacrolimus

Medicinal product *[Mechanism of interaction]*	**Interaction Geometric mean changes (%)**	**Recommendations concerning co-administration**
		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)	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.
Methadone (32-100 mg QD) *[CYP3A4 substrate]*	R-methadone (active) C_{max} ↑ 31% R-methadone (active) AUC_{τ} ↑ 47% S-methadone C_{max} ↑ 65% S-methadone AUC_{τ} ↑ 103%	Frequent monitoring for adverse 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 AUC_{τ} ↑ 280% Voriconazole C_{max} ↑ 15% Voriconazole AUC_{τ} ↑ 41% Other proton pump inhibitors that are CYP2C19 substrates may also be inhibited by voriconazole and may result in increased plasma concentrations of these	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.

Medicinal product *[Mechanism of interaction]*	**Interaction Geometric mean changes (%)**	**Recommendations concerning co-administration**
	medicinal products.	
Oral Contraceptives* *[CYP3A4 substrate; CYP2C19 inhibitor]* Norethisterone/ethinyles radiol (1 mg/0.035 mg QD)	Ethinylestradiol C_{max} ↑ 36% Ethinylestradiol AUC_{τ} ↑ 61% Norethisterone C_{max} ↑ 15% Norethisterone AUC_{τ} ↑ 53% Voriconazole C_{max} ↑ 14% Voriconazole AUC_{τ}↑46%	Monitoring for adverse reactions related to oral contraceptives, in addition to those for voriconazole, is recommended.
Short-acting Opiates *[CYP3A4 substrates]* Alfentanil (20 µg/kg single dose, with concomitant naloxone) Fentanyl (5 µg/kg single dose)	Alfentanil $AUC_{0-\infty}$ ↑ 6-fold 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 clinically, voriconazole is likely to increase the plasma concentrations of statins that are metabolised by CYP3A4 and could lead to rhabdomyolysis.	Dose reduction of statins should be considered.
Sulfonylureas (e.g. tolbutamide, glipizide, glyburide) *[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.
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.

Medicinal product ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
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 medicinal 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 medicinal toxicity and/or lack of efficacy and dose adjustment may be needed.
Cimetidine (400 mg BID) *[non-specific CYP450 inhibitor and increases gastric pH]*	Voriconazole C_{max}↑18% VoriconazoleAUC$_\tau$↑23%	No dose adjustment
Digoxin (0.25 mg QD) *[P-gp substrate]*	Digoxin C_{max} ↔ Digoxin AUC$_\tau$ ↔	No dose adjustment
Indinavir (800 mg TID) *[CYP3A4 inhibitor and substrate]*	Indinavir C_{max} ↔ Indinavir AUC$_\tau$ ↔ Voriconazole C_{max} ↔ Voriconazole AUC$_\tau$ ↔	No dose adjustment
Macrolide antibiotics Erythromycin (1 g BID) *[CYP3A4 inhibitor]* Azithromycin (500 mg QD)	 Voriconazole C_{max} and AUC$_\tau$ ↔ Voriconazole C_{max} and AUC$_\tau$ ↔ The effect of voriconazole on either erythromycin or azithromycin is unknown.	No dose adjustment

Medicinal product ***[Mechanism of interaction]***	**Interaction** **Geometric mean changes (%)**	**Recommendations concerning co-administration**
Mycophenolic acid (1 g single dose) *[UDP-glucuronyl transferase substrate]*	Mycophenolic acid C_{max} ↔ Mycophenolic acid AUC_t ↔	No dose adjustment
Corticosteroids Prednisolone (60 mg single dose) *[CYP3A4 substrate]*	Prednisolone C_{max} ↑ 11% Prednisolone $AUC_{0-\infty}$ ↑ 34%	No dose adjustment Patients on long-term treatment with voriconazole and corticosteroids (including inhaled corticosteroids e.g., budesonideand 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 AUC_τ ↔	No dose adjustment

4.6 Pregnancy and lactation

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

Voriconazole 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.

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

Tabulated list of adverse reactions

Frequency categories are expressed as: Very common; Common; Uncommon; Rare; Very rare; Not known.

