



SUMMARY OF DRUG INTERACTIONS^{1,2}

NOXAFIL[®] 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.

NOXAFIL[®] is indicated for the treatment of oropharyngeal candidiasis (OPC), including OPC refractory to itraconazole and/or fluconazole.

Adapted from Prescribing Information.
Please see Important Safety Information inside.
Please see accompanying full Prescribing Information.

 **NOXAFIL[®]**
posaconazole Oral Suspension

Concomitant drug dosing considerations¹

Interaction	Drugs	Recommendations
NOXAFIL® plasma concentrations may be reduced	Cimetidine, efavirenz	Avoid concomitant use unless the benefit outweighs the risks.
NOXAFIL® plasma concentrations may be reduced and the plasma concentration of the concomitant drug may be increased	Rifabutin	Avoid concomitant use unless the benefit outweighs the risks; however, if concomitant administration is required, frequent monitoring of whole blood counts and adverse events (eg, uveitis, leukopenia) due to increased rifabutin levels is recommended.
	Phenytoin	Avoid concomitant use unless the benefit outweighs the risks. Frequent monitoring of phenytoin concentrations should be performed while coadministered with NOXAFIL® and dose reductions of phenytoin should be considered.
Plasma concentrations of the concomitant drug may be increased	Sirolimus	Coadministration of NOXAFIL® with sirolimus is contraindicated.
	Cyclosporine	Increased cyclosporine concentrations resulted in cyclosporine dose reductions in heart transplant patients coadministered NOXAFIL®. At initiation of NOXAFIL® therapy, reduce cyclosporine to approximately three fourths of the original dose. Frequent monitoring of cyclosporine whole blood trough concentrations should be performed during and at discontinuation of NOXAFIL® therapy and the cyclosporine dose adjusted accordingly. Cases of elevated cyclosporine levels resulting in rare serious adverse events, including nephrotoxicity, leukoencephalopathy, and death were reported in clinical efficacy studies.
	Tacrolimus	NOXAFIL® has been shown to increase C _{max} and AUC of tacrolimus significantly. At initiation of NOXAFIL® therapy, reduce tacrolimus to approximately one third of the original dose. Frequent monitoring of tacrolimus whole blood trough concentrations should be performed during and at discontinuation of NOXAFIL® therapy and the tacrolimus dose adjusted accordingly.
	Midazolam	Frequent monitoring of adverse events of benzodiazepines metabolized by CYP3A4 should be performed and dose reduction of these benzodiazepines should be considered during coadministration with NOXAFIL®. A clinical study in healthy volunteers demonstrated a >5-fold increase in midazolam AUC.
	Ritonavir	Frequent monitoring of adverse effects and toxicity of ritonavir should be performed during coadministration with NOXAFIL®.
	Atazanavir, atazanavir/ritonavir boosted regimen	Frequent monitoring of adverse effects and toxicity of atazanavir should be performed during coadministration with NOXAFIL®.
Drugs not studied <i>in vitro</i> or <i>in vivo</i> , but likely to result in significant drug interactions—Plasma concentrations of concomitant drug may be affected	Terfenadine, astemizole, pimozone, cisapride, halofantrine, quinidine	Increased plasma concentrations of these drugs can lead to QT prolongation with rare occurrences of torsades de pointes. Coadministration with NOXAFIL® is contraindicated.
	Ergot alkaloids (ergotamine and dihydroergotamine)	NOXAFIL® may increase plasma concentrations of ergot alkaloids, which may lead to ergotism. Coadministration with NOXAFIL® is contraindicated.
	Vinca alkaloids (eg, vincristine and vinblastine)	NOXAFIL® may increase plasma concentrations of vinca alkaloids, which may lead to neurotoxicity. Therefore, it is recommended that dose adjustment of the vinca alkaloid be considered.
	HMG-CoA reductase inhibitors (statins) metabolized through CYP3A4	It is recommended that dose reduction of statins be considered during coadministration. Increased statin concentrations in plasma can be associated with rhabdomyolysis.
	Calcium channel blockers (CCBs) metabolized through CYP3A4	Frequent monitoring for adverse events and toxicity related to CCBs is recommended during coadministration. Dose reduction of CCBs may be needed.
	Digoxin	Increased plasma concentrations of digoxin have been reported in patients receiving digoxin and NOXAFIL®. Therefore, monitoring of digoxin plasma concentrations is recommended during coadministration.
No clinically relevant effect on NOXAFIL® bioavailability and/or plasma concentrations	Antacids, glipizide, ritonavir, proton pump inhibitors, and H ₂ receptor antagonists other than cimetidine	Dose adjustment of NOXAFIL® not required. NOXAFIL® administration with glipizide does not require a dose adjustment in either drug; however, glucose concentrations decreased in some healthy volunteers administered the combination. Therefore, glucose concentrations should be monitored in accordance with the current standard of care for patients with diabetes when NOXAFIL® is coadministered with glipizide.
No clinically significant effects on concomitant drug	Zidovudine, lamivudine, indinavir, caffeine	No dose adjustments of these concomitant drugs are required when coadministered with NOXAFIL® 200 mg QD.

