Vortimal Voriconazole 200mg POWDER FOR SOLUTION FOR INFUSION
Voriconazole 200mg

Product Description

White to off-white lyophilized powder.
After reconstitution and dilution: The solution for infusion is clear, colourless and free from visible particles.

Composition

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

Pharmacodynamics

Mechanism 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 demethylations, 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.

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 a 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 the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

EUCAST Breakpoints

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

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

[2] In clinical studies, response to voriconazole in patients with *C glabrata* infections was 21% lower compared to *C. albicans*, *C. parapsilosis* and *C. tropicalis*. However, this reduced response was not correlated with elevated MICs.

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

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

Pharmacokinetics

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 (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 patients.

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 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%.

Biotransformation

Voriconazole is metabolised by the hepatic cytochrome P 450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4.
The inter-individual variability of voriconazole pharmacokinetics is high.

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 were similar. Therefore, no dosage adjustment based on gender is necessary.

Older people

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 older (see section *Recommended Dose*).

Paediatric population

The higher intravenous maintenance dose in paediatric 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. Based on the population pharmacokinetic analysis, 12- to 14-year-old adolescents weighing less than 50 kg should receive children's doses (see section *Recommended Dose*).

Renal impairment

The plasma protein binding of voriconazole was similar with different degrees of renal impairment. See section *Recommended Dose* and section *Warnings and Precautions.*

In patients with normal renal function, the pharmacokinetic profile of hydroxypropylbetadex, an ingredient of Voriconazole 200 mg powder for solution for infusion, 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 haemodialysis, with a clearance of 37.5 ± 24 ml/min.

Hepatic impairment

Protein binding of voriconazole was not affected by impaired hepatic function (See section *Recommended Dose* and section *Warnings and Precautions*).

Indication

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 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.

Recommended Dosage

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. 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.

	Intravenous	**Oral**	
		Patients 40 kg and above	**Patients less than 40 kg**
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	200 mg (5 mL) every 12 hours	100 mg (2.5 mL) every 12 hours
- Fluconazole-resistant serious invasive *Candida*/ Invasive aspergillosis/ *Scedosporium* and *Fusarium* infections/ Prophylaxis of invasive fungal infections	4 mg/kg every 12 hours	200 mg (5 mL) every 12 hours	100 mg (2.5 mL) every 12 hours
- Candidemia in non-neutropenic patients and other deep tissue C*andida* infections	3 – 4 mg/kg every 12 hours	200 mg (5 mL) every 12 hours	100 mg (2.5 mL) every 12 hours
-Esophageal candidiasis	Not evaluated	200 mg (5 mL) every 12 hours	100 mg (2.5 mL) every 12 hours

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

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

Phenytoin may be co-administered with voriconazole if the maintenance dose of voriconazole is increased to 5 mg/kg intravenously every 12 hours (see sections Warnings and Precautions and section Interactions with Other Medicaments).

Treatment duration depends upon patients' clinical and mycological response.

Elderly: No dose adjustment is necessary for elderly patients.

Patients with Renal Impairment:
In patients with moderate to severe renal dysfunction (creatinine clearance <50 mL/min), accumulation of the intravenous vehicle, hydroxypropylbetadex, 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, hydroxypropylbetadex, is hemodialyzed with a clearance of 37.5 ± 24 mL/min.

Patients with Hepatic Impairment: No dose adjustment is necessary for 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 is 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.

Paediatrics: Use in Children (2 to <12 years) and Young Adolescents (12 to 14 years and <50 kg): The recommended dosing regimen is as follows. (See table below).

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

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 have not been established. Therefore, voriconazole is not recommended for children less than 2 years of age. Use in paediatric patients aged 2 to <12 years with hepatic or renal insufficiency has not been studied (see sections Pharmacokinetics and Side Effects).

Use in All Other Adolescents (12 to 14 Years and ≥50 kg; 15 to 16 Years Regardless of Bodyweight): Voriconazole should be dosed as adults.
Dosage Adjustment: If patient response 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 patients are 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).

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 treatment Tables previously.
Duration of Prophylaxis: The safety and efficacy of voriconazole use for longer than 180 days has not been adequately studied in clinical trials.

