VORIF

(Voriconazole Tablets 50mg & 200mg)

COMPOSITION

Each film coated tablet contains: Voriconazole 50mg and 200mg respectively.
Ferozsons Specifications

DRUG DESCRIPTION

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

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 wall 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.

Pharmacodynamics/Kinetics

Absorption: Well absorbed after oral administration; administration of crushed tablets is considered bioequivalent to whole tablets
Distribution: V_d: 4.6 L/kg; Protein binding:58%
Metabolism: Hepatic, via CYP2C19 (major pathway) and CYP2C9 and CYP3A4 (less significant); saturable (may demonstrate nonlinearity).
Bioavailability: 96%
Half-life elimination: Variable, dose-dependent
Time to peak: Oral: 1-2 hours; 0.5 hours (crushed tablet)
Excretion: Urine (as inactive metabolites; <2% as unchanged drug.

INDICATIONS

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

1. Invasive aspergillosis
2. Esophageal candidiasis
3. Candidemia (in non-neutropenic patients)
4. Disseminated *Candida* infections of the skin and viscera
5. Serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* spp (including *Fusarium solani*) in patients intolerant of, or refractory to, other therapy.

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

DOSAGE AND ADMINISTRATION:

VORIF Tablets should 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
Therapy must be initiated with the specified loading dose regimen of tablets **VORIF** to achieve plasma concentrations on Day 1 that are close to steady state.

Recommended Adult Dose

	Tablets	
	Patients 40kg and above	Patients less than 40kg
Dose for the first 24 hours (Loading Dose)	400mg every 12 hours for the first 24 hours	200mg every 12 hours for the first 24 hours
Dose after the first 24 hours (Maintenance Dose)	200mg twice a day	100mg twice a day

Recommended Dose in Children and Teenagers

	Tablets	
	Children aged 2 to less than 12 years and teenagers aged 12 to 14 years weighing less than 50kg	Teenagers aged 12 to 14 years weighing 50kg or more; and all teenagers older than 14
Dose for the first 24 hours (Loading Dose)	Your treatment will be started as an infusion	400mg every 12 hours for the first 24 hours
Dose after the first 24 hours (Maintenance Dose)	9mg/kg twice a day (a maximum dose of 350mg twice daily)	200mg twice a day

Duration of treatment: Patients should be treated for a minimum of 14 days and for at least 7 days following resolution of symptoms. Treatment should be as short as possible depending on the patients' clinical and mycological response. For long term treatment greater than 6 months, a careful assessment of the benefit-risk balance should be considered.

Dosing in Special Populations:

Patients with Renal Insufficiency: Oral dosage form of Voriconazole is poorly dialyzed; no supplemental dose or dosage adjustment necessary, including patients on intermittent hemodialysis, peritoneal dialysis, or continuous renal replacement therapy (eg, CVVHD)
Patient with Hepatic Insufficiency: Mild-to-moderate hepatic dysfunction (Child-Pugh class A or B): Following standard loading dose, reduce maintenance dosage by 50%
Severe hepatic impairment: Should only be used if benefit outweighs risk; monitor closely for toxicity
Dosage adjustment in patients unable to tolerate treatment: Dose may be reduced in 50 mg decrements to a minimum dosage of 200 mg every 12 hours in patients weighing ≥40 kg (100 mg every 12 hours in patients <40 kg
Elderly: Refer to adult dosing.
Dosage adjustment in patients receiving concomitant CYP450 enzyme inducers or substrates: Efavirenz: Increase maintenance dose of voriconazole to 400 mg every 12 hours and reduce efavirenz dose to 300 mg once daily; upon discontinuation of voriconazole, return to the initial dose of efavirenz
Phenytoin: Increase voriconazole dose to 400 mg every 12 hours in patients ≥40 kg (200 mg every 12 hours in patients <40 kg

