Triazole Administration Guidance

	Formulations at VUH	Dosing	Administration	Drug Interactions	Therapeutic Drug Monitoring
Fluconazole	Tablet: (50 mg, 100 mg, 150 mg, 200 mg) Oral Suspension (40 mg/mL) IV	100-1,200 mg daily Renal: CrCl ≤ 50 mL/min reduce dose by 50% CRRT: double the daily dose Obesity: Use actual bodyweight	• Food and gastric pH do not affect absorption. Enteral Feeding Tube: • Hold enteral nutrition during administration. Flush tube w/ purified water before administration. Ensure the container is rinsed and total medication dose is given. Flush tube prior to restarting enteral nutrition. • Oral suspension: shake suspension prior to drawing up dose for dilution; dilute with at least equivalent vol with purified water. • Tablet: crush into fine powder and disperse in 10mL purified water; administer immediately IV: Infuse over 1 to 2 hours. Do not exceed 200 mg/hr.	Inhibits 2C19 (strong), 2C9 (moderate), 3A4 (moderate) Prolongs QTc	• Rarely performed and not routinely recommended
Itraconazole	Oral solution: (10mg/mL) Capsule: (100 mg)	200 mg q8h x 9 doses, then 200 mg q12h No adjustments made for renal or hepatic dysfunction, or obesity	Oral solution: • Administer on empty stomach. • Enteral feeding tube: stop enteral feeds 2 hours before dose and hold 1 hour after dose. Capsule: • Administer with full meal or acidic beverage; do not crush, break, or chew. • Avoid acid suppressing agents. • Do NOT open capsules for enteral tube administration.	Drug-disease interaction: heart failure Inhibits 3A4 (strong) and p-gp; 3A4 substrate (major) Prolongs QTc	• Obtain trough or random level 10- 14 days after starting therapy or 5-7 days with loading dose. • Target: ≥ 1 mcg/mL (itraconazole component only) • Toxicity: 3-4 mcg/mL • Active metabolite hydroxy-itraconazole may be reported, however, there is mixed data on how to clinically utilize its value.
Voriconazole *Restricted to ID	Tablet (50 mg, 200 mg) Oral suspension (40 mg/mL) IV (contains cyclodextrin)*	6 mg/kg q12h x 2 doses, then 4 mg/kg q12h Usual PO maintenance: 200-300 mg q12h Obesity: Use adjusted body weight Hepatic: Child-Pugh class A or B: considering reducing maintenance dose by 50%	• Bioavailability is reduced by high-fat meals. • Absorption is not pH dependent; however, omeprazole may increase voriconazole level due to CYP interactions. Oral: • Administer 1 hour before or 2 hours after a meal. Enteral feeding tube: • Hold enteral feeds 1 hour before and 2 hours after dose. Tablets can be crushed for enteral administration.	Inhibits 2C19 (moderate), 2C9 (weak), 3A4 (strong) Substrate of 2C19, 2C9, and 3A4 Prolongs QTc	• Obtain trough level in 5-7 days after initiation or dose changes. • Nonlinear pharmacokinetics • Target: 1-5.5 mcg/mL • Toxicity: >5.5 mcg/mL

Created by Ramsey Shane, PharmD
Last Updated: October 2024

		Child-Pugh class C: consider benefits vs. risks	IV: Infuse over 1 to 3 hours (rate not to exceed 3 mg/kg/hour). Do not infuse concomitantly with other drugs, concentrated electrolyte solutions or blood products. May be infused simultaneously with nonconcentrated electrolytes or TPN through a separate IV line.		
Posaconazole *Restricted to ID	Tablet, delayed release (100 mg) Oral Suspension (40 mg/mL) IV ($$$) (contains cyclodextrin)*	No adjustments made for renal or hepatic dysfunction, or obesity **Oral suspension is not interchangeable with IV or delayed release tablet formulations**	Delayed release tablet: • Not affected by acid suppressing agents or food. Suspension: • Unpredictable and variable absorption; requires fed state or acidic beverage. Avoid acid suppressing agents. Enteral feeding tube: • Manufacturers recommend to NOT crush DR tabs, but case studies have reported successful crushed administration with close TDM monitoring (higher dosing may be necessary). Crush into fine powder, dilute with 30 mL of purified water, administer immediately, and flush with 10mL purified water. • Suspension: give immediately after feed or during a feed infusion; utilize TDM. IV: Infuse over 90 minutes via a central venous line. Must be infused through an in-line filter.	Inhibits 3A4 (strong) and p-gp Substrate of p-gp Prolongs QTc	• Obtain trough levels 5 days after initiation with loading dose or 7 days without a loading dose. • Target: ≥1-1.5 mcg/mL • Prophylaxis: ≥0.7 mcg/mL • Toxicity: >3-3.75 mcg/mL
Isavuconazole *Restricted to ID	Capsule ($$$) (186 mg) IV ($$$)	186 mg isavuconazonium sulfate = 100mg isavuconazole 372 mg q8h x 6 doses, then 372 mg q24h starting 12-24 hrs after last loading dose No adjustments for renal or hepatic dysfunction, or obesity	Capsule: • Can be taken with or without food. Acid suppressing agents do not affect bioavailability. • Capsules may be opened and administered via enteral feeding tube. Administer within 1 hour of reconstitution; follow with a flush of 3x 5mL rinses of water. IV: Infuse over a minimum of 1 hour with an in-line filter.	Inhibits 3A4 (moderate) and p-gp 3A4 substrate Shortens the QTc	• Not routinely collected; can consider if concern for malabsorption, administration of capsules via enteral tube, drug-drug interactions, critical illness, extremes of weight, or other factors anticipated to alter pharmacokinetics. • Obtain level ~5-7 days after initiation with loading dose or 10-14 days after initiation without a loading dose. • Target concentrations not established, but experts consider Target: ≥1-2 mcg/mL, Toxicity: >4.6- 5.1 mcg/mL.