Administration: Voriconazole requires reconstitution and dilution (see Instruction for Use) prior to administration as an intravenous infusion.
Voriconazole powder for solution for infusion is not recommended for bolus injection.
It is recommended that voriconazole is administered at a maximum rate of 3 mg/kg per hour over 1 to 3 hours.

Route of Administration

Intravenous.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients used in Vortimal
- Coadministration with CYP3A4 substrates, terfenadine, astemizole, cisapride, pimozide or quinidine since increased plasma concentrations of these medicinal products can lead to QTc prolongation and rare occurrences of torsades de pointes (see section *Interactions with Other Medicaments*).
- Coadministration with rifampicin, carbamazepine and phenobarbital since these medicinal products are likely to decrease plasma voriconazole concentrations significantly (see section *Interactions with Other Medicaments*).
- Coadministration of standard doses of voriconazole with efavirenz doses of 400 mg once daily or higher is contraindicated because efavirenz significantly decreases plasma voriconazole concentrations in healthy subjects at these doses. Voriconazole also significantly increases efavirenz plasma concentrations (see section *Interactions with Other Medicaments*, for lower doses see section *Warning and Precautions*).
- Coadministration with high-dose ritonavir (400 mg and above twice daily) because ritonavir significantly decreases plasma voriconazole concentrations in healthy subjects at this dose (see section *Interactions with Other Medicaments*, for lower doses see section *Warning and Precautions*).
- Coadministration with ergot alkaloids (ergotamine, dihydroergotamine), which are CYP3A4 substrates, since increased plasma concentrations of these medicinal products can lead to ergotism (see section *Interactions with Other Medicaments*).
- Coadministration with sirolimus since voriconazole is likely to increase plasma concentrations of sirolimus significantly (see section *Interactions with Other Medicaments*).
- Coadministration with St John's Wort (see section *Interactions with Other Medicaments*).

Warnings and Precautions

Hypersensitivity

Caution should be used in prescribing Vortimal to patients with hypersensitivity to other azoles (see also section *Side Effects*).

Duration of treatment

The duration of treatment with the intravenous formulation should be no longer than 6 months

Cardiovascular

Voriconazole has been associated with QT_C interval prolongation. There have been rare cases of torsades de pointes in patients taking voriconazole who had risk factors, such as a 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 QT_C prolongation
- Cardiomyopathy, in particular when heart failure is present
- Sinus bradycardia
- Existing symptomatic arrhythmias
- Concomitant medicinal product that is known to prolong QT_C intervals Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy (see section *Recommended Dose*).

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 *Side Effects*).

Hepatic toxicity

There have been uncommon 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 *Side Effects*).

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, is based on the benefit-risk assessment the treatment is continued (see section *Recommended Dose*), 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.

Visual adverse reactions

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

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 *Side Effects*).

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.

Dermatological adverse reactions

Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome, during treatment with voriconazole. If a patient develops a rash he should be monitored closely and voriconazole discontinued if lesions progress.

In addition, voriconazole has been associated with phototoxicity 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).

Long-term treatment

Long-term exposure treatment or prophylaxis) grated 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 section *Pharmacodynamics* and section *Recommended Dose*). The following severe adverse events have been reported in relation to long-term voriconazole treatment.

Squamous cell carcinoma of the skin (SCC) has been reported in patients, some of whom have reported prior phototoxic reactions. If phototoxic reactions occur, multidisciplinary advice should be sought and the patient should be referred to a dermatologist. Voriconazole discontinuation and use of alternative antifungal agents should be considered. Dermatologic evaluation should be performed on a systematic and regular basis, whenever voriconazole is continued despite the occurrence of phototoxicity-related lesions, to allow early detection and management of premalignant lesions. Voriconazole should be discontinued if premalignant skin lesions or squamous cell carcinoma are identified.

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.

Paediatric population

Safety and effectiveness in paediatric subjects below the age of two years have not been established (see section *Pharmacodynamics* and section *Side Effects*). Voriconazole is indicated for paediatric patients aged two years or older. 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.

