UCSF Health Adult Azole Therapeutic Drug Monitoring Reference Document

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Disclaimer: Practice guidelines are intended to assist with clinical decision-making for common situations but cannot replace personalized evaluation and management decisions based on individual patient factors. All patients should be carefully evaluated and treated for suspected focal infection if identified. Consult ID or ASP if you have clinical questions or questions about antibiotic selection. Additionally, the information reflects the best available data at the time the guideline was prepared. The results of future studies may prompt revisions of these guidelines to reflect new data.

Revision History:

- 1/2025: Modified itraconazole administration instructions

Antifungal Drug Information and Monitoring Chart

¥ ¥ = Conversion between formulations is NOT 1:1, please reach out to ASP/ID pharmacy when converting between the two formulations.

Drug	Formulations	Administration	Therapeutic Drug Monitoring	Adverse Reactions
				Class Effect Hepatotoxicity
Fluconazole (IDMP)	IV Enteral Suspension Tablet	Enteral formulations can be given with or without meal	Not routinely recommended	QT Prolongation
Voriconazole (IDMP)	IV Enteral Suspension Tablet	Food decreases absorption of enteral formulations Must be taken 1 hr before or after meal	Obtain trough after steady state (3-5 days) - Prophylaxis trough goal: 2-6 mcg/mL - Treatment trough goal: 2-6 mcg/mL Serum levels > 4 mcg/L are associated with visual hallucinations/risk of neurotoxicity and may be associated with hepatotoxicity	QT Prolongation Photosensitivity Visual Disturbances <u>Rare (<1%):</u> Skeletal Fluorosis Dermatologic Complications
Posaconazole (IDMP)	¥ ¥ Delayed Release Tablet	Increased bioavailability when taken with meal May crush and give via a feeding tube if patient unable to swallow pills If crushing is needed, crush tablet into a fine powder, dilute with 30 mL purified water, allow to dissolve for 10 min, administer, and flush tube with an additional 10 mL purified water.	Obtain first trough after steady state (5-7 days) - 6 days for IV & delayed-release tablet - 7-10 days for the IR enteral suspension - Prophylaxis trough goal: ≥ 0.7 mcg/mL - Treatment trough goal: ≥ 1.25 mcg/mL	QT Prolongation <u>Rare (<1%):</u> Pseudohyperaldosteroinism
	IV (Restricted to ID/ASP)			
	¥ ¥ IR Suspension	Not recommended due to unpredictable bioavailability		

Drug	Formulations	Administration	Therapeutic Drug Monitoring	Adverse Reactions
				Class Effect Hepatotoxicity
		- Administer with high-fat meals to improve bioavailability and avoid concomitant acid-suppression therapy		
Isavuconazole (IDMP)	IV Capsule	Enteral formulations can be given with or without meals Crushing instructions for capsule: - Open capsules and mix contents with saline or tube feed formulations for administration via enteral feeding tubes. Then administer 15 mL of water afterwards.	TDM is generally **not** recommended unless concern for toxicity, therapeutic failure, or altered absorption; consult ID/ASP for further guidance if indicated Obtain first trough after steady state (5-7 days) - Treatment trough goal: 2-5 mcg/mL	
Itraconazole	¥ ¥ Solution ¥ ¥ Capsule (Sporanox) ¥ ¥ Capsule (Tolsura)	- Administer capsules with a meal and avoid acid-suppressing agents - Administer oral solution on an empty stomach	Obtain first trough after steady state (10-14 days) - Prophylaxis trough goal: > 0.5 mcg/mL - Treatment trough goal: >1-2 mcg/mL	Heart Failure
Flucytosine (IDMP)	Capsule	Food can decrease rate of absorption	TDM is generally **not** indicated unless under the guidance of ID/ASP Obtain peak level after day 3 of therapy ~2 hours after administration - Treatment peak goal: 50-75 mcg/mL	

Red = Nonformulary Item

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Note: Timing of labs and other additional information regarding drug levels are available in the lab manual here. Reference ranges may vary by lab and must be interpreted according to specific assays utilized.

