PRESCRIBING INFORMATION

(For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only)

VORITROP 50 / 200
(Voriconazole Tablets 50 mg / 200 mg**)**

1. Name and strength of active ingredient

VORITROP 50/200; Voriconazole 50 mg & 200 mg

2. Product Description

VORITROP 50/200; 50 mg & 200 mg:

50 mg: White to off white, round, film coated tablets, debossed with 'V50' on one side and plain on the other Side.

200 mg: White to off white, oval, film coated tablets, debossed with 'V200' on one side and plain on the other side.

3. Pharmacological Properties

Pharmacodynamic Properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC: J02A C03.

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

Pharmacokinetic/Pharmacodynamic Relationship
A positive association between mean, maximum or minimum plasma Voriconazole concentration and efficacy was not found and this relationship has not been explored in prophylaxis studies.

Positive associations have been identified between plasma Voriconazole concentrations and both liver function test abnormalities and visual disturbances. Dose adjustments have not been explored.

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 by day 6 in the majority of subjects.

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

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 P450 isoenzymes, CYP2C19, CYP2C9 and CYP3A4.

The inter-individual variability of voriconazole pharmacokinetics is high.
CYP2C19 is significantly involved in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism. For example, 15-20 % of Asian populations maybe expected to be poor metabolisers. For Caucasians and Blacks the prevalence of poor metabolisers is 3-5 %. Caucasian and Japanese healthy subjects have shown that poor metabolisers have, on average, 4-fold higher voriconazole exposure (AUC_τ) than their homozygous extensive metaboliser counterparts. Subjects who are heterozygous extensive metabolisers have on average 2-fold higher voriconazole exposure than their homozygous extensive metaboliser counterparts.

The major metabolite of voriconazole is the N-oxide, which accounts for 72% of the circulating radio labeled 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 radio labelled dose of voriconazole, approximately 80% of the radioactivity is recovered in the urine after multiple intravenous dosing and 83% in the urine after multipleoral 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 dosage adjustment based on gender is necessary.

Elderly
The safety profile of voriconazole in young and elderly patients was similar and, therefore, no dosage adjustment is necessary for the elderly.

Pediatric population
Voriconazole exposures in the majority of adolescent patients were comparable to those in adults receiving the same dosing regimens. However, lower voriconazole exposure was observed in some young adolescents with low body weight compared to adults. It is likely that these subjects may metabolize voriconazole more similarly to children than to adults. 12 to14-year-old adolescents weighing less than 50 kg should receive children's doses.

Renal impairment
The plasma protein binding of voriconazole was similar in subjects with different degrees of renal impairment.

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

4. 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 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.

5. Posology and method of administration

Posology
Voriconazole film-coated tablets is to be taken at least one hour before, or one hour following a meal.
Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy.

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

	Intravenous	**Oral**	
		Patients 40 kg and above	Patients less than 40 kg
Loading Dose Regimen 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 *Candida* infections	3-4 mg/kg every 12 hours[c]	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

Oral administration:

If patient response is inadequate, the maintenance dose may be increased from 200 mg every 12 hours (similar to 3 mg/kg IV every 12 hours) to 300 mg every 12 hours (similar to 4 mg/kg IV every 12 hours) for oral administration. For patients less than 40 kg the oral dose may be increased from 100 mg to 150 mg every 12 hours.

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

Phenytoin may be co-administered with voriconazole if the maintenance dose of voriconazole is increased from 200 mg to 400 mg orally, every 12 hours (from 100 mg to 200 mg orally, every 12 hours in patients less than 40 kg).

When voriconazole is co-administered with adjusted doses of efavirenz, voriconazole maintenance dose should be increased to 400 mg every 12 hours.

Treatment duration depends upon patients' clinical and mycological response.

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

Use in patients with renal impairment
Film-coated tablets:
The pharmacokinetics of orally administered voriconazole are not affected by renal impairment. Therefore, no adjustment is necessary for oral dosing for patients with mild to

severe renal impairment.
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	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.

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

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.

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 (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 the treatment tables above.

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

6. Route of Administration

For oral use only. Voriconazole tablets are to be taken at least one hour before, or one hour following, a meal

7. Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Co-administration 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.

Co-administration with rifampicin, carbamazepine and phenobarbital since these medicinal products are likely to decrease plasma voriconazole concentrations significantly.

Co-administration 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.

