

Bon Secours Richmond  
Pharmacy and Therapeutics Committees  
Posaconazole (Noxafil®)  
2/2007

**Recommendations:**

- Posaconazole (Noxafil®) suspension is recommended for formulary addition for the following FDA approved indications:
  - Posaconazole oral suspension, 105 ml with 40 mg/ml, is indicated for prophylaxis of invasive *Aspergillus* and *Candida* infections in patients 13 years of age and older who are at high risk of developing these infections due to being severely immunocompromised, such as *hematopoietic stem cell transplant (HSCT) recipients with Graft versus Host Disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy*
    - Hematopoietic stem cell transplant (HSCT) recipients with Graft versus Host Disease (GVHD): Posaconazole was not shown to be statistically superior to fluconazole
    - Hematologic malignancies with prolonged neutropenia from chemotherapy: Posaconazole was shown to be statistically superior to fluconazole
  - Treatment of oropharyngeal candidiasis refractory to fluconazole or itraconazole.
  - Patients previously receiving the medication will be asked to bring their medication from home for use during their hospitalization

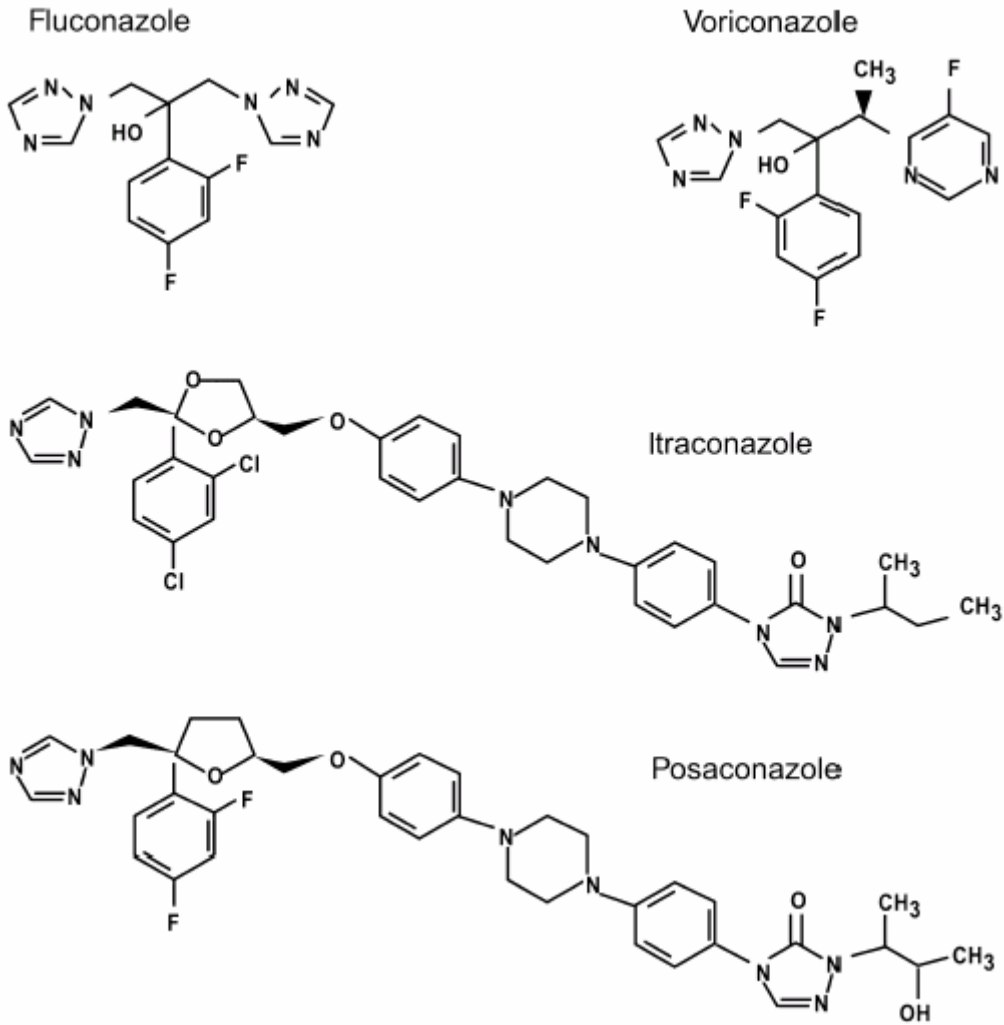
Drug	Dose	Condition	Conc. average ng/ml	AUC ng*h/ml
Posaconazole Suspension	200 mg TID	Neutropenic Chemotherapy Patients	583 ± 381	15,900 (0-24 hour)
Posaconazole Suspension	200 mg TID	GVDH (Chronic, Acute Disease)	1470, 958 (CV 57%, 68%)	
Posaconazole Suspension	400 mg BID		723	9,093 (0-12 hour)
Itraconazole Capsule	200 mg BID		2068	22,569 (0-12 hour)

- Pharmacy Monitoring
  - Pharmacy will ensure that orders are entered to be given with food to increase the bioavailability.
    - The package insert recommends each dose to be given with a full meal or liquid nutritional supplement such as Boost Plus.
    - Posaconazole's prophylaxis should start 24 hours after the last anthracycline dose in patients receiving chemotherapy
  - Pharmacy will monitor for interacting drugs and notify the physician as needed.
    - Posaconazole should not be administered with rifabutin, phenytoin, and cimetidine due to a 50% decrease in posaconazole serum levels. (Note: other H<sub>2</sub> antagonist and PPIs do not interact)
    - Contraindicated with ergot alkaloids as ergotism may result; cisapride, pimozide (Orap), halofantrine (antimalarial), and quinidine due to increase serum levels of these drugs which may lead to increased QTc interval and torsades de pointes.
    - Cyclosporin and tacrolimus require dosage reductions as their levels are increased.
  - Patients allergic to itraconazole will probably react to posaconazole. Physicians will be contacted if patients are allergic to itraconazole.
  - Doses above 800 mg per day are not recommended as higher serum levels and AUC are not achieved.
  - A serum level is recommended 5-8 days after starting therapy to verify absorption. If levels are lower than 500 ng/ml a dosage increase, change in time of administration, or increased frequency of administration is needed.

<b>Cost Comparison of Oral Antifungals used for prevention of invasive fungal infections</b>			
Indication	Posaconazole	Itraconazole	Fluconazole
Prophylaxis of Invasive Fungal Infections	200 mg PO TID \$66.62 per day	Not FDA Approved	400 mg/day Cost/day = \$5.72/day
Oropharyngeal Candidiasis Refractory to Itraconazole or fluconazole	400 mg BID \$88.82 per day		
Oropharyngeal Candidiasis	100 mg BID, then 100 mg daily for 13 days \$11.21 per day	200 mg/day \$14.14	200 mg x1; 100 mg/day Cost/day = \$0.4/day
Treatment of Invasive Fungal Infection (not FDA)	200 mg QID until improvement, then 400 mg BID	200-400 mg/day	400-800 mg/day \$5.72-\$11.44

approved)	\$88.82 per day	\$14-28	
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Note: Voriconazole (Vfend) 200 mg q12 hours cost \$60 per day for oral and \$199 per day for IV.



**Spectrum of Activity of the Azole Antifungals**

	Ketoconazole	Fluconazole	Itraconazole	Voriconazole	Posaconazole
<i>Candida albicans</i>	++	+++	+++	+++	+++
<i>Candida glabrata</i>	-	++	++	+++	+++
<i>Candida krusei</i>	-	+	++	+++	+++
Dimorphic fungi	-	++	++	+++	+++
<i>Aspergillus fumigatus</i>	-	+	++	+++	+++
<i>Aspergillus terreus</i>	-	+	-	+++	+++
<i>Fusarium</i> spp.	-	-	-	++	++
Dematiaceous fungi	-	-	+	++	++
Zygomycetes	-	-	+	+	++

Organism	N	MIC <sub>90</sub> (mcg/ml)				
		Posaconazole	Itraconazole	Fluconazole	Voriconazole	Amphotericin
<i>Candida. albicans</i>	3525	0.063	0.25	2	0.063	1
<i>Aspergillus fumigatus</i>	1119	0.5	1		0.5	1

TABLE 1. In vitro activities of posaconazole, itraconazole, fluconazole, voriconazole, and amphotericin B against all fungi, molds, and yeasts tested

Antifungal agent	In vitro activity against <sup>a</sup> :								
	All fungi			All molds			All yeasts		
	n	MIC (µg/ml)		n	MIC (µg/ml)		n	MIC (µg/ml)	
		50%	90%		50%	90%		50%	90%
POS	22,850	0.063	1.0	4,499	0.125	1.0	18,351	0.063	1.0
ITC	18,877	0.125	1.0	3,204	0.5	4.0	15,673	0.125	1.0
FLC	17,884	0.5	128.0	1,779	256.0	256.0	16,105	0.5	16.0
VRC	9,598	0.031	0.5	1,826	0.25	2.0	7,772	0.031	0.5
AMB	16,567	1.0	1.0	3,013	1.0	2.0	13,554	1.0	1.0

<sup>a</sup> n is the number of MICs determined. 50% and 90%, MIC<sub>50</sub> and MIC<sub>90</sub>, respectively.

## Findings:

- Indication: Posaconazole is indicated for prophylaxis of invasive *Aspergillus* and *Candida* infections in patients 13 years of age and older who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with Graft versus Host Disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy.
- Posaconazole has shown *in vitro* activity against most strains of *Candida* (including some fluconazole resistant strains) and *Aspergillus*. It has good activity against dermatophytes, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*, and *Cryptococcus neoformans*. It is also active against *Scedosporium apiospermum* and has variable activity *Fusarium*. Unlike other azoles it has good activity against *Zygomycetes*.
- *Aspergillus* is the most common mould infection in immunocompromised patients
  - Significant morbidity and mortality
  - Primarily respiratory tract infections
- Primary antifungal prophylaxis in patients with hematologic malignancies
  - The incidence of invasive fungal infections is substantially higher in hematologic malignancies as compared to solid tumors.
  - Fluconazole doses less than 400 mg per day have not demonstrated any significant efficacy in the prophylaxis of invasive fungal disease in allogenic bone marrow or hematopoietic stem cell transplants.
  - Fluconazole is ineffective against molds and *Candida krusei*, and its activity against *Candida glabrata* is dose-dependent.
  - Itraconazole suspension has an unpleasant taste and erratic serum levels requiring plasma levels with target level above 500 ng/ml
- Mechanism of action: Blocks ergosterol synthesis through the inhibition of the enzyme lanosterol 14 $\alpha$ -demethylase and accumulation of methylated sterol precursors. Amphotericin binds to ergosterol and increases membrane permeability (fungicidal). Combination of amphotericin B with posaconazole is not recommended due to potential inhibition of activity.
- Voriconazole has replaced amphotericin B as the treatment of choice for invasive aspergillosis.
- Echinocandins (anidulafungin, caspofungin, micafungin) are active against most *Candida* and *Aspergillus*, but are inactive against *Zygomycetes*.
- Posaconazole and Amphotericin B are the only products available for treatment of *Zygomycetes*.
- Posaconazole ADR's reported in the package insert appear to lower than itraconazole and similar to fluconazole. As the structure of posaconazole and itraconazole are similar this finding is not expected.
- Dosing: Posaconazole is available as an oral suspension that delivers 40 mg/mL. Recommended dosing for prophylaxis is 200 mg (5 mL) by mouth three times a day. Treatment doses are 400 mg twice a day.
- How Supplied: Posaconazole is available in a 4 oz bottle that contains 105 mL of suspension. At the recommended dosing, this is enough suspension to provide one week of therapy. Each bottle also comes with a dosing spoon that is calibrated to measure volumes of 2.5 and 5 mLs.
- Side effects most common in clinical trials were nausea, vomiting, diarrhea, abdominal pain, and headache. Liver enzyme elevations occur; cholestasis or hepatic failure with fatalities have been reported.
- Risk factors for Invasive Fungal Infections: 3 or more antibiotics, broad spectrum antibiotics for 4 or more days, central venous catheter, GI or cardiac surgery, High APACHE II scores, ICU stay for 4 or more days, burn patients, premature birth, PRN, mechanical ventilation for more than 48 hours, neutropenia, steroids, HIV, diabetes, candida colonization of 2 or more sites, thrush, candiduria.

- **Contraindications:**
  - Co-administration with ergot alkaloids (ergotamine and dihydroergotamine) which may lead to ergotism.
  - Co-administration with CYP3A4 substrates terfenadine (Not available in the U. S.), astemizole (Not available in the U. S.), cisapride, pimozone, halofantrine, or quinidine as this could lead to increased plasma concentrations of these substrates. Increased plasma concentrations may then lead to QTc prolongation and possibly torsades de pointes.
- **Warnings:**
  - There is no information regarding the cross-sensitivity between posaconazole and other azole antifungals. Caution is advised if a patient is hypersensitive to another azole antifungal.
  - LFTs should be monitored at the start and during posaconazole therapy.
  - In clinical efficacy studies, elevated cyclosporine levels were responsible for rare cases of nephrotoxicity, leukoencephalopathy, and death. Dose reduction of cyclosporine is recommended.
- **Precautions: Arrhythmias and QT Prolongation**
  - Posaconazole, as well as other azole antifungals, have been associated with QTc prolongation on ECG.
  - There was one case of torsades de pointes in a patient taking posaconazole during clinical development.
    - Per Package Insert, this patient was seriously ill with a history of cardiotoxic chemotherapy and palpitations, hypokalemia, hypomagnesemia, and use of concomitant medications that may have contributed. However, the manufacturer does not include what concomitant medications this patient was on.
  - In patients with potentially proarrhythmic conditions, posaconazole should be given with caution and should not be given with drugs that are metabolized by CYP3A4 and are known to prolong the QTc interval.
  - The manufacturer recommends that rigorous attempts to correct potassium, magnesium, and calcium should be made before starting posaconazole.
  - In an ECG evaluation of healthy subjects, no one had a QTc(F) interval  $\geq 500$  msec or an increase  $\geq 60$  msec in their QTc(F) interval from baseline.
- **Pharmacokinetics:**
  - Absorption: Tmax of 3-5 hours
  - Distribution: Vd = 1,774L; >98% protein bound (predominately albumin)
  - Metabolism: Primarily circulates as parent compound. Of circulating metabolites, the majority are formed by UDP glucuronidation (phase 2). There are no major oxidative metabolites. Metabolites account for ~17% of administered radiolabeled dose.
  - Excretion: Elimination half-life (t1/2) of 35 hours. Total body clearance (CL/F) of 32 L/hr. Predominately eliminated in the feces (71%) with minor elimination renally (13%).

	Posaconazole	Itraconazole
Tmax (Hours)	3-5	3-4
Bioavailability	No Data as no IV formulation for comparison Doses above 800 mg per day do not increase serum levels or AUC 58% increase in exposure by dividing 800 mg daily dose to 200 mg QID versus 400 mg BID	24-32% for capsule 55% for oral solution
Volume of Distribution (liters)	1774 (no IV formulation, true value unknown)	796 (IV formulation use as comparator)
Protein Binding %	98%	99.8%
Half-Life (hours)	35 (20-66)	21-64
CNS Penetration	Poor	
Metabolism	UDP (uridine diphosphate glucuronidation) and P-glycoprotein efflux	CYP3A4
Excretion	Urine & Feces as metabolites 17% Urine < 0.2% as parent drug Fecal 71%, 66% as parent drug	Urine 40% of dose as inactive metabolites Fecal 3-18% excreted unchanged
Average Serum Level ng/ml	583 (200 mg TID) 723 (400 mg BID)	2068 (200 BID)
AUC ng*h/ml	200 mg TID: 15,900 (24 hours)	200 mg BID: 22,569 (12 hours)

- Posaconazole should be given with a full meal or a nutritional supplement in order to enhance absorption. The mean AUC is approximately 3 times higher with a nonfat meal and 4 times higher with a high fat meal (~50 grams of fat) than the mean AUC in the fasted state. A liquid nutritional supplement (14 grams of fat) provides a mean AUC that is approximately 3 times higher than the mean AUC in the fasted state.
  - Monitor closely for infection or use alternate antifungal therapy if a patient cannot tolerate a meal or supplement.

