Stanford MEDICINE

Antifungal Reference Document for Adult Patients at Stanford Health Care

<table>
<tr><th>Voriconazole</th><th colspan="2">Formulations Available at SHC</th><th>Therapeutic Drug Monitoring</th><th>Dose Adjustments</th><th>Clinical Pearls</th></tr>
<tr><td rowspan="3"></td><td>Tablets
(50 mg, 200 mg)</td><td rowspan="2">Administer on an empty stomach*</td><td rowspan="3"><u>When to consider TDM</u>

Recommended for all patients receiving voriconazole given inter- and intra-patient variability and exposure-response and toxicity profile

<u>Type of level</u>
Trough (i.e. prior to the next dose or ~10-12 hours after the last dose)

<u>When to get a level</u>
Day ≥ 4

<u>Prophylaxis</u>
≥1 to ≤ 5.5 mg/L

<u>Treatment</u>
≥ 1 to ≤ 5.5 mg/L (may consider > 2 mg/L in certain clinical scenarios in consultation with ID)

<u>When to consider additional levels</u>
• After a change in dose
• Introduction or discontinuation of drugs with significant interaction potential
• Severe diarrhea and receiving oral formulations
• Disease progression
• Concern for non-adherence
• Concern for toxicity</td><td rowspan="3"><u>Trough level < 1 mg/L</u>:
Non-linear pharmacokinetics: dose adjustments do not lead to proportional changes in serum levels. Increase daily dose by 50 – 100 mg & re-check a level in 4-7 days

<u>Trough level > 5.5 mg/L:</u>
Decrease daily dose by 50 – 100 mg & re-check a level in 4-7 days. May need to consider holding dose(s) in certain clinical scenarios

Discuss with ID consult service or clinical pharmacist as needed.</td><td rowspan="3"><u>PK/PD</u>
Enteral formulations have high bioavailability (especially on an empty stomach); consider tablets or suspension for patients unless contraindicated.

Serum levels > 5.5 mg/L are associated with visual hallucinations/risk of neurotoxicity and may be associated with hepatotoxicity

Significant interpatient variability in serum levels due to polymorphisms in CYP2C19

Use adjusted body weight in setting of obesity¥

<u>Drug-Drug Interactions</u>
Clinically significant drug-drug interactions.

<u>Adverse Drug Reactions</u>
Use has been associated with transient visual disturbances, QTc prolongation, transaminase abnormalities, and, with long-term use, fluorosis and dermatological complications, including cutaneous malignancies</td></tr>
<tr><td>Oral suspension
(40 mg/mL)</td></tr>
<tr><td>Intravenous</td><td>Formulated in sulfobutylether-β-cyclodextrin. Clinical significance of accumulation in renal insufficiency is debated. Toxicity has only been demonstrated in animal models and at doses far above normal human doses. Weigh risk vs benefit and consider enteral therapy when appropriate</td></tr>
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*Administer 1 hour before or 1 hour after meals
¥Refer to Antimicrobial Dosing Reference Guide for dosing recommendations

Posaconazole	Formulations Available at SHC		Therapeutic Drug Monitoring	Dose Adjustments	Clinical Pearls
	Delayed Release tablet (DRT) (100 mg)	Administer with food.	**When to consider TDM** Recommended for patients receiving posaconazole for treatment. For prophylaxis, TDM may not be necessary if receiving DRT/IV formulations. Consider TDM on a case-by-case basis (e.g. extremes of body weight, concern for breakthrough infection, crushing DRTs etc.), as per protocol, or in consultation with ID **Type of level** 'Trough" (random level acceptable) **When to get a level*** Day 5 – 7 **Prophylaxis** ≥ 700 ng/mL** **Treatment** ≥ 1,000 ng/mL (≥ 1,250 ng/mL may be considered in certain clinical scenarios in consultation with ID) **When to consider additional levels** • After a change in dose • Morbid obesity • Introduction or discontinuation of drugs with significant interaction potential • Diarrhea and receiving oral formulations • Disease progression • Concern for non-adherence • Concern for toxicity	**Trough level below target and on DR tablet/intravenous formulation:** Assume linear/proportional pharmacokinetics. Increase dose in 100 mg increments if near target. In patients with very low levels (e.g. < 500 ng/mL), larger dose adjustments and more frequent dosing intervals may be necessary (e.g., q12hr dosing). Re-check a level in 5 – 7 days Discuss with ID consult service or clinical pharmacist as needed. No toxicity threshold has been established. Limited data suggest an association with higher serum posaconazole concentrations and pseudohypoaldosteronism. Some licensing authorities suggest an upper end of 3,750 ng/mL be considered	**PK/PD** DRTs have high bioavailability (especially when administered with food) and should be considered for patients unless contraindicated*** Posaconazole suspension (non-formulary) is not interchangeable with the DRT/IV preparations due to saturable absorption & erratic pharmacokinetics. For patients without central access & NG tube in place, consider alternative antifungal options or crushing DRTs. There is limited data to support crushing the posaconazole DRT for administration via feeding tubes. If this is done, TDM should be performed **Drug-Drug Interactions** Clinically significant drug-drug interactions. **Adverse Drug Reactions** Use has been associated with GI disturbances, QTc prolongation, transaminase abnormalities, and metabolic side effects
	Intravenous (IV)	Administer via a central line. Formulated in sulfobutylether-β-cyclodextrin. Clinical significance of accumulation in renal insufficiency is debated. Toxicity has only been demonstrated in animal models and at doses far above normal human doses. Weigh risk vs benefit and consider enteral therapy when appropriate			

