



## ANTIFUNGAL THERAPEUTIC DRUG MONITORING RECOMMENDATIONS FOR ADULT AND PEDIATRIC PATIENTS

### VORICONAZOLE

#### Serum trough goals based on indication:

- Treatment: 1 to 5.5 mcg/mL: Routine monitoring recommended in all patients.
- Prophylaxis: 1 to 5.5 mcg/mL: A steady-state level is recommended, then a level is needed only if occurrence of persistent diarrhea, GVHD, possible hepatotoxicity or neurotoxicity, or breakthrough infection, once therapeutic

#### When To Get Trough Levels:

- First level should be drawn at Day 5-7 (steady state), if received load may check as early as Day 2
- Trough levels are recommended
- Follow-up levels may be performed once monthly
- **Reasons for checking trough levels more frequently:**
  - Changes in voriconazole dosing or route, GvHD with diarrhea, addition or withdrawal of interacting medications, diarrhea, or perceived fungal disease progression or toxicity, suspected toxicity or concerns regarding non-adherence.

#### \*Adult Dose adjustment:

- If the level is very low (< 0.5 mcg/ml), consider alternative agents as patient may be rapid metabolizer. Otherwise, if level is less than desired, increase daily dose by 50-100 mg and recheck level in 1 week. Make sure the patient is taking the drug on an empty stomach.
- Levels greater than 5.5 mcg/mL should prompt dose reduction to minimize neurotoxicity and hepatotoxicity
- If the level is greater than 5.5 decrease daily dose by 100 mg and recheck level in 1 week

### ISAVUCONAZOLE

#### Serum goals based on indication:

- Treatment: > 1,000 ng/mL: Routine monitoring recommended in all patients.
- Prophylaxis: > 1,000 ng/mL: No routine monitoring required for isavuconazole, except for morbid obesity, diarrhea for > 72 hours, possible toxicity, receiving opened capsules via feeding tubes, or breakthrough fungal infection.

#### When To Get Levels:

- First level should be drawn at Day 5-7 if received loading dose, 10-14 days without loading dose
- Follow-up levels may be performed once monthly
- Trough levels are preferred but random levels are acceptable given prolonged half-life
- **Reasons for checking levels more frequently**
  - Changes in the dosage or formulation delivery, addition or withdrawal of interacting medications, perceived fungal disease progression, toxicity or concerns regarding non-adherence.

#### \*Adult Dose Adjustment:

- Although no data are available to inform therapeutic target levels or levels associated with toxicity, therapeutic drug monitoring is recommended to ensure that patients are absorbing drug. Troughs < 1,000 ng/mL may warrant a dose increase, depending on the patient's clinical response to therapy. Ensure that patients with low levels are taking correct dose (2- 186 mg capsules). Dose changes can be made assuming linear pharmacokinetics (i.e., double the dose or decrease interval to q12 in patient with level 0.5 mcg/mL).

### POSACONAZOLE

#### Serum trough goals based on indication:

- Treatment: 1,250 to 4,000 ng/mL: Routine monitoring recommended in all patients.
- Prophylaxis: > 700 to 4,000 ng/mL: No routine monitoring required for posaconazole tablets, except for morbid obesity, diarrhea for > 72 hours, receiving crushed tablets, possible toxicity or breakthrough fungal infection. Monitoring is recommended for posaconazole suspension

#### When To Get Trough Levels:

- First level should be drawn at Day 5 if loading dose was used, -7 days if not loaded
- Follow-up levels may be performed once monthly
- Trough levels are preferred; random levels are acceptable
- **Reasons for checking levels more frequently:**
  - Changes in the dosage, addition or withdrawal of interacting medications particularly PPIs, perceived fungal disease progression, development of mucositis, diarrhea or vomiting, suspected toxicity, concerns regarding non-adherence.

