Patients	200	30	N/D	5570 (32)	954 (44)	N/D	N/D
	300	22	N/D	8240 (26)	1590 (62)	N/D	N/D
$AUC_{0-\infty}$ = Area under the plasma concentration-time curve from time zero to infinity; AUC_{0-12} = Area under the plasma concentration-time curve from time zero to 12 hr after the first dose on Day 1; C_{max} = maximum observed concentration; $t_{½}$ = terminal phase half-life; CL = total body clearance; N/D = Not Determined							

Table 19 displays the pharmacokinetic parameters of posaconazole in patients following administration of Noxafil injection 300 mg taken once a day for 10 or 14 days following twice daily dosing on Day 1.

Table 19: Arithmetic Mean (%CV) of PK Parameters in Serial PK-Evaluable Patients Following Dosing of Noxafil Injection (300 mg)*

Day	N	C_{max} (ng/mL)	T_{max}† (hr)	AUC_{0-24} (ng*hr/mL)	Cav (ng/mL)	C_{min} (ng/mL)
10/14	49	3280 (74)	1.5 (0.98-4.0)	36100 (35)	1500 (35)	1090 (44)

AUC_{0-24} = area under the concentration-time curve over the dosing interval (i.e. 24 hours); Cav= time-averaged concentrations (i.e., AUC_{0-24h}/24hr);

C_{min} = POS trough level immediately before a subject received the dose of POS on the day specified in the protocol; C_{max} = observed maximum plasma concentration; CV = coefficient of variation, expressed as a percent (%); Day = study day on treatment; T_{max} = time of observed maximum plasma concentration.

* 300 mg dose administered over 90 minutes once a day following twice daily dosing on Day 1

† Median (minimum-maximum)

Noxafil Delayed-Release Tablets

Noxafil delayed-release tablets exhibit dose proportional pharmacokinetics after single and multiple dosing up to 300 mg. The mean pharmacokinetic parameters of posaconazole at steady state following administration of Noxafil delayed-release tablets 300 mg twice daily on Day 1, then 300 mg once daily thereafter in healthy volunteers and in neutropenic patients who are receiving cytotoxic chemotherapy for AML or MDS or HSCT recipients with GVHD are shown in **Table 20**.

Table 20: Arithmetic Mean (%CV) of Steady State PK Parameters in Healthy Volunteers and Patients Following Administration of Noxafil Delayed-Release Tablets (300 mg)*

	N	$AUC_{0-24\ hr}$ (ng·hr/mL)	Cav† (ng/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)	T_{max}‡ (hr)	$t_{1/2}$ (hr)	CL/F (L/hr)
Healthy Volunteers	12	51618 (25)	2151 (25)	2764 (21)	1785 (29)	4 (3-6)	31 (40)	7.5 (26)
Patients	50	37900 (42)	1580 (42)	2090 (38)	1310 (50)	4 (1.3-8.3)	-	9.39 (45)

CV = coefficient of variation expressed as a percentage (%CV); AUC_{0-T} = Area under the plasma concentration-time curve from time zero to 24 hr; C_{max} = maximum observed concentration; C_{min} = minimum observed plasma concentration; T_{max} = time of maximum observed concentration; $t_{½}$ = terminal phase half-life; CL/F = Apparent total body clearance

*300 mg twice daily on Day 1, then 300 mg once daily thereafter

† Cav = time-averaged concentrations (i.e., $AUC_{0-24\ hr}$/24hr)

‡ Median (minimum-maximum)

Noxafil Oral Suspension

Dose-proportional increases in plasma exposure (AUC) to Noxafil oral suspension were observed following single oral doses from 50 mg to 800 mg and following multiple-dose administration from 50 mg twice daily to 400 mg twice daily in healthy volunteers. No further increases in exposure were observed

when the dose of the oral suspension increased from 400 mg twice daily to 600 mg twice daily in febrile neutropenic patients or those with refractory invasive fungal infections.