- Monitor closely for infection if severe diarrhea or vomiting occurs.
- There was a greater variability in AUC in patients compared to healthy subjects.
- Dosage Adjustments:
  - Gender: No adjustment necessary
  - Race: No adjustment necessary
  - Geriatric: No adjustment necessary in elderly patients based on age ( $\geq 65$  years of age)
  - Pediatric: Only indicated for patients  $\geq 13$  years of age; safety and effectiveness in patients  $< 13$  years of age have not been established
  - **Hepatic Impairment:** Use caution; there is insufficient data to determine if adjustment is necessary in hepatic impairment.
  - **Renal Impairment:** No adjustment is necessary, however, in patients with severe renal impairment ( $CL_{Cr} < 20$  mL/min/1.73m<sup>2</sup>) patients should be monitored for breakthrough fungal infections due to a large variability in AUC seen among these patients (Coefficient of Variation 96%). Serum levels may need to be monitored.
  - Also, posaconazole is not removed by hemodialysis.
- Pregnancy Category C: There are no adequate, well-controlled studies in pregnant women. Use only if potential benefit justifies the potential risk to the fetus.
- Lactation: The excretion of posaconazole into human breast milk has not been studied. Use only if the potential benefit to the mother outweighs the potential risk to the infant.
- Posaconazole is a moderate **inhibitor** of CYP3A4.
- **Drug Interactions:**

Drugs that were found to decrease posaconazole concentrations in healthy volunteers		
Co-administered Drug (Postulated Mechanism of Interaction)	Change in Mean AUC of Posaconazole	Recommendations
Rifabutin (UDP-G Induction)	↓49%	<b>Avoid</b> unless benefits outweigh risks.
Phenytoin (UDP-G Induction)	↓50%	<b>Avoid</b> unless benefits outweigh risks.
Cimetidine (Alteration of Gastric pH)	↓39%	<b>Avoid</b> unless benefits outweigh risks.

**Note:** For these studies, 200 mg posaconazole tablets were used rather than the suspension.

Drugs that are affected by posaconazole in healthy volunteers		
Co-administered Drug (Postulated Mechanism of Interaction)	Effect on Bioavailability of Co-administered Drugs	Recommendations
Cyclosporine (Inhibition of CYP3A4)	Increase cyclosporine whole blood trough concentrations: <i>dose reductions of up to 29% were required</i>	<i>Reduce cyclosporine dose to approximately 3/4 of original dose at initiation of posaconazole.</i> Frequently monitor whole blood trough concentrations of cyclosporine during and at discontinuation of treatment with posaconazole.
Tacrolimus (Inhibition of CYP3A4)	<i>AUC increase of 358%</i>	<i>Reduce tacrolimus dose to approximately 1/3 of the original dose at initiation of posaconazole.</i> Frequently monitor whole blood trough concentrations of tacrolimus during and at discontinuation of treatment with posaconazole.
Rifabutin (Inhibition of CYP3A4)	<i>AUC increase of 72%</i>	Avoid unless benefits outweigh risks. If co-administered monitor for rifabutin full blood counts and adverse effects frequently.
Midazolam (Inhibition of CYP3A4)	AUC increase of 83%	Monitor for AEs of benzodiazepines that are substrates of CYP3A4 and consider dose reduction of benzodiazepines
Phenytoin (Inhibition of CYP3A4)	AUC increase of 16%	Frequently monitor phenytoin concentrations and consider dose reduction of phenytoin

**Note:** For these studies, 200 mg posaconazole tablets were used rather than the suspension.

**TABLE 9. Drugs Not Studied in vitro or in vivo but Likely to Result in Significant Drug Interactions**

<b>Drug or Drug Class (CYP3A4 Substrates)</b>	<b>Recommendations</b>
Terfenadine, Astemizole, Pimozide, Cisapride, Quinidine	Increased plasma concentrations of these drugs can lead to QT prolongation with rare occurrences of torsade de pointes. <b>Co-administration with posaconazole is contraindicated.</b> (See <b>CONTRAINDICATIONS</b> )
Ergot Alkaloids	Posaconazole may increase the plasma concentration of ergot alkaloids (ergotamine and dihydroergotamine) which may lead to ergotism. <b>Co-administration of posaconazole with ergot alkaloids is contraindicated.</b> (See <b>CONTRAINDICATIONS</b> )
Vinca Alkaloids	Posaconazole may increase the plasma concentrations of vinca alkaloids (eg, vincristine and vinblastine) which may lead to neurotoxicity. Therefore, it is recommended that the dose adjustment of the vinca alkaloid be considered.
Sirolimus	Frequent monitoring of sirolimus whole blood trough concentrations should be performed upon initiation, during co-administration, and at discontinuation of posaconazole treatment, with sirolimus doses reduced accordingly.
HMG-CoA reductase inhibitors (statins) metabolized through CYP3A4	It is recommended that dose reduction of statins be considered during co-administration. Increased statin concentrations in plasma can be associated with rhabdomyolysis.
Calcium Channel Blockers metabolized through CYP3A4	Frequent monitoring for adverse events and toxicity related to calcium channel blockers is recommended during co-administration. Dose reduction of calcium channel blockers may be needed.

Cytochrome P450 Effect of the Azole Antifungals		
Drug	CYP450 Inhibitors	CYP450 Substrates
Fluconazole	CYP1A2 (weak), 2C9 (strong), 2C19 (strong), 3A4 (moderate)	
Itraconazole	CYP3A4 (strong)	CYP3A4 (major)
Voriconazole	CYP2C9 (weak), 2C19 (weak), 3A4 (moderate)	CYP2C9 (major), 2C19 (major), 3A4 (minor)
Posaconazole	CYP3A4 (moderate)	

**Note:** None of these drugs are inducers of CYP450.

Contraindicated Drug Products with Selected Azole Antifungals				
	Fluconazole	Voriconazole	Itraconazole	Posaconazole
Drugs that cause an increase in Azole antifungal concentrations				
Drugs that cause a decrease in Azole antifungal concentrations		Carbamazepine, Long-acting Barbiturates, <b>Rifabutin</b> , Rifampin, High-dose Ritonavir (400 mg Q12H), <b>Efavirenz</b>		Rifabutin Cimetidine phenytoin
Drugs that have increased drug concentrations when administered with Azole antifungals	Terfenadine, Cisapride	Astemizole, Cisapride, Ergot Alkaloids, Pimozide, Quinidine, <b>Rifabutin</b> , Sirolimus, Terfenadine, <b>Efavirenz</b>	Cisapride, Oral Midazolam, Nisoldipine, Pimozide, Quinidine, Dofetilide, Triazolam, Levacetylmethadol (levomeperidol), HMG CoA-reductase inhibitors metabolized by CYP3A4 such as lovastatin and simvastatin, Ergot alkaloids	Ergot alkaloids (Ergotamine and Dihydroergotamine), CYP3A4 substrates Terfenadine (Not available in the U. S.), Astemizole (Not available in the U. S.), Cisapride, Pimozide, Halofantrine, or Quinidine

<b>Drug Interactions With Selected Azole Antifungals</b>				
	<b>Fluconazole</b>	<b>Voriconazole</b>	<b>Itraconazole</b>	<b>Posaconazole</b>
Medications in which a dose reduction is needed or recommended when co-administered	Short-acting benzodiazepines (consider decreasing benzodiazepine dosage)	Cyclosporine and Tacrolimus (initially decrease dose, then frequently monitor and increase dose as necessary), Omeprazole (reduce dose by ½ in patients stable on 40mg or greater; also watch other Proton Pump Inhibitors)		Cyclosporine, Tacrolimus, Benzodiazepines that are CYP3A4 substrates (consider), Phenytoin (consider); <b>Not Studied but likely to have an interaction:</b> Vinca alkaloids, sirolimus, HMG CoA-reductase inhibitors metabolized through CYP3A4, Calcium Channel Blockers metabolized through CYP3A4
Medications that decrease concentrations of azole antifungals	Rifampin (enhances metabolism: consider increasing fluconazole dose)	<b>Phenytoin</b> (Increase voriconazole dose)	Phenytoin, <b>Carbamazepine</b> , Phenobarbital, The Antimycobacterials <b>Rifabutin</b> , Rifampin, and Isoniazid (Coadministration is not recommended), Antacids, H <sub>2</sub> -receptor antagonists, Proton Pump Inhibitors, Nevirapine (Coadministration is not recommended)	<b>Avoid unless benefits outweigh risks:</b> Rifabutin, Phenytoin, Cimetidine
Medications that increase concentrations of azole antifungals			Clarithromycin, Erythromycin, <b>Indinavir, Ritonavir</b>	
Medications that require careful monitoring	Tolbutamide, Glyburide, Glipizide, or other Sulfonylureas, Coumarin-type anticoagulants, Phenytoin, Cyclosporine, Theophylline, Astemizole, Rifabutin, Tacrolimus	Methadone (dose reduction may be needed), <b>Phenytoin</b> , Ethinyl Estradiol and Norethindrone containing Oral Contraceptives, Warfarin (PT time increased), Benzodiazepines, HMG-CoA Reductase Inhibitors, Dihydropyridine Calcium Channel Blockers, Sulfonylureas, and Vinca Alkaloids (dose adjustment may be needed)	Disopyramide, Digoxin, <b>Carbamazepine</b> , <b>Rifabutin</b> , Busulfan, Docetaxel, Vinca Alkaloids, parenteral Midazolam, Alprazolam, Diazepam, Dihydropyridine Calcium Channel Blockers and Verapamil (increased risk of CHF), Cyclosporine, Tacrolimus, Sirolimus, Oral hypoglycemics, <b>Indinavir, Ritonavir</b> , Saquinavir, Halofantrine, Alfentanil, Buspirone, Methylprednisolone, Budesonide, Dexamethasone, Trimextrate, Warfarin, Cilostazol, Eletriptan, Fentanyl	

**Study Results: Prophylaxis of *Aspergillus* and *Candida* Infections**

• **Study 1:**

- Randomized, double-blind trial comparing Posaconazole oral suspension 200 mg TID vs. Fluconazole capsules 400 mg QD as prophylaxis against invasive fungal infections in allogeneic hematopoietic stem cell transplant (HSCT) recipients with Graft versus Host Disease (GVHD). Patients were 13 years of age or older and weighted more than 34 kg.
- Proven/Probable invasive fungal infections, death, or treatment with systemic anti-fungal therapy were a composite endpoint for treatment failure to evaluate the efficacy of prophylaxis of posaconazole.
- The mean duration of therapy was 80 days for those patients taking posaconazole and 77 days for those taking fluconazole.
- The frequency of study drug discontinuation because of an adverse reaction was similar in the two groups(34% posaconazole, 38% in fluconazole).
- A high rate of treatment related discontinuation occurred because of the severity of underlying disease. 46% of the patients in posaconazole and 41% of the patients in fluconazole groups completed the full 16 weeks of treatment.
- The results are shown in the following table.

**TABLE 5. Results from Blinded Clinical Study 1 in Prophylaxis of IFI in All Randomized Patients with hematopoietic stem cell transplant (HSCT) and graft-vs-host disease (GVHD)**

	<b>Posaconazole n =301</b>	<b>Fluconazole n = 299</b>
<b>On therapy plus 7 days</b>		
Clinical Failure <sup>a</sup>	50 (17%)	55 (18%)
Failure due to:		
Proven/Probable IFI	7 (2%)	22 (7%)
( <i>Aspergillus</i> )	3 (1%)	17 (6%)
( <i>Candida</i> )	1 (<1%)	3 (1%)
(Other)	3 (1%)	2 (1%)
All Deaths	22 (7%)	24 (8%)
Proven / probable fungal infection prior to death	2 (<1%)	6 (2%)
SAF <sup>b</sup>	27 (9%)	25 (8%)
<b>Through 16 weeks</b>		
Clinical Failure <sup>a,c</sup>	99 (33%)	110 (37%)
Failure due to:		
Proven/Probable IFI	16 (5%)	27 (9%)
( <i>Aspergillus</i> )	7 (2%)	21 (7%)
( <i>Candida</i> )	4 (1%)	4 (1%)
(Other)	5 (2%)	2 (1%)
All Deaths	58 (19%)	59 (20%)
Proven / probable fungal infection prior to death	10 (3%)	16 (5%)
SAF <sup>b</sup>	26 (9%)	30 (10%)
Event free lost to follow-up <sup>d</sup>	24 (8%)	30 (10%)
<p>a: Patients may have met more than one criteria defining failure.  b: Use of systemic antifungal therapy (SAF) criterion is based on protocol definitions (empiric/IFI usage &gt;4 consecutive days).  c: 95% confidence interval (posaconazole-fluconazole) = (-11.5%, +3.7%)  d: Patients who are lost to follow-up (not observed for 112 days), and who did not meet another clinical failure endpoint. These patients were considered failures.</p>		

**Note:** IFI = invasive fungal infections, SAF = treatment with systemic antifungal therapy



**Study 2:**

- Randomized, open-label study that compared posaconazole oral suspension 200 mg TID versus fluconazole suspension 400 mg QD or itraconazole oral solution 200 mg BID as prophylaxis against IFIs in patients expected to be neutropenic for 7 days or more after receiving cytotoxic chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes. Regimens continued until neutrophil recovery or occurrence of invasive fungal infection, for up to 12 weeks.
- Proven/Probable invasive fungal infections, death, or treatment with systemic anti-fungal therapy were a composite endpoint for treatment failure to evaluate the efficacy of prophylaxis of posaconazole.
- The mean duration of therapy in this study was 29 days for patients receiving posaconazole and 25 days for patients receiving fluconazole or itraconazole.
- The results are summarized in the following table.
- Note only 58 patients received itraconazole.

**TABLE 6. Results from Open-Label Clinical Study 2 in Prophylaxis of IFI in All Randomized Patients with Hematologic Malignancy and Prolonged Neutropenia**

	Posaconazole n=304	Fluconazole/Itraconazole n=298
<i>On therapy plus 7 days</i>		
<b>Clinical Failure<sup>a,b</sup></b>	82 (27%)	126 (42%)
<b>Failure due to:</b>		
Proven/Probable IFI	7 (2%)	25 (8%)

**TABLE 6. Results from Open-Label Clinical Study 2 in Prophylaxis of IFI in All Randomized Patients with Hematologic Malignancy and Prolonged Neutropenia (cont)**

	Posaconazole n=304	Fluconazole/Itraconazole n=298
<i>On therapy plus 7 days</i>		
( <i>Aspergillus</i> )	2 (1%)	20 (7%)
( <i>Candida</i> )	3 (1%)	2 (1%)
(Other)	2 (1%)	3 (1%)
<b>All Deaths</b>	17 (6%)	25 (8%)
Proven/probable fungal infection prior to death	1 (<1%)	2 (1%)
SAF <sup>c</sup>	67 (22%)	98 (33%)
<i>Through 100 days post-randomization</i>		
<b>Clinical Failure<sup>a</sup></b>	158 (52%)	191 (64%)
<b>Failure due to:</b>		
Proven/Probable IFI	14 (5%)	33 (11%)
( <i>Aspergillus</i> )	2 (1%)	26 (9%)
( <i>Candida</i> )	10 (3%)	4 (1%)
(Other)	2 (1%)	3 (1%)
<b>All Deaths</b>	44 (14%)	64 (21%)
Proven/probable fungal infection prior to death	2 (1%)	16 (5%)
SAF <sup>c</sup>	98 (32%)	125 (42%)
Event-free lost to follow-up <sup>d</sup>	34 (11%)	24 (8%)

<sup>a</sup> 95% confidence interval (posaconazole-fluconazole/itraconazole) = (-22.9%, -7.8%).

