



Antifungal Drug Level Monitoring

TEST CODE:
See Table 2

CPT CODE:
80299

CATEGORY
Antifungal Drug Level Monitoring

Clinical Utility

Voriconazole LC-MS/MS

Monitoring trough levels of voriconazole is suggested in patients with impaired liver function, patients with pharmacogenomic polymorphisms associated with lower metabolism of voriconazole (e.g. genotypes CYP2C19*2 and CYP2C19*3), and in patients taking other medications that affect CYP2C19 activity. Additionally, results may be clinically useful to determine if current dosing levels have achieved adequate therapeutic concentrations when treating at-risk patients prophylactically or when treating patients with invasive fungal infections. Results may also be used to evaluate reasons for therapeutic failure due to suboptimal drug levels or for toxicity potentially attributable to voriconazole.

Posaconazole LC-MS/MS

Patient variability in the pharmacokinetics of posaconazole supports quantitative monitoring of blood drug levels, particularly due to its variable absorption. Monitoring trough levels of posaconazole is suggested in patients with suboptimal nutritional intake (and therefore requiring food and liquid nutritional supplementation), or in patients with gastrointestinal disease such as mucositis, diarrhea, vomiting or GvHD. Monitoring trough levels of posaconazole is also suggested in patients treated with other drugs that either induce or inhibit CYP450 isoenzymes or that serve as substrates for these isoenzymes. Results may be clinically useful to determine if current dosing levels have achieved adequate therapeutic concentrations of posaconazole.

Itraconazole LC-MS/MS

Patient variability in the pharmacokinetics of itraconazole supports quantitative monitoring of blood drug levels, particularly due to its variable absorption. Monitoring trough levels of itraconazole and hydroxyitraconazole (the metabolite of itraconazole) is suggested in the first one to two weeks of treatment to ensure therapeutic levels have been achieved. Results may be clinically useful to determine if current dosing levels require adjustment for ongoing treatment.

Isavuconazole (CRESEMBA®) LC-MS/MS

Isavuconazole is for the treatment of life threatening fungal infections, specifically invasive aspergillosis and invasive mucormycosis.¹ There is a significant need for alternative antifungal therapies that address some of the limitations of voriconazole, such as reduced potential for nephrotoxicity for the intravenous formulation², in addition to other dose-related toxicities.³ Given the difficulty in diagnosis and similarity with which infections may present, having an antifungal that is effective for both indications would be particularly useful to physicians treating immunocompromised patients.

Background

The successful management of invasive fungal infections (IFI) continues to pose a difficult challenge for physicians treating immunocompromised patients, and despite recent advances in therapy, the morbidity and mortality due to IFI remains unacceptably high.⁴ Triazole antifungal drugs are commonly used to either prevent or treat IFI in at-risk patients. However, extensive intra- and inter-patient variability is observed in the pharmacokinetics of triazole antifungal drugs. This variability supports quantitative monitoring, i.e., therapeutic drug monitoring of triazole blood drug levels.^{4,5}

By using drug level monitoring with timely results, the physician is able to individualize drug dosage to improve efficacy and reduce toxicity. Drug monitoring of triazoles is included in the Infectious Diseases Society of America guidelines for treating aspergillosis and candidiasis.^{6,7} Recommendations indicate that blood samples should be obtained one to two weeks after the start of therapy, immediately before the next dose (“trough time”) and repeated following a change in dosage, formulation, initiation or discontinuation of an interacting medication, potential treatment failure or non-adherence to dosing schedule. Patients with altered hepatic and/or renal clearance will also benefit from drug level monitoring of triazoles.

Several triazole drugs are commonly used to treat IFI in immunocompromised patients. Voriconazole is used in treatment for a broad range of fungal infections, including invasive aspergillosis, candidiasis and other emerging IFI. Posaconazole is a broad spectrum triazole antifungal agent for treatment and prophylaxis of fungal and mold infections, including candidiasis, aspergillosis and zygomycosis. Itraconazole is used as therapy for a variety of invasive and non-invasive fungal infections, and is approved for the treatment of histoplasmosis, aspergillosis, esophageal candidiasis, and oropharyngeal candidiasis. Isavuconazole (CRESEMBA) is used to treat invasive aspergillosis and mucormycosis.¹

Specimen Requirements

- Ship frozen on dry ice Monday through Friday. Label Friday shipments for Saturday delivery.
- Specimens collected in serum or plasma gel tubes or specimen types other than those listed are not accepted and are cause for rejection.
- Recommended specimen collection time is immediately before the next scheduled dose of drug ("trough time").