The mean (%CV) [min-max] Noxafil oral suspension average steady-state plasma concentrations (Cavg) and steady-state pharmacokinetic parameters in patients following administration of 200 mg three times a day and 400 mg twice daily of the oral suspension are provided in **Table 21.**

Table 21: The Mean (%CV) [min-max] Posaconazole Steady-State Pharmacokinetic Parameters in Patients Following Oral Administration of Noxafil Oral Suspension 200 mg Three Times a Day and 400 mg Twice Daily

Dose*	Cavg (ng/mL)	AUC† (ng·hr/mL)	CL/F (L/hr)	V/F (L)	$t_{½}$ (hr)
200 mg three times a day‡ (n=252)	1103 (67) [21.5-3650]	ND§	ND§	ND§	ND§
200 mg three times a day¶ (n=215)	583 (65) [89.7-2200]	15,900 (62) [4100-56,100]	51.2 (54) [10.7-146]	2425 (39) [828-5702]	37.2 (39) [19.1-148]
400 mg twice daily# (n=23)	723 (86) [6.70-2256]	9093 (80) [1564-26,794]	76.1 (78) [14.9-256]	3088 (84) [407-13,140]	31.7 (42) [12.4-67.3]

Cavg = the average posaconazole concentration when measured at steady state
* Oral suspension administration
† AUC (0-24 hr) for 200 mg three times a day and AUC (0-12 hr) for 400 mg twice daily
‡ HSCT recipients with GVHD
§ Not done
¶ Neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes
# Febrile neutropenic patients or patients with refractory invasive fungal infections, Cavg n=24
The variability in average plasma posaconazole concentrations in patients was relatively higher than that in healthy subjects.

Absorption:

Noxafil Delayed-Release Tablets

When given orally in healthy volunteers, Noxafil delayed-release tablets are absorbed with a median T_{max} of 4 to 5 hours. Steady-state plasma concentrations are attained by Day 6 at the 300 mg dose (once daily after twice daily loading dose at Day 1). The absolute bioavailability of the oral delayed-release tablet is approximately 54% under fasted conditions. The C_{max} and AUC of posaconazole following administration of Noxafil delayed-release tablets is increased 16% and 51%, respectively, when given with a high fat meal compared to a fasted state (see **Table 22**).

Table 22: Statistical Comparison of Plasma Pharmacokinetics of Posaconazole Following Single Oral Dose Administration of 300 mg Noxafil Delayed-Release Tablet to Healthy Subjects under Fasting and Fed Conditions

	Fasting Conditions		Fed Conditions (High Fat Meal)*		Fed/Fasting
Pharmacokinetic Parameter	**N**	**Mean (%CV)**	**N**	**Mean (%CV)**	**GMR (90% CI)**
C_{max} (ng/mL)	14	935 (34)	16	1060 (25)	1.16 (0.96, 1.41)
AUC_{0-72hr} (hr·ng/mL)	14	26200 (28)	16	38400 (18)	1.51 (1.33, 1.72)
T_{max}† (hr)	14	5.00 (3.00, 8.00)	16	6.00 (5.00, 24.00)	N/A

GMR=Geometric least-squares mean ratio; CI=Confidence interval
* 48.5 g fat
† Median (Min, Max) reported for T_{max}

Concomitant administration of Noxafil delayed-release tablets with drugs affecting gastric pH or gastric motility did not demonstrate any significant effects on posaconazole pharmacokinetic exposure (see **Table 23**).

Table 23: The Effect of Concomitant Medications that Affect the Gastric pH and Gastric Motility on the Pharmacokinetics of Noxafil Delayed-Release Tablets in Healthy Volunteers