ADVERSE REACTIONS

>10%:
Central nervous system: Hallucinations (4% to 12%; auditory and/or visual and likely serum concentration-dependent)
Ocular: Visual changes (dose related; photophobia, color changes, increased or decreased visual acuity, or blurred vision occur in ~21%)
Renal: Creatinine increased (1% to 21%)
2% to 10%:
Cardiovascular: Tachycardia (≤2%)
Central nervous system: Fever (≤6%), chills (≤4%), headache (≤3%)
Dermatologic: Rash (≤7%)
Endocrine & metabolic: Hypokalemia (≤2%)
Gastrointestinal: Nausea (1% to 5%), vomiting (1% to 4%)
Hepatic: Alkaline phosphatase increased (4% to 5%), AST increased (2% to 4%), ALT increased (2% to 3%), cholestatic jaundice (1% to 2%)
Ocular: Photophobia (2% to 3%)
<2% (Limited to important or life-threatening): Acute tubular necrosis, adrenal cortical insufficiency, allergic reaction, alopecia, anaphylactoid reaction, ataxia, atrial arrhythmia, atrial fibrillation, AV block, bigeminy, bone marrow depression, bone necrosis, bradycardia, brain edema, bundle branch block, cardiac arrest, cardiomegaly, cardiomyopathy, cerebral hemorrhage, cerebral ischemia, cerebrovascular accident, chest pain, CHF, cholecystitis, cholelithiasis, chromatopsia, color blindness, coma, cyanosis, delirium, dementia, depersonalization, depression, diabetes insipidus, diarrhea, DIC, discoid lupus erythematosus, duodenal ulcer perforation, DVT, dyspnea, edema, encephalopathy, endocarditis, erythema multiforme, exfoliative dermatitis, extrapyramidal symptoms, fixed drug eruption, gastrointestinal hemorrhage, glucose tolerance decreased, Guillain-Barré syndrome, hepatic failure, hepatitis, hydronephrosis, hypercholesterolemia, hypoxia, intestinal perforation, intracranial hypertension, lung edema, lymphadenopathy, lymphangitis, melanoma,

MI, multiorgan failure, myasthenia, myopathy, nephritis, nephrosis, neuropathy, night blindness, nodal arrhythmia, oculogyric crisis, optic atrophy, optic neuritis, orthostatic hypotension, osteomalacia, osteoporosis, palpitation, pancreatitis, papilledema, paresthesia, peripheral edema, peritonitis, petechia, photosensitivity, pleuraleffusion, pseudomembraneous colitis, pseudoporphyria, psychosis, pulmonary embolus, purpura, QT interval prolongation, renal failure (acute), respiratory distress syndrome, retinal hemorrhage, seizure, sepsis, spleen enlarged, squamous cell carcinoma, Stevens-Johnson syndrome, suicidal ideation, supraventricular extrasystoles, supraventricular tachycardia, syncope, thrombophlebitis, thrombotic thrombocytopenic purpura, toxic epidermal necrolysis, uremia, urinary retention, uveitis, vasodilation, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia, visual field defect.

CONTRAINDICATIONS:

Hypersensitivity to voriconazole or any component of the formulation (cross-reaction with other azole antifungal agents may occur but has not been established, use caution); coadministration of CYP3A4 substrates which may lead to QT_c prolongation (cisapride, pimozide, or quinidine); coadministration with barbiturates (long acting), carbamazepine, efavirenz (with standard [eq, not adjusted] voriconazole and efavirenz doses), ergot derivatives, rifampin, rifabutin, ritonavir (≥800 mg/day), sirolimus, St John's wort.

WARNINGS/PRECAUTIONS

Concerns related to adverse effects:

• Arrhythmias/QT prolongation: QT interval prolongation has been associated with voriconazole use; rare cases of arrhythmia (including torsade de pointes), cardiac arrest, and sudden death have been reported, usually in seriously ill patients with comorbidities and/or risk factors (eg, prior cardiotoxic chemotherapy, cardiomyopathy, electrolyte imbalance, or concomitant QT_c-prolonging drugs). Use with caution in these patient populations; correct electrolyte abnormalities (eg, hypokalemia, hypomagnesemia, hypocalcemia) prior to initiating therapy.

• Dermatologic reactions: Rare cases of malignancy (melanoma, squamous cell carcinoma) have been reported in patients (mostly immunocompromised) with prior onset of severe photosensitivity reactions and exposure to long-term voriconazole therapy. Other serious exfoliative cutaneous reactions, including Stevens-Johnson syndrome, have also been reported. Patients should avoid strong, direct exposure to sunlight; may cause photosensitivity, especially with long-term use. Discontinue use in patients who develop an exfoliative cutaneous reaction or a skin lesion consistent with squamous cell carcinoma or melanoma. Periodic total body skin examinations should be performed, particularly with prolonged use.

• Hallucinations: Visual and/or auditory hallucinations have been observed. Possibly dependent on serum concentrations and may be more common with the I.V. formulation.

• Ocular effects: Visual changes, including blurred vision, changes in visual acuity, color perception, and photophobia, are commonly associated with treatment; postmarketing cases of optic neuritis and papilledema (lasting >1 month) have also been reported. Patients should be warned to avoid tasks which depend on vision, including operating machinery or driving. Changes are reversible on discontinuation following brief exposure/treatment regimens (≤28 days); reversibility following long-term administration has not been evaluated.