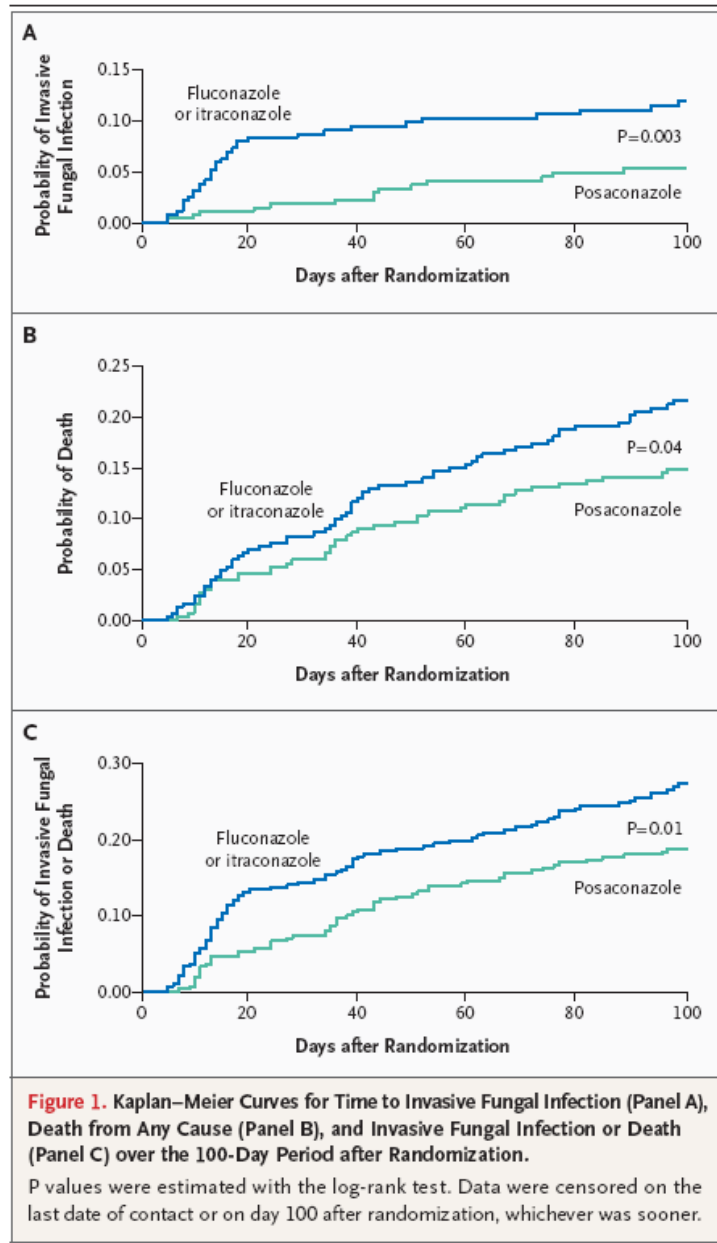
<sup>b</sup> Patients may have met more than one criterion defining failure.

<sup>c</sup> Use of systemic antifungal therapy (SAF) criterion is based on protocol definitions (empiric/IFI usage >3 consecutive days).

<sup>d</sup> Patients who are lost to follow-up (not observed for 100 days), and who did not meet another clinical failure endpoint. These patients were considered failures.

**Note:** IFI = invasive fungal infections, SAF = treatment with systemic antifungal therapy

- It was found that patients prophylaxed with posaconazole in both studies had fewer breakthrough infections that were caused by *Aspergillus*



**Laboratory Value Changes:**

- The information contained in the following table was obtained from the two studies mentioned previously.

**TABLE 13. Study 1 and Study 2. Changes in Liver Function Test Results from CTC Grade 0, 1, or 2 at Baseline to Grade 3 or 4**

Laboratory Parameter	Number (%) of Patients With Change <sup>a</sup>	
	Study 1	
	Posaconazole N=301	Fluconazole N=299
AST	11/266 (4)	13/266 (5)
ALT	47/271 (17)	39/272 (14)
Bilirubin	24/271 (9)	20/275 (7)
Alkaline Phosphatase	9/271 (3)	8/271 (3)
	Study 2	
	Posaconazole (n=304)	Fluconazole/Itraconazole (n=298)
AST	9/286 (3)	5/280 (2)
ALT	18/289 (6)	13/284 (5)
Bilirubin	20/290 (7)	25/285 (9)
Alkaline Phosphatase	4/281 (1)	1/276 (<1)

a: Change from Grade 0 to 2 at Baseline to Grade 3 or 4 during the study. These data are presented in the form X/Y, where X represents the number of patients who met the criterion as indicated, and Y represents the number of patients who had a baseline observation and at least one post-baseline observation.

CTC = Common Toxicity Criteria; AST= Aspartate Aminotransferase; ALT= Alanine Aminotransferase.

• **Study 3**

- Randomized, controlled, evaluator-blinded study in HIV-infected patient with oropharyngeal candidiasis.
- Either posaconazole or fluconazole oral suspension, 100 mg twice daily x 1 day, then 100 mcg daily for 13 days
- Clinical and mycological outcomes were assessed after 14 days of treatment and at 4 weeks after the end of treatment.

**TABLE 7. Clinical Success, Mycological Eradication, and Relapse Rates in Oropharyngeal Candidiasis**

	Posaconazole	Fluconazole
Clinical Success at End of Therapy (Day 14)	155/169 (91.7%)	148/160 (92.5%)
Clinical Relapse (4 Weeks after End of Therapy)	45/155 (29.0%)	52/148 (35.1%)
Mycological Eradication (absence of CFU) at End of Therapy (Day 14)	88/169 (52.1%)	80/160 (50.0%)
Mycological Relapse (4 Weeks after End of Treatment)	49/88 (55.6%)	51/80 (63.7%)

Mycologic response rates, using a criterion for success as a post-treatment quantitative culture with  $\leq 20$  colony-forming units (CFU/mL) were also similar between the two groups (posaconazole 68.0%, fluconazole 68.1%). The clinical significance of this finding is unknown.

**Study 4**

- Non-comparative study of posaconazole oral suspension in HIV-infected subjects with OPC that was refractory to treatment with fluconazole or itraconazole.
- Posaconazole 400 mg BID for 3 days, then 400 mg every day for 25 days with an option for further treatment with 400 mg BID for 3 months.
- The clinical success rate 74.2%

**Adverse Reactions:**

- Bilirubinemia, increased hepatic enzymes, hepatocellular damage, nausea, and vomiting were the most common treatment-related serious adverse events in the prophylaxis studies (1% each).
- Adrenal insufficiency and allergic/hypersensitivity reactions occurred rarely during clinical trials.

- Hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and pulmonary embolus have been reported mainly in patients that were also receiving cyclosporine or tacrolimus for transplant rejection or graft versus host disease.
- The one case of torsade de pointes was discussed earlier under precautions.
- The package insert states that the safety of posaconazole has been studied in 1,844 patients, however the data that is presented in the following tables is only for the 605 patients that were included in the two prophylaxis studies discussed earlier.

**TABLE 10** presents treatment-emergent adverse events observed at an incidence >10% in the posaconazole prophylaxis studies.

**TABLE 10. Study 1 and Study 2. Number (%) of Randomized Subjects Reporting Treatment Emergent Adverse Events: Frequency of At Least 10% in the POS or FLU Treatment Groups (Pooled Prophylaxis Safety Analysis)**

	Posaconazole n=605		Fluconazole n=539		Itraconazole n=58	
<b>Subjects Reporting any Adverse Event</b>	<b>595</b>	<b>(98)</b>	<b>531</b>	<b>(99)</b>	<b>58</b>	<b>(100)</b>
<b>Body as a Whole - General Disorders</b>						
Fever	274	(45)	254	(47)	32	(55)
Headache	171	(28)	141	(26)	23	(40)
Rigors	122	(20)	87	(16)	17	(29)
Fatigue	101	(17)	98	(18)	5	(9)
Edema Legs	93	(15)	67	(12)	11	(19)
Anorexia	92	(15)	94	(17)	16	(28)
Dizziness	64	(11)	56	(10)	5	(9)
Edema	54	(9)	68	(13)	8	(14)
Weakness	51	(8)	52	(10)	2	(3)
<b>Cardiovascular Disorders, General</b>						
Hypertension	106	(18)	88	(16)	3	(5)
Hypotension	83	(14)	79	(15)	10	(17)
<b>Disorders of Blood and Lymphatic System</b>						
Anemia	149	(25)	124	(23)	16	(28)
Neutropenia	141	(23)	122	(23)	23	(40)
Febrile Neutropenia	118	(20)	85	(16)	23	(40)
<b>Disorders of the Reproductive System and Breast</b>						
Vaginal Hemorrhage <sup>a</sup>	24	(10)	20	(9)	3	(12)

	Posaconazole n=605		Fluconazole n=539		Itraconazole n=58	
<b>Gastro-Intestinal System Disorders</b>						
Diarrhea	256	(42)	212	(39)	35	(60)
Nausea	232	(38)	198	(37)	30	(52)
Vomiting	174	(29)	173	(32)	24	(41)
Abdominal Pain	161	(27)	147	(27)	21	(36)
Constipation	126	(21)	94	(17)	10	(17)
Mucositis NOS	105	(17)	68	(13)	15	(26)
Dyspepsia	61	(10)	50	(9)	6	(10)
<b>Heart Rate and Rhythm Disorders</b>						
Tachycardia	72	(12)	75	(14)	3	(5)
<b>Infection and Infestations</b>						
Bacteremia	107	(18)	98	(18)	16	(28)
Herpes Simplex	88	(15)	61	(11)	10	(17)
Cytomegalovirus Infection	82	(14)	69	(13)	0	
Pharyngitis	71	(12)	60	(11)	12	(21)
Upper Respiratory Tract Infection	44	(7)	54	(10)	5	(9)
<b>Liver and Biliary System Disorders</b>						
Bilirubinemia	59	(10)	51	(9)	11	(19)
<b>Metabolic and Nutritional Disorders</b>						
Hypokalemia	181	(30)	142	(26)	30	(52)
Hypomagnesemia	110	(18)	84	(16)	11	(19)
Hyperglycemia	68	(11)	76	(14)	2	(3)
Hypocalcemia	56	(9)	55	(10)	5	(9)
<b>Musculo-Skeletal System Disorders</b>						
Musculo-Skeletal Pain	95	(16)	82	(15)	9	(16)
Arthralgia	69	(11)	67	(12)	5	(9)
Back Pain	63	(10)	66	(12)	4	(7)
<b>Platelet, Bleeding and Clotting Disorders</b>						
Thrombocytopenia	175	(29)	146	(27)	20	(34)
Petechiae	64	(11)	54	(10)	9	(16)
<b>Psychiatric Disorders</b>						
Insomnia	103	(17)	92	(17)	11	(19)
Anxiety	52	(9)	61	(11)	9	(16)
<b>Respiratory System Disorders</b>						
Coughing	146	(24)	130	(24)	14	(24)
Dyspnea	121	(20)	116	(22)	15	(26)
Epistaxis	82	(14)	73	(14)	12	(21)
<b>Skin and Subcutaneous Tissue Disorders</b>						
Rash	113	(19)	96	(18)	25	(43)
Pruritus	69	(11)	62	(12)	11	(19)

a: Percentages of sex-specific adverse events are based on the number of males/females.  
NOS = not otherwise specified.

**TABLES 11 and 12** present treatment-related adverse events observed at an incidence  $\geq 2\%$  in the posaconazole prophylaxis studies.

**TABLE 11. Study 1. Treatment-Related Adverse Events, Occurring in Greater Than or Equal to 2% of Patients in Posaconazole or Fluconazole Treatment Group**

Body System/Preferred Term	Posaconazole N=301	Fluconazole N=299
	n (%)	n (%)
<b>Subjects Reporting Any Adverse Event</b>	<b>107 (36)</b>	<b>115 (38)</b>
<b>Body as a Whole – General Disorders</b>		
Drug Level Altered	5 (2)	2 (1)
Dizziness	4 (1)	5 (2)
Fatigue	4 (1)	6 (2)
Anorexia	3 (1)	7 (2)
Headache	3 (1)	8 (3)
Weakness	3 (1)	5 (2)
<b>Cardiovascular Disorders, General</b>		
Hypertension	2 (1)	5 (2)
<b>Central and Peripheral Nervous System Disorders</b>		
Tremor	4 (1)	6 (2)
<b>Disorders of the Eye</b>		
Vision Blurred	3 (1)	5 (2)
<b>Gastrointestinal System Disorders</b>		
Nausea	22 (7)	28 (9)
Vomiting	13 (4)	15 (5)
Diarrhea	8 (3)	12 (4)
Abdominal Pain	4 (1)	7 (2)
Dyspepsia	3 (1)	6 (2)
Constipation	1 (<1)	5 (2)
<b>Liver and Biliary System Disorders</b>		
SGPT Increased	9 (3)	4 (1)
GGT Increased	9 (3)	7 (2)
Bilirubinemia	8 (3)	5 (2)
Hepatic Enzymes Increased	8 (3)	7 (2)
SGOT Increased	8 (3)	3 (1)
<b>Metabolic and Nutritional Disorders</b>		
Phosphatase Alkaline Increased	5 (2)	5 (2)
<b>Renal and Urinary System Disorders</b>		
Blood Creatinine Increased	6 (2)	5 (2)
<b>Special Senses Other, Disorders</b>		
Taste Perversion	3 (1)	5 (2)

GGT = gamma-glutamyl transpeptidase; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

**TABLE 12. Study 2. Treatment-Related Adverse Events, Occurring in Greater Than or Equal to 2% of Patients in Posaconazole or Fluconazole/Itraconazole Treatment Group**

Body System/Preferred Term	Number (%) of Patients			
	Posaconazole (n=304)	Fluconazole/ Itraconazole (n=298)	Fluconazole (n=240)	Itraconazole (n=58)
<b>Subjects Reporting Any Adverse Event</b>	102 (34)	101 (34)	71 (30)	30 (52)
<b>Body as a Whole - General Disorders</b>				
Headache	5 (2)	1 (<1)	0	1 (2)
<b>Gastrointestinal System Disorders</b>				
Nausea	22 (7)	25 (8)	17 (7)	8 (14)
Diarrhea	20 (7)	21 (7)	12 (5)	9 (16)
Vomiting	14 (5)	20 (7)	14 (6)	6 (10)
Abdominal Pain	9 (3)	9 (3)	8 (3)	1 (2)
Mucositis NOS	7 (2)	0	0	0
Dyspepsia	5 (2)	3 (1)	3 (1)	0
Constipation	3 (1)	7 (2)	7 (3)	0
<b>Heart Rate and Rhythm Disorders</b>				
QT/QTc Prolongation	12 (4)	9 (3)	5 (2)	4 (7)
<b>Liver and Biliary System Disorders</b>				
Bilirubinemia	7 (2)	8 (3)	5 (2)	3 (5)
Hepatic Enzymes Increased	7 (2)	3 (1)	3 (1)	0
SGPT Increased	7 (2)	5 (2)	4 (2)	1 (2)
SGOT Increased	6 (2)	5 (2)	4 (2)	1 (2)
GGT Increased	5 (2)	2 (1)	1 (<1)	1 (2)
<b>Metabolic and Nutritional Disorders</b>				
Hypokalemia	9 (3)	6 (2)	5 (2)	1 (2)
<b>Skin and Subcutaneous Tissue Disorders</b>				
Rash	9 (3)	11 (4)	10 (4)	1 (2)

GGT = gamma-glutamyl transpeptidase; NOS = not otherwise specified; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