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

Undesirable effects reported after receiving voriconazole:

System Organ Class	Very common	Common	Uncommon	Rare	Not known
Infections and infestations		sinusitis	pseudomembranous colitis		
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)					squamous cell carcinoma*

Blood and lymphatic system disorders		agranulocyosis[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	torsades de pointes, atrioventricular block complete, bundle branch block, nodal rhythm	

			QTprolonged, supraventricular tachycardia		
Vascular disorders		hypotension, phlebitis	thrombophlebitis, lymphangitis		
Respiratory, thoracic and mediastinal disorders	Respiratory distress[9]	acute respiratory distress syndrome, pulmonary oedema			
Gastrointestinal disorders	diarrhoea, vomiting, abdominal pain, nausea	cheilitis, dyspepsia, constipation, gingivitis	peritonitis, pancreatitis, swollen tongue, duodenitis, gastroenteritis, glossitis		
Hepatobiliary disorders	liver function test abnormal	jaundice, jaundice cholestatic, hepatitis[10]	hepatic failure, hepatomegaly, cholecystitis, cholelithiasis		
Skin and subcutaneous tissue disorders	rash	dermatitis exfoliative, alopecia, rash maculo-papular, pruritus, erythema	Stevens-Johnson syndrome[8], phototoxicity, purpura, urticaria, dermatitis allergic, rash papular, rash macular, eczema	toxic epidermal necrolysis[8], angioedema, actinic keratosis*, pseudoporphyria, erythema multiforme, psoriasis, medicinal eruption, drug reaction with eosinophilia and systemic symptoms (DRESS)[8]	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 medicinal product-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
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. 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.

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

Dermatological reactions
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 discontinued if lesions progress.

Photosensitivity reactions such as ephelides, lentigo and actinic keratosis have been reported, especially during long-term therapy (see section 4.4).

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

Liver function tests
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, anaphylactoid-type reactions, including flushing, fever, sweating, tachycardia, chest tightness, dyspnoea, faintness, nausea, pruritus and rash have occurred. Symptoms appeared immediately upon initiating the infusion (see section 4.4).

Paediatric population

Overall, the safety profile of voriconazole in paediatric population was similar to that in adults.
Post-marketing data suggest there might be a higher occurrence of skin reactions (especially erythema) in the paediatric population compared to adults. There have been post-marketing reports of pancreatitis in paediatric patients.

4.9 Overdose

There is no known antidote to voriconazole.

Voriconazole is haemodialysed with a clearance of 121 mL/min. The intravenous vehicle, hydroxypropylbetadex, is haemodialysed with a clearance of 37.5 ± 24 mL/min. In an overdose, haemodialysis may assist in the removal of voriconazole and hydroxypropylbetadex from the body.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism 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 P450 enzymes than for various mammalian cytochrome P450 enzyme systems.

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

Clinical efficacy defined as partial or complete response has been demonstrated for

Aspergillus spp., including *A. flavus, A. fumigatus, A. terreus, A. niger, A. nidulans; Candida* spp., including *C. albicans, C. glabrata, C. krusei, C. parapsilosis* and *C. tropicalis;* and limited numbers of *C. dubliniensis, C. inconspicua* and *C. guilliermondii, Scedosporium* spp., including *S. apiospermum, S. prolificans;* and *Fusarium* spp.

Other treated fungal infections (often with either partial or complete response) included isolated cases of *Alternaria* spp., *Blastomyces dermatitidis, Blastoschizomyces capitatus, Cladosporium* spp., *Coccidioides immitis, Conidiobolus coronatus, Cryptococcus neoformans, Exserohilum rostratum, Exophiala spinifera, Fonsecaea pedrosoi, Madurella mycetomatis, Paecilomyces lilacinus, Penicillium* spp., including *P. 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 species 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]
[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.

5.2 Pharmacokinetic properties

General pharmacokinetic characteristics

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 mostly by Day 6.

Long-term safety of hydroxypropylbetadex in humans is limited to 21 days (250 mg/kg/day).

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

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

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

Biotransformation

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

The inter-individual variability of voriconazole pharmacokinetics is high.

In vivo studies indicated that CYP2C19 is significantly involved in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism. For example, 15-20 % of Asian populations may be expected to be poor metabolisers. For Caucasians and Blacks the prevalence of poor metabolisers is 3-5 %.