Please see Important Safety Information inside.
Please see accompanying full Prescribing Information.

Important Safety Information

NOXAFIL® has been shown to interact with several medications, including drugs that suppress the immune system, and these reactions may be serious. The product label should be consulted when other drugs are prescribed with NOXAFIL®.

Coadministration with sirolimus or ergot alkaloids is contraindicated. Coadministration with the CYP3A4 substrates terfenadine, astemizole, cisapride, pimozide, halofantrine, or quinidine, is also contraindicated since this may result in increased plasma concentrations of these medicinal products, leading to QTc prolongation and rare occurrences of torsades de pointes.

Serious and rare fatal toxicity from cyclosporine has occurred when taken in combination with NOXAFIL® and therefore reduction of the dose of drugs like cyclosporine or tacrolimus and frequent monitoring of drug levels of these medications are necessary when taking them in combination with NOXAFIL®.

In clinical trials, there were infrequent cases of hepatic reactions (eg, mild to moderate elevations in ALT, AST, alkaline phosphatase, total bilirubin, and/or clinical hepatitis). Rarely, more severe hepatic reactions including cholestasis or hepatic failure including fatalities were reported in patients with serious underlying medical conditions (eg, hematologic malignancies) during treatment with posaconazole. Liver function tests should be monitored at the start of and during the course of therapy. Discontinuation of NOXAFIL® must be considered in patients who experience symptoms consistent with liver disease that may be attributable to NOXAFIL®.

The safety and effectiveness of NOXAFIL® in patients below the age of 13 years old have not been established.

The most common treatment-related serious adverse events (1% each) in the combined prophylaxis studies were bilirubinemia, increased hepatic enzymes, hepatocellular damage, nausea, and vomiting.

In the pooled prophylaxis safety analysis, fever, headache, anemia, diarrhea, nausea, vomiting, abdominal pain, hypokalemia, and thrombocytopenia were frequently reported treatment-emergent adverse events.

In clinical studies of OPC and refractory OPC, adverse events were reported more frequently in the pool of patients with refractory OPC. The most commonly reported serious adverse events in refractory OPC patients included fever (13%) and neutropenia (10%).

Please see accompanying full Prescribing Information.

CYP drug interactions^{1,2}

- NOXAFIL® is not a substrate for CYP450 enzymes¹
 - Minimally metabolized by CYP2C19, CYP2C9, or CYP3A4
- NOXAFIL® inhibits only CYP3A4^{1,2}

Renal and hepatic interactions¹

- No dosage adjustment is recommended for patients with renal dysfunction
 - However, the range of the NOXAFIL® AUC estimates was highly variable (CV=96%) in subjects with severe renal insufficiency as compared to that in the other renal impairment groups (CV<40%)
 - Due to the variability in exposure, patients with severe renal impairment should be monitored closely for breakthrough invasive fungal infections (IFIs)
- The pharmacokinetic data in subjects with hepatic impairment were not sufficient to determine if dose adjustment is necessary in patients with hepatic dysfunction
 - It is recommended that NOXAFIL® be used with caution in patients with hepatic impairment and discontinuation of NOXAFIL® must be considered in patients who experience symptoms consistent with liver disease that may be attributable to NOXAFIL®
 - Rarely, more severe hepatic reactions including cholestasis or hepatic failure including fatalities were reported in patients with serious underlying medical conditions (eg, hematologic malignancies) during treatment with NOXAFIL®. Liver function tests should be monitored at start of and during course of therapy

References: 1. NOXAFIL® (posaconazole) Prescribing Information. Schering Corporation; Kenilworth, NJ; June 2008. 2. Wexler D, Courtney R, Richards W, Banfield C, Lim J, Laughlin M. Effect of posaconazole on cytochrome P450 enzymes: a randomized, open-label, two-way crossover study. *Eur J Pharm Sci.* 2004;21:645-653.



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