Table 1. Specimen Details

Specimen Type	Volume	Special Instructions
Serum (preferred specimen type)	1 mL	<ul style="list-style-type: none"> • Collect 4-5 mL whole blood in serum tube (red top without gel). • Allow to clot for 30 to 60 minutes, centrifuge, transfer 1 mL of serum to sterile tube and freeze immediately (-70° C).
Plasma	1 mL	<ul style="list-style-type: none"> • Collect 4-5 mL whole blood in EDTA tubes (lavender top without gel). • Within 30 minutes of draw time, centrifuge, transfer 1 mL of plasma to sterile tube and freeze immediately (-70° C).

Units and Normal Reference Ranges

Analytical sensitivity

Voriconazole, posaconazole, itraconazole and metabolites, and isavuconazole – the analytical measuring range is 0.1 — 10.0 mcg/mL.

Table 2. Therapeutic Range

Test Code	Test Name	Drug Name	Therapeutic Range (mcg/mL)	Toxic Level (mcg/mL)
3310 / 3301 Serum / Plasma	Voriconazole LC-MS/MS *	Voriconazole	1.0 — 5.5	>6.0
4210 Serum	Posaconazole LC-MS/MS *	Posaconazole	>0.7	Not established
2810 / 2801 Serum / Plasma	Itraconazole LC-MS/MS *	Itraconazole/ Hydroxyitraconazole	*Localized: >0.5 *Systemic: >1.0	Not established
4910 / 4901 Serum / Plasma	Isavuconazole (CRESEMBA) LC-MS/MS *	Isavuconazole (CRESEMBA)	Not established	Not established

*Test available for NY samples. Result values must be summed for itraconazole and hydroxyitraconazole to determine the active circulating concentration

Method

Voriconazole, posaconazole, itraconazole or hydroxyitraconazole, and isavuconazole are extracted from serum or plasma by protein precipitation with methanol followed by centrifugation. Chromatographic separation and quantitative analysis of the supernatant are performed using reversed-phase UPLC-MS/MS. These tests have not been cleared or approved for diagnostic use by the U.S. Food and Drug Administration.

Turnaround Time

Same day (within 8 to 12 hours of specimen receipt), Monday through Saturday.

References

1. Astellas Pharma US, Inc., CRESEMBA® Package Insert.
2. von Mach MA1, Burhenne J, Weilemann LS. 2006. Accumulation of the solvent vehicle sulphobutylether beta cyclodextrin sodium in critically ill patients treated with intravenous voriconazole under renal replacement therapy. BMC Clin Pharmacol. 2006 6:6.
3. Pascual A1, Calandra T, Bolay S, Bucin T, Bille J, Marchetti O. 2008. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. Clin Infect Dis. 46(2):201-11.
4. Andes D, Pascual A, Marchetti O. Antifungal Therapeutic Drug Monitoring: Established and Emerging Indications. Antimicrob Agents Chemother. 2009 Jan; 53(1):24–34.
5. Goodwin ML, Drew RH. Antifungal serum concentration monitoring: an update. J Antimicrob Chemother. 2008 Jan; 61(1):17–25.
6. Pappas PG¹, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009 Mar 1; 48(5):503-35.
7. Walsh TJ¹, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis. 2008 Feb 1; 46(3):326-60.

The CPT codes provided are based on Viracor Eurofins' interpretation of the American Medical Association's Current Procedural Terminology (CPT) codes and are provided for informational purposes only. CPT coding is the sole responsibility of the billing party. Questions regarding coding should be addressed to your local Medicare carrier. Viracor Eurofins assumes no responsibility for billing errors due to reliance on the CPT codes illustrated in this material.

MM 0016 REV7 1116