**Sanford Guide To Antimicrobial Therapy 2006**

	% of Isolates	Risk Factors	Fluconazole	Itraconazole	Voriconazole	Amphotericin B	Caspofungin	Micafungin Anidulafungin
C. albicans	45-63	HIV/AIDS, surgery	97% S	93% S	99% S	> 95% S	S	S
C. glabrata	12-24	Heme malignancies, azole prophylaxis	85-90% (S-DD)	50% R	92% S-I	> 95% S-I	S	S
C. parapsilosis	11-29	Azole prophylaxis, neonates, foreign bodies	99% S	4% S-DD	99% S	> 95% S	S-I	S-I
C. tropicalis	6-19	Neutropenia	98 S	58% S	99% S	>95% S	S	S
C. krusei	1-5	Heme malignancies, azole prophylaxis	5% R	69% S	99% S-I	> 95% S-I	S	S
C. guilliermondii	1	Azole prophylaxis, previous amphotericin	> 95% S	? S	> 95% S	? R	S	S
C. lusitanae	1	Previous amphotericin	> 95% S	? S	> 95% S	? R	S	S

**FDA Approved Indications and Dosage**

	Anidulafungin	Micafungin	Caspofungin	Fluconazole
Aspergillus			70 mg x1; 50 mg/day Cost/day = \$198.00	
Esophageal Candidiasis	100 mg x1; 50 mg/day Cost/day = \$90 Minimum of 14 days, 7 days past resolution of symptoms	150 mg/day Cost/day = \$238.44	50 mg/day Cost/day = \$198.00	200 mg x1; 100 mg/day Cost/day = \$0.4-\$15/day
Candidemia	200 mg x1; 100 mg/day Cost/day = \$180.00 Continue 14 days past last positive blood culture		70 mg x1; 50 mg/day Cost/day = \$198.00	400 mg/day Cost/day = \$0.8-\$30/day
Other Candida Infections (intra-abdominal abscess and peritonitis)	200 mg x1; 100 mg/day Cost/day = \$180.00		70 mg x1; 50 mg/day Cost/day = \$198.00	400 mg/day Cost/day = \$0.4-\$15/day
Candida prophylaxis in hematopoietic stem cell transplantation		50 mg/day Cost/day = \$79.48		400 mg/day Cost/day = \$0.4-\$15/day
Febrile Neutropenia; empiric therapy			70 mg x1; 50 mg/day Cost/day = \$198.00	400-800 mg/day Cost/day = \$0.4-\$15/day

<b>Drugs Contraindicated with voriconazole</b>		
Drug	Effect on voriconazole	Effect on drug in 1 <sup>st</sup> column
Astemizole		Increased drug level
Carbamazepine	Decreased drug level	
Cisapride		Increased drug level
Ergot Alkaloids		Increased drug level
Long-acting Barbiturates	Decreased drug level	
Pimozide		Increased drug level
Quinidine		Increased drug level
Rifabutin	Decreased drug level ↓ AUC 79%	Increased drug level 400% ↑ AUC
Rifampin	Decreased drug level 96% ↓ AUC	
Sirolimus		Increased drug level 700% ↑ AUC
Terfenadine		Increased drug level

<b>Voriconazole Drug Interactions requiring dosage change and/or monitoring</b>		
<b>Agent</b>	<b>Dose change</b>	<b>Monitor</b>
Phenytoin	Increase Voriconazole IV dose from 4 to 5mg/kg IV or double oral dose	Phenytoin plasma level AUC ↑ 80%, adverse events (Aes)
Tacrolimus	Decrease tacrolimus dose to one third	Drug level
Cyclosporine	Decrease cyclosporine dose to one half	Drug level
Omeprazole (doses > 40mg)	Decrease omeprazole dose to one half	
Statins	Consider	Drug toxicity, AEs
Calcium Channel Blockers	Consider	Drug toxicity, AEs
Benzodiazepines	Consider	Drug toxicity, AEs
Vinca alkaloids	Consider	Drug toxicity, AEs
Sulfonylureas	Consider	Blood glucose, hypoglycemia
Warfarin	Consider	Prothrombin time
HIV protease inhibitor (except indinavir)	None	Drug toxicity, AEs
NNRTIs	None	Drug toxicity, AEs

**Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease.**

[Ullmann AJ](#), [Lipton JH](#), [Vesole DH](#), [Chandrasekar P](#), [Langston A](#), [Tarantolo SR](#), [Greinix H](#), [Morais de Azevedo W](#), [Reddy V](#), [Boparai N](#), [Pedicone L](#), [Patino H](#), [Durrant S](#).

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**BACKGROUND:** Invasive fungal infections are an important cause of morbidity and mortality after allogeneic hematopoietic stem-cell transplantation. **METHODS:** In an international, randomized, double-blind trial, we compared oral posaconazole with oral fluconazole for prophylaxis against invasive fungal infections in patients with graft-versus-host disease (GVHD) who were receiving immunosuppressive therapy. The primary end point was the incidence of proven or probable invasive fungal infections from randomization to day 112 of the fixed treatment period of the study. **RESULTS:** Of a total of 600 patients, 301 were assigned to posaconazole and 299 to fluconazole. *At the end of the fixed 112-day treatment period, posaconazole was found to be as effective as fluconazole in preventing all invasive fungal infections (incidence, 5.3% and 9.0%, respectively; odds ratio, 0.56; 95 percent confidence interval [CI], 0.30 to 1.07; P=0.07) and was superior to fluconazole in preventing proven or probable invasive aspergillosis (2.3% vs. 7.0%; odds ratio, 0.31; 95% CI, 0.13 to 0.75; P=0.006). While patients were receiving study medications (exposure period), in the posaconazole group, as compared with the fluconazole group, there were fewer breakthrough invasive fungal infections (2.4% vs. 7.6%, P=0.004), particularly invasive aspergillosis (1.0% vs. 5.9%, P=0.001). Overall mortality was similar in the two groups, but the number of deaths from invasive fungal infections was lower in the posaconazole group (1%, vs. 4% in the fluconazole group; P=0.046). The incidence of treatment-related adverse events was similar in the two groups (36% in the posaconazole group and 38% in the fluconazole group), and the rates of treatment-related serious adverse events were 13% and 10%, respectively.* **CONCLUSIONS:** Posaconazole was similar to fluconazole for prophylaxis against fungal infections among patients with GVHD. It was superior in preventing invasive aspergillosis and reducing the rate of deaths related to fungal infections. (ClinicalTrials.gov number, NCT00034645 [ClinicalTrials.gov]). Copyright 2007 Massachusetts Medical Society.

**Table 2. Proven or Probable Invasive Fungal Infections during the Fixed Treatment Period and the Exposure Period, According to Pathogen, among Patients Assigned to a Study Drug.**

Pathogen or Pathogen Group	Posaconazole	Fluconazole	Odds Ratio (95% CI)	P Value
	Group (N= 301)	Group (N= 299)		
	<i>no. (%)</i>			
<b>Fixed treatment period</b>				
All proven and probable invasive fungal infections*	16 (5.3)	27 (9.0)	0.56 (0.30–1.07)	0.07
All invasive aspergillosis	7 (2.3)	21 (7.0)	0.31 (0.13–0.75)	0.006
Aspergillus (not otherwise specified)	0	5		
Aspergillus galactomannan antigen index	5	6		
<i>A. fumigatus</i>	2	5		
<i>A. flavus</i>	0	3		
<i>A. niger</i>	0	1		
<i>A. terreus</i>	0	1		
All candida species	4	4		
<i>C. krusei</i>	1	1		
<i>C. albicans</i>	0	1		
<i>C. glabrata</i>	2	1		
<i>C. parapsilosis</i>	0	1		
Candida (not otherwise specified)	1	0		
Other fungi	5	2		
<i>Pseudallescheria boydii</i>	1	0		
<i>Rhizomucor miehei</i>	0	1		
<i>Trichosporon beigelii</i>	1	0		
<i>Scedosporium prolificans</i>	1	0		
Mold (not otherwise specified)	2	1		

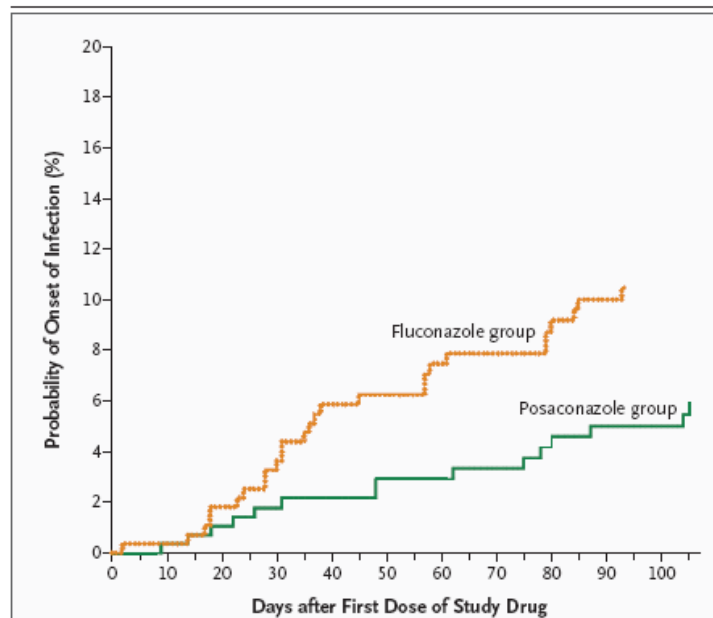
Table 2. (Continued.)				
Pathogen or Pathogen Group	Posaconazole Group	Fluconazole Group	Odds Ratio (95% CI)	P Value
	(N= 291)	(N= 288)		
	<i>no. (%)</i>			
<b>Exposure period†</b>				
All proven and probable invasive fungal infections*	7 (2.4)	22 (7.6)	0.30 (0.12–0.71)	0.004
All invasive aspergillosis	3 (1.0)	17 (5.9)	0.17 (0.05–0.57)	0.001
Aspergillus (not otherwise specified)	0	4		
Aspergillus galactomannan antigen index	3	4		
<i>A. fumigatus</i>	0	6‡		
<i>A. flavus</i>	0	2		
<i>A. niger</i>	0	0		
<i>A. terreus</i>	0	1		
All candida species	1	3		
<i>C. krusei</i>	0	1		
<i>C. albicans</i>	0	1		
<i>C. glabrata</i>	1	1		
<i>C. parapsilosis</i>	0	0		
Candida (not otherwise specified)	0	0		
Other fungi	3	2		
<i>P. boydii</i>	1	0		
<i>R. miehei</i>	0	1		
<i>T. beigelii</i>	1	0		
<i>S. prolificans</i>	0	0		
Mold (not otherwise specified)	1	1		

\* Cases of probable invasive aspergillosis confirmed on aspergillus galactomannan immunossay (Platelia Aspergillus EIA, Bio-Rad Laboratories) were included in this category.

† The total numbers of patients for the analysis of invasive fungal infections during the exposure period were 291 in the posaconazole group and 288 in the fluconazole group.

‡ An invasive fungal infection that developed in one patient on day 113 (while the patient was receiving the study drug) was not counted as occurring during the fixed treatment period (the interval beginning on the date of randomization and ending on day 112).

Table 4. Treatment-Related Adverse Events and All-Cause Mortality during the Observation Period.*		
Event	Posaconazole Group (N= 301)	Fluconazole Group (N= 299)
	<i>no. (%)</i>	
<b>Adverse events</b>		
Total	107 (36)	115 (38)
Headache	3 (1)	8 (3)
Gastrointestinal disorders		
Diarrhea	8 (3)	12 (4)
Nausea	22 (7)	28 (9)
Vomiting	13 (4)	15 (5)
Liver and biliary disorders		
Bilirubinemia	8 (3)	5 (2)
Increased $\gamma$ -glutamyltransferase	9 (3)	7 (2)
Increased hepatic enzymes	8 (3)	7 (2)
Increased aspartate aminotransferase	8 (3)	3 (1)
Increased alanine aminotransferase	9 (3)	4 (1)
<b>Serious adverse events</b>		
Total	40 (13)	29 (10)
Increased hepatic enzymes	6 (2)	1 (<1)
Increased $\gamma$ -glutamyltransferase	5 (2)	3 (1)
Hepatocellular damage	4 (1)	0
Bilirubinemia	3 (1)	3 (1)
Abnormal hepatic function	0	3 (1)
Vomiting	4 (1)	1 (<1)
Nausea	4 (1)	0



**Figure 1. Time to Proven or Probable Invasive Fungal Infection.**

All events not related to invasive fungal infections were considered censored; data on all patients were censored as of the end of the treatment period (day 112). The mean day of the onset of invasive fungal infection was day 102 in the posaconazole group and day 88 in the fluconazole group (P=0.048).

**Table 4. Treatment-Related Adverse Events and All-Cause Mortality during the Observation Period.\***

Event	Posaconazole Group (N= 301)	Fluconazole Group (N= 299)
	<i>no. (%)</i>	
<b>Adverse events</b>		
Total	107 (36)	115 (38)
Headache	3 (1)	8 (3)
<b>Gastrointestinal disorders</b>		
Diarrhea	8 (3)	12 (4)
Nausea	22 (7)	28 (9)
Vomiting	13 (4)	15 (5)
<b>Liver and biliary disorders</b>		
Bilirubinemia	8 (3)	5 (2)
Increased $\gamma$ -glutamyltransferase	9 (3)	7 (2)
Increased hepatic enzymes	8 (3)	7 (2)
Increased aspartate aminotransferase	8 (3)	3 (1)
Increased alanine aminotransferase	9 (3)	4 (1)
<b>Serious adverse events</b>		
Total	40 (13)	29 (10)
Increased hepatic enzymes	6 (2)	1 (<1)
Increased $\gamma$ -glutamyltransferase	5 (2)	3 (1)
Hepatocellular damage	4 (1)	0
Bilirubinemia	3 (1)	3 (1)
Abnormal hepatic function	0	3 (1)
Vomiting	4 (1)	1 (<1)
Nausea	4 (1)	0

Table 4. (Continued.)		
Event	Posaconazole Group (N = 301)	Fluconazole Group (N = 299)
	no. (%)	
<b>Deaths</b>		
All causes		
During the observation period	76 (25)	84 (28)
During the fixed treatment period	58 (19)	59 (20)
During the exposure period†	22 (8)	24 (8)
Cause of death		
Adverse event	39 (13)‡	37 (12)
Invasive fungal infection		
Complications of infection‡	4 (1)	12 (4)
Proven or probable infection§	2 (1)	11 (4)
Possible infection	2 (1)	1 (<1)
Progression of underlying disease or GVHD	31 (10)	33 (11)
Other	2 (1)	2 (1)

\* Treatment-related adverse events were those that occurred at a frequency of at least 3% in either of the two groups. Treatment-related serious adverse events were those that occurred in at least three patients. Actual totals are also shown. (For further details on treatment-related serious events, see the Supplementary Appendix.) Deaths from all causes were those that occurred during the 24-week observation period. Invasive fungal infections were adjudicated by the data review committee in a blinded fashion. The cause of death was assessed by an investigator as one of the following: an invasive fungal infection, a cause other than an invasive fungal infection but in the presence of an invasive fungal infection, or a cause other than an invasive fungal infection (without evidence on autopsy of invasive fungal infection or with clinical evidence of the resolution of an invasive fungal infection).

† Data are for 291 patients in the posaconazole group and 288 in the fluconazole group. Only one adverse event was considered by an investigator to be related to the study drug. Ninety days after posaconazole was discontinued, only a single death from multiple-organ failure occurred after cyclosporine-associated thrombotic thrombocytopenic purpura-like syndrome developed; the death was considered by the investigator to be possibly related to treatment with posaconazole.

‡ P=0.046 by the log-rank test.

§ P=0.01 by the chi-square test.

[N Engl J Med.](#) 2007 Jan 25;356(4):348-59

### Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia.