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 *Interaction with Other Medicaments*).

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 *Recommended Dose*, *Contraindications* and section *Interaction with Other Medicaments*).

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 *Interaction with Other Medicaments*).

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 section *Contraindications* and section *Interaction with Other Medicaments*).

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 sub to allow dosing recommendations in this situation (see section *Interaction with Other Medicaments*).

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 *Interaction with Other Medicaments*).

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 *Interaction with Other Medicaments)*. As the half-life of alfentanil is prolonged in a 4-fold manner when alfentanil is coadministered with voriconazole, and in an independent published study, concomitant use of voriconazole with fentanyl resulted in an increase in the mean AUC 0-∞ of fentanyl frequent monitoring for opiate-associated adverse reactions (including a longer respiratory monitoring period) may be necessary.

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

Fluconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor)
Coadministration of oral voriconazole and oral fluconazole resulted in a significant increase in Cmax and AUCτ 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 *Interaction with Other Medicaments*).

Sodium content
Each vial of Vortimal contains 225.6 mg of sodium chloride. This should be taken into consideration for patients on a controlled sodium diet.

Interactions with Other Medicaments

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

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

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

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. AUCτ, AUC_t 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.
The interactions in the table are presented in the following order: contraindications, those requiring a 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 and terfenadine [*CYP3A4 substrates]*	Although not studied, increased plasma concentrations of these medicinal products can lead to QT_C prolongation and rare occurrences of torsades de pointes.	Contraindicated (see section *Contraindications*)
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 *Contraindications*)

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 AUCτ ↑ 44% Voriconazole C_{max} ↓ 61% Voriconazole AUCτ ↓ 77%	Use of standard doses of voriconazole with efavirenz doses of 400 mg QD or higher is contraindicated (see section *Contraindications*).
Efavirenz 300 mg QD, coadministered with voriconazole 400 mg BID*	Compared to Efavirensz 600 mg QD, Efavirenz C_{max} ↔ Efavirenz AUCτ ↑ 17% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 23% Voriconazole AUCτ ↓ 7%	Voriconazole may be coadministered with efavirenz if the voriconazole maintenance dose is increased to 400 mg BID and the efavirenz dose is decreased to 300 mg QD. When voriconazole treatment is stopped, the initial dose of efavirenze should be restored (see section *Recommended Dose* and section *Warnings and Precautions*).
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 *Contraindications*)
Rifabutin *[potent CYP450 inducer]* 300 mg QD	Voriconazole C_{max} ↓ 69% Voriconazole AUCτ ↓ 78%	Concomitant use of voriconazole and rifabutin 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 AUCτ ↓ 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 *Recommended Dose*).
300 mg QD (co-administered with voriconazole 400 mg BID)*	Rifabutin C_{max} ↑ 195% Rifabutin AUCτ ↑ 331% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 104% Voriconazole AUCτ ↑ 87%	Careful monitoring of full blood counts and adverse reactions to rifabutin (e.g., uveitis) are recommended when rifabutin is coadministered with voriconazole.
Rifampicin (600 mg QD) *[potent CYP450 inducer]*	Voriconazole C_{max} ↓ 93% Voriconazole AUCτ ↓ 96%	Contraindicated (see section *Contraindications*)

