

Azole Antifungal Therapeutic Drug Monitoring Guidance

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The purpose of this document is to provide guidance on when to perform therapeutic drug monitoring (TDM) and obtain serum concentrations of azole antifungals. For additional guidance on monitoring for adverse effects and lab frequency, see the “[Antimicrobial Monitoring](#)” document in the Housestaff Manual.

The general intent of azole antifungal TDM is to improve efficacy by achieving a therapeutic serum concentration based on evidence and guidelines, monitor adherence, and improve safety by identifying suprathreshold serum concentrations that may increase the risk of toxicity. Of note, other antifungals, including amphotericin products and echinocandins do not require TDM.

Currently, plasma or serum specimens are sent to an outside laboratory for analysis. Stanford Clinical Laboratory is validating high-performance liquid chromatography (HPLC) to perform azole antifungal TDM in-house on a thrice weekly basis (M/W/F) soon (early 2023).

All serum concentration goals below are based on a trough concentration, which is the lowest concentration in the body before the next dose. All blood collections should occur 30 minutes prior to administration of the next dose at steady state to obtain a clinically relevant and interpretable serum concentration.

Azole antifungal	Serum trough goals	Analytical measurement range	When to perform TDM	How to perform TDM	Adverse effects and comments
Voriconazole	<p><u>Treatment</u>: 1 – 5.5 mcg/mL¹ (some experts recommend ≥ 2 mcg/mL for severe disease)</p> <p><u>Prophylaxis</u>: 1 – 5.5 mcg/mL¹</p>	0.4 – 7 mcg/mL	<p>Routine monitoring for all treatment courses</p> <p>Consider obtaining steady state TDM for prophylaxis courses</p>	<p>Measure serum concentration on day 5 of consecutive therapy (presumed steady state) and 4 days after change in dose</p> <p>Repeat one week after initial trough to confirm within therapeutic range</p> <p>Repeat for any of the following changes:</p> <ul style="list-style-type: none"> • Patient’s clinical condition (e.g., disease progression, diarrhea with enteral formulation, GVHD, concern for non-adherence) • Concomitant interacting medications • Suspected toxicity (e.g., neurotoxicity, hepatotoxicity) 	<p>Hepatotoxicity, QTc prolongation, visual disturbances (e.g., hallucinations, skin photosensitivity), SJS, TEN, periostitis due to fluorosis, and with long-term use, dermatological complications (e.g., cutaneous malignancies)</p> <p>Serum levels >5.5 mcg/mL may be associated with increased risk of visual disturbances, neurotoxicity, and hepatotoxicity</p> <p>IV formulation contains sulfobutylether-beta-cyclodextrin which undergoes renal elimination and may accumulate when CrCl <50 ml/min</p> <p>Drug-drug interactions: Strong inhibitor and substrate of CYP3A4 (e.g., vincristine metabolism inhibition), moderate inhibitor and substrate of CYP2C19 and weak inhibitor of CYP2C9</p>

Azole antifungal	Serum trough goals	Analytical measurement range	When to perform TDM	How to perform TDM	Adverse effects and comments
Posaconazole	<u>Treatment:</u> >1 mcg/mL (1000 ng/mL) ¹ (some experts recommend >1.25 mcg/mL (>1250 ng/mL) for salvage therapy) ² <u>Prophylaxis:</u> >0.7 mcg/mL (>700 ng/mL) ^{1,2}	0.25 – 4.5 mcg/mL (250 - 4500 ng/mL)	Routine monitoring for all treatment and prophylaxis courses	Measure serum concentration on day 5 of therapy (presumed steady state) and 4 days after change in dose Repeat TDM as clinically relevant, such as: <ul style="list-style-type: none"> • Patient's clinical condition (e.g., disease progression, diarrhea with enteral formulation, GVHD, concern for non-adherence) • Concomitant interacting medications • Suspected toxicity (e.g., QTc prolongation, hepatotoxicity) 	Hepatotoxicity, QTc prolongation, thrombocytopenia, leukopenia, electrolyte abnormalities, dermatological complications (e.g., rash) Serum levels > 3.75 mcg/mL (>3750 ng/mL) have not been well studied and may be associated with adverse effects ³ Delayed release tablets are not interchangeable with immediate release oral suspension due to dose differences (bioavailability improved with high fat meals and/or acidic beverage) Drug-drug interactions: Strong CYP3A4 inhibitor, e.g., vincristine contraindicated ⁴
Isavuconazole	<u>Treatment:</u> Not established, consider targeting levels 1 – 7 mcg/mL (some experts recommend 3 – 6 mcg/mL) ^{5,6} <u>Prophylaxis:</u> NA	0.5 – 20 mcg/mL	Given predictable attainment of serum concentration and lack of concentration-dependent relationships for efficacy or safety, routine monitoring is not required	(Continued from previous row)	Hepatotoxicity, QTc shortening Intravenous and enteral formulations are interchangeable Drug-drug interactions: Major substrate of CYP3A4 and moderate inhibitor
Fluconazole	<u>Treatment:</u> Not established, AUC: MIC > 100 may be an appropriate target ⁷ <u>Prophylaxis:</u> NA	0.8 – 17 mcg/mL	Predictable attainment of serum concentration Rare circumstances to consider TDM include CNS disease, renal replacement therapy, treatment of an organism with a high MIC, or adherence	(Continued from previous row)	Hepatotoxicity, QTc prolongation Primarily renally eliminated, dose adjustment advised for CrCl <50 mL/min Drug-drug interactions: Strong inhibitor of CYP2C19, moderate inhibitor of CYP3A4 and CYP2C9
Itraconazole*	Add the itraconazole and hydroxy-itraconazole levels to assess target serum concentration <u>Treatment:</u> 1 – 4 mcg/mL ⁸	0.2 – 1.8 mcg/mL Hydroxy-itraconazole: 0.25 – 2.5 mcg/mL	Routine monitoring for all treatment and prophylaxis courses	Because of the long half-life, serum concentrations vary little during a 24-h dosing interval and blood specimen can be collected at any time. Measure serum concentration after 2 weeks of therapy (presumed steady state)	Hepatotoxicity, QTc prolongation, heart failure exacerbation, CNS depression, neuropathy Formulations are not interchangeable. Oral solution bioavailability taken on an empty stomach improves absorption while capsules should be taken after meals.

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	Prophylaxis: 0.5 – 4 mcg/mL				<p>Our HPLC procedure for measuring drug concentration is preferred over bioassay which may be the analytic assay used at other institutions/labs.⁹ Results are not interchangeable as bioassays typically run 2 to 10 times higher than HPLC results.</p> <p>Drug-drug interactions: Strong inhibitor and substrate of CYP3A4</p>

* Non-formulary at LPCHS

HPLC: high-performance liquid chromatography GVHD: Graft versus host disease; NA: Not available; SJS: Stevens-Johnson syndrome; TDM: Therapeutic drug monitoring; TEN: Toxic epidermal necrolysis

References

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