[Cornely OA](#), [Maertens J](#), [Winston DJ](#), [Perfect J](#), [Ullmann AJ](#), [Walsh TJ](#), [Helfgott D](#), [Holowiecki J](#), [Stockelberg D](#), [Goh YT](#), [Petrini M](#), [Hardalo C](#), [Suresh R](#), [Angulo-Gonzalez D](#).

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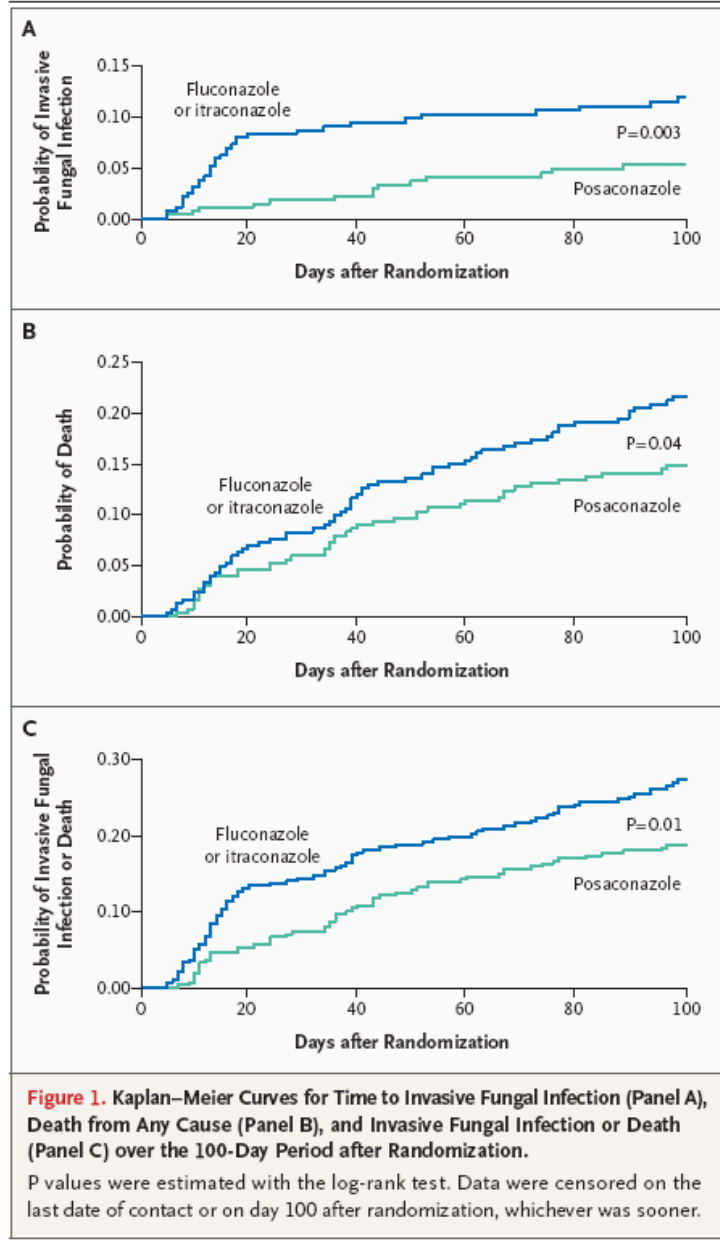
**BACKGROUND:** Patients with neutropenia resulting from chemotherapy for acute myelogenous leukemia or the myelodysplastic syndrome are at high risk for difficult-to-treat and often fatal invasive fungal infections. **METHODS:** In this randomized, multicenter study involving evaluators who were unaware of treatment assignments, we compared the efficacy and safety of posaconazole with those of fluconazole or itraconazole as prophylaxis for patients with prolonged neutropenia. Patients received prophylaxis with each cycle of chemotherapy until recovery from neutropenia and complete remission, until occurrence of an invasive fungal infection, or for up to 12 weeks, whichever came first. We compared the incidence of proven or probable invasive fungal infections during treatment (the primary end point) between the posaconazole and fluconazole or itraconazole groups; death from any cause and time to death were secondary end points. **RESULTS:** A total of 304 patients were randomly assigned to receive posaconazole, and 298 patients were randomly assigned to receive fluconazole (240) or itraconazole (58). Proven or probable invasive fungal infections were reported in 7 patients (2%) in the posaconazole group and 25 patients (8%) in the fluconazole or itraconazole group (absolute reduction in the posaconazole group, -6%; 95% confidence interval, -9.7 to -2.5%; P<0.001), fulfilling statistical criteria for superiority. Significantly fewer patients in the posaconazole group had invasive aspergillosis (2 [1%] vs. 20 [7%], P<0.001). Survival was significantly longer among recipients of posaconazole than among recipients of fluconazole or itraconazole (P=0.04). Serious adverse events possibly or probably related to treatment were reported by 19 patients (6%) in the posaconazole group and 6 patients (2%) in the fluconazole or itraconazole group (P=0.01). The most common treatment-related adverse events in both groups were gastrointestinal tract disturbances. **CONCLUSIONS:** In patients undergoing chemotherapy for acute myelogenous leukemia or the myelodysplastic syndrome, posaconazole prevented invasive fungal infections more effectively than did either fluconazole or itraconazole and improved overall survival. There were more serious adverse events possibly or

probably related to treatment in the posaconazole group. (ClinicalTrials.gov number, NCT00044486 [ClinicalTrials.gov]).  
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Publication Types:

- [Research Support, Non-U.S. Gov't](#)

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**Table 2. Proven or Probable Invasive Fungal Infection during the Treatment Phase.\***

Invasive Fungal Infection	Posaconazole (N=304)	Fluconazole or Itraconazole (N=298)	Fluconazole (N=240)	Itraconazole (N=58)	P Value	95% CI
		number (percent)				
Proven or probable†	7 (2)	25 (8)	19 (8)	6 (10)	<0.001	-9.7 to -2.5
Mold						
Invasive aspergillosis	2 (1)	20 (7)	15 (6)	5 (9)	<0.001	-9.1 to -3.1
<i>Aspergillus fumigatus</i>	0	2	1	1		
<i>A. flavus</i>	0	2	2	0		
Aspergillus species‡	2	16	12	4		
Rhizopus species	0	1	1	0		
<i>Pseudallescheria boydii</i>	0	1	1	0		
Mold, not otherwise specified	1	0	0	0		
Yeast						
Invasive candidiasis	3 (1)	2 (<1)	2 (<1)	0		
<i>Candida glabrata</i>	2	1	1	0		
<i>C. krusei</i>	0	1§	1§	0		
<i>C. parapsilosis</i>	0	1§	1§	0		
<i>C. tropicalis</i>	1	0	0	0		
Other						
<i>Pneumocystis jirovecii</i> ¶	1	1	0	1		

\* The treatment phase was defined as the period from randomization to 7 days after the last dose of the study drug had been administered during the last cycle of chemotherapy. P values were calculated with the use of the chi-square test. P values and 95% confidence intervals (CIs) are reported for the posaconazole group as compared with the pooled fluconazole and itraconazole groups.

† The global distribution of invasive fungal infection was as follows: United States, 7 patients (posaconazole group, 1 of 81; fluconazole or itraconazole group, 6 of 78), Europe, 15 patients (posaconazole, 3 of 125; fluconazole or itraconazole, 12 of 127), Canada, 0 patients, Far East, 5 patients (posaconazole, 2 of 18; fluconazole or itraconazole, 3 of 21), and Latin America, 5 patients (posaconazole, 1 of 66; fluconazole or itraconazole, 4 of 58).

‡ Microbiologic criteria for proven or probable infection with aspergillus species included a positive test for aspergillus galactomannan antigen ( $\geq 0.5$  on the galactomannan index), not necessarily a positive culture, or compatible histopathological findings.

§ Two infections were in one patient; therefore, they are counted as a single infection.

¶ *Pneumocystis pneumonia* was included even though there is no evidence that azoles, including the study drugs, act against *P. jirovecii*.

**Table 3. Clinical Response and Reasons for Failure during the Treatment Phase.\***

Clinical Response	Posaconazole (N= 304)	Fluconazole or Itraconazole (N= 298)	P Value	95% CI
	<i>no. (%)</i>			
Clinical success	195 (64)	160 (54)		
Clinical failure†	109 (36)	138 (46)	0.009	-18.3 to -2.6
Proven or probable invasive fungal infection	7 (2)	25 (8)	<0.001	-9.7 to -2.5
Use of systemic antifungal agent for ≥4 consecutive days for a suspected fungal infection‡	68 (22)	101 (34)	0.002	-18.7 to -4.3
Adverse event possibly or probably related to study treatment, resulting in discontinuation	25 (8)	25 (8)	0.94	
Use of intravenous study drug for ≥4 consecutive days or for 10 days in total	6 (2)§	12 (4)	0.14	
Withdrawal for any reason and loss to follow-up	8 (3)	1 (<1)	0.02	0.0 to 4.2

\* The treatment phase was defined as the period from randomization to 7 days after the last dose of the study drug had been administered during the last cycle of chemotherapy. P values were calculated with the use of the chi-square test. P values are reported for the posaconazole group as compared with the pooled fluconazole and itraconazole groups; related 95% confidence intervals (CIs) are provided when significance was achieved.

† Clinical failure was also defined as randomization without subsequent treatment, which accounted for 7 of the 304 patients (2%) in the posaconazole group and 6 of the 298 patients (2%) in the fluconazole or itraconazole group. Numbers of patients in each subcategory do not sum to the total because some patients had more than one type of clinical failure.

‡ Amphotericin B was the systemic antifungal agent most frequently administered to patients in both groups.

§ Seventeen patients in the posaconazole group received amphotericin B intravenously as an alternative to posaconazole; however, only six of them received it for 4 consecutive days or more or for 10 days in total.

<b>Table 4. Summary of Serious Adverse Events.*</b>				
Event	Posaconazole (N = 304)	Fluconazole or Itraconazole (N = 298)	Fluconazole (N = 240)	Itraconazole (N = 58)
Any event†				
Total	159 (52)	175 (59)	143 (60)	32 (55)
Neutropenia	22 (7)	23 (8)	18 (8)	5 (9)
Gastrointestinal hemorrhage	8 (3)	3 (1)	2 (1)	1 (2)
Bilirubinemia	7 (2)	5 (2)	4 (2)	1 (2)
Hypotension	10 (3)	21 (7)	17 (7)	4 (7)
Cardiac failure	6 (2)	3 (1)	3 (1)	0
Cardiac arrest	4 (1)	6 (2)	5 (2)	1 (2)
Cardiorespiratory arrest	4 (1)	5 (2)	4 (2)	1 (2)
Atrial fibrillation	2 (1)	6 (2)	5 (2)	1 (2)
Event possibly or probably related to treatment				
Total	19 (6)	6 (2)	4 (2)	2 (3)
Bilirubinemia	5 (2)	3 (1)	2 (1)	1 (2)
Increased hepatic enzymes	3 (1)	1 (<1)	1 (<1)	0
Increased alanine aminotransferase	1 (<1)	1 (<1)	0	1 (2)
Hepatic failure	1 (<1)	0	0	0
Hepatitis	1 (<1)	0	0	0
Hepatocellular damage	1 (<1)	0	0	0
Jaundice	1 (<1)	0	0	0
Diarrhea	1 (<1)	0	0	0
Atrial fibrillation	1 (<1)	0	0	0
Syncope	2 (1)	0	0	0
Decreased ejection fraction	1 (<1)	0	0	0
QT or QTc prolongation‡	1 (<1)	0	0	0
Torsades de pointes	1 (<1)	0	0	0
Diplopia	0	1 (<1)	1 (<1)	0

\* Events are listed for the period from randomization until 30 days after the last dose of the study drug had been administered. For a complete listing, see the Supplementary Appendix. Numbers for subentries may not sum to the total numbers because patients could have more than 1 event. QTc denotes the QT interval corrected for heart rate.

† Events listed are those with a 2% or greater incidence in the posaconazole group or in the fluconazole or itraconazole group.

‡ Prolongation was defined as a period of more than 450 msec for men and more than 470 msec for women.

[Eur J Haematol.](#) 2007 Jan 23;

### **Evaluating prophylaxis of invasive fungal infections in patients with haematologic malignancies.**

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Objective: Patients with hematologic malignancies are at substantial risk of developing invasive fungal infections (IFI) that are associated with substantial morbidity and mortality. This article reviews the epidemiology, risk factors, and efficacy of antifungal prophylaxis in patients with hematologic malignancies. Methods: A PubMed search was conducted to identify relevant studies with special emphasis on meta-analyses and direct comparisons between antifungal agents. Results: The epidemiology of IFI has changed substantially in recent years with *Candida albicans* becoming less common owing to the widespread prophylactic use of azole antifungals. Invasive aspergillosis, fusariosis, and zygomycosis have increased in frequency. This change is at least partly related to the use of broad-spectrum antifungal agents, either as prophylaxis or as empirical treatment. Other risk factors for IFI include prior fungal exposure, immunosuppression, underlying disease, graft-vs.-host disease, and organ dysfunction. Inconsistent results have been reported in studies evaluating the efficacy of antifungal prophylaxis in patients at risk of IFI. Meta-analyses found that antifungals, such as fluconazole and itraconazole,

are effective in decreasing IFI and IFI-related mortality, primarily owing to yeast infections in patients with more severe immunosuppression (i.e. patients undergoing bone marrow transplantation), but do not decrease the overall mortality. The European Conference on Infections in Leukemia (ECIL) guidelines currently recommend fluconazole (AI, ie. strongly recommended, based on at least 1 well-executed, randomized trial) and itraconazole (BI, ie. generally recommended, based on at least 1 well-executed, randomized trial) in allogeneic transplant recipients. Posaconazole, a triazole antifungal, has been recently shown to decrease IFI incidence and overall mortality in some high-risk patients compared with standard azoles. Based on preliminary data, a provisional AI ECIL recommendation has been given. Conclusions: Because of the substantial morbidity and mortality associated with IFI, there is a need to accurately define patient groups at greatest risk of IFI and, when appropriate, to initiate effective antifungal prophylaxis.

PMID: 17241370 [PubMed - as supplied by publisher]

[Clin Infect Dis](#). 2007 Jan 1;44(1):2-12. Epub 2006 Nov 28.

**Treatment of invasive aspergillosis with posaconazole in patients who are refractory to or intolerant of conventional therapy: an externally controlled trial.**

[Walsh TJ](#), [Raad I](#), [Patterson TF](#), [Chandrasekar P](#), [Donowitz GR](#), [Graybill R](#), [Greene RE](#), [Hachem R](#), [Hadley S](#), [Herbrecht R](#), [Langston A](#), [Louie A](#), [Ribaud P](#), [Segal BH](#), [Stevens DA](#), [van Burik JA](#), [White CS](#), [Corcoran G](#), [Gogate J](#), [Krishna G](#), [Pedicone L](#), [Hardalo C](#), [Perfect JR](#).

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**BACKGROUND:** Invasive aspergillosis is an important cause of morbidity and mortality in immunocompromised patients. Current treatments provide limited benefit. Posaconazole is an extended-spectrum triazole with in vitro and in vivo activity against *Aspergillus* species. **METHODS:** We investigated the efficacy and safety of posaconazole oral suspension (800 mg/day in divided doses) as monotherapy in an open-label, multicenter study in patients with invasive aspergillosis and other mycoses who were refractory to or intolerant of conventional antifungal therapy. Data from external control cases were collected retrospectively to provide a comparative reference group. **RESULTS:** Cases of aspergillosis deemed evaluable by a blinded data review committee included 107 posaconazole recipients and 86 control subjects (modified intent-to-treat population). The populations were similar and balanced with regard to prespecified demographic and disease variables. The overall success rate (i.e., the data review committee-assessed global response at the end of treatment) was 42% for posaconazole recipients and 26% for control subjects (odds ratio, 4.06; 95% confidence interval, 1.50-11.04; P=.006). The differences in response between the modified intent-to-treat treatment groups were preserved across additional, prespecified subsets, including infection site (pulmonary or disseminated), hematological malignancy, hematopoietic stem cell transplantation, baseline neutropenia, and reason for enrollment (patient was refractory to or intolerant of previous antifungal therapy). An exposure-response relationship was suggested by pharmacokinetic analyses. **CONCLUSIONS:** Although the study predates extensive use of echinocandins and voriconazole, these findings demonstrate that posaconazole is an alternative to salvage therapy for patients with invasive aspergillosis who are refractory to or intolerant of previous antifungal therapy.