* Clinicians often avoid IV voriconazole when CrCl <50 ml/min due to accumulation of cyclodextrin that could cause nephrotoxicity. However, recent studies showed the polysubstituted derivative, SBECD, does not accumulate or affect the renal epithelial cells. Therefore, IV voriconazole can be used when needed in patients with renal impairment.

References

1. McCreary EK, Davis MR, Narayanan N, et al. Utility of triazole antifungal therapeutic drug monitoring: Insights from the Society of Infectious Diseases Pharmacists. *Pharmacotherapy*. 2023; 43: 1043-1050.
2. Thompson GR. Antifungal drugs: azoles. In: Bennett JE, Dolin R, Blaser MJ, ed. *Mandell, Douglass, and Bennett's Principles and Practice of Infectious Diseases*. Elsevier; 2022: 501-508.
3. Fluconazole [package insert]. New York City, NY: Pfizer; 2024.
4. Cresemba [package insert]. Northbrook, IL: Astellas Pharma US, Inc; 2024.
5. Voriconazole [package insert]. New York City, NY: Pfizer; 2010.
6. Itraconazole [package insert]. Raritan, NJ: Jassen; 2023.
7. Posaconazole [package insert]. Webster Groves, MO: Mallinckrodt; 2022.
8. Dodds Ashley ES, Zaas AK, Fang AF, Damle B, Perfect JR. Comparative pharmacokinetics of voriconazole administered orally as either crushed or whole tablets. Antimicrob Agents Chemother 2007; 51(3): 877–880
9. Andes D, Pascual A, Marchetti O. Antifungal therapeutic drug monitoring: established and emerging indications. Antimicrob Agents Chemother. 2009 Jan;53(1):24-34. doi: 10.1128/AAC.00705-08. Epub 2008 Oct 27. PMID: 18955533; PMCID: PMC2612175.
10. Adamsick ML, Elshaboury RH, Gift T, Mansour MK, Kotton CN, Gandhi RG. Therapeutic drug concentrations of isavuconazole following the administration of isavuconazonium sulfate capsules via gastro-jejunum tube: A case report. Transpl Infect Dis. 2019 Apr;21(2):e13048. doi: 10.1111/tid.13048. Epub 2019 Jan 29. PMID: 30636363.
11. McCreary EK, Nguyen MH, Davis MR, Borlagdan J, Shields RK, Anderson AD, Rivosecchi RM, Marini RV, Sacha LM, Silveira FP, Andes DR, Lepak AJ. Achievement of clinical isavuconazole blood concentrations in transplant recipients with isavuconazonium sulphate capsules administered via enteral feeding tube. J Antimicrob Chemother. 2020 Oct 1;75(10):3023-3028. doi: 10.1093/jac/dkaa274. PMID: 32710097; PMCID: PMC7778376.
12. Ryan W Stevens, Casey O'Connell, Angie Huang, Kevin L Epps, Dan Ilges, Therapeutic drug monitoring following crushed administration of delayed-release posaconazole tablets via enteral feeding tubes, *Journal of Antimicrobial Chemotherapy*, Volume 78, Issue 2, February 2023, Pages 553–555, https://doi.org/10.1093/jac/dkac427
13. Manesh A, Devasagayam E, Bhanuprasad K, et al. Efficacy of Crushed Delayed-Release Posaconazole Tablets in Rhino-Orbito-Cerebral Mucormycosis. *Antimicrob Agents Chemother.* 2022;66(12):e0108522.
14. Kane N, Rikard R, McCrory K, Marx A. Crushed Posaconazole Delayed-Release Tablets Via Enteral Feeding Tubes: A Cautionary Tale. *Ann Pharmacother.* Published online April 30, 2024.
15. Kim S, Kwon J, Park C, Han S, Yim D, Choi J, Cho S, et al. Therapeutic drug monitoring and safety of intravenous voriconazole formulated with sulfobutylether B-cyclodextrin in haematological patients with renal impairment. *Mycoses*. 2016 June; 59 (10): 644-651. https://doi.org/10.1111/myc.12517

Created by Ramsey Shane, PharmD

Last Updated: October 2024