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

The safety profile and plasma concentrations observed in male and female patients were similar.
Therefore, no dose adjustment based on gender is necessary.

Elderly

The safety profile of voriconazole in young and elderly patients was similar and, therefore, no dose adjustment is necessary for the elderly (see section 4.2).

Paediatric population

Paediatric patients relative to adults have a higher intravenous maintenance dose which 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 young adolescents may metabolize voriconazole more similarly to children than to adolescents/adults. Based on the population pharmacokinetic analysis, 12- to 14-year-

old adolescents weighing less than 50 kg should receive children's doses (see section 4.2).

Renal impairment

In patients with normal renal function, the pharmacokinetic profile of hydroxypropylbetadex, an ingredient of voriconazole intravenous formulation, has a short half-life of 1 to 2 hours and demonstrates no accumulation following successive daily doses. In patients with mild to severe renal insufficiency, the majority (>85%) of an 8 g dose of hydroxypropylbetadex is eliminated in the urine. In patients with mild, moderate and severe renal impairment, half-life values were increased over normal values by approximately two-, four- and six-fold, respectively. In these patients, successive infusions may result in accumulation of hydroxypropylbetadex until steady state is reached. Hydroxypropylbetadex is removed by hemodialysis, with a clearance of 37.5 ± 24 mL/min.

Hepatic impairment

Protein binding of voriconazole was not affected by impaired hepatic function.

No pharmacokinetic data are available for patients with severe hepatic cirrhosis (Child-Pugh C) (see sections 4.2 and 4.4).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropylbetadex
Sodium chloride
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

Voriconazole must not be infused into the same line or cannula concomitantly with other intravenous products. When the Voriconazole 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 hypokalemia, hypomagnesemia and hypocalcemia should be corrected prior to initiation of voriconazole therapy (see sections 4.2 and 4.4). Voriconazole 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 Voriconazole 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 Voriconazole. Voriconazole must not be diluted with 4.2 % Sodium Bicarbonate Infusion. Compatibility with other concentrations is unknown.

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

6.3 Shelf life

3 years.

Chemical and physical in-use stability has been demonstrated for 72 hours at 25 °C and at 2

°C - 8 °C.

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 - 8 °C (in a refrigerator), unless reconstitution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store at or below 30°C
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Each carton contains 1 vial.
25 mL clear Type I glass vial with a grey, chlorobutyl rubber stopper and aluminium cap with plastic red flip-off seal.

6.6 Special precautions for disposal and other handling

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

The powder is reconstituted with either 19 mL of water for injections or 19 mL of sodium chloride 9 mg/mL (0.9 %) solution for injection to obtain an extractable volume of 20 mL of clear concentrate containing 10 mg/mL of voriconazole. Discard the Voriconazole 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 sodium chloride 9 mg/mL (0.9 %) solution for injection 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 below) to obtain a final voriconazole solution containing 0.5- 5 mg/mL.

Dilution
Voriconazole must be infused over 1 to 3 hours, at a concentration of 5 mg/mL or less. Therefore, the required volume of the 10 mg/mL voriconazole concentrate should be further diluted as follows (appropriate diluents listed below):

1. Calculate the volume of 10 mg/mL voriconazole concentrate required based on the patient's weight (see table below).
2. In order to allow the required volume of voriconazole concentrate to be added, withdraw and discard at least an equal volume of diluent from the infusion bag or bottle to be used. The volume of diluent remaining in the bag or bottle should be such that when the 10 mg/mL voriconazole concentrate is added, the final concentration is not less than 0.5 mg/mL nor greater than 5 mg/mL
3. Using a suitable size syringe and aseptic technique, withdraw the required volume of voriconazole concentrate from the appropriate number of vials and add to the infusion bag or bottle. DISCARD PARTIALLY USED VIALS.

The final voriconazole solution must be infused over 1 to 3 hours at a maximum rate of 3 mg/kg per hour.

Required Volumes of 10 mg/mL Voriconazole Concentrate

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

Voriconazole is a single dose unpreserved sterile lyophile. Therefore, from a microbiological point of view, the product must be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

The reconstituted solution can be diluted with:
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 Sodium Chloride 9 mg/mL (0.9 %) Solution for Injection

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

7 MANUFACTURER

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8 PRODUCT REGISTRATION HOLDER

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