Publication Types:

- [Clinical Trial](#)
- [Multicenter Study](#)
- [Research Support, Non-U.S. Gov't](#)

PMID: 17143808 [PubMed - indexed for MEDLINE]

[Curr Opin Microbiol](#). 2006 Oct;9(5):483-8. Epub 2006 Aug 9

**Clinical efficacy of new antifungal agents.**

[Kauffman CA](#).

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Several new options are now available for treating serious fungal infections. All three echinocandin agents currently available have been shown in randomized, blinded clinical trials to be efficacious in treating candidemia and invasive candidiasis. By contrast, the demonstrated efficacy of the echinocandins for the treatment of invasive aspergillosis has been based on

historically controlled salvage treatment trials in patients failing or intolerant of other therapies. The new triazole agents, voriconazole and posaconazole, have a broad spectrum of antifungal activity. Voriconazole has become the agent of choice for invasive aspergillosis. On the basis of compassionate treatment data, posaconazole appears to be effective for treatment of zygomycosis. These agents have also been shown to be effective in the treatment of non-Aspergillus mould infections, several of the endemic mycoses and serious Candida infections.

[Med Mycol.](#) 2005 Mar;43(2):179-85

**In vitro activities of posaconazole, ravuconazole, terbinafine, itraconazole and fluconazole against dermatophyte, yeast and non-dermatophyte species.**

[Gupta AK](#), [Kohli Y](#), [Batra R](#).

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The in vitro activities of two new triazole antifungal agents with broad-spectrum antifungal activity, posaconazole and ravuconazole, were compared with those of three well-established antifungal agents, terbinafine, itraconazole and fluconazole, against 184 clinical isolates. These included 129 dermatophyte isolates (twelve species), 25 yeast isolates (five species) and 28 non-dermatophyte isolates (nine species). In vitro testing was conducted using microdilution plates with RPMI 1640 and National Committee for Clinical Laboratory Standards (NCCLS) guidelines (M27-38P) were followed, except for the preparation of the dermatophyte inoculum. Both posaconazole and ravuconazole showed similar broad-spectrum activity against dermatophyte, yeast and non-dermatophyte species. Mean inhibitory concentrations (MIC) at which 90% [MIC<sub>90</sub>] of the isolates were inhibited by posaconazole and ravuconazole were 0.25 and 0.5 microg/ml for dermatophytes, 0.5 and 0.25 microg/ml for yeasts, and >4 and 8 microg/ml for non-dermatophytes. The MIC ranges against Trichophyton (six species), Microsporum (five species) and Epidermophyton floccosum were: posaconazole (0.007-1.0/0.007-0.25/0.007-1.0 microg/ml), ravuconazole (0.015-8.0/0.015-1.0/0.015-1.0 microg/ml), itraconazole (0.015->8.0/0.015-0.5/0.015-8.0 microg/ml), fluconazole (0.125- >64.0/4.0 >64.0/0.5-64.0 microg/ml) and terbinafine (0.003 >2.0/0.007-2.0/0.007 >2.0 microg/ml). Overall ranking of the antifungal activity of the five antifungal agents was: terbinafine > posaconazole > ravuconazole > itraconazole > fluconazole, for dermatophytes; ravuconazole > posaconazole > itraconazole > fluconazole > terbinafine, against yeasts; and posaconazole > ravuconazole > terbinafine > itraconazole > fluconazole, for non-dermatophytes.

Publication Types:

- [Comparative Study](#)

PMID: 15832561 [PubMed - indexed for MEDLINE]

[Clin Infect Dis.](#) 2006 Jun 15;42(12):1726-34. Epub 2006 May 8.

**Safety of long-term oral posaconazole use in the treatment of refractory invasive fungal infections.**

[Raad II](#), [Graybill JR](#), [Bustamante AB](#), [Cornely OA](#), [Gaona-Flores V](#), [Afif C](#), [Graham DR](#), [Greenberg RN](#), [Hadley S](#), [Langston A](#), [Negroni R](#), [Perfect JR](#), [Pitisuttithum P](#), [Restrepo A](#), [Schiller G](#), [Pedicone L](#), [Ullmann AJ](#).

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**BACKGROUND:** Invasive fungal infections are found most frequently in immunosuppressed and critically ill hospitalized patients. Antifungal therapy is often required for long periods. Safety data from the clinical development program of the triazole antifungal agent, posaconazole, were analyzed. **METHODS:** A total of 428 patients with refractory invasive fungal infections (n = 362) or febrile neutropenia (n = 66) received posaconazole in 2 phase II/III open-label clinical trials. Also, 109 of these patients received posaconazole therapy for > or = 6 months. Incidences of treatment-emergent, treatment-related, and serious adverse events and abnormal laboratory parameters were recorded during these studies. **RESULTS:** Treatment-emergent, treatment-related adverse events were reported in 38% of the overall patient population. *The most common treatment-related adverse events were nausea (8%) and vomiting (6%). Treatment-related serious adverse events occurred in 8% of patients. Low rates of treatment-related corrected QT interval and/or QT interval prolongation (1%) and elevation of hepatic enzymes (2%) were reported as adverse events.* Treatment-emergent, treatment-related adverse events occurred at similar rates in patients who received posaconazole therapy for < 6 months and > or = 6 months. **CONCLUSIONS:** Prolonged posaconazole treatment was associated with a generally favorable safety profile in seriously ill patients with refractory invasive fungal infections. Long-term therapy did not increase the risk of any individual adverse event, and no unique adverse event was observed with longer exposure to posaconazole.

Publication Types:

- [Controlled Clinical Trial](#)

PMID: 16705579 [PubMed - indexed for MEDLINE]

[Antimicrob Agents Chemother.](#) 2006 May;50(5):1881-3

**Effect of a nutritional supplement on posaconazole pharmacokinetics following oral administration to healthy volunteers.**

[Sansone-Parsons A](#), [Krishna G](#), [Calzetta A](#), [Wexler D](#), [Kantesaria B](#), [Rosenberg MA](#), [Saltzman MA](#).

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We conducted a randomized, crossover study in healthy adults to examine the effects of a nutritional supplement (Boost Plus) on posaconazole pharmacokinetics. In this study, coadministration of posaconazole with Boost Plus increased the maximum concentration of posaconazole in serum and area under the concentration-time curve from 0 to 72 h values 3.4- and 2.6-fold, respectively, compared to those for the fasted state.

Publication Types:

- [Randomized Controlled Trial](#)

PMID: 16641468 [PubMed - indexed for MEDLINE]

[Clin Infect Dis.](#) 2006 May 15;42(10):1398-403. Epub 2006 Apr 11

**Posaconazole as salvage treatment for invasive fusariosis in patients with underlying hematologic malignancy and other conditions.**

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**BACKGROUND:** Conventional amphotericin B-based antifungal therapy for invasive fusariosis in patients with a hematologic malignancy results in a > or = 70% failure rate. Posaconazole is a broad-spectrum antifungal agent with in vitro and in vivo activity against *Fusarium* species. **METHODS:** In this retrospective analysis of patients from 3 open-label clinical trials, we evaluated posaconazole for the treatment of invasive fusariosis. Twenty-one patients with proven or probable invasive fusariosis who had disease refractory to or who were intolerant of standard antifungal therapy received oral posaconazole suspension (800 mg per day in divided doses) as salvage therapy. **RESULTS:** *Successful outcome occurred in 10 (48%) of all 21 patients. Among patients with leukemia who received posaconazole therapy for >3 days, the overall success rate was 50%; for patients who recovered from myelosuppression, the success rate was 67%, compared with 20% for those with persistent neutropenia.* **CONCLUSION:** These results suggest that posaconazole is useful for the treatment of invasive fusariosis.

Publication Types:

- [Clinical Trial](#)
- [Multicenter Study](#)

PMID: 16619151 [PubMed - indexed for MEDLINE]

[Clin Infect Dis.](#) 2006 Apr 15;42(8):1179-86. Epub 2006 Mar 14.

Comment in:

- [Clin Infect Dis. 2006 Apr 15;42\(8\):1187-8.](#)

**A multicenter randomized trial evaluating posaconazole versus fluconazole for the treatment of oropharyngeal candidiasis in subjects with HIV/AIDS.**

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**BACKGROUND:** Oropharyngeal candidiasis is the most common opportunistic infection among persons infected with human immunodeficiency virus (HIV). Use of some agents is hampered by lack of efficacy, emergence of resistance, adverse events, and need for intravenous administration. Posaconazole is an extended-spectrum triazole with potent in vitro activity against *Candida* species, including *Candida albicans*, *Candida glabrata*, and *Candida krusei* (including fluconazole-resistant strains). **METHODS:** This multicenter, randomized, evaluator-blinded study of subjects with HIV infection and oropharyngeal candidiasis compared efficacy of posaconazole with that of fluconazole. Subjects received either 200 mg of posaconazole or fluconazole oral suspension on day 1, followed by 100 mg/day for 13 days. The primary study end point--clinical success (cure or improvement) on day 14--was evaluated for 329 subjects. Durability of clinical success was evaluated on day 42. **RESULTS:** Three hundred fifty subjects received posaconazole (n = 178) or fluconazole (n = 172). Clinical success occurred in 155 (91.7%) of 169 posaconazole recipients and in 148 (92.5%) of 160 fluconazole recipients (95% confidence interval, -6.61% to 5.04%), indicating that posaconazole was not inferior to fluconazole. On day 14, mycological success was 68% in both arms, but by day 42, significantly more posaconazole recipients than fluconazole recipients continued to have mycological success (40.6% vs. 26.4%; P=.038). Fewer posaconazole recipients than fluconazole recipients experienced clinical relapse (31.5% vs. 38.2%). Adverse events were similar between treatment arms. **CONCLUSIONS:** Results demonstrate that posaconazole was as effective as fluconazole in producing a successful clinical outcome. However, posaconazole was more effective in sustaining clinical success after treatment was stopped.

Publication Types:

- [Multicenter Study](#)
- [Randomized Controlled Trial](#)

PMID: 16575739 [PubMed - indexed for MEDLINE]  
[Rev Inst Med Trop Sao Paulo](#). 2005 Nov-Dec;47(6):339-46.

**Posaconazole treatment of refractory eumycetoma and chromoblastomycosis.**

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Eumycetoma and chromoblastomycosis are chronic, disfiguring fungal infections of the subcutaneous tissue that rarely resolve spontaneously. Most patients do not achieve sustained long-term benefits from available treatments; therefore, new therapeutic options are needed. We evaluated the efficacy of posaconazole, a new extended-spectrum triazole antifungal agent, in 12 patients with eumycetoma or chromoblastomycosis refractory to existing antifungal therapies. Posaconazole 800 mg/d was given in divided doses for a maximum of 34 months. Complete or partial clinical response was considered a success; stable disease or failure was considered a nonsuccess. All 12 patients had proven infections refractory to standard therapy. Clinical success was reported for five of six patients with eumycetoma and five of six patients with chromoblastomycosis. Two patients were reported to have stable disease. As part of a treatment-use extension protocol, two patients with eumycetoma who initially had successful outcome were successfully retreated with posaconazole after a treatment hiatus of > 10 months. Posaconazole was well tolerated during long-term administration (up to 1015 d). Posaconazole therapy resulted in successful outcome in most patients with eumycetoma or chromoblastomycosis refractory to standard therapies, suggesting that posaconazole may be an important treatment option for these diseases.

Publication Types:

- [Case Reports](#)
- [Multicenter Study](#)

PMID: 16553324 [PubMed - indexed for MEDLINE]

[Antimicrob Agents Chemother](#). 2006 Feb;50(2):658-66

**Pharmacokinetics, safety, and efficacy of posaconazole in patients with persistent febrile neutropenia or refractory invasive fungal infection.**

[Ullmann AJ](#), [Cornely OA](#), [Burchardt A](#), [Hachem R](#), [Kontoviannis DP](#), [Topelt K](#), [Courtney R](#), [Wexler D](#), [Krishna G](#), [Martinho M](#), [Corcoran G](#), [Raad I](#).

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The pharmacokinetic profiles, safety, and efficacies of different dosing schedules of posaconazole oral suspension in patients with possible, probable, and proven refractory invasive fungal infection (rIFI) or febrile neutropenia (FN) were evaluated in a multicenter, open-label, parallel-group study. Sixty-six patients with FN and 32 patients with rIFI were randomly assigned to one of three posaconazole regimens: 200 mg four times a day (q.i.d.) for nine doses, followed by 400 mg twice a day (b.i.d.); 400 mg q.i.d. for nine doses, followed by 600 mg b.i.d.; or 800 mg b.i.d. for five doses, followed by 800 mg once a day (q.d.). Therapy was continued for up to 6 months in patients with rIFI or until neutrophil recovery occurred in patients with FN. *The 400-mg-b.i.d. dose provided the highest overall mean exposure, with 135% ( $P = 0.0004$ ) and 182% ( $P < 0.0001$ ) greater exposure than the 600-mg-b.i.d. and 800-mg-q.d. doses, respectively.* However, exposure in allogeneic bone marrow transplant (BMT) recipients ( $n = 12$ ) was 52% lower than in non-BMT patients. Treatment-related adverse events (occurring in 24% of patients) were mostly gastrointestinal in nature. Twenty-four percent of patients had adverse events leading to premature discontinuation (none were treatment related). In efficacy-evaluable patients, successful clinical response was observed in 43% with rIFI (56% of patients receiving 400 mg b.i.d., 17% receiving 600 mg b.i.d., and 50% receiving 800 mg q.d.) and 77% with FN (74% receiving 400 mg b.i.d., 78% receiving 600 mg b.i.d., and 81% receiving 800 mg q.d.). Posaconazole is well tolerated and absorbed. Divided doses of 800 mg (400 mg b.i.d.) provide the greatest posaconazole exposure.

Publication Types:

- [Multicenter Study](#)
- [Randomized Controlled Trial](#)

PMID: 16436724 [PubMed - indexed for MEDLINE]

[Antimicrob Agents Chemother.](#) 2006 Jan;50(1):126-33

**Posaconazole as salvage therapy for zygomycosis.**

[Greenberg RN](#), [Mullane K](#), [van Burik JA](#), [Raad I](#), [Abzug MJ](#), [Anstead G](#), [Herbrecht R](#), [Langston A](#), [Marr KA](#), [Schiller G](#), [Schuster M](#), [Wingard JR](#), [Gonzalez CE](#), [Revankar SG](#), [Corcoran G](#), [Krvscio RJ](#), [Hare R](#).

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Zygomycosis, an infection that is associated with significant morbidity and mortality, is becoming common in immunocompromised patients. Posaconazole is a new extended-spectrum azole antifungal that has demonstrated in vitro and in vivo activity against zygomycetes. This report provides the results from the first 24 patients with active zygomycosis who were enrolled in two open-label, nonrandomized, multicentered compassionate trials that evaluated oral posaconazole as salvage therapy for invasive fungal infections. Posaconazole was usually given as an oral suspension of 200 mg four times a day or 400 mg twice a day. Eleven (46%) of the infections were rhinocerebral. Duration of posaconazole therapy ranged from 8 to 1,004 days (mean, 292 days; median, 182 days). Rates of successful treatment (complete cure and partial response) were 79% in 19 subjects with zygomycosis refractory to standard therapy and 80% in 5 subjects with intolerance to standard therapy. Overall, 19 of 24 subjects (79%) survived infection. Survival was also associated with surgical resection of affected tissue and stabilization or improvement of the subjects' underlying illnesses. Failures either had worsening of underlying illnesses or requested all therapy withdrawn; none of the failures received more than 31 days of posaconazole. Posaconazole oral solution was well tolerated and was discontinued in only one subject due to a drug rash. Posaconazole appears promising as an oral therapy for zygomycosis in patients who receive required surgery and control their underlying illness.

