Voriderm™

Voriconazole

Presentation
Voriderm™ 50 mg tablet: Each tablet contains Voriconazole BP 50 mg.
Voriderm™ 200 mg tablet: Each tablet contains Voriconazole BP 200 mg.
Voriderm™ IV Injection: Each vial contains Voriconazole BP 200 mg as lyophilized cake or powder.

Description
Voriconazole is an azole 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.

Indication
Voriconazole is an antifungal indicated for use in the treatment of:
• Invasive Aspergillosis
• Candidemia (nonneutropenics) and disseminated candidiasis in skin, abdomen, kidney, bladder wall, and wounds
• Esophageal candidiasis
• Serious infections caused by *Scedosporium apiospermum* and Fusarium species including *Fusarium solani*, in patients intolerant of, or refractory to, other therapy.

Dosage and Administration
Voriconazole Tablet is to be taken at least one hour before or one hour following a meal.

Recommended Dosing Regimen:

Adult

Infection	Loading Dose	Maintenance Dose	
	Intravenous infusion	Intravenous infusion	Oral
Invasive Aspergillosis	6 mg/kg every 12 hours for the first24 hours	4 mg/kg every 12 hours	200 mg every 12 hours
Candidemia in nonneutropenic patients and other deep tissue Candida infections	6 mg/kg every 12 hours for the first 24 hours	3-4 mg/kg every 12 hours	200 mg every 12 hours
Esophageal Candidiasis	Not Evaluated	Not Evaluated	200 mg every 12 hours
Scedosporiosis and Fusariosis	6 mg/kg every 12 hours for the first 24 hours	4 mg/kg every 12 hours	200 mg every 12 hours

Pediatric (2 to less than 12 years of age and 12 to 14 years of age with body weight less than 50 kg)

Infection	Loading Dose	Maintenance Dose	
	Intravenous infusion	Intravenous infusion	Oral
Invasive Aspergillosis	9 mg/kg every 12 hours for the first 24 hours	8 mg/kg every 12 hours after the first 24 hours	9 mg/kg every 12 hours (maximum dose of 350 mg every 12 hours)
Candidemia in nonneutropenics and other deep tissue Candida infections			
Scedosporiosis and Fusariosis			
Esophageal Candidiasis	Not Evaluated	4 mg/kg every 12 hours	9 mg/kg every 12 hours (maximum dose of 350 mg every 12 hours)

Pediatric patients 12 to 14 years of age weighing greater than or equal to 50 kg and 15 years of age and older regardless of body weight: the optimal method for titrating dosage recommended for adults is used.

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
The overall safety profile of the elderly patients was similar to that of the young so no dosage adjustment is recommended.

Treatment duration depends upon patients' clinical and mycological response.

Dose adjustment
Adult
If patient's response is inadequate, the oral maintenance dose may be increased from 200 mg every 12 hours (similar to 3 mg/kg intravenously every 12 hours) to 300 mg every 12 hours (similar to 4 mg/kg intravenously every 12 hours). For adult patients weighing less than 40 kg, the oral maintenance dose may be increased from 100 mg every 12 hours to 150 mg every 12 hours. If patient is unable to tolerate 300 mg orally every 12 hours, reduce the oral maintenance dose by 50 mg steps to a minimum of 200 mg every 12 hours (or to 100 mg every 12 hours for adult patients weighing less than 40 kg).
If patient is unable to tolerate 4 mg/kg intravenously every 12 hours, the intravenous maintenance should be reduced dose to 3 mg/kg every 12 hours.

Pediatric
If patient response is inadequate and the patient is able to tolerate the initial intravenous maintenance dose, the maintenance dose may be increased by 1 mg/kg steps. If patient response is inadequate and the patient is able to tolerate the oral maintenance dose, the dose may be increased by 1 mg/kg steps or 50 mg steps to a maximum of 350 mg every 12 hours. If patients are unable to tolerate the initial intravenous maintenance dose, the dose may be reduced by 1 mg/kg steps. If patients are unable to tolerate the oral maintenance dose, the dose may be reduced by 1 mg/kg or 50 mg steps.

Patients with hepatic impairment: Only the maintenance dose is recommended to be halved in adult patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B).

Patients with renal impairment: No adjustment is necessary for oral dosing in patients with mild to severe renal impairment. In adult patients with moderate to severe renal impairment intravenous administration should be avoid.

Co-administered with Phenytoin or Efavirenz: Maintenance dose of Voriconazole should be increased when co-administered with Phenytoin or Efavirenz.

Pregnancy and lactation
Pregnancy Category D: Voriconazole can cause fetal harm when administered to a pregnant woman. The excretion of Voriconazole in breast milk has not been investigated. Voriconazole should not be used by nursing mothers unless the benefit clearly outweighs the risk.

Reconstitution
For Voriderm IV: 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 (19.0 mL) of Water for Injection is dispensed. The vial should be shacked 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 nor 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.

