

## UCSF Health Adult Azole Therapeutic Drug Monitoring Reference Document

### Table of Contents

1. Antifungal Drug Information and Monitoring Chart
2. When to Obtain an Additional Level
3. Considerations Prior to Dose Adjustment
4. Instructions for Dose Adjustment Based Upon Levels
5. Azole Drug-Drug Interaction Chart
6. MIC Interpretation Chart

**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
- 7/2025: Modified itraconazole trough timing (5-7 days if load given)

### 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<br>Hepatotoxicity                                            |
| <b>Fluconazole</b><br>(IDMP)  | IV                         | Enteral formulations can be given with or without meal                                                                                                                                                                                                                                                                            | Not routinely recommended                                                                                                                                                                                                                     | QT Prolongation                                                           |
|                               | Enteral Suspension         |                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                               |                                                                           |
|                               | Tablet                     |                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                               |                                                                           |
| <b>Voriconazole</b><br>(IDMP) | IV                         | Food decreases absorption of enteral formulations                                                                                                                                                                                                                                                                                 | Obtain trough after steady state (3-5 days)<br>- Prophylaxis trough goal: 2-6 mcg/mL<br>- Treatment trough goal: 2-6 mcg/mL                                                                                                                   | QT Prolongation<br>Photosensitivity<br>Visual Disturbances                |
|                               | Enteral Suspension         | Must be taken 1 hr before or after meal                                                                                                                                                                                                                                                                                           | Serum levels > 4 mcg/L are associated with visual hallucinations/risk of neurotoxicity and may be associated with hepatotoxicity                                                                                                              | <u>Rare (&lt;1%):</u><br>Skeletal Fluorosis<br>Dermatologic Complications |
|                               | Tablet                     |                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                               |                                                                           |
| <b>Posaconazole</b><br>(IDMP) | ¥ ¥ Delayed Release Tablet | Increased bioavailability when taken with meal<br><br>May crush and give via a feeding tube if patient unable to swallow pills<br><br>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)<br>- 6 days for IV & delayed-release tablet<br>- 7-10 days for the IR enteral suspension<br><br>- Prophylaxis trough goal: $\geq 0.7$ mcg/mL<br>- Treatment trough goal: $\geq 1.25$ mcg/mL | QT Prolongation<br><br><u>Rare (&lt;1%):</u><br>Pseudohyperaldosteronism  |
|                               | IV (Restricted to ID/ASP)  |                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                                                                                               |                                                                           |
|                               | ¥ ¥ IR Suspension          | Not recommended due to unpredictable bioavailability<br>- Administer with high-fat meals to improve bioavailability and avoid concomitant acid-suppression therapy                                                                                                                                                                |                                                                                                                                                                                                                                               |                                                                           |

| Drug                                           | Formulations                                                            | Administration                                                                                                                                                                                                                                                       | Therapeutic Drug Monitoring                                                                                                                                                                                                                                       | Adverse Reactions              |
|------------------------------------------------|-------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
|                                                |                                                                         |                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                   | Class Effect<br>Hepatotoxicity |
| <b>Isavuconazole</b><br><a href="#">(IDMP)</a> | IV<br><br>Capsule                                                       | Enteral formulations can be given with or without meals<br><br>Crushing instructions for capsule:<br>- 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 <b>not</b> recommended unless concern for toxicity, therapeutic failure, or altered absorption; consult ID/ASP for further guidance if indicated<br><br>Obtain first trough after steady state (5-7 days)<br>- Treatment trough goal: 2-5 mcg/mL |                                |
| <b>Itraconazole</b>                            | ¥ ¥ Solution<br><br>¥ ¥ Capsule (Sporanox)<br><br>¥ ¥ Capsule (Tolsura) | - Administer capsules with a meal and avoid acid-suppressing agents<br>- Administer oral solution on an empty stomach                                                                                                                                                | Obtain first trough after steady state (5-7 days if loading dose given, 10-14 days if no loading dose given)<br>- Prophylaxis trough goal: > 0.5 mcg/mL<br>- Treatment trough goal: > 1-2 mcg/mL                                                                  | Heart Failure                  |
| <b>Flucytosine</b><br><a href="#">(IDMP)</a>   | Capsule                                                                 | Food can decrease rate of absorption                                                                                                                                                                                                                                 | TDM is generally <b>not</b> indicated unless under the guidance of ID/ASP<br><br>Obtain peak level after day 3 of therapy ~2 hours after administration<br>- Treatment peak goal: 50-75 mcg/mL                                                                    |                                |

Red = Nonformulary Item

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

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<br>Recheck trough level after steady state achieved (3-5 days)<br>- 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<br>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<br>Recheck trough level after steady state achieved<br>- If toxicity remains, consider alternative agent |
| >8                                   | Hold dose<br>Recheck trough and restart at 50% dose reduction when trough is therapeutic<br>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 <b>WITH symptoms of toxicity</b> | Decrease dose by 100 mg<br>Consider holding 1-2 doses and rechecking trough after steady state achieved<br>- 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 <b>WITH symptoms of toxicity</b> | Consider holding 1-2 doses and rechecking trough level after steady state achieved<br>Decrease dose by 100 mg<br>- 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      | <b>Increased Monitoring:</b> Rivaroxaban<br><b>Dose Adjustment:</b> Immunosuppressive agents (mTOR, CNI); apixaban, methadone, venetoclax (see prescribing information for specific dose adjustments in combination with azole therapy)<br><b>Change in Therapy:</b> Lovastatin, simvastatin<br><b>Change in Azole:</b> Vincristine |

## Sources:

- Arendrup MC, Friberg N, Mares M, et al. How to interpret MICs of antifungal compounds according to the revised clinical breakpoints v. 10.0 European committee on antimicrobial susceptibility testing (Eucast). *Clinical Microbiology and Infection*. 2020;26(11):1464-1472.
- Howard SJ, Lass-Flörl C, Cuenca-Estrella M, Gomez-Lopez A, Arendrup MC. Determination of isavuconazole susceptibility of aspergillus and candida species by the eucast method. *Antimicrob Agents Chemother*. 2013;57(11):5426-5431
- Jørgensen KM, Astvad KMT, Hare RK, Arendrup MC. Eucast susceptibility testing of isavuconazole: mic data for contemporary clinical mold and yeast isolates. *Antimicrob Agents Chemother*. 2019;63(6):e00073-19.
- Jørgensen KM, Guinea J, Meletiadis J, Hare RK, Arendrup MC. Revision of EUCAST breakpoints: consequences for susceptibility of contemporary Danish mould isolates to isavuconazole and comparators. *Journal of Antimicrobial Chemotherapy*. 2020;75(9):2573-2581.
- Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the infectious diseases society of america. *Clinical Infectious Diseases*. 2016;62(4):e1-e50.
- Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america. *Clinical Infectious Diseases*. 2010;50(3):291-322.
- Perreault S, McManus D, Anderson A, Lin T, Ruggiero M, Topal JE. Evaluating a voriconazole dose modification guideline to optimize dosing in patients with hematologic malignancies. *J Oncol Pharm Pract*. 2019;25(6):1305-1311.
- Takesue Y, Hanai Y, Oda K, et al. Clinical practice guideline for the therapeutic drug monitoring of voriconazole in non-asian and asian adult patients: consensus review by the japanese society of chemotherapy and the japanese society of therapeutic drug monitoring. *Clin Ther*. 2022;44(12):1604-1623.
- Turner RB, Martello JL, Malhotra A. Worsening renal function in patients with baseline renal impairment treated with intravenous voriconazole: A systematic review. *Int J Antimicrob Agents*. 2015;46(4):362-366.