Coadministered Drug	Administration Arms	Change in C_{max} (ratio estimate*; 90% CI of the ratio estimate)	Change in $AUC_{0\text{-}last}$ (ratio estimate*; 90% CI of the ratio estimate)
Mylanta® Ultimate strength liquid (Increase in gastric pH)	25.4 meq/5 mL, 20 mL	↑6% (1.06; 0.90 -1.26)↑	↑4% (1.04; 0.90 -1.20)
Ranitidine (Zantac®) (Alteration in gastric pH)	150 mg (morning dose of 150 mg Ranitidine twice daily)	↑4% (1.04; 0.88 -1.23)↑	↓3% (0.97; 0.84 -1.12)
Esomeprazole (Nexium®) (Increase in gastric pH)	40 mg (every morning for 5 days, Day -4 to 1)	↑2% (1.02; 0.88-1.17)↑	↑5% (1.05; 0.89 -1.24)
Metoclopramide (Reglan®) (Increase in gastric motility)	15 mg four times daily for 2 days (Day -1 and 1)	↓14% (0.86, 0.73,1.02)	↓7% (0.93, 0.803,1.07)

* Ratio Estimate is the ratio of coadministered drug plus Noxafil to Noxafil alone for C_{max} or $AUC_{0\text{-}last}$.

Noxafil PowderMix for Delayed-Release Oral Suspension

The absolute bioavailability of the Noxafil PowderMix for delayed-release oral suspension is approximately 70-80%. The effect of food on the pharmacokinetics of the Noxafil PowderMix for delayed-release oral suspension has not been determined.

Concomitant administration of Noxafil PowderMix for delayed-release oral suspension with drugs affecting gastric pH or gastric motility would not be expected to demonstrate any significant effects on posaconazole pharmacokinetic exposure based on similarity to the delayed-release tablets.

An *in vitro* dissolution study was conducted to evaluate the impact of alcohol (5, 10, 20, and 40%) on the dissolution of Noxafil PowderMix delayed-release oral suspension. The study showed alcohol-induced dose-dumping potential with the Noxafil PowderMix delayed-release oral suspension *[see Dosage and Administration (2.1) and Drug Interactions (7.15)]*.

Noxafil Oral Suspension

Noxafil oral suspension is absorbed with a median T_{max} of ~3 to 5 hours. Steady-state plasma concentrations are attained at 7 to 10 days following multiple-dose administration.

Following single-dose administration of 200 mg, the mean AUC and C_{max} of posaconazole are approximately 3-times higher when the oral suspension is administered with a nonfat meal and approximately 4-times higher when administered with a high-fat meal (~50 gm fat) relative to the fasted state. Following single-dose administration of Noxafil oral suspension 400 mg, the mean AUC and C_{max} of posaconazole are approximately 3-times higher when administered with a liquid nutritional supplement (14 gm fat) relative to the fasted state (see **Table 24**). In addition, the effects of varying gastric administration conditions on the C_{max} and AUC of Noxafil oral suspension in healthy volunteers have been investigated and are shown in **Table 25**.

In order to assure attainment of adequate plasma concentrations, it is recommended to administer Noxafil oral suspension during or immediately following a full meal. In patients who cannot eat a full meal, Noxafil oral suspension should be taken with a liquid nutritional supplement or an acidic carbonated beverage (e.g., ginger ale).

Table 24: The Mean (%CV) [min-max] Posaconazole Pharmacokinetic Parameters Following Single-Dose Noxafil Oral Suspension Administration of 200 mg and 400 mg Under Fed and Fasted Conditions

Dose (mg)	C_{max} (ng/mL)	T_{max}* (hr)	AUC (I) (ng·hr/mL)	CL/F (L/hr)	$t_{½}$ (hr)

200 mg fasted (n=20)†	132 (50) [45-267]	3.50 [1.5-36‡]	4179 (31) [2705-7269]	51 (25) [28-74]	23.5 (25) [15.3-33.7]
200 mg nonfat (n=20)†	378 (43) [131-834]	4 [3-5]	10,753 (35) [4579-17,092]	21 (39) [12-44]	22.2 (18) [17.4-28.7]
200 mg high fat (54 gm fat) (n=20)†	512 (34) [241-1016]	5 [4-5]	15,059 (26) [10,341-24,476]	14 (24) [8.2-19]	23.0 (19) [17.2-33.4]
400 mg fasted (n=23)§	121 (75) [27-366]	4 [2-12]	5258 (48) [2834-9567]	91 (40) [42-141]	27.3 (26) [16.8-38.9]
400 mg with liquid nutritional supplement (14 gm fat) (n=23)§	355 (43) [145-720]	5 [4-8]	11,295 (40) [3865-20,592]	43 (56) [19-103]	26.0 (19) [18.2-35.0]