Co-administration with high dose ritonavir (400 mg and above twice daily) because ritonavir significantly decreases plasma voriconazole concentrations in healthy subjects at this dose.

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

Co-administration with sirolimus since voriconazole is likely to increase plasma concentrations of sirolimus significantly.

Co-administration with St John's Wort.

8. Special Warnings & Precautions

Hypersensitivity

Caution should be used in prescribing Voriconazole to patients with hypersensitivity to other azoles.

Cardiovascular

Voriconazole has been associated with QT 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 QT-prolongation
- Cardiomyopathy, in particular when heart failure is present
- Sinus bradycardia
- Existing symptomatic arrhythmias
- Concomitant medicinal product that is known to prolong QT interval. Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be monitored and corrected, if necessary, prior to initiation and during voriconazole therapy.

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.

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, 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.

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.

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 developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome, during treatment with voriconazole. If patients develop a rash they 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 intense or prolonged 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) 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. The following severe adverse events have been reported in relation with 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 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 has not been established. Voriconazole is indicated for paediatric patients aged two years or older. A higher frequency of liver enzyme elevations was observed in the paediatric population. Hepatic function should be monitored in both children and adults. Oral bioavailability may be limited in paediatric patients aged 2-<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 photo protection 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.

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 that of efavirenz should be decreased to 300 mg every 24 hours.

Rifabutin (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.

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 justifies the use of voriconazole.

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.

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 co-administration of voriconazole. Dose reduction of methadone may be needed.

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. As the half-life of alfentanil is prolonged in a 4-fold manner when alfentanil is coadministered with voriconazole and concomitant use of voriconazole with fentanyl resulted in an increase in the mean $AUC_{0-\infty}$ of fentanyl, frequent monitoring for opiate-associated adverse reactions (including a longer respiratory monitoring period) may be necessary.

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

Fluconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor)
Co-administration of oral Voriconazole and oral fluconazole resulted in a significant increase in Cmax and AUCτ of voriconazole in healthy subjects. The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole associated adverse reactions is recommended if voriconazole is used sequentially after fluconazole.

Voriconazole tablets contain lactose and should not be given to patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

9. 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.

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.

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]***	**Recommendations concerning co-administration**
Astemizole, cisapride, pimozide, quinidine and terfenadine *[CYP3A4 substrates]*	**Contraindicated**
Carbamazepine and long-acting barbiturates (e.g., phenobarbital, mephobarbital) *[potent CYP450 inducers]*	**Contraindicated**
Efavirenz (a non-nucleoside reverse transcriptase inhibitor) *[CYP450 inducer; CYP3A4 inhibitor and substrate]* Efavirenz 400 mg QD, coadministered with voriconazole 200 mg BID* Efavirenz 300 mg QD, coadministered with voriconazole 400 mg BID*	Use of standard doses of voriconazole with efavirenz doses of 400 mg QD or higher is **contraindicated**. 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.
Ergot alkaloids (e.g., ergotamine and dihydroergotamine) *[CYP3A4 substrates]*	**Contraindicated**
Rifabutin *[potent CYP450 inducer]* 300 mg QD 300 mg QD (co-administered with voriconazole 350 mg BID)*	Concomitant use of voriconazole and rifabutin should be avoided unless the benefit outweighs the risk. The maintenance dose of voriconazole may be increased to 5 mg/kg intravenously BID or from 200 mg to 350 mg orally BID (100 mg to 200 mg orally BID in patients less than 40 kg). Careful monitoring of full blood counts and adverse

