VORCAZ™ 50mg 200mg
[Voriconazole]
Tablets J.P.

ورکاز ۵۰ ملی گرام ۲۰۰ ملی گرام
(وورِیکونازول)
ٹیبلٹس جے۔پی۔

QUALITATIVE AND QUANTITATIVE COMPOSITION
Vorcaz™ Tablet 50mg J.P.
Each film-coated tablet contains:
Voriconazole 50mg
Vorcaz™ Tablet 200mg J.P.
Each film-coated tablet contains:
Voriconazole 200mg

DESCRIPTION
Voriconazole, a triazole antifungal agent, Voriconazole is designated chemically as (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1H -1,2,4-triazol-1-yl)-2-butanol with an empirical formula of C16H14F3N5O and a molecular weight of 349.3.

CLINICAL PHARMACOLOGY
Pharmacodynamics: Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02AC03
Pharmacokinetics: General pharmacokinetic characteristics During oral administration of 200 mg or 300 mg twice daily for 14 days in patients at risk of aspergillosis (mainly patients with malignant neoplasms of lymphatic or haematopoietic tissue), the observed pharmacokinetic characteristics of rapid and consistent absorption, accumulation and non-linear pharmacokinetics were in agreement with those observed in healthy subjects. The pharmacokinetics of voriconazole are non-linear due to saturation of its metabolism. Greater than proportional increase in exposure is observed with increasing dose. It is estimated that, on average, increasing the oral dose from 200 mg twice daily to 300 mg twice daily leads to a 2.5-fold increase in exposure (AUCτ). The oral maintenance dose of 200 mg (or 100 mg for patients less than 40 kg) achieves a voriconazole exposure similar to 3 mg/kg IV. A 300 mg (or 150 mg for patients less than 40 kg) oral maintenance dose achieves an exposure similar to 4 mg/kg IV. When the recommended intravenous or oral loading dose regimens are administered, plasma concentrations close to steady state are achieved within the first 24 hours of dosing. Without the loading dose, accumulation occurs during twice daily multiple dosing with steady-state plasma voriconazole concentrations being achieved by Day 6 in the majority of subjects. **Absorption:** Voriconazole is rapidly and almost completely absorbed following oral administration, with maximum plasma concentrations (Cmax) achieved 1-2 hours after dosing. The absolute bioavailability of voriconazole after oral administration is estimated to be 96%.
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%. **Elimination:** Voriconazole is eliminated via hepatic metabolism with less than 2% of the dose excreted unchanged in the urine.
The terminal half-life of voriconazole depends on dose and is approximately 6 hours at 200 mg (orally).

INDICATIONS AND USAGE
Voriconazole, is a broad-spectrum, triazole antifungal agent and is indicated in adults and children aged 2 years and above as follows:
Treatment of invasive aspergillosis. Treatment of candidaemia in non-neutropenic patients. Treatment of fluconazole-resistant serious invasive Candida infections (including *C. krusei*). Treatment of serious fungal infections caused by Scedosporium spp. and Fusari-

um spp. Voriconazole should be administered primarily to patients with progressive, possibly life-threatening infections. Prophylaxis of invasive fungal infections in high risk allogeneic hematopoietic stem cell transplant (HSCT) recipients.

CONTRAINDICATIONS: Hypersensitivity to the active substance or to any of the excipients listed in section 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. Coadministration with rifampicin, carbamazepine and phenobarbital since these medicinal products are likely to decrease plasma voriconazole concentrations significantly. 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. Coadministration with high-dose ritonavir (400 mg and above twice daily) because ritonavir significantly decreases plasma voriconazole concentrations in healthy subjects at this dose. Coadministration with ergot alkaloids (ergotamine, dihydroergotamine), which are CYP3A4 substrates, since increased plasma concentrations of these medicinal products can lead to ergotism. Coadministration with sirolimus since voriconazole is likely to increase plasma concentrations of sirolimus significantly. Coadministration with St. John's Wort.

INTERACTIONS: 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), coadministration is contraindicated.