* Median [min-max].
† n=15 for AUC (I), CL/F, and $t_{½}$
‡ The subject with T_{max} of 36 hrs had relatively constant plasma levels over 36 hrs (1.7 ng/mL difference between 4 hrs and 36 hrs).
§ n=10 for AUC (I), CL/F, and $t_{½}$

Table 25: The Effect of Varying Gastric Administration Conditions on the C_{max} and AUC of Noxafil Oral Suspension in Healthy Volunteers*

Study Description	Administration Arms	Change in C_{max} (ratio estimate†; 90% CI of the ratio estimate)	Change in AUC (ratio estimate†; 90% CI of the ratio estimate)
400-mg single dose with a high-fat meal relative to fasted state (n=12)	5 minutes before high-fat meal	↑96% (1.96; 1.48-2.59)	↑111% (2.11; 1.60-2.78)
	During high-fat meal	↑339% (4.39; 3.32-5.80)	↑382% (4.82; 3.66-6.35)
	20 minutes after high-fat meal	↑333% (4.33; 3.28-5.73)	↑387% (4.87; 3.70-6.42)
400 mg twice daily and 200 mg four times daily for 7 days in fasted state and with liquid nutritional supplement (BOOST®) (n=12)	400 mg twice daily with BOOST	↑65% (1.65; 1.29-2.11)	↑66% (1.66; 1.30-2.13)
	200 mg four times daily with BOOST	No Effect	No Effect
Divided daily dose from 400 mg twice daily to 200 mg four times daily for 7 days regardless of fasted conditions or with BOOST (n=12)	Fasted state	↑136% (2.36; 1.84-3.02)	↑161% (2.61; 2.04-3.35)
	With BOOST	↑137% (2.37; 1.86-3.04)	↑157% (2.57; 2.00-3.30)
400-mg single dose with carbonated acidic beverage (ginger ale) and/or proton pump inhibitor (esomeprazole) (n=12)	Ginger ale	↑92% (1.92; 1.51-2.44)	↑70% (1.70; 1.43-2.03)
	Esomeprazole	↓32% (0.68; 0.53-0.86)	↓30% (0.70; 0.59-0.83)
400-mg single dose with a prokinetic agent (metoclopramide 10 mg three times a day for 2 days) + BOOST or	With metoclopramide + BOOST	↓21% (0.79; 0.72-0.87)	↓19% (0.81; 0.72-0.91)
	With loperamide + BOOST	↓3%	↑11%

an antikinetic agent (loperamide 4-mg single dose) + BOOST (n=12)		(0.97; 0.88-1.07)	(1.11; 0.99-1.25)
400-mg single dose either orally with BOOST or via an NG tube with BOOST (n=16)	Via NG tube‡	↓19% (0.81; 0.71-0.91)	↓23% (0.77; 0.69-0.86)
* In 5 subjects, the C_{max} and AUC decreased substantially (range: -27% to -53% and -33% to -51%, respectively) when Noxafil was administered via an NG tube compared to when Noxafil was administered orally. It is recommended to closely monitor patients for breakthrough fungal infections when Noxafil is administered via an NG tube because a lower plasma exposure may be associated with an increased risk of treatment failure. † Ratio Estimate is the ratio of coadministered drug plus Noxafil to coadministered drug alone for C_{max} or AUC. ‡ NG = nasogastric			

Concomitant administration of Noxafil oral suspension with drugs affecting gastric pH or gastric motility results in lower posaconazole exposure. (See **Table 26**.)