300 mg QD (co-administered with voriconazole 400 mg BID)*	reactions to rifabutin (e.g., uveitis) is recommended when rifabutin is coadministered with voriconazole.
Rifampicin (600 mg QD) *[potent CYP450 inducer]*	**Contraindicated**
Ritonavir (protease inhibitor) *[potent CYP450 inducer; CYP3A4 inhibitor and substrate]* High dose (400 mg BID) Low dose (100 mg BID)*	 Co-administration of voriconazole and high doses of ritonavir (400 mg and above BID) is **contraindicated**. 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; Pgp inducer]* 300 mg TID (co-administered with voriconazole 400 mg single dose)	**Contraindicated**.
Everolimus *[CYP3A4 substrate, P-gP substrate]*	Co-administration of voriconazole with everolimus is not recommended because voriconazole is expected to significantly increase everolimus concentrations.
Fluconazole (200 mg QD) *[CYP2C9, CYP2C19 and CYP3A4 inhibitor]*	The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole-associated adverse reactions is recommended if voriconazole is used sequentially after fluconazole.
Phenytoin *[CYP2C9 substrate and potent CYP450 inducer]* 300 mg QD 300 mg QD (co-administered with voriconazole 400 mg BID)*	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).
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]*	Close monitoring of prothrombin time or other suitable anticoagulation tests is recommended and the dose of anticoagulants should be adjusted accordingly.
Benzodiazepines (e.g., midazolam, triazolam, alprazolam) *[CYP3A4 substrates]*	Dose reduction of benzodiazepines should be considered.
Immuno-suppressants *[CYP3A4 substrates]* Sirolimus (2 mg single dose) Ciclosporin (In stable renal transplant recipients receiving chronic ciclosporin therapy) Tacrolimus (0.1 mg/kg single dose)	 Co-administration of voriconazole and sirolimus is **contraindicated.** When initiating voriconazole in patients already on ciclosporin it is recommended that the ciclosporin dose be halved and ciclosporin level carefully monitored. Increased ciclosporin levels have been associated with nephrotoxicity. <u>When voriconazole is discontinued, ciclosporin levels must be carefully monitored and the dose increased as necessary.</u> When initiating voriconazole in patients already on tacrolimus, it is recommended that the tacrolimus dose be reduced to a third of the original dose and tacrolimus level carefully monitored. Increased tacrolimus levels have been associated with nephrotoxicity. <u>When voriconazole is discontinued, tacrolimus levels must be carefully monitored and the dose increased as necessary.</u>
Long Acting Opiates *[CYP3A4 substrates]* Oxycodone (10 mg single dose)	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]*	Frequent monitoring for adverse reactions and toxicity related to methadone, including QT prolongation, is recommended. Dose reduction of methadone may be needed.
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	

[CYP2C9 substrates] Ibuprofen (400 mg single dose) Diclofenac (50 mg single dose)	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]*	No dose adjustment of voriconazole is recommended. When initiating voriconazole in patients already receiving omeprazole doses of 40 mg or above, it is recommended that the omeprazole dose be halved.
Oral Contraceptives* *[CYP3A4 substrate; CYP2C19 inhibitor]* Norethisterone/ethinylestradiol (1 mg/0.035 mg QD)	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)	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]*	Dose reduction of statins should be considered.
Sulfonylureas (e.g., tolbutamide, glipizide, glyburide) *[CYP2C9 substrates]*	Careful monitoring of blood glucose is recommended. Dose reduction of sulfonylureas should be considered.
Vinca Alkaloids (e.g., vincristine and vinblastine) *[CYP3A4 substrates]*	Dose reduction of vinca alkaloids should be considered.
Other HIV Protease Inhibitors (e.g., saquinavir, amprenavir and nelfinavir)* *[CYP3A4 substrates and 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]*	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 inhibitorand*	No dose adjustment

increases gastric pH]	
Digoxin (0.25 mg QD) *[P-gp substrate]*	No dose adjustment
Indinavir (800 mg TID) *[CYP3A4 inhibitor and substrate]*	No dose adjustment
Macrolide antibiotics Erythromycin (1 g BID) *[CYP3A4 inhibitor]* Azithromycin (500 mg QD)	No dose adjustment
Mycophenolic acid (1 g single dose) *[UDP-glucuronyl transferase substrate]*	No dose adjustment
Prednisolone (60 mg single dose) *[CYP3A4 substrate]*	No dose adjustment
Ranitidine (150 mg BID) *[increases gastric pH]*	No dose adjustment

10. Fertility, Pregnancy and Lactation

Pregnancy
There are no adequate data from the use of voriconazole in pregnant women.
The potential risk for humans is unknown.
Voriconazole must not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus.

Women of 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.

11. 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.

12. Undesirable effects

Summary of safety profile

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

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

Tabulated list of adverse reactions

Undesirable effects reported in subjects receiving voriconazole:

System Organ Class	Adverse Reactions
Infections and infestations	sinusitis, pseudomembranous colitis
Blood and lymphatic system disorders	agranulocytosis[1], pancytopenia, thrombocytopenia[2], leukopenia, anaemia, bone marrow failure, lymphadenopathy, eosinophilia, disseminated intravascular coagulation
Immune system disorders	hypersensitivity, anaphylactoid reaction
Endocrine disorders	adrenal insufficiency, hypothyroidism, hyperthyroidism
Metabolism and nutrition disorders	oedema peripheral, hypoglycaemia, hypokalaemia, hyponatraemia
Psychiatric disorders	depression, hallucination, anxiety, insomnia, agitation, confusional state
Nervous system disorders	headache, convulsion, syncope, tremor, hypertonia[3], paraesthesia, somnolence, dizziness, brain oedema, encephalopathy[4], extrapyramidal disorder[5], neuropathy peripheral, ataxia, hypoaesthesia, dysgeusia, hepatic encephalopathy, Guillain-Barre syndrome, nystagmus
Eye disorders	visual impairment[6], retinal haemorrhage, papilloedema, oculogyric crisis, diplopia, scleritis, blepharitis, optic atrophy, corneal opacity
Ear and labyrinth disorders	hypoacusis, vertigo, tinnitus

System Organ Class	Adverse Reactions
Cardiac disorders	arrhythmia supraventricular, tachycardia, bradycardia, ventricular fibrillation, ventricular extrasystoles, ventricular tachycardia, electrocardiogram QT prolonged, supraventricular tachycardia, torsades de pointes, atrioventricular block complete, bundle branch block, nodal rhythm
Vascular disorders	hypotension, phlebitis, thrombophlebitis, lymphangitis
Respiratory, thoracic and mediastinal disorders	respiratory distress[9], acute respiratory distress syndrome, pulmonary oedema
Gastrointestinal disorders	Diarrhoea, vomiting, abdominal pain, nausea, cheilitis, dyspepsia, constipation, gingivitis, peritonitis, pancreatitis, swollen tongue, duodenitis, gastroenteritis, glossitis.
Hepatobiliary disorders	Liver function 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, phototoxicity, purpura, urticaria, dermatitis allergic, rash papular, rash macular, eczema, toxic epidermal necrolysis, angioedema, pseudoporphyria erythema multiforme, psoriasis, drug eruption.
Musculoskeletal and connective tissue disorders	back pain, arthritis
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.

[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 8.
[9] Includes dyspnoea and dyspnoea exertional.
[10] Includes drug-induced liver injury, hepatitis toxic, hepatocellular injury and hepatotoxicity.
[11] Includes periorbital oedema, lip oedema, and oedema mouth

Description of selected adverse reactions

Visual impairment
Visual impairments (including blurred vision, photophobia, chloropsia, chromatopsia, colour blindness, cyanopsia, eye disorder, halo vision, night blindness, oscillopsia, photopsia, scintillating scotoma, visual acuity reduced, visual brightness, visual field defect, vitreous

floaters, and xanthopsia) with voriconazole were very common. These visual *impairments* were transient and fully reversible, with the majority spontaneously resolving within 60 minutes and no clinically significant long-term visual effects were observed. There was evidence of attenuation with repeated doses of voriconazole. The visual impairment were generally mild, rarely resulted in discontinuation and were not associated with long-term sequelae. Visual impairment 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.

Dermatological reactions
The majority of rashes were of mild to moderate severity. Patients have developed serious cutaneous reactions, including Stevens-Johnson syndrome (uncommon), toxic epidermal necrolysis (rare) and erythema multiforme (rare) during treatment with voriconazole.

If patients develop 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.

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.

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.

13. Overdose & Treatment

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

There is no known antidote to voriconazole.

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

14. Ingredients

Tablet core
Voriconazole
Lactose monohydrate,
Pre gelatinized starch,
Croscarmellose sodium,
Povidone,
Magnesium Stearate.

Film-coating (50 mg)
Hypromellose
Lactose monohydrate
Triacetin,
Titanium dioxide

Film-coating (200 mg)
Opadry II White 30K580005

15. Storage Conditions

Store below 30 °C.

16. Dosage forms and packaging available

Voriconazole Tablets 50 mg & 200 mg available in clear PVC-Alu blister pack of 10 Tablets.

17. Name and address of manufacturer

INTAS PHARMACEUTICALS LTD.
Plot No. 457 & 458, Village Matoda, Bavla road,
And Plot No. 191/218 P, Village Chacharwadi,
Ta -Sanand, Dist. Ahmedabad, Gujarat,
382210 India.

18. Product Registration Holder

Accord Healthcare Sdn Bhd
26-6, Menara 1MK, Kompleks One Mont' Kiara
No. 1, Jalan Kiara, Mont' Kiara,
50480 Kuala Lumpur, Malaysia

19. Date of revision of PI

02/02/2021