Vori™

Voriconazole

COMPOSITION
Vori™ 50 Tablet: Each Tablet contains Voriconazole USP 50 mg.
Vori™ 200 Tablet: Each Tablet contains Voriconazole USP 200 mg.
Vori™ IV Injection: Each Vial Contains Voriconazole USP 200 mg as sterile lyophilized powder.

PHARMACOLOGY
Voriconazole is a triazole antifungal agent. Its primary mode of action is the inhibition of fungal cytochrome P-450-mediated 14α-lanosterol demethylation, an essential step in ergosterol biosynthesis. Voriconazole is more selective than some other azole drugs for fungus as opposed to various mammalian cytochrome P-450 enzyme systems. The subsequent loss of normal sterols correlates with the accumulation of 14α-methyl sterols in fungi and may be responsible for its fungistatic/fungicidal activity.

INDICATION
Voriconazole is indicated in adults and pediatric patients (2 years of age and older) for the treatment of following fungal infections:
- Invasive aspergillosis
- Candidemia in non-neutropenics and other deep tissue *Candida* infections
- Esophageal candidiasis
- Serious fungal infections caused by *Scedosporium apiospermum* & *Fusarium species* including *Fusarium solani*, in patients intolerant of, or refractory to, other therapy

DOSAGE & ADMINISTRATION
Voriconazole tablets to be taken at least one hour before or one hour following a meal. Voriconazole injection requires reconstitution and dilution prior to administration as an intravenous infusion.
Adults
Therapy must be initiated with the specified loading dose regimen of either intravenous or oral Voriconazole to achieve plasma concentrations on Day 1. Switching between intravenous & oral administration is appropriate when clinically indicated.
Detailed information on dosage recommendations is provided in the following table:

	Intravenous	Oral	
		Patients 40 kg & above*	Patients less than 40 kg*
Loading dose regimen (first 24 hours)	6 mg/kg every 12 hours	400 mg every 12 hours	200 mg every 12 hours
Maintenance dose (after first 24 hours)	4 mg/kg twice daily	200 mg twice daily	100 mg twice daily

* This also applies to patients aged 15 years and older
Duration of treatment
Treatment duration should be as short as possible depending on the patient's clinical and mycological response. Long term exposure to Voriconazole greater than 180 days (6 months) requires careful assessment of the benefit-risk balance.
Dosage adjustment (Adults)
If patient is unable to tolerate intravenous treatment at 4 mg/kg twice daily, reduce the dose to 3 mg/kg twice daily. 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.
Children (2 to <12 years) and young adolescents with low body weight (12 to 14 years and <50 kg)

	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.
Renal impairment
In patients with moderate to severe renal dysfunction (creatinine clearance < 50 ml/min), accumulation of the intravenous vehicle, SBECD, occurs. Oral voriconazole should be administered to these patients, unless an assessment of the risk benefit to the patient justifies the use of intravenous Voriconazole. Serum creatinine levels should be closely monitored in these patients and, if increases occur, consideration should be given to changing to oral Voriconazole therapy.
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.
Reconstitution: for Vori IV Injection
The powder is reconstituted with 19 ml of Water for Injection to obtain an extractable volume of 20 ml of clear concentrate containing 10 mg/ml of Voriconazole. It is recommended that a standard 20 ml syringe be used to ensure that the exact amount (19 ml) of Water for Injection is dispensed. The vial should be shaked until all the powder is dissolved. Voriconazole must be infused over 1 to 3 hours, at a concentration of 5 mg/ml or less. Therefore, the required volume of the 10 mg/ml Voriconazole concentrate should be further diluted as follows:
1. The volume of 10 mg/ml Voriconazole concentrate required based on the patient's weight is calculated.
2. In order to allow the required volume of Voriconazole concentrate to be added, at least an equal volume of diluent from the infusion bag or bottle to be used should be withdrawn and discarded. The volume of diluent remaining in the bag or bottle should be such that when the 10 mg/ml Voriconazole concentrate is added, the final concentration is not less than 0.5 mg/ml or greater than 5 mg/ml.
3. Using a suitable size syringe and aseptic technique, the required volume of Voriconazole concentrate from the appropriate number of vials should be withdrawn and added to the infusion bag or bottle. Partially Used Vials should be discarded. The final Voriconazole solution must be infused over 1 to 3 hours at a maximum rate of 3 mg/kg per hour.

CONTRAINDICATIONS
In patients with known hypersensitivity to Voriconazole or to any of the excipients. Coadministration of CYP3A4 substrates, Terfenadine, Astemizole, Cisapride, Pimozide or Quinidine, Sirolimus, Rifampin, Carbamazepine and long-acting barbiturates, high-dose Ritonavir (400 mg Q12h), Rifabutin, Ergot alkaloids, St. John's Wort with Voriconazole is also contraindicated.

SIDE EFFECTS
The most frequently reported side effects in the therapeutic trials were visual disturbances, fever, rash, vomiting, nausea, diarrhea, headache, sepsis, peripheral edema, abdominal pain, and respiratory disorder. The treatment-related side effects which most often led to discontinuation of Voriconazole therapy were elevated liver function tests, rash, and visual disturbances.

WARNINGS & PRECAUTIONS
Long term exposure (treatment or prophylaxis) greater than 180 days requires careful assessment of the benefit-risk balance. Squamous cell carcinoma of the skin (SCC) has been reported in relation with long-term Voriconazole treatment.

DRUG INTERACTIONS
Voriconazole is metabolized by the human hepatic cytochrome P450 enzymes CYP2C19, CYP2C9, and CYP3A4. Results of in vitro metabolism studies indicate that the affinity of Voriconazole is highest for CYP2C19, followed by CYP2C9, and is appreciably lower for CYP3A4. Inhibitors or inducers of these three enzymes may increase or decrease the plasma concentration of Voriconazole respectively.

PREGNANCY & LACTATION
Voriconazole can cause fetal harm when administered to a pregnant woman.
It is not known whether Voriconazole is excreted in the milk of laboratory animals or in human breast milk. Voriconazole must not be used in nursing mothers unless the benefit clearly outweighs the risk.

PEDIATRIC USE
Safety and effectiveness in pediatric patients below the age of 2 years has not been established. Therefore, Voriconazole is not recommended for pediatric patients less than 2 years of age.

GERIATRIC USE
No dose adjustment is necessary for geriatric patients.

STORAGE CONDITION
Store below 30° C. Keep out of reach of children. Reconstituted solution should be used immediately, or store at refrigeration (2° to 8°C) for 24 hours maximum.

HOW SUPPLIED
Vori™ 50 Tablet: Each pack contains 10 Tablets (in Alu-PVC Blister).
Vori™ 200 Tablet: Each pack contains 10 Tablets (in Alu-PVC Blister).
Vori™ IV Injection: Each box contains a blister pack containing one vial of 200 mg Voriconazole as sterile lyophilized powder and two ampoules of 20 ml water for injections BP and a complementary pouch comprising one 20 ml sterile disposable syringe, one infusion set with butterfly needle, one alcohol pad and one first aid bandage.

Manufactured by
SQUARE
PHARMACEUTICALS PLC.
Bangladesh