Table 26: The Effect of Concomitant Medications that Affect the Gastric pH and Gastric Motility on the Pharmacokinetics of Noxafil Oral Suspension in Healthy Volunteers

Coadministered Drug (Postulated Mechanism of Interaction)	**Coadministered Drug Dose/Schedule**	**Noxafil Dose/Schedule**	**Effect on Bioavailability of Posaconazole**	
			Change in Mean C_{max} (ratio estimate*; 90% CI of the ratio estimate)	**Change in Mean AUC** (ratio estimate*; 90% CI of the ratio estimate)
Cimetidine (Alteration of gastric pH)	400 mg twice daily × 10 days	200 mg (tablets) once daily × 10 days†	↓ 39% (0.61; 0.53-0.70)	↓ 39% (0.61; 0.54-0.69)
Esomeprazole (Increase in gastric pH)‡	40 mg every morning × 3 days	400 mg (oral suspension) single dose	↓ 46% (0.54; 0.43-0.69)	↓ 32% (0.68; 0.57-0.81)
Metoclopramide (Increase in gastric motility)‡	10 mg three times a day × 2 days	400 mg (oral suspension) single dose	↓ 21% (0.79; 0.72-0.87)	↓ 19% (0.81; 0.72-0.91)
* Ratio Estimate is the ratio of coadministered drug plus Noxafil to coadministered drug alone for C_{max} or AUC. † The tablet refers to a non-commercial tablet formulation without polymer. ‡ The drug interactions associated with the oral suspension are also relevant for the delayed-release tablet with the exception of Esomeprazole and Metoclopramide.				

Distribution:

The mean volume of distribution of posaconazole after intravenous solution administration was 261 L and ranged from 226-295 L between studies and dose levels.

Posaconazole is highly bound to human plasma proteins (>98%), predominantly to albumin.

Metabolism:

Posaconazole primarily circulates as the parent compound in plasma. Of the circulating metabolites, the majority are glucuronide conjugates formed via UDP glucuronidation (phase 2 enzymes). Posaconazole does not have any major circulating oxidative (CYP450 mediated) metabolites. The excreted metabolites in urine and feces account for ~17% of the administered radiolabeled dose.

Posaconazole is primarily metabolized via UDP glucuronidation (phase 2 enzymes) and is a substrate for p-glycoprotein (P-gp) efflux. Therefore, inhibitors or inducers of these clearance pathways may affect posaconazole plasma concentrations. A summary of drugs studied clinically with the oral suspension or an early tablet formulation, which affect posaconazole concentrations, is provided in **Table 27**.

Table 27: Summary of the Effect of Coadministered Drugs on Noxafil in Healthy Volunteers

Coadministered Drug (Postulated	**Coadministered Drug Dose/Schedule**	**Noxafil Dose/Schedule**	**Effect on Bioavailability of Posaconazole**

Mechanism of Interaction)			Change in Mean C_{max} (ratio estimate*; 90% CI of the ratio estimate)	Change in Mean AUC (ratio estimate*; 90% CI of the ratio estimate)
Efavirenz (UDP-G Induction)	400 mg once daily × 10 and 20 days	400 mg (oral suspension) twice daily × 10 and 20 days	↓45% (0.55; 0.47-0.66)	↓ 50% (0.50; 0.43-0.60)
Fosamprenavir (unknown mechanism)	700 mg twice daily x 10 days	200 mg once daily on the 1st day, 200 mg twice daily on the 2nd day, then 400 mg twice daily x 8 Days	↓21% 0.79 (0.71-0.89)	↓23% 0.77 (0.68-0.87)
Rifabutin (UDP-G Induction)	300 mg once daily x 17 days	200 mg (tablets) once daily × 10 days†	↓ 43% (0.57; 0.43-0.75)	↓ 49% (0.51; 0.37-0.71)
Phenytoin (UDP-G Induction)	200 mg once daily x 10 days	200 mg (tablets) once daily × 10 days†	↓ 41% (0.59; 0.44-0.79)	↓ 50% (0.50; 0.36-0.71)

* Ratio Estimate is the ratio of coadministered drug plus Noxafil to Noxafil alone for C_{max} or AUC.
† The tablet refers to a non-commercial tablet formulation without polymer.