Required Volumes of 10 mg/mL Voriconazole 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 mL (1)	-	8 mL (1)	9 mL (1)
15	-	6 mL (1)	-	12 mL (1)	13.5 mL (1)
20	-	8 mL (1)	-	16 mL (1)	18 mL (1)
25	-	10 mL (1)	-	20 mL (1)	22.5 mL (2)
30	9 mL (1)	12 mL (1)	18 mL (1)	24 mL (2)	27 mL (2)
35	10.5 mL (1)	14 mL (1)	21 mL (2)	28 mL (2)	31.5 mL (2)
40	12 mL (1)	16 mL (1)	24 mL (2)	32 mL (2)	36 mL (2)
45	13.5 mL (1)	18 mL (1)	27 mL (2)	36 mL (2)	40.5 mL (3)
50	15 mL (1)	20 mL (1)	30 mL (2)	40 mL (2)	45 mL (3)
55	16.5 mL (1)	22 mL (2)	33 mL (2)	44 mL (3)	49.5 mL (3)
60	18 mL (1)	24 mL (2)	36 mL (2)	48 mL (3)	54 mL (3)
65	19.5 mL (1)	26 mL (2)	39 mL (2)	52 mL (3)	58.5 mL (3)
70	21 mL (2)	28 mL (2)	42 mL (3)	-	-
75	22.5 mL (2)	30 mL (2)	45 mL (3)	-	-
80	24 mL (2)	32 mL (2)	48 mL (3)	-	-
85	25.5 mL (2)	34 mL (2)	51 mL (3)	-	-
90	27 mL (2)	36 mL (2)	54 mL (3)	-	-
95	28.5 mL (2)	38 mL (2)	57 mL (3)	-	-
100	30 mL (2)	40 mL (2)	60 mL (3)	-	-

The reconstituted solution can be diluted with:

0.9% Sodium Chloride USP
Lactated Ringers USP
5% Dextrose and Lactated Ringers USP
5% Dextrose and 0.45% Sodium Chloride USP
5% Dextrose USP
5% Dextrose and 20 mEq Potassium Chloride USP
0.45% Sodium Chloride USP
5% Dextrose and 0.9% Sodium Chloride USP

Contraindications
• Hypersensitivity to Voriconazole or its excipients
• Coadministration with Terfenadine, Astemizole, Cisapride, Pimozide or Quinidine, Sirolimus due to risk of serious adverse reactions
• Coadministration with Rifampin, Carbamazepine, long-acting barbiturates, Efavirenz, Ritonavir, Rifabutin, ergot alkaloids, and St. John's Wort due to risk of loss of efficacy

Warnings and Precautions
Liver function should be evaluated at start of and during Voriconazole therapy. Patients with Hereditary Galactose Intolerance, Lapp Lactase deficiency or glucose-galactose malabsorption should not use Voriconazole. Patients with proarrhythmic conditions should use with caution.
It should be discontinued for exfoliative cutaneous reactions or phototoxicity. Fluorosis and periostitis can occur with long-term Voriconazole therapy.

Blood products and concentrated electrolytes:
Voriconazole IV must not be infused concomitantly with any blood product or short-term infusion of concentrated electrolytes, even if the two infusions are running in separate intravenous lines (or cannulas). Electrolyte disturbances such as hypokalemia, hypomagnesemia and hypocalcemia should be corrected prior to initiation of and during Voriconazole therapy.

Intravenous solutions containing (non-concentrated) electrolytes:
Voriconazole IV 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 IV 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 IV.

Side effects
Most common adverse reactions are visual disturbances, fever, nausea, rash, vomiting, chills, headache, liver function test abnormality, tachycardia & hallucinations.

Drug Interactions
• CYP3A4, CYP2C9, and CYP2C19 inhibitors and inducers: Adjust Voriconazole dosage and monitor for adverse reactions or lack of efficacy
• Voriconazole may increase the concentrations and activity of drugs that are CYP3A4, CYP2C9 and CYP2C19 substrates. Reduce dosage of these other drugs and monitor for adverse reactions
• Phenytoin or Efavirenz: For co-administration, increase maintenance oral and intravenous dosage of Voriconazole

Storage

For Voriderm IV: Do not store above 30°C. Keep away from light and out of the reach of children.
After reconstitution reconstituted solution can be stored for 24 hours at 2-8 ^{0}C.

Commercial Pack
Voriderm™ 50 mg tablet: Each box contains 1 blister strip of 10 tablets.
Voriderm™ 200 mg tablet: Each box contains 1 blister strip of 10 tablets.
Voriderm™ IV Injection: Each box contains a blister pack containing one vial of 200 mg Voriconazole as lyophilized cake or powder and two ampoules of 10 ml Water for injection and a complimentary pouch comprising one 20 ml sterile disposable syringe, one butterfly needle, one alcohol pad and one first aid bandage.

Manufactured by
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