Ritonavir (protease inhibitor) *[potent CYP450 inducer; CY P3A4 inhibitor and substrate]* High dose (400 mg BID)	Ritonavir C_{max} and AUCτ ↔ Voriconazole C_{max} ↓ 66% Voriconazole AUCτ ↓ 82%	Coadministration of voriconazole and high doses of ritonavir (400 mg and above BID) is contraindicated (see section *Contraindications*).
Low dose (100 mg BID)*	Ritonavir C_{max} ↓ 25% Ritonavir AUCτ ↓13% Voriconazole C_{max} ↓ 24% Voriconazole AUCτ ↓ 39%	Coadministration of voriconazole and low dose of ritonavir (100 mg BID) should be avoided unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.
St John's Wort *[CYP450 inducer; P-gp inducer]* 300 mg TID (co-administered with voriconazole 400 mg single dose)	In an independent published study, Voriconazole AUC0-$_{\infty}$ ↓ 59%	Contraindicated (see section *Contraindications*)
Everolimus *[CYP3A4 substrate, P-gP substrate]*	Although not studied, voriconazole is likely to significantly increase the plasma concentrations of everolimus.	Coadministration of voriconazole with everolimus is not recommended because voriconazole is expected to significantly increase everolimus concentrations (see section *Warnings and Precautions*).
Fluconazole (200 mg QD) *[CYP2C9, CYP2C19 and CYP3A4 inhibitor]*	Voriconazole C_{max} ↑ 57% Voriconazole AUCτ ↑ 79% Fluconazole C_{max} ND Fluconazole AUCτ ND	The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect has not been established. Monitoring for voriconazole- associated adverse reactions are recommended if voriconazole is used sequentially after fluconazole.
Phenytoin *[CYP2C9 substrate and potent CYP450 inducer]* 300 mg QD	Voriconazole C_{max} ↓ 49% Voriconazole AUCτ ↓ 69%	Concomitant use of voriconazole and phenytoin should be avoided unless the benefit outweighs the risk. Careful monitoring of phenytoin plasma levels is recommended.
300 mg QD (co-administered with voriconazole 400 mg BID)*	Phenytoin C_{max} ↑ 67% Phenytoin AUCτ ↑ 81% Compared to voriconazole 200 mg BID, Voriconazole C_{max} ↑ 34% Voriconazole AUCτ ↑ 39%	Phenytoin may be 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 *Recommended Dose*).

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 ti me or other suitable anticoagulation tests are recommended, and the dose of anticoagulants should be adjusted accordingly.
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.
Immunosuppressants *[CYP3A4 substrates]* Sirolimus (2 mg single dose) Ciclosporin (In stable renal transplant recipients receiving chronic ciclosporin therapy) Tacrolimus (0.1 mg/kg single dose)	 In an independent published study, Sirolimus C_{max} ↑ 6.6-fold Sirolimus AUC0-$_\infty$ ↑ 11-fold Ciclosporin C_{max} ↑ 13% Ciclosporin AUCτ ↑ 70% Tacrolimus C_{max} ↑ 117% Tacrolimus AUCt ↑ 221%	 Co-administration of voriconazole and sirolimus is contraindicated (see section *Contraindications*). 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. When initiating voriconazole in patients already on tacrolimus, it is recommended that the tacrolimus dose is reduced to a third of the original dose and tacrolimus level carefully monitored. Increased tacrolimus levels have been associated with nephrotoxicity. When voriconazole is discontinued, tacrolimus levels must be carefully monitored and the dose increased as necessary.
Long Acting Opiates *[CYP3A4 substrates]* Oxycodone (10 mg single dose)	 In an independent published study, Oxycodone C_{max} ↑ 1.7-fold Oxycodone AUC0-$_\infty$ ↑ 3.6-fold	Dose reduction in oxycodone and other long-acting opiates metabolized by CYP3A4 (e.g.: hydrocodone) should be considered. Frequent monitoring of opiate-associated adverse reactions may be necessary.