USE IN SPECIFIC POPULATION

Pregnancy Category D: Voriconazole can cause fetal harm when administered to a pregnant woman. 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. **Patients with Renal or Hepatic Impairment** Dose reduction may be necessary in patients with significant impairment of renal or hepatic function. Clozapine concentrations may be increased in these patients, because clozapine is almost completely metabolized and then excreted. **WARNINGS AND PRECAUTIONS** **Hypersensitivity:** Caution should be used in prescribing Voriconazole to patients with hypersensitivity to other azoles. **Cardiovascular:** Voriconazole has been associated with QTc interval prolongation. There have been rare cases of torsades de pointes in patients taking voriconazole who had risk factors, such as history of cardiotoxic chemotherapy, cardiomyopathy, hypokalaemia and concomitant medicinal products that may have been contributory. **Hepatic toxicity:** In clinical trials, there have been cases of serious hepatic reactions during treatment with voriconazole (including clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities). **Serious dermatological adverse reactions: Phototoxicity: Squamous cell carcinoma of the skin (SCC): Severe cutaneous adverse reactions: Long-term treatment:** Squamous cell carcinoma of the skin (SCC) has been reported in relation with long-term voriconazole treatment. **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. **Paediatric population:** Safety and effectiveness in paediatric subjects below the age of two years has not been established. **DRUG INTERACTIONS 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. **Phenytoin (CYP2C9 substrate and potent CYP450 inducer):** Careful monitoring of phenytoin levels is recommended when coadministered. **Rifabutin (Potent CYP450 inducer):** Careful monitoring of full blood counts and adverse reactions to rifabutin (e.g., uveitis) is recommended when coadministered. **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. **Everolimus (CYP3A4 substrate, P-gp substrate):** Coadministration of voriconazole with everolimus is not recommended because voriconazole is expected to significantly increase everolimus concentrations. **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. **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, **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. Frequent monitoring for opiate-associated adverse reactions may be necessary. **Fluconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor):** Coadministration of oral voriconazole and oral fluconazole resulted in a significant increase in Cmax and AUC 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. **ADVERSE REACTIONS:** 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.

DOSAGE AND ADMINISTRATION Adults: Therapy must be initiated with the specified loading dose regimen of VORICONAZOLE to achieve plasma concentrations on Day 1 that are close to steady state.

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

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

* This also applies to patients aged 15 years and older

Duration of treatment

Depending on the patient's clinical and mycological response.

Dosage adjustment (Adults)

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

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

In case of use as prophylaxis, refer below.
Children (2 to <12 years) and young adolescents with low body weight (12 to 14 years and <50 kg) Voriconazole should be dosed as children as these young adolescents may metabolize voriconazole more similarly to children than to adults.
The recommended dosing regimen is as follows:

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

All other adolescents (12 to 14 years and ≥50 kg; 15 to 17 years regardless of body weight) Voriconazole should be dosed as adults. **Dosage adjustment (Children [2 to <12 years] and young adolescents with low body weight [12 to 14 years and <50 kg])** Dose can be adjusted from 50 mg TO 350 mg **Prophylaxis in Adults and Children** Prophylaxis should be initiated on the day of transplant and may be administered for up to 100 days. **Duration of prophylaxis** The safety and efficacy of voriconazole use for longer than 180 days has not been adequately studied in clinical trials.
Elderly No dose adjustment is necessary for elderly patients **Renal impairment** The pharmacokinetics of orally administered voriconazole are not affected by renal impairment. **Hepatic impairment** It is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh A and B) receiving voriconazole. **Method of administration** VORICONAZOLE tablets are to be taken at least one hour before, or one hour following, a meal. **Overdose:** There is no known antidote to voriconazole.

DOSAGE: As directed by the physician. **INSTRUCTIONS:** Store below 30°C. Protect from heat, light and moisture. Keep all medicines out of the reach of children. **For oral use only.**

PRESENTATION
Vorcaz Tablet 50mg: Available in Alu/PVC Blister of 1 X 10's, Packed in carton box.
Vorcaz Tablet 200mg: Available in Alu/PVC Blister of 1 X 10's, Packed in carton box.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
ہدایات: ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
گرمی، روشنی اور نمی سے محفوظ رکھیں۔ تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔
صرف کھانے کیلئے استعمال کریں۔

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