#### \*Adult Dose Adjustment:

- Main toxicity concern with high levels is pseudohyperaldosteronism, monitor for new/worsening hypertension, hypokalemia.
- **Delayed release tablet:** Dose changes can be made assuming linear pharmacokinetics, consider q12h interval in very low levels.
- **Oral suspension:** Dosing at 200 mg four times daily will result in higher levels than 400 mg BID. Increasing the dose (> 200 mg PO four times daily) will not generally result in a linear increase in levels as this drug has saturable absorption. Oral suspension should be taken with a fatty meal and acidic beverage such as cola. Use of acid suppression should be avoided.

### **ITRACONAZOLE**

#### **Serum level goals based on indication:**

- Treatment: itraconazole > 1 or itraconazole plus hydroxyitraconazole level > 2 mcg/mL
- Prophylaxis: itraconazole > 0.5 or itraconazole plus hydroxyitraconazole level > 1 mcg/mL
- Routine monitoring recommended in all patients.

<p><b>When To Get Levels:</b></p> <ul style="list-style-type: none"> <li>• First level should be drawn 5-7 days after starting therapy if loading dose used, 10-14 days after starting therapy if not loaded.</li> <li>• Follow-up levels may be performed once monthly</li> <li>• Trough levels preferred, but random levels are acceptable because of long half-life</li> <li>• <b>Reasons for checking levels more frequently</b> <ul style="list-style-type: none"> <li>• Changes in the dosage or delivery of itraconazole, addition or withdrawal of interacting medications, perceived fungal disease progression, suspected toxicity, or concerns regarding non-adherence.</li> </ul> </li> </ul>	<p><b>*Adult Dose Adjustment:</b></p> <ul style="list-style-type: none"> <li>• No clear correlation between levels and toxicity</li> <li>• <b>Capsules:</b> Optimal absorption is dependent on administration <i>with food</i>. Also, absorption is dependent on gastric acidity, so discontinue unnecessary proton pump inhibitor (PPI) or H-2 antagonist therapy. Absorption can be increased by taking the capsules with an acidic drink, such as Coca-Cola. Avoid capsules in patients requiring PPI therapy. If patient has low levels on capsules despite the above measures, consider changing to solution.</li> <li>• <b>Solution:</b> Absorption is not affected by gastric pH. Optimal absorption dependent on administration in the <i>fasting</i> state.</li> <li>• <b>Tolsura Capsules:</b> Absorption not significantly affected by gastric pH or fasting/fed state. Dosed differently than other formulations (65 mg Tolsura= 100 mg capsule (fed state))</li> </ul>
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### **FLUCYTOSINE**

#### **Serum peak level goal: between 50-75 mcg/mL**

<p><b>When To Get Levels:</b></p> <ul style="list-style-type: none"> <li>• First level should be drawn on day 3 after starting therapy, and peak should be obtained 2 hours after oral administration</li> <li>• Peak levels &gt; 100 mcg/mL are associated with myelosuppression and hepatotoxicity</li> <li>• Follow-up levels may be performed as needed based on concerns for toxicity, perceived fungal disease progression, or changes in renal function/support.</li> </ul>	<p><b>*Adult Dose Adjustment:</b></p> <ul style="list-style-type: none"> <li>• Pharmacodynamics suggests linear kinetics, and dose adjustments are proportional to the goal level. However, changes in fluid status and renal function should be accounted for when making large dose adjustments.</li> </ul>
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**\* Goal drug levels and recommendations for monitoring apply to both adult and pediatric patients. Please consult a clinical pharmacy specialist regarding dose adjustments for patients <18 years.**

**\*\*The first day of antifungal is day 1**

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P&T Approval: 12/2023	Last Revised: 12/2023
<p>Revision History: 05/2022: Updated isavuconazole goals and flucytosine instructions 12/2023: Updated detail around timing of levels</p>	

*The recommendations in this guide are meant to serve as treatment guidelines for use at Michigan Medicine facilities. If you are an individual experiencing a medical emergency, call 911 immediately. These guidelines should not replace a provider's professional medical advice based on clinical judgment, or be used in lieu of an Infectious Diseases consultation when necessary. As a result of ongoing research, practice guidelines may from time to time change. The authors of these guidelines have made all attempts to ensure the accuracy based on current information, however, due to ongoing research, users of these guidelines are strongly encouraged to confirm the information contained within them through an independent source.*

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