Methadone (32-100 mg QD) *[CYP3A4 substrate]*	R-methadone (active) C_{max} ↑ 31% R-methadone (active) AUCτ ↑ 47% S-methadone C_{max} ↑ 65% S-methadone AUCτ ↑ 103%	Frequent monitoring for adverse rea ctions and toxicity related to methadone, including QTc prolonga tion, 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 AUC0-$_\infty$ ↑ 100% Diclofenac C_{max} ↑ 114% Diclofenac AUC0-$_\infty$ ↑ 78%	Frequent monitoring for adverse rea ctions and toxicity related to NSAIDs is recommended. Dose reduction of NSAIDs may be needed.
Omeprazole (40 mg QD)* *[CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate]*	Omeprazole C_{max} ↑ 116% Omeprazole AUCτ ↑ 280% Voriconazole C_{max} ↑ 15% Voriconazole AUCτ ↑ 41% Other proton pump inhibitors that are CYP2C19 substrates may also be inhibited by voriconazole and may result in increased plasma concentrations of these medicinal products.	No dose adjustment of voriconazole is recommended. When initiating voriconazole in patients already receiving omeprazole doses of 40 mg or above, it is recommended that the omeprazole dose is halved.
Oral Contraceptives* *[CYP3A4 substrate; CYP2C19 inhibitor]* Norethisterone/ ethinylestradiol (1 mg/0.035 mg QD)	Ethinylestradiol C_{max} ↑ 36% Ethinylestradiol AUCτ ↑ 61% Norethisterone C_{max} ↑ 15% Norethisterone AUCτ ↑ 53% Voriconazole C_{max} ↑ 14% Voriconazole AUCτ ↑ 46%	Monitoring for adverse reactions related to oral contraceptives, in addition to those for voriconazole is recommended.
Short-Acting Opiates *[CYP3A4 substrates]* Alfentanil (20 μg/kg single dose, with concomitant naloxone) Fentanyl (5 μg/kg single dose)	 In an independent published study, Alfentanil AUC0-$_\infty$ ↑ 6-fold In an independent published study, Fentanyl AUC0-$_\infty$ ↑ 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 are 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.
Sulphonylureas (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.

Other HIV Protease Inhibitors (e.g., saquinavir, amprenavir and nelfinavir)* *[CYP3A4 substrates and inhibitors]*	Not studied clinically. *In vitro* studies show that voriconazole may inhibit the metabolism of HIV protease inhibitors and the metabolism of voriconazole may also be inhibited by HIV protease inhibitors.	Careful monitoring for any occurrence of drug toxicity and/or lack of efficacy, and dose adjustment may be needed.
Other Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (e.g., delavirdine, nevirapine)* *[CYP3A4 substrates, inhibitors or CYP450 inducers]*	Not studied clinically. *In vitro* studies show that the metabolism of voriconazole may be inhibited by NNRTIs and voriconazole may inhibit the metabolism of NNRTIs. The findings of the effect of efavirenz on voriconazole suggest that the metabolism of voriconazole may be induced by an NNRTI.	Careful monitoring for any occurrence of drug toxicity and/or lack of efficacy, and dose adjustment may be needed.
Cimetidine (400 mg BID) *[non-specific CYP450 inhibitor and increases gastric pH]*	Voriconazole C_{max} ↑ 18% Voriconazole AUCτ ↑ 23%	No dose adjustment
Digoxin (0.25 mg QD) *[P-gp substrate]*	Digoxin C_{max} ↔ Digoxin AUCτ ↔	No dose adjustment
Indinavir (800 mg TID) *[CYP3A4 inhibitor and substrate]*	Indinavir C_{max} ↔ Indinavir AUCτ ↔ Voriconazole C_{max} ↔ Voriconazole AUCτ ↔	No dose adjustment
Macrolide antibiotics Erythromycin (1 g BID) *[CYP3A4 inhibitor]* Azithromycin (500 mg QD)	 Voriconazole Cmax and AUCτ ↔ Voriconazole Cmax and AUCτ ↔ The effect of voriconazole on either erythromycin or azithromycin is unknown.	No dose adjustment
Mycophenolic acid (1g single dose) *[UDP-glucuronyl transferase substrate]*	Mycophenolic acid C_{max} ↔ Mycophenolic acid AUCt ↔	No dose adjustment
Prednisolone (60 mg single dose) *[CYP3A4 substrate]*	Prednisolone C_{max} ↑ 11% Prednisolone AUC0-$_\infty$ ↑ 34%	No dose adjustment
Ranitidine (150 mg BID) *[increases gastric pH]*	Voriconazole C_{max} and AUCτ ↔	No dose adjustment

Pregnancy and Lactation

Pregnancy

There are no adequate data from the use of voriconazole in pregnant women. Vortimal 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.

Breastfeeding

The excretion of voriconazole into breast milk has not been investigated. Breastfeeding must be stopped on initiation of treatment with Vortimal.