In vitro studies with human hepatic microsomes and clinical studies indicate that posaconazole is an inhibitor primarily of CYP3A4. A clinical study in healthy volunteers also indicates that posaconazole is a strong CYP3A4 inhibitor as evidenced by a >5-fold increase in midazolam AUC. Therefore, plasma concentrations of drugs predominantly metabolized by CYP3A4 may be increased by posaconazole. A summary of the drugs studied clinically, for which plasma concentrations were affected by posaconazole, is provided in **Table 28** *[see Contraindications (4)* and *Drug Interactions (7.1) including recommendations]*.

Table 28: Summary of the Effect of Noxafil on Coadministered Drugs in Healthy Adult Volunteers and Patients

Coadministered Drug (Postulated Mechanism of Interaction is Inhibition of CYP3A4 by posaconazole)	Coadministered Drug Dose/Schedule	Noxafil Dose/ Schedule	Effect on Bioavailability of Coadministered Drugs	
			Change in Mean C_{max} (ratio estimate*; 90% CI of the ratio estimate)	Change in Mean AUC (ratio estimate*; 90% CI of the ratio estimate)
Sirolimus	2-mg single oral dose	400 mg (oral suspension) twice daily x 16 days	↑ 572% (6.72; 5.62-8.03)	↑ 788% (8.88; 7.26-10.9)
Cyclosporine	Stable maintenance dose in heart transplant recipients	200 mg (tablets) once daily x 10 days†	↑ cyclosporine whole blood trough concentrations Cyclosporine dose reductions of up to 29% were required	
Tacrolimus	0.05-mg/kg single oral dose	400 mg (oral suspension) twice daily × 7 days	↑ 121% (2.21; 2.01-2.42)	↑ 358% (4.58; 4.03-5.19)
Simvastatin	40-mg single oral dose	100 mg (oral suspension) once daily x 13 days	Simvastatin ↑ 841% (9.41, 7.13-12.44) Simvastatin Acid ↑ 817% (9.17, 7.36-11.43)	Simvastatin ↑ 931% (10.31, 8.40-12.67) Simvastatin Acid ↑634% (7.34, 5.82-9.25)
		200 mg (oral suspension) once daily x 13 days	Simvastatin ↑ 1041% (11.41, 7.99-16.29) Simvastatin Acid ↑851%	Simvastatin ↑ 960% (10.60, 8.63-13.02) Simvastatin Acid ↑ 748%

			(9.51, 8.15-11.10)	(8.48, 7.04-10.23)
Midazolam	0.4-mg single intravenous dose‡	200 mg (oral suspension) twice daily x 7 days	↑ 30% (1.3; 1.13-1.48)	↑ 362% (4.62; 4.02-5.3)
	0.4-mg single intravenous dose‡	400 mg (oral suspension) twice daily x 7 days	↑62% (1.62; 1.41-1.86)	↑524% (6.24; 5.43-7.16)
	2-mg single oral dose‡	200 mg (oral suspension) once daily x 7 days	↑ 169% (2.69; 2.46-2.93)	↑ 470% (5.70; 4.82-6.74)
	2-mg single oral dose‡	400 mg (oral suspension) twice daily x 7 days	↑ 138% (2.38; 2.13-2.66)	↑ 397% (4.97; 4.46-5.54)
Rifabutin	300 mg once daily x 17 days	200 mg (tablets) once daily × 10 days†	↑ 31% (1.31; 1.10-1.57)	↑ 72% (1.72;1.51-1.95)
Phenytoin	200 mg once daily PO x 10 days	200 mg (tablets) once daily x 10 days†	↑ 16% (1.16; 0.85-1.57)	↑ 16% (1.16; 0.84-1.59)
Ritonavir	100 mg once daily x 14 days	400 mg (oral suspension) twice daily x 7 days	↑ 49% (1.49; 1.04-2.15)	↑ 80% (1.8;1.39-2.31)
Atazanavir	300 mg once daily x 14 days	400 mg (oral suspension) twice daily x 7 days	↑ 155% (2.55; 1.89-3.45)	↑ 268% (3.68; 2.89-4.70)
Atazanavir/ ritonavir boosted regimen	300 mg/100 mg once daily x 14 days	400 mg (oral suspension) twice daily x 7 days	↑ 53% (1.53; 1.13-2.07)	↑ 146% (2.46; 1.93-3.13)
* Ratio Estimate is the ratio of coadministered drug plus Noxafil to coadministered drug alone for C_{max} or AUC. † The tablet refers to a non-commercial tablet formulation without polymer. ‡ The mean terminal half-life of midazolam was increased from 3 hours to 7 to 11 hours during coadministration with Noxafil.				