General Dosing Considerations

- If patient has previous history of being on a triazole, please review medication history and prior levels to determine dosing before reinitiation
- If patient has past medical history involving hepatic impairment (cirrhosis, acute liver failure, etc.), consider initiating voriconazole at a reduced dose
    - Voriconazole is extensively metabolized by liver and patients with hepatic impairment (cirrhosis, acute liver failure, etc.) are susceptible to overexposure and adverse reactions

When to Obtain an Additional Level

- Change in dose
- Change in body habitus (morbid obesity, etc.)
- Introduction or discontinuation of drugs with significant interactions
- Disease progression
- Toxicity concern
- Concern for non-adherence

How Often to Obtain Levels Once Therapeutic

- Once level is within goal, can check intermittently, deferring to primary clinical team judgement, unless patient undergoes change that qualifies them for an additional level (see above)

Considerations Prior to Dose Adjustment

- New drug-drug interactions
- Altered absorption (i.e. diarrhea, vomiting, tube feedings, etc.)
- Erratic administration/missed doses
- Incorrect trough draws (not at steady state, drawn after dose administered, etc.)

Voriconazole CYP2C19 polymorphisms (per PharmKGB)

- Poor metabolizer: consider use of alternate agent OR if unable to switch, use 50% of standard dose and monitor serum concentrations
- Normal, intermediate metabolizer: monitor serum concentrations
- Ultrarapid metabolizer: consider use of alternate agent OR if unable to switch, use 150% of standard dose and monitor serum concentrations

Instructions for Dose Adjustment Based Upon Levels

Voriconazole: Based upon Expert Opinion and Trial Data

Voriconazole Trough Level (mcg/mL)	Intervention
<0.1-1.9	Increase total daily dose by 100 mg Recheck trough level after steady state achieved (3-5 days) - Consider adding omeprazole to boost level if still subtherapeutic after 2+ dose increases
2.0-6.0*	No change
6.1-7.9 WITHOUT symptoms of toxicity	Consider decreasing total daily dose by 100 mg Recheck trough level after steady state achieved
6.1-7.9 WITH symptoms of toxicity	Hold 1-2 doses/until toxicity resolved, recheck trough, then restart at total daily dose 100 mg less when trough is no longer supratherapeutic Recheck trough level after steady state achieved - If toxicity remains, consider alternative agent
>8	Hold dose Recheck trough and restart at 50% dose reduction when trough is therapeutic Recheck trough level after steady state achieved

* If patient is experiencing symptoms of toxicity, see row with symptoms of toxicity

Posaconazole (Prophylaxis) - Delayed Release Capsules: Based on Expert Opinion

Posaconazole Trough Level (mcg/mL)	Intervention
<0.7	Increase dose by 100 mg, recheck trough level after steady state achieved (5-7 days)
0.7-4.9	No change
>5 **WITH symptoms of toxicity**	Decrease dose by 100 mg Consider holding 1-2 doses and rechecking trough after steady state achieved - If toxicity remains, consider alternative agent

Posaconazole (Treatment) - Delayed Release Capsules: Based on Expert Opinion

Posaconazole Trough Level (mcg/mL)	Intervention
<1.0	Increase dose by 100 mg, recheck trough level after steady state achieved (5-7 days)

1.0-4.9	No change
>5 **WITH symptoms of toxicity**	Consider holding 1-2 doses and rechecking trough level after steady state achieved Decrease dose by 100 mg - If toxicity remains, consider alternative agent

Azole Drug-Drug Interaction Table:

This table highlights established DDIs but is not meant to be a comprehensive list. **Be sure to run all patient medications for interactions.** Please evaluate the significance of the interaction on a case-by-case basis weighing benefits and risks of therapy. Check the package insert for specific dosing instructions with interacting medications.

Interactions with increased azole concentration			
Drug Class	Examples	Affected Azoles	Management
CYP2C9/2C19 inhibitors	Fluvoxamine	Voriconazole	Consider modifying treatment to avoid combined use of CYP inhibitor with azole
CYP3A inhibitors	Ritonavir, Cobicistat, Clarithromycin	Isavuconazole, itraconazole	
Interactions with decreased azole concentration			
Drug Class	Examples	Affected Azoles	Management
CYP inducers	Rifampin, carbamazepine, phenobarbital, phenytoin, St. John's wort	Voriconazole, posaconazole, isavuconazole, or itraconazole	Consider modifying treatment to avoid combined use of CYP3A inducer with azole
Interactions with increased concentration of co-administered drug			
Drug Class	Examples	Affected Azoles	Management
CYP3A substrates	Apixaban, cyclosporine, dronedarone, everolimus, lovastatin, methadone, rivaroxaban, simvastatin, sirolimus, tacrolimus, venetoclax, vincristine	Fluconazole, posaconazole, voriconazole, itraconazole	**Increased Monitoring:** Rivaroxaban **Dose Adjustment:** Immunosuppressive agents (mTOR, CNI); apixaban, methadone, venetoclax (see prescribing information for specific dose adjustments in combination with azole therapy) **Change in Therapy:** Lovastatin, simvastatin **Change in Azole**: Vincristine

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Sources:

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