Side Effects

System Organ Class	Adverse drug reactions
Infections and infestation	
Common	Gastroenteritis, sinusitis, gingivitis
Uncommon	Pseudomembranous colitis, lymphangitis, peritonitis
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	
Not known	Squamous cell carcinoma*
Blood and lymphatic system disorders	
Common	Agranulocytosis, pancytopenia, thrombocytopenia, anaemia
Uncommon	Disseminated intravascular coagulation, bone marrow failure, leukopenia, lymphadenopathy, eosinophilia
Immune system disorders	
Common	Hypersensitivity
Uncommon	Anaphylactoid reaction
Endocrine disorders	
Uncommon	Adrenal insufficiency, hypothyroidism
Rare	Hyperthyroidism
Metabolism and nutrition disorders	
Very common	Oedema peripheral
Common	Hypoglycaemia, hypokalaemia, hyponatraemia
Psychiatric disorders	
Common	Depression, hallucination, anxiety, insomnia, agitation, confusion state
Nervous system disorders	
Very common	Headache
Common	Convulsion, tremor, paraesthesia, hypertonia, somnolence, syncope, dizziness
Uncommon	Brain oedema, encephalopathy, extrapyramidal disorder, neuropathy peripheral, ataxia, hypoaesthesia, dysgeusia, nystagmus
Rare	Hepatic, encephalopathy, Guillain-Barre syndrome
Eye disorders	
Very common	Visual impairment (including blurred vision [see section Warnings and Precautions], chromatopsia and photophobia)
Common	Retinal haemorrhage
Uncommon	Oculogyric crisis, Optic nerve disorder (including optic neuritis, see section *Warnings and Precautions*), Papilloedema (see section *Warnings and Precautions*). scleritis, blepharitis, diplopia
Rare	Optic atrophy, corneal opacity
Ear and labyrinth disorders	
Uncommon	Hypoacusis, vertigo, tinnitus
Cardiac disorders	
Common	Arrhythmia supraventricular, tachycardia, bradycardia

Uncommon	Ventricular fibrillation, ventricular extrasystole supraventricular tachycardia, ventricular tachycardia
Rare	Torsades de pointes, atrioventricular complete block, bundle branch block, nodal rhythm
Vascular disorders	
Common	Hypotension phlebitis
Uncommon	Thrombophlebitis
Respiratory, thoracic and mediastinal disorders	
Very common	Respiratory distress
Common	Acute respiratory distress syndrome, pulmonary oedema
Gastrointestinal disorders	
Very common	Abdominal pain, nausea, vomiting, diarrhoea
Common	Dyspepsia, constipation, cheilitis
Uncommon	Pancreatitis, duodenitis, glossitis, swollen tongue
Hepato-biliary disorders	
Very common	Liver function test abnormal (including AST, ALT, alkaline phosphatase, gamma-glutamyl transpeptidase [GGT], lactate dehydrogenase [LDH], bilirubin
Common	Jaundice, jaundice cholestatic, hepatitis
Uncommon	Hepatic failure, hepatomegaly, cholecystitis
Skin and subcutaneous tissue disorders	
Very common	Rash
Common	Dermatitis exfoliative, rash, maculopapular, pruritus, alopecia, erythema
Uncommon	Toxic epidermal necrolysis, Stevens-Johnson syndrome, Erythema multiforme, angioedema, psoriasis, urticaria, dermatitis allergic, phototoxicity, rash macular, rash papular, purpura, eczema
Rare	Pseudoporphyria, fixed drug eruption
Not known	Cutaneous lupus erythematosus*
Musculoskeletal and connective tissue disorders	
Common	Back pain
Uncommon	Arthritis
Not known	Periostitis*
Renal and urinary disorders	
Common	Renal failure acute, haematuria
Uncommon	Renal tubular necrosis, proteinuria, nephritis
General disorders and administration site conditions	
Very common	Pyrexia
Common	Chest pain, face oedema, asthenia, influenza-like illness, chills
Uncommon	Injection site reaction
Investigations	
Common	Blood creatinine increased
Uncommon	Electrocardiogram QTc prolonged, blood urea increased, blood cholesterol increased

*Undesirable events identified during post-approval use

Description of selected adverse reactions

Visual disturbances
Visual impairments with voriconazole were very common. The visual disturbances include altered/enhanced visual perception, blurred vision, colour vision change or photophobia. These visual disturbances 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 disturbances were generally mild, rarely resulted in discontinuation and were not associated with long-term sequelae. Visual disturbances 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 *Warnings and Precautions*).