Additional clinical studies demonstrated that no clinically significant effects on zidovudine, lamivudine, indinavir, or caffeine were observed when administered with Noxafil 200 mg once daily; therefore, no dose adjustments are required for these coadministered drugs when coadministered with Noxafil 200 mg once daily.

Excretion:

Following administration of Noxafil oral suspension, posaconazole is predominantly eliminated in the feces (71% of the radiolabeled dose up to 120 hours) with the major component eliminated as parent drug (66% of the radiolabeled dose). Renal clearance is a minor elimination pathway, with 13% of the radiolabeled dose excreted in urine up to 120 hours (<0.2% of the radiolabeled dose is parent drug).

Noxafil injection is eliminated with a mean terminal half-life ($t_{½}$) of 27 hours and a total body clearance (CL) of 7.3 L/h.

Noxafil delayed-release tablet is eliminated with a mean half-life ($t_{½}$) ranging between 26 to 31 hours.

Noxafil oral suspension is eliminated with a mean half-life ($t_{½}$) of 35 hours (range: 20-66 hours).

Specific Populations

No clinically significant differences in the pharmacokinetics of posaconazole were observed based on age, sex, renal impairment, and indication (prophylaxis or treatment).

Race/Ethnicity:

In a population pharmacokinetic analysis of posaconazole, AUC was found to be 25% higher in Chinese patients relative to patients from other races/ethnicities. This higher exposure is not expected to be clinically relevant given the expected variability in posaconazole exposure.

Patients Weighing More Than 120 kg:

Weight has a clinically significant effect on posaconazole clearance. Relative to 70 kg patients, the Cavg is decreased by 25% in patients greater than 120 kg. Patients administered Noxafil weighing more than 120 kg may be at higher risk for lower posaconazole plasma concentrations compared to lower weight patients *[see Use in Specific Populations (8.10)]*.

Pediatric Patients

The mean pharmacokinetic parameters after multiple-dose administration of Noxafil injection and Noxafil PowderMix for delayed-release oral suspension in neutropenic pediatric patients 2 to less than 18 years of age are shown in **Table 29**. Patients were enrolled into 2 age groups and received Noxafil injection and Noxafil PowderMix for delayed-release oral suspension doses at 6 mg/kg (0.6 to 1 times the recommended dose) with a maximum 300 mg dose once daily (twice daily on Day 1) *[see Adverse Reactions (6.1)]*.

Table 29: Summary of Steady-State Geometric Mean Pharmacokinetic Parameters (% Geometric CV) After Multiple Dosing with Noxafil Injection and Noxafil PowderMix for Delayed-Release Oral Suspension 6 mg/kg* in Pediatric Patients with Neutropenia or Expected Neutropenia

Age Group	Dose Type	N	$AUC_{0\text{-}24\ hr}$ (ng·hr/mL)	Cav† (ng/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)	T_{max}‡ (hr)	CL/F§ (L/hr)
2 to <7 years	IV	17	31100 (48.9)	1300 (48.9)	3060 (54.1)	626 (104.8)	1.75 (1.57-1.83)	3.27 (49.3)
	PFS	7	23000 (47.3)	960 (47.3)	1510 (43.4)	542 (68.8)	4.00 (2.17-7.92)	4.60 (35.2)
7 to 17 years	IV	24	44200 (41.5)	1840 (41.5)	3340 (39.4)	1160 (60.4)	1.77 (1.33-6.00)	4.76 (55.7)
	PFS	12	25000 (184.3)	1040 (184.3)	1370 (178.5)	713 (300.6)	2.78 (0.00-4.00)	8.39 (190.3)