Publication Types:

- [Controlled Clinical Trial](#)

PMID: 16377677 [PubMed - indexed for MEDLINE]

[J Clin Microbiol](#). 2005 Oct;43(10):5243-6 **Quality control and reference guidelines for CLSI broth microdilution susceptibility method (M 38-A document) for amphotericin B, itraconazole, posaconazole, and voriconazole.**

[Espinel-Ingroff A](#), [Fothergill A](#), [Ghannoum M](#), [Manavathu E](#), [Ostrosky-Zeichner L](#), [Pfaller M](#), [Rinaldi M](#), [Schell W](#), [Walsh T](#).

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Although standard conditions are available for testing the susceptibilities of filamentous fungi to antifungal agents by the Clinical and Laboratory Standards Institute (CLSI; formerly National Committee for Clinical Laboratory Standards) broth microdilution assay, quality control (QC) MIC limits have not been established for any mold-agent combination. This multicenter (eight-center) study documented the reproducibility of tests for one isolate of *Paecilomyces variotii* ATCC MYA-3630 and 11 other mold isolates (three isolates of *Aspergillus fumigatus*; two isolates of *A. terreus*; one isolate each of *A. flavus*, *A. nidulans*, *Fusarium moniliforme*, and *F. solani*; and two isolates of *Scedosporium apiospermum*) by the CLSI reference broth microdilution method (M 38-A document). Control limits (amphotericin B, 1 to 4 microg/ml; itraconazole, 0.06 to 0.5 microg/ml; posaconazole, 0.03 to 0.25 microg/ml; voriconazole, 0.015 to 0.12 microg/ml) for the selected QC *P. variotii* ATCC MYA-3630 were established by the analysis of replicate MIC results. Reference isolates and corresponding MIC ranges were also established for 6 of the 12 molds evaluated. MIC limits were not proposed for the other five molds tested due to low testing reproducibility for these isolates.

Publication Types:

- [Multicenter Study](#)

PMID: 16207990 [PubMed - indexed for MEDLINE]

[J Clin Microbiol](#). 2005 Sep;43(9):4535-40

**Comparison of visual 24-hour and spectrophotometric 48-hour MICs to CLSI reference microdilution MICs of fluconazole, itraconazole, posaconazole, and voriconazole for *Candida* spp.: a collaborative study.**

[Espinel-Ingroff A](#), [Barchiesi F](#), [Cuenca-Estrella M](#), [Fothergill A](#), [Pfaller MA](#), [Rinaldi M](#), [Rodriguez-Tudela JL](#), [Verweij PE](#).

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A multicenter (six-center) study evaluated the performance (interlaboratory reproducibility, compatibility with reference methods, and categorical agreement) of 24-h visual and 48-h spectrophotometric MICs. MICs of fluconazole, itraconazole, voriconazole, and posaconazole were compared to reference 48-h microdilution broth visual MICs (CLSI [formerly NCCLS] M27-A2 document) for 71 isolates of *Candida* spp. that included 10 fluconazole-resistant strains. Twenty readings (5%) were reported as showing no growth at 24 h, mostly for *Candida dubliniensis* and from a single center. The overall interlaboratory agreement of 24-h visual readings and 48-h spectrophotometric MICs, as well their compatibility with reference values, were excellent with the four triazoles for most of the species (93 to 99%, within 3 dilutions). The categorical agreement between the investigational reading conditions and reference values was good with fluconazole and voriconazole (93 to 97%) but lower with itraconazole (86 to 88%), due primarily to minor errors. There were only 0 to 3% very major errors with these three triazoles; the number of substantial errors (more than three dilutions) was also low (<2%) with posaconazole. These data suggest that the performance of both investigational MIC readings gives results similar to those of reference MICs. Since spectrophotometric MICs are more objective and the 24-h time period would shorten the MIC determination of azoles, the description of either of these two reading conditions in the M27-A2 document should be considered by the CLSI subcommittee in addition to or instead of the longer, less practical, and more subjective 48-h visual MIC reading.

Publication Types:

- [Evaluation Studies](#)
- [Multicenter Study](#)

PMID: 16145103 [PubMed - indexed for MEDLINE]

[J Antimicrob Chemother.](#) 2005 Oct;56(4):745-55. Epub 2005 Aug 31

**Activity of posaconazole in the treatment of central nervous system fungal infections.**

[Pitisuttithum P.](#), [Negroni R.](#), [Graybill JR.](#), [Bustamante B.](#), [Pappas P.](#), [Chapman S.](#), [Hare RS.](#), [Hardalo CJ.](#)

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**OBJECTIVES:** A multinational, multicentre, open-label clinical trial was conducted to evaluate the safety and efficacy of posaconazole, an extended-spectrum triazole antifungal agent, in subjects with invasive fungal infections who had refractory disease or who were intolerant of standard antifungal therapy. In this subanalysis, we report on those subjects in this trial who had a fungal infection that involved the CNS. **METHODS:** Subjects received posaconazole oral suspension 800 mg/day in divided doses for up to 1 year; however, subjects could receive additional therapy as part of a treatment-use extension protocol. A blinded, third-party data review committee determined subject eligibility and outcome. **RESULTS:** Of the 330 subjects who enrolled in the study, 53 had infections of the CNS, of which 39 were considered evaluable for efficacy. Most had refractory disease (37 of 39) and underlying HIV infection (29 of 39). Twenty-nine subjects had cryptococcal infections, and 10 had infections caused by other fungal pathogens [*Aspergillus* spp. (four), *Pseudallescheria boydii* (two), *Coccidioides immitis* (one), *Histoplasma capsulatum* (one), *Ramichloridium mackenziei* (one), and *Apophysomyces elegans* plus a *Basidiomycetes* sp. (one)]. Successful outcomes were observed in 14 of 29 (48%) subjects with cryptococcal meningitis and five of 10 (50%) subjects with CNS infections due to other fungal pathogens. Posaconazole was well tolerated. **CONCLUSIONS:** These data suggest that posaconazole, as an oral medication, has clinical activity against fungal infections of the CNS and may provide a valuable alternative to parenteral therapy in patients failing existing antifungal agents.

Publication Types:

- [Clinical Trial](#)
- [Multicenter Study](#)

PMID: 16135526 [PubMed - indexed for MEDLIN]

[J Clin Microbiol.](#) 2005 Aug;43(8):3884-9

**International and multicenter comparison of EUCAST and CLSI M27-A2 broth microdilution methods for testing susceptibilities of *Candida* spp. to fluconazole, itraconazole, posaconazole, and voriconazole.**

[Espinell-Ingroff A.](#), [Barchiesi F.](#), [Cuenca-Estrella M.](#), [Pfaller MA.](#), [Rinaldi M.](#), [Rodriguez-Tudela JL.](#), [Verweij PE.](#)

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The aim of this study was to compare MICs of fluconazole, itraconazole, posaconazole, and voriconazole obtained by the European Committee on Antibiotic Susceptibility Testing (EUCAST) and CLSI (formerly NCCLS) methods in each of six centers for 15 *Candida albicans* (5 fluconazole-resistant and 4 susceptible-dose-dependent [S-DD] isolates), 10 *C. dubliniensis*, 7 *C. glabrata* (2 fluconazole-resistant isolates), 5 *C. guilliermondii* (2 fluconazole-resistant isolates), 10 *C. krusei*, 9 *C. lusitanae*, 10 *C. parapsilosis*, and 5 *C. tropicalis* (1 fluconazole-resistant isolate) isolates. CLSI MICs were obtained visually at 24 and 48 h and spectrophotometric EUCAST MICs at 24 h. The agreement (within a 3-dilution range) between the methods was species, drug, and incubation time dependent and due to lower EUCAST than CLSI MICs: overall, 94 to 95% with fluconazole and voriconazole and 90 to 91% with posaconazole and itraconazole when EUCAST MICs were compared against 24-h CLSI results. The agreement was lower (85 to 94%) against 48-h CLSI endpoints. The overall interlaboratory reproducibility by each method was  $\geq 92\%$ . When the comparison was based on CLSI breakpoint categorization, the agreement was 68 to 76% for three of the four species that included fluconazole-resistant and S-DD isolates; 9% very major discrepancies ( $< \text{or} = 8$  microg/ml versus  $> \text{or} = 64$  microg/ml) were observed among fluconazole-resistant isolates and 50% with voriconazole ( $< \text{or} = 1$  microg/ml versus  $> \text{or} = 4$  microg/ml). Similar results were observed with itraconazole for seven of the eight species evaluated (28 to 77% categorical agreement). Posaconazole EUCAST MICs were also substantially lower than CLSI MIC modes (0.008 to 1 microg/ml versus 1 to  $> \text{or} = 8$  microg/ml) for some of these

isolates. Therefore, the CLSI breakpoints should not be used to interpret EUCAST MIC data.

Publication Types:

- [Multicenter Study](#)

PMID: 16081926 [PubMed - indexed for MEDLINE]

[Clin Infect Dis](#). 2005 Jun 1;40(11):1684-8. Epub 2005 Apr 29

**Posaconazole as salvage therapy in patients with chronic granulomatous disease and invasive filamentous fungal infection.**

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Chronic granulomatous disease (CGD) is characterized by life-threatening bacterial and fungal infections. Treatment with posaconazole led to a complete response in 7 of 8 patients with CGD with invasive mold infections (7 proven cases and 1 possible case) after failure or intolerance of treatment with standard antifungal agents. In this preliminary study, salvage treatment with posaconazole was safe and effective.

Publication Types:

- [Clinical Trial](#)

PMID: 15889369 [PubMed - indexed for MEDLINE]

[J Clin Microbiol](#). 2005 May;43(5):2163-7

**Global trends in the antifungal susceptibility of *Cryptococcus neoformans* (1990 to 2004).**

[Pfaller MA](#), [Messer SA](#), [Boyken L](#), [Rice C](#), [Tendolkar S](#), [Hollis RJ](#), [Doern GV](#), [Diekema DJ](#).

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The antifungal susceptibilities of 1,811 clinical isolates of *Cryptococcus neoformans* obtained from 100 laboratories in 5 geographic regions worldwide between 1990 and 2004 were determined. The MICs of amphotericin B, flucytosine, fluconazole, voriconazole, posaconazole, and ravuconazole were determined by the National Committee for Clinical Laboratory Standards broth microdilution method. Isolates were submitted to a central reference laboratory (University of Iowa) from study centers in Africa (5 centers, 395 isolates), Europe (14 centers, 102 isolates), Latin America (14 centers, 82 isolates), the Pacific region (7 centers, 50 isolates), and North America (60 centers, 1,182 isolates). Resistance to amphotericin B, flucytosine, and fluconazole was  $\leq 1\%$  overall. Susceptibility to flucytosine (MIC,  $\leq 4$  microg/ml) ranged from 35% in North America to 68% in Latin America. Similarly, only 75% of isolates from North America were susceptible to fluconazole (MIC,  $\leq 8$  microg/ml) compared to 94 to 100% in the other regions. Isolates remained highly susceptible to amphotericin B (99% susceptibility at a MIC of  $\leq 1$  microg/ml) over the entire 15-year period. Susceptibility to flucytosine (MIC,  $\leq 4$  microg/ml) increased from 34% in 1990 to 1994 to 66% in 2000 to 2004. Susceptibility to fluconazole (MIC,  $\leq 8$  microg/ml) increased from 72% in 1990 to 1994 to 96% in 2000 to 2004. Voriconazole, posaconazole, and ravuconazole all were very active (99% of isolates susceptible at MIC of  $\leq 1$  microg/ml) against this geographically diverse collection of isolates. We conclude that in vitro resistance to antifungal agents used in the treatment of cryptococcosis remains uncommon among isolates of *C. neoformans* from five broad geographic regions and has not increased over a 15-year period.

Publication Types:

- [Multicenter Study](#)

PMID: 15872236 [PubMed - indexed for MEDLINE]

[Clin Pharmacokinet](#). 2005;44(2):211-20.

**Oral bioavailability of posaconazole in fasted healthy subjects: comparison between three regimens and basis for clinical dosage recommendations.**

[Ezzet F](#), [Wexler D](#), [Courtney R](#), [Krishna G](#), [Lim J](#), [Laughlin M](#).

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**BACKGROUND AND OBJECTIVE:** Posaconazole is a potent, extended-spectrum triazole antifungal agent currently in clinical development for the treatment of invasive fungal infections. This study was conducted to compare the bioavailability and resulting serum concentrations of posaconazole 800 mg following administration of three different dose regimens to fasting adults. **STUDY DESIGN:** This was a randomised, open-label, three-way crossover study. **METHODS:** Subjects fasted 12 hours before and 48 hours after the administration of posaconazole oral suspension (800 mg) given as a single dose (regimen A), 400 mg every 12 hours (regimen B) or 200 mg every 6 hours (regimen C). Plasma posaconazole concentrations were determined for 48 hours after the initial dose and subjects completed a 1-week washout period between treatment regimens. A one-compartment oral model with first-order rate of absorption and first-order rate of elimination was fitted to the plasma concentration-time data. Differences in exposure were investigated by allowing the bioavailability fraction to vary among regimens. **STUDY PARTICIPANTS:** A total of 18 healthy men were enrolled in and completed the study. **MAIN OUTCOME MEASURES AND RESULTS:** Posaconazole relative bioavailability was estimated to be significantly different among regimens ( $p < 0.0001$ ) and increased with the number of doses, such that regimen B/regimen A = 1.98 +/- 0.35, representing a 98% increase, and regimen C/regimen A = 3.20 +/- 0.69, or a 220% increase. With use of the one-compartment model, the population steady-state values for area under the concentration-time curve over 24 hours were predicted to be 3900, 7700 and 12 400 microg.h/L, with average plasma concentrations of 162, 320 and 517 microg/L for regimens A, B and C, respectively. **CONCLUSION:** These data suggest that divided daily dose administration (every 12 or 6 hours) significantly increases posaconazole exposure under fasted conditions.

Publication Types:

- [Clinical Trial](#)
- [Randomized Controlled Trial](#)

PMID: 15656699 [PubMed - indexed for MEDLINE]

[J Clin Pharmacol](#). 2005 Feb;45(2):185-92

**Posaconazole pharmacokinetics, safety, and tolerability in subjects with varying degrees of chronic renal disease.**

[Courtney R](#), [Sansone A](#), [Smith W](#), [Marbury T](#), [Statkevich P](#), [Martinho M](#), [Laughlin M](#), [Swan S](#).

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Posaconazole is a triazole antifungal in development for the treatment of invasive fungal infections. The authors evaluated the pharmacokinetics and safety of posaconazole in healthy subjects and in those with mild ( $CL(CR) = 50-80$  mL/min), moderate ( $CL(CR) = 20-49$  mL/min), and severe chronic renal disease ( $CL(CR) < 20$  mL/min; receiving outpatient hemodialysis) ( $n = 6$ /group). Subjects received one 400-mg dose of posaconazole oral suspension with a standardized high-fat breakfast. For hemodialysis-dependent subjects, this dose was given on a nonhemodialysis day, and a second 400-mg dose was given 6 hours before hemodialysis. Blood samples were collected before dose and up to 120 hours postdose. For hemodialysis-dependent subjects following the second dose, additional samples (predialyzed and postdialyzed) were collected before, during, and after dialysis. There was no correlation between posaconazole pharmacokinetics and mild to moderate renal disease; the slopes of the linear regressions for creatinine clearance versus posaconazole AUC,  $C(max)$ ,  $CL/F$ , and  $t_{1/2}$  values were not significantly different from zero ( $P > .130$ ). Mean  $CL/F$  values before and during hemodialysis were comparable. Furthermore, the difference in the predialyzed and postdialyzed posaconazole concentrations was only approximately 3%, supporting that posaconazole was not removed by hemodialysis. Protein binding was similar in all groups (approximately 98%) and was unaffected by hemodialysis. Posaconazole was generally well tolerated. One patient had elevated liver function test results that were not present at baseline and were thought to be possibly related to posaconazole. Results of this single-dose study indicate that dosage adjustments for patients with varying degrees of renal disease are not required.