Disease-related concerns:

• Hepatic impairment: Serious (and rarely fatal) hepatic toxicity (eg, hepatitis, cholestasis, fulminant failure) has been observed with azole therapy. Use with caution in patients with pre-existing hepatic impairment; monitor liver function closely and dosage adjustment or discontinuation may be warranted.

• Pancreatitis: Monitor pancreatic function in patients (children and adults) at risk for acute pancreatitis (eg, recent chemotherapy or hematopoietic stem cell transplantation). There have been postmarketing reports of pancreatitis in children.

• Renal impairment: Acute renal failure has been observed in severely ill patients; use with caution in patients receiving concomitant nephrotoxic medications.

Concurrent drug therapy issues:

• High potential for interactions: Use caution in patients taking strong cytochrome P450 inducers, CYP2C9 inhibitors, and major 3A4 substrates (see Drug Interactions); consider alternative agents that avoid or lessen the potential for CYP-mediated interactions.

Other warnings/precautions:

Pregnancy Risk Factor: D

Voriconazole was teratogenic and embryotoxic in animal studies, and lowered plasma estradiol in animal models. Women of childbearing potential should use effective contraception during treatment. Should be used in pregnant woman only if benefit to mother justifies potential risk to the fetus.

Lactation: Excretion in breast milk unknown/not recommended

DRUG INTERACTIONS

The systemic exposure to voriconazole is significantly reduced or is expected to be reduced by the concomitant administration of the following agents and their use is contraindicated:

Rifampin (potent CYP450 inducer), Ritonavir (potent CYP450 inducer; CYP3A4 inhibitor and substrate), Carbamazepine and long-acting barbiturates (potent CYP450 inducers)

Significant drug interactions that may require voriconazole dosage adjustment, or frequent monitoring of voriconazole-related adverse events/toxicity:

Fluconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor)

Minor or no significant pharmacokinetic interactions that do not require dosage adjustment:

Cimetidine (non-specific CYP450 inhibitor and increases gastric pH),Ranitidine (increases gastric pH), Macrolide antibiotics

The systemic exposure of the following drugs is significantly increased or is expected to be significantly increased by coadministration of voriconazole and their use is contraindicated:

Sirolimus (CYP3A4 substrate), Terfenadine, astemizole, cisapride, pimozide and quinidine (CYP3A4 substrates), Ergot alkaloid

Coadministration of voriconazole with the following agents results in increased exposure or is expected to result in increased exposure to these drugs. Therefore, careful monitoring and/or dosage adjustment of these drugs is needed:

Alfentanil (CYP3A4 substrate), Fentanyl (CYP3A4 substrate), Oxycodone (CYP3A4 substrate), Cyclosporine (CYP3A4 substrate), Methadone (CYP3A4, CYP2C19, CYP2C9 substrate), Tacrolimus (CYP3A4 substrate), Warfarin (CYP2C9 substrate), Oral Coumarin Anticoagulants (CYP2C9, CYP3A4 substrates), Statins (CYP3A4 substrates), Benzodiazepines (CYP3A4 substrates), Calcium Channel Blockers(CYP3A4 substrates), Sulfonylurea's (CYP2C9 substrates), Vinca Alkaloids (CYP3A4 substrates), Non-Steroidal Anti-Inflammatory Drugs(NSAIDs; CYP2C9 substrates)

Two-Way Interactions

Concomitant use of the following agents with voriconazole is contraindicated:

Rifabutin (potent CYP450 inducer)

Significant drug interactions that may require dosage adjustment, frequent monitoring of drug levels and/or frequent monitoring of drug-related adverse events/toxicity:

Efavirenz, a non-nucleoside reverse transcriptase inhibitor (CYP450 inducer; CYP3A4 inhibitor and substrate) Phenytoin (CYP2C9 substrate and potent CYP450 inducer), Omeprazole (CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate), Oral Contraceptives (CYP3A4 substrate; CYP2C19 inhibitor)

STORAGE

Store at 15-30°C in a dry and dark place. Keep out of the reach of children.

HOW SUPPLIED

Vorif 50mg & 200mg Tablets are available in 1x10's Blister Pack.

Tablet Vorif 50mg	Regn. No. 069764
Tablet Vorif 200mg	Regn. No. 069765

Please read the contents cautiously before use. This package insert is regularly and timely updated.

Manufactured by:
FEROZSONS
LABORATORIES LIMITED
P. O. Ferozsons, Nowshera-Pakistan
Mfg. Lic. No. 000038

02-09-0163