Voriconazole:

Class: Antifungal.

Indications:
Treatement of invasive aspergillosis; treatment of esophageal candidiasis; treatment of candidemia (in non-neutropenic patients); treatment of disseminated Candida infections of the skin and viscera; treatment of serious fungal infections caused by Scedosporium apiospermum and Fusarium spp (including Fusarium solani) in patients intolerant of, or refractory to, other therapy

Available dosage form in the hospital: 200MG FILM-COATED TABLETS, 200MG VIAL.

Dosage:

- **Aspergillosis, invasive, including disseminated and extrapulmonary infection**: Duration of therapy should be a minimum of 6-12 weeks or throughout period of immunosuppression (Walsh, 2008):
  - I.V.: Initial: Loading dose: 6 mg/kg every 12 hours for 2 doses; followed by maintenance dose of 4 mg/kg every 12 hours
  - Oral: Maintenance dose:
    - Manufacturer’s recommendations:
      - Patients <40 kg: 100 mg every 12 hours; maximum: 300 mg/day
      - Patients ≥40 kg: 200 mg every 12 hours; maximum: 600 mg/day
    - IDSA recommendations (Walsh, 2008): May consider oral therapy in place of I.V. with dosing of 4 mg/kg (rounded up to convenient tablet dosage form) every 12 hours; however, I.V. administration is preferred in serious infections since comparative efficacy with the oral formulation has not been established.

- **Scedosporiosis, fusariosis**:
  - I.V.: Initial: Loading dose: 6 mg/kg every 12 hours for 2 doses; followed by maintenance dose of 4 mg/kg every 12 hours
  - Oral: Maintenance dose:
    - Patients <40 kg: 100 mg every 12 hours; maximum 300 mg/day
    - Patients ≥40 kg: 200 mg every 12 hours; maximum: 600 mg/day

- **Candidemia and other deep tissue Candida infections**: Treatment should continue for a minimum of 14 days following resolution of symptoms or following last positive culture, whichever is longer.
  - I.V.: Initial: Loading dose 6 mg/kg every 12 hours for 2 doses; followed by maintenance dose of 3-4 mg/kg every 12 hours
-Oral:

-Manufacturer’s recommendations: Maintenance dose:

  -Patients <40 kg: 100 mg every 12 hours; maximum: 300 mg/day
  -Patients ≥40 kg: 200 mg every 12 hours; maximum: 600 mg/day

-IDSA recommendations (Pappas, 2009): Initial: Loading dose: 400 mg every 12 hours for 2 doses; followed by 200 mg every 12 hours

-Endophthalmitis, fungal (unlabeled use; Pappas, 2009): I.V.: 6 mg/kg every 12 hours for 2 doses, then 3-4 mg/kg every 12 hours

-Esophageal candidiasis: Oral: Treatment should continue for a minimum of 14 days, and for at least 7 days following resolution of symptoms:

  -Patients <40 kg: 100 mg every 12 hours; maximum: 300 mg/day
  -Patients ≥40 kg: 200 mg every 12 hours; maximum: 600 mg/day

-Meningitis (secondary to contaminated [eg, Exserohilum rostratum ] steroid products) (unlabeled use) (CDC [parameningeal], 2012; Kauffman, 2013): Note: Consult an infectious disease specialist and current CDC guidelines for specific treatment recommendations. Therapy duration is ≥3 months; trough serum concentrations must be maintained between 2-5 mcg/mL.

  -I.V.: 6 mg/kg every 12 hours. If patient does not improve or has severe disease, consider adding amphotericin B (liposomal)

  -Oral (only in mild disease in adherent patients whose trough concentrations/response to therapy can be closely monitored): 6 mg/kg every 12 hours (CDC [parameningeal], 2012)

-Osteoarticular infection involving the spine, discitis, epidural abscess or vertebral osteomyelitis (secondary to contaminated [eg, Exserohilum rostratum ] steroid products) (unlabeled use) (CDC [osteoarticular], 2012; Kauffman, 2013): I.V.: 6 mg/kg every 12 hours for ≥3 months. Note: Consult an infectious disease specialist and current CDC guidelines for specific treatment recommendations. Trough serum concentrations must be maintained between 2-5 mcg/mL. If patient has severe disease, consider adding amphotericin B (liposomal). Patients may be switched to oral therapy if condition has improved or stabilized.

-Osteoarticular infection not involving the spine (secondary to contaminated [eg, Exserohilum rostratum ] steroid products) (unlabeled use) (CDC [osteoarticular], 2012; Kauffman, 2013): Note: Consult an infectious disease specialist and current CDC guidelines for specific treatment recommendations. Therapy duration is ≥3 months. Trough serum concentrations must be maintained between 2-5 mcg/mL.

  -I.V.: 6 mg/kg every 12 hours for 2 doses, then 4 mg/kg every 12 hours. If patient has severe disease, consider adding amphotericin B (liposomal)

  -Oral (only in mild disease in adherent patients whose trough concentrations/response to therapy can be closely monitored): 6 mg/kg every 12 hours for 2 doses, then 4 mg/kg every 12 hours
Dosage adjustment in patients unable to tolerate treatment:
- I.V.: Dose may be reduced to 3-4 mg/kg every 12 hours, depending upon condition
- Oral: 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).

Dosage adjustment in patients receiving concomitant CYP450 enzyme inducers or substrates:
- Efavirenz: Oral: 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:
  - I.V.: Increase voriconazole maintenance dosage to 5 mg/kg every 12 hours
  - Oral: Increase voriconazole dose to 400 mg every 12 hours in patients ≥40 kg (200 mg every 12 hours in patients <40 kg).

Renal Impairment:
- In patients with Cl\textsubscript{cr} <50 mL/minute, accumulation of the intravenous vehicle (cyclodextrin) occurs. After initial I.V. loading dose, oral voriconazole should be administered to these patients, unless an assessment of the benefit:risk to the patient justifies the use of I.V. voriconazole. Monitor serum creatinine and change to oral voriconazole therapy when possible.
- Oral: Poorly dialyzed; no supplemental dose or dosage adjustment necessary, including patients on intermittent hemodialysis, peritoneal dialysis, or continuous renal replacement therapy (eg, CVVHD).
Note: I.V. dosing NOT recommended since cyclodextrin vehicle is cleared at half the rate of voriconazole and may accumulate.

Hepatic Impairment:
- 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.

Common side effect:
- Central nervous system: Hallucination (2% to 12%; auditory and/or visual and likely serum concentration-dependent), headache.
- Ophthalmic: Visual disturbance
- Renal: Increased serum creatinine.
- Cardiovascular: Tachycardia
- Dermatologic: Skin rash.
- Endocrine & metabolic: Hypokalemia.

Pregnancy Risk Factor: D