Publication Types:

- [Clinical Trial](#)
- [Controlled Clinical Trial](#)

PMID: 15647411 [PubMed - indexed for MEDLINE]

[Antimicrob Agents Chemother](#). 2004 Sep;48(9):3543-51

**Disposition of posaconazole following single-dose oral administration in healthy subjects.**

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Posaconazole is a potent, broad-spectrum triazole antifungal agent currently in clinical development for the treatment of refractory invasive fungal infections. Eight healthy male subjects received a single 399-mg (81.7 microCi) oral dose of [(14)C]posaconazole after consuming a high-fat breakfast. Urine, feces, and blood samples were collected for up to 336 h postdose and assayed for total radioactivity; plasma and urine samples were also assayed for parent drug. Posaconazole was orally bioavailable, with a median maximum posaconazole concentration in plasma achieved by 10 h postdose. Thereafter, posaconazole was slowly eliminated, with a mean half-life of 20 h. The greatest peak in the radioactivity profile of pooled plasma extracts was due to posaconazole, with smaller peaks due to a monoglucuronide, a diglucuronide, and a smaller fragment of the molecule. The mean total amount of radioactivity recovered was 91.1%; the cumulative excretion of radioactivity in feces and in urine was 76.9 and 14.0% of the dose, respectively. Most of the fecal radioactivity was associated with posaconazole, which accounted for 66.3% of the administered dose; however, urine contained only trace amounts of unchanged posaconazole. The radioactivity profile of pooled urine extracts included two monoglucuronide conjugates and a diglucuronide conjugate of posaconazole. These observations suggest that oxidative (phase 1) metabolism by cytochrome P450 isoforms represents only a minor route of elimination for posaconazole, and therefore cytochrome P450-mediated drug interactions should have a limited potential to impact posaconazole pharmacokinetics.

Publication Types:

- [Clinical Trial](#)

PMID: 15328123 [PubMed - indexed for MEDLINE]

[Eur J Pharm Sci](#). 2004 Apr;21(5):645-53

**Effect of posaconazole on cytochrome P450 enzymes: a randomized, open-label, two-way crossover study.**

[Wexler D](#), [Courtney R](#), [Richards W](#), [Banfield C](#), [Lim J](#), [Laughlin M](#).

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Posaconazole is an antifungal with a wide-spectrum of activity against common and emerging fungal pathogens. In this randomised, open-label, two-way crossover study, the potential for drug interactions with posaconazole via the cytochrome P450 (CYP450) enzyme pathway was evaluated. Thirteen subjects received posaconazole tablets (2 x 100 mg) once daily for 10 days or no treatment; following a 14-day washout period, subjects were crossed over to the alternate treatment. The inhibition spectra of posaconazole were examined using a cocktail of the following probe substrates: caffeine (CYP1A2), tolbutamide (CYP2C8/9), dextromethorphan (CYP2D6 and total CYP3A4), chlorzoxazone (CYP2E1), and midazolam (hepatic CYP3A4). Except for midazolam, which was intravenously infused on Day 10, the cocktail probes were administered simultaneously on Day 9 during both treatment periods. Blood and urine samples were collected at specified times to quantitate probe substrates and/or metabolites. Based on insignificant differences in mean probe ratios, posaconazole did not inhibit CYP1A2, 2C8/9, 2D6, or 2E1. However, the midazolam AUC((tf)) was higher in the posaconazole than no-

treatment group (93.4 ng/ml versus 51.4 ng/ml,  $P < 0.01$ ), indicating inhibition of hepatic CYP3A4. Drug interactions mediated by various CYP450 are common with the currently available triazole antifungals, however these results suggest that posaconazole may have an improved and more narrow drug interaction profile (CYP3A4 only) compared with other triazoles.

Publication Types:

- [Clinical Trial](#)
- [Randomized Controlled Trial](#)

PMID: 15066665 [PubMed - indexed for MEDLINE]

[Antimicrob Agents Chemother.](#) 2004 Mar;48(3):804-8

**Pharmacokinetics of posaconazole coadministered with antacid in fasting or nonfasting healthy men.**

[Courtney R](#), [Radwanski E](#), [Lim J](#), [Laughlin M](#).

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Posaconazole is a potent broad-spectrum azole antifungal agent in clinical development for the treatment of invasive fungal infections. This study evaluated the potential for a pH-dependent pharmacokinetic interaction between posaconazole and an antacid (Mylanta), under fasting and nonfasting conditions. Twelve men completed this randomized, four-period crossover, single-dose study. Subjects received 200 mg of posaconazole following a 10-h fast, with 20 ml of Mylanta and a 10-h fast, with 20 ml of Mylanta and a high-fat breakfast, and with a high-fat breakfast alone. Antacid coadministration had no statistically significant effects on posaconazole bioavailability under fasting or nonfasting conditions. In the fasting state, antacid slightly increased the relative oral bioavailability of posaconazole by 15% ( $P = 0.296$ ); in the nonfasting state, antacid decreased the relative bioavailability of posaconazole by 12% ( $P = 0.352$ ). Food increased the relative oral bioavailability of posaconazole by 400% ( $P = 0.001$ ). In conclusion, the effect of antacid on posaconazole exposure in the fasting or nonfasting state was small and is not considered clinically significant.

Publication Types:

- [Clinical Trial](#)
- [Randomized Controlled Trial](#)

PMID: 14982768 [PubMed - indexed for MEDLINE]

[J Clin Microbiol.](#) 2004 Feb;42(2):718-21

**Multicenter comparison of the Sensititre YeastOne colorimetric antifungal panel with the NCCLS M27-A2 reference method for testing new antifungal agents against clinical isolates of *Candida* spp.**

[Espinel-Ingroff A](#), [Pfaller M](#), [Messer SA](#), [Knapp CC](#), [Holliday N](#), [Killian SB](#).

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A multicenter (three centers) study compared MICs obtained by the Sensititre YeastOne Colorimetric Antifungal plate to reference microdilution broth (NCCLS M27-A2 document) MICs of three new triazoles (posaconazole, ravuconazole, and voriconazole) and the echinocandin caspofungin acetate for 100 isolates of *Candida* spp. In addition, amphotericin B and fluconazole were tested as control drugs. Colorimetric MICs of caspofungin and amphotericin B corresponded to the first blue well (no growth), and MICs of the other agents corresponded to the first slightly purple or blue well. Two comparisons

of MIC pairs by the two methods were evaluated: 24-h colorimetric MICs were compared to NCCLS MICs at 24 and at 48 h. The interlaboratory reproducibility of YeastOne and reference MICs was also examined. The best performance of the YeastOne plate was with 24-h MICs (overall, 95 to 99% agreement) for all the species and antifungal agents. These results suggest the potential value of the YeastOne plate for use in the clinical laboratory for the four new antifungal agents evaluated.

Publication Types:

- [Multicenter Study](#)

PMID: 14766842 [PubMed - indexed for MEDLINE]

[Br J Clin Pharmacol](#). 2004 Feb;57(2):218-22

**Effect of food on the relative bioavailability of two oral formulations of posaconazole in healthy adults.**

[Courtney R](#), [Wexler D](#), [Radwanski E](#), [Lim J](#), [Laughlin M](#).

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**AIMS:** This randomized, crossover, single-dose study evaluated the relative oral bioavailability of posaconazole suspension and coprecipitate tablet formulations. Additionally, the study determined whether systemic exposure to posaconazole was affected by prandial status or by the fat content of a meal. **METHODS:** This was a randomized, open-label, four-way crossover, single-dose study in 20 healthy men. Posaconazole pharmacokinetics were evaluated over 72 h following a single oral dose of posaconazole suspension (200 mg/5 ml) administered with a high-fat meal, a nonfat breakfast, or after a 10 h fast, or posaconazole tablets (2 x 100 mg) administered with a high-fat meal. **RESULTS:** The posaconazole suspension showed a significant increase in bioavailability compared with the tablet (increase in AUC(0,72 h) = 137% (90% confidence interval (CI) 119%, 156% and Cmax = 123% (90% CI 104%, 146%). The mean increases in AUC(0,72 h) and Cmax values were about 400% when administered with a high-fat meal compared with administration of the suspension in the fasting state (AUC(0,72 h) 90% CI 343%, 448%; Cmax 90% CI 352%, 493%). Administration of the suspension with a nonfat meal enhanced exposure, resulting in an increase in AUC(0,72 h) of 264% (90% CI 231%, 302%) and in Cmax of 296% (90% CI 250%, 350%) relative to the fasted state. **CONCLUSIONS:** The suspension formulation of posaconazole was associated with enhanced systemic exposure and increased relative bioavailability compared with the tablet. Food substantially enhanced the rate and extent of posaconazole absorption in healthy subjects.

Publication Types:

- [Clinical Trial](#)
- [Randomized Controlled Trial](#)

PMID: 14748822 [PubMed - indexed for MEDLINE]

[Antimicrob Agents Chemother](#). 2003 Sep;47(9):2788-95

**Pharmacokinetics, safety, and tolerability of oral posaconazole administered in single and multiple doses in healthy adults.**

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The pharmacokinetics, safety, and tolerability of posaconazole, an investigational triazole antifungal, were evaluated following the administration of rising single and multiple oral doses. A total of 103 healthy adults were enrolled in two phase I trials. Each study had a double-blind, placebo-controlled, parallel-group design with a rising single-dose (RSD) or rising multiple-dose (RMD) scheme. In the RSD study, subjects received single doses of posaconazole oral tablets (50 to 1200 mg) or placebo. In the RMD study, subjects received posaconazole oral tablets (50 to 400 mg) or placebo twice daily for 14 days. By using model-independent methods, the area under the plasma concentration-time curve and the maximum concentration in

plasma were determined and used to assess dose proportionality. In the RSD study, the levels of posaconazole in plasma increased proportionally between the 50- and 800-mg dose range, with saturation of absorption occurring above 800 mg. Dose proportionality was also observed in the RMD study. In both studies, the apparent volume of distribution was large (range, 343 to 1341 liters) and the terminal-phase half-life was long (range, 25 to 31 h). Posaconazole was well tolerated at all dose levels, and the adverse events were not dose dependent. No clinically significant changes in clinical laboratory test values or electrocardiograms were observed. Following the administration of single and twice-daily rising doses, the level of posaconazole exposure increased in a dose-proportional manner. The long elimination-phase half-life of posaconazole supports once- or twice-daily dosing in clinical trials; however, additional studies are required to determine if further division of the dose will enhance exposure.

Publication Types:

- [Clinical Trial](#)
- [Randomized Controlled Trial](#)

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[J Chemother.](#) 2002 Jun;14(3):246-52.

**Effect of medium composition on static and cidal activity of amphotericin B, itraconazole, voriconazole, posaconazole and terbinafine against *Aspergillus fumigatus*: a multicenter study.**

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The effect of the medium composition on the fungistatic (MIC) and fungicidal (MLC) activity of amphotericin B, itraconazole, voriconazole, posaconazole and terbinafine against four *Aspergillus fumigatus* strains has been investigated by four European laboratories. MICs were determined by broth microdilution, using RPMI 1640 and Antibiotic Medium 3 (AM3), three times in three independent determinations by the four laboratories. MLCs were determined for the three independent determinations by the four laboratories, subculturing 100 microl from each well showing no visible growth after 48 hours. Except for a 2-dilution difference observed in three cases, no differences were observed between MICs determined on the two media. In contrast, a 3- to 6-dilution discrepancy between the MLCs was observed for the azoles. Endpoints on RPMI were higher than those on AM3. A 1-2 dilution difference was noted between both the endpoints of amphotericin B and of terbinafine. The highest inter- and intra-laboratory agreements were reached on AM3. The azoles showed a medium-dependent fungicidal activity.

Publication Types:

- [Multicenter Study](#)

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**Optimal susceptibility testing conditions for detection of azole resistance in *Aspergillus* spp.: NCCLS collaborative evaluation. National Committee for Clinical Laboratory Standards.**

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The most important role of susceptibility testing is to identify potentially resistant isolates for the agent being evaluated. Standard testing guidelines recently have been proposed for antifungal susceptibility testing of filamentous fungi (molds). This collaborative (eight centers) study evaluated further newly proposed guidelines (NCCLS, proposed standard M38-P, 1998) and other testing conditions for antifungal susceptibility testing of *Aspergillus* spp. to itraconazole and three new triazoles, posaconazole (SCH56592), ravuconazole (BMS-207147), and voriconazole. MICs of itraconazole, posaconazole, ravuconazole, and voriconazole for 15 selected isolates of three species of *Aspergillus* (*A. fumigatus*, *A. flavus*, and *A. terreus*) with well documented in vitro, clinical, or animal data were determined in each center by using four medium formulations (standard RPMI-1640 [RPMI], RPMI with 2% dextrose, antibiotic medium 3 [M3], and M3 with 2% dextrose)

and two criteria of MIC determination (complete [MIC-0s] and prominent [MIC-2s] growth inhibition) at 24, 48, and 72 h. The highest reproducibility (92 to 99%) was seen with the standard RPMI and M3 media. Moreover, the distinction between itraconazole-resistant (MICs of >8 microg/ml for clinically resistant strains) and -susceptible (MICs of 0.03 to 1 microg/ml) isolates, as well as between a voriconazole-resistant laboratory mutant and other isolates (voriconazole MICs of 2 to >8 versus 0.12 to 2 microg/ml), was more consistently evident with the standard RPMI medium and when MIC-0s were determined at 48 h. These results provide further refinement of the testing guidelines for susceptibility testing of *Aspergillus* spp. and warrant consideration for inclusion in the future NCCLS document M38-A.

Publication Types:

- [Clinical Trial](#)
- [Multicenter Study](#)

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[Chirality](#). 2000 Jul;12(7):590-7

**Chiral high-performance liquid chromatographic analysis of antifungal SCH 56592 and evaluation of its chiral inversion in animals and humans.**

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SCH 56592 is a novel triazole antifungal agent that is active both orally and intravenously in animal models of infection. This compound is in Phase II-III clinical trials for the treatment of systemic fungal infections. SCH 56592 is a single enantiomer with four stereogenic centers; therefore, it was necessary to evaluate the possible chiral inversion of this drug candidate in animals and humans. Thus, chiral high-performance liquid chromatographic (HPLC) methods have been developed to separate SCH 56592 from its diastereomers and to evaluate its chiral inversion in rats, dogs, cynomolgus monkeys, and humans. Chiral HPLC analysis involved the use of a Chiralcel OD column set at 39 degrees C with a mobile phase of hexane-ethanol-diethylamine and a fluorescence detector set at an excitation wavelength of 270 nm and an emission wavelength of 390 nm. Plasma or serum samples were subjected to solid phase extraction on a C(2) cartridge followed by HPLC analysis. The method was sensitive with a limit of quantitation of 0.1 microg/ml in dog serum. The linearity was satisfactory, as shown by correlations of >0.997 and by visual examination of the calibration curves. The precision and accuracy were satisfactory, as indicated by coefficients of variation (CV) ranging from 1.1 to 12.1% and bias values ranging from -11.0 to 9.0%. Chiral HPLC analysis indicated that SCH 56592 was not subjected to chiral inversion in rats, dogs, cynomolgus monkeys, and humans. Copyright 2000 Wiley-Liss, Inc.

Publication Types:

- [Clinical Trial](#)

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