* Serum levels obtained at day three may be considered as a surrogate for steady-state levels on a case-by-case basis
**Based on a pooled analysis of PK data from two Phase III clinical trials. Some studies and consensus guidelines have suggested that a lower target of > 500 ng/mL may be acceptable
***Refer to Pharmacist-Managed Intravenous to Oral Therapy Interchange Protocol
¥Refer to Antimicrobial Dosing Reference Guide for dosing recommendations

Itraconazole	Formulations Available at SHC		Therapeutic Drug Monitoring	Dose Adjustments*	Clinical Pearls
	Capsule (100 mg)	Administer with a full meal and/or acidic beverage Acid suppression (e.g. PPI or H2RA) should be avoided	**When to consider TDM** Recommended for all patients **Type of level** "Trough" (random level acceptable) HPLC assay measures itraconazole **and** hydroxyitraconazole levels. Both values should be added to evaluate true level. **When to get a level** Day 5 – 7 if loading dose administered Day 10 – 14 if no loading dose administered **Prophylaxis**** >0.5 mg/L – < 5 mg/L **Treatment** >1 mg/L – < 5 mg/L (may consider > 2 mg/L in certain clinical scenarios) **When to consider additional levels** • After a change in dose • Introduction or discontinuation of drugs with significant interaction potential • Diarrhea and receiving oral formulations • Disease progression • Concern for non-adherence • Concern for toxicity	**Random level < 0.5 mg/L:** Increase total daily dose by 100 – 200 mg **Random level> 5 mg/L:** Consider dose reduction if the patient is experiencing an adverse event or transition to an alternative antifungal if clinically appropriate	**PK/PD** Oral solution has higher bioavailability relative to the capsule but may not be well tolerated due to GI side effects. Given differences in relative bioavailability, these products are not directly interchangeable Some centers measure itraconazole levels by bioassay; these levels are **not** interchangeable with HPLC A new formulation of itraconazole (Tolsura®) with enhanced oral bioavailability was FDA approved in 2018 (not on SHC formulary) **Drug-Drug Interactions** Clinically significant drug-drug interactions. **Adverse Drug Reactions** Use has been associated with GI disturbances, QTc prolongation, heart failure (rare cases of new onset & exacerbation mostly described with IV preparation)
	Oral Solution (10 mg/mL)	Administer on an empty stomach*			

*Administer 1 hour before or 1 hour after meals
**Non-linear pharmacokinetics; dose adjustments do not lead to proportional changes in serum levels
HPLC = high-performance liquid chromatography

Isavuconazole	Formulations Available at SHC		Therapeutic Drug Monitoring	Dose Adjustments	Clinical Pearls
	Capsule (186 mg)	Administer without regards to meals	**When to consider TDM** Not routinely recommended. Clinical scenarios necessitating TDM should be discussed with ID and/or ASP (e.g. if capsules are opened for administration via feeding tube, concern for breakthrough fungal infection, etc) No exposure-efficacy or exposure-toxicity thresholds have been established		**PK/PD** Capsules have high bioavailability and should be considered for patients unless contraindicated* Isavuconazole PK are linear and dose proportional **Drug-Drug Interactions** Clinically significant drug-drug interactions. **Adverse Drug Reactions** Use has been associated with a shortened QT interval, transaminase abnormalities, GI disturbances, peripheral edema, and hypokalemia Emerging data to suggest that opening capsules and administering via NG tubes leads to comparable exposures to administration of intact capsules. Consider TDM if this is pursued.
	Intravenous (IV)	Infuse with an in-line filter (pore size 0.2 to 1.2 micron)			

*Refer to Pharmacist-Managed Intravenous to Oral Therapy Interchange Protocol

Flucytosine	Formulations Available at SHC		Therapeutic Drug Monitoring	Dose Adjustments**	Clinical Pearls
	Capsule (250 mg, 500 mg)	To reduce or avoid nausea and vomiting, administer a few capsules at a time over 15 minutes until full dose is taken	**When to consider TDM** Recommended for most patients* **Type of level*** Peak (i.e. 2 hours post-dose) **When to get a level** Within 72 hours of initiation or after 3 to 5 doses **Target Peak** 25 – 100 mg/L Levels > 100 mg/L increase risk of bone marrow suppression and hepatic dysfunction	**Peak level < 25 mg/L:** Limited data, consider increasing total daily dose by 50% (use clinical judgment) **Peak level > 100 mg/L:** Hold dose(s) as needed. If due to renal impairment, decrease dosing frequency Acute changes in renal function should prompt consideration for empiric dose adjustment	**PK/PD** > 90% of drug excreted unchanged in urine. Dose-adjust in patients with renal insufficiency¥ Used in combination with other antifungals for synergy; avoid use as monotherapy given rapid development of resistance **Adverse Drug Reactions** Use has been associated with hematologic (e.g. leukopenia, thrombocytopenia), hepatic, and GI adverse events
	Oral Suspension	Not commercially available; may be compounded on an as needed basis (discuss with pharmacy)			

*This is a send out lab that takes several days to result. It is important to time level appropriately so that it is clinically actionable
**Demonstrates linear pharmacokinetics
¥Refer to Antimicrobial Dosing Reference Guide for dosing recommendations

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