Dermatological reactions
Dermatological reactions were common in patients treated with voriconazole and were receiving multiple concomitant medicinal products. The majority of rashes were of mild to moderate severity. Patients have rarely developed serious cutaneous reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme during treatment with voriconazole.

If a patient develops a rash they should be monitored closely and voriconazole discontinued if lesions progress. Photosensitivity reactions have been reported, especially during long-term therapy (see section *Warnings and Precautions)*.

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 *Warnings and Precautions*).

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 infrequently associated with cases of serious hepatic toxicity in patients with other serious underlying conditions. This includes cases of jaundice, and rare cases of hepatitis and hepatic failure leading to death (see section *Warnings and Precautions*).

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 *Warnings and Precautions*).

Prophylaxis
Discontinuation of voriconazole treatment has been reported in other study comparing voriconazole and itraconazole as primary prophylaxis in adult and adolescent allogeneic HSCT recipients without prior proven or probable IFI, following adverse effects and treatment-emergent hepatic side effects.

Paediatric population
The adverse reaction profile of the paediatric patients 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.

Symptoms and Treatment of Overdose

A single adverse reaction of photophobia of 10 minutes duration was reported to be associated with overdose of voriconazole.

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.

Effects on Ability to Drive and Use Machine

Vortimal has a 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.

Instructions for Use

The powder is reconstituted with about 19 ml Water for Injections to obtain an extractable volume of 20 ml of clear concentrate containing 10 mg/ml of voriconazole. Discard the vial if the vacuum does not pull the diluent into the vial. This medicinal product is for single use only and any unused solution should be discarded and only clear solutions without particles should be used.

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

The reconstituted solution can be diluted with:

1. 0.9% Sodium Chloride Intravenous Infusion
2. Compound Sodium Lactate Intravenous Infusion
3. 5% Glucose and Compound Sodium Lactate Intravenous Infusion
4. 5% Glucose and 0.45% Sodium Chloride Intravenous Infusion
5. 5% Glucose Intravenous Infusion
6. 5% Glucose in 20 mEq Potassium Chloride Intravenous Infusion
7. 0.45% Sodium Chloride Intravenous Infusion
8. 5% Glucose and 0.9% Sodium Chloride Intravenous Infusion

Required Volumes of 10 mg/ml Vortimal 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 (2)
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)	-	-

The final voriconazole solution must be infused at a maximum rate of 3 mg/kg per hour over 1 to 3 hours.
The compatibility of voriconazole with diluents other than described previously or in Incompatibilities as follows is unknown.

Incompatibilities

Vortimal must not be infused into the same line or cannula concomitantly with other intravenous products. When the Vortimal infusion is complete, the line may be used for administration of other intravenous products.

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

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 Interactions with Other).

Vortimal 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 previously.

Storage Conditions

Store at below 30 °C. Store in the original package in order to protect from light.
After reconstitution: Store at 2 – 8 °C for 24 hours. After further dilution: Store at 25 °C for 24 hours.

Shelf Life

2 years.
After reconstitution: 24 hours at 2 – 8 °C. After further dilution: 24 hours at 25 °C.

Dosage Forms and Packaging
Box contains 1 vial@ 200mg powder for solution for infusion.

Registration Number

Vortimal Voriconazole 200mg POWDER FOR SOLUTION FOR INFUSION - **MALXXXXXXXA**

Name and Address of Manufacturer

Anfarm Hellas S.A.
61st km NAT. RD. Athens-Lamia,
Schimatari Viotias,
32009 Greece.

Product Registration Holder

Averroes Pharmaceuticals Sdn. Bhd.
03-08-01 & 03-09-01, Block 3,
Presint Alami, Worldwide Business Center II,
Persiaran Akuatik, Seksyen 13
40100 Shah Alam, Selangor
Malaysia
Tel : +603 5511 1433
Fax: +603 5511 1431

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