IV= Noxafil injection; PFS= Noxafil PowderMix for delayed-release oral suspension; $AUC_{0\text{-}24}$ = Area under the plasma concentration-time curve from time zero to 24 hr; C_{max} = maximum observed concentration; C_{min} = minimum observed plasma concentration; T_{max} = time of maximum observed concentration; CL /F = apparent total body clearance

* 0.6 to 1 times the recommended dose

† Cav = time-averaged concentrations (i.e., $AUC_{0\text{-}24\ hr}$/24hr)

‡ Median (minimum-maximum)

§ Clearance (CL for IV and CL/F for PFS)

Based on a population pharmacokinetic model evaluating posaconazole pharmacokinetics and predicting exposures in pediatric patients, the exposure of steady-state posaconazole average concentration greater than or equal to 700 ng/mL in approximately 90% of patients is attained with the recommended dose of Noxafil injection and Noxafil PowderMix for delayed-release oral suspension.

The population pharmacokinetic analysis of posaconazole in pediatric patients suggests that age, sex, renal impairment and ethnicity have no clinically meaningful effect on the pharmacokinetics of posaconazole.

A total of 12 patients 13 to 17 years of age received 600 mg/day (200 mg three times a day) of Noxafil oral suspension for prophylaxis of invasive fungal infections. Based on pharmacokinetic data in 10 of these pediatric patients, the mean steady-state Cav was similar between these patients and adults (≥18 years of age). In a study of 136 neutropenic pediatric patients 11 months to less than 18 years treated with Noxafil oral suspension, the exposure target of steady-state posaconazole Cavg between 500 ng/mL and less than 2500 ng/mL was attained in approximately 50% of patients instead of the pre-specified 90% of patients.

12.4 Microbiology

Mechanism of Action:

Posaconazole blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent enzyme lanosterol 14α-demethylase responsible for the conversion of lanosterol to ergosterol in the fungal cell membrane. This results in an accumulation of methylated sterol precursors and a depletion of ergosterol within the cell membrane thus weakening the structure and function of the fungal cell membrane. This may be responsible for the antifungal activity of posaconazole.

Resistance:

Clinical isolates of *Candida albicans* and *Candida glabrata* with decreased susceptibility to posaconazole were observed in oral swish samples taken during prophylaxis with posaconazole and

fluconazole, suggesting a potential for development of resistance. These isolates also showed reduced susceptibility to other azoles, suggesting cross-resistance between azoles. The clinical significance of this finding is not known.

Antimicrobial Activity:

Posaconazole has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections *[see Indications and Usage (1)]*.

Microorganisms:

Aspergillus spp. and *Candida spp.*

Susceptibility Testing:

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see:
https://www.fda.gov/STIC .

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No drug-related neoplasms were recorded in rats or mice treated with posaconazole for 2 years at doses higher than the clinical dose. In a 2-year carcinogenicity study, rats were given posaconazole orally at doses up to 20 mg/kg (females), or 30 mg/kg (males). These doses are equivalent to 3.9- or 3.5-times the exposure achieved with a 400-mg twice daily oral suspension regimen, respectively, based on steady-state AUC in healthy volunteers administered a high-fat meal (400-mg twice daily oral suspension regimen). In the mouse study, mice were treated at oral doses up to 60 mg/kg/day or 4.8-times the exposure achieved with a 400-mg twice daily oral suspension regimen.

Mutagenesis

Posaconazole was not genotoxic or clastogenic when evaluated in bacterial mutagenicity (Ames), a chromosome aberration study in human peripheral blood lymphocytes, a Chinese hamster ovary cell mutagenicity study, and a mouse bone marrow micronucleus study.

Impairment of Fertility

Posaconazole had no effect on fertility of male rats at a dose up to 180 mg/kg (1.7 x the 400-mg twice daily oral suspension regimen based on steady-state plasma concentrations in healthy volunteers) or female rats at a dose up to 45 mg/kg (2.2 x the 400-mg twice daily oral suspension regimen).

13.2 Animal Toxicology and/or Pharmacology

In a nonclinical study using intravenous administration of posaconazole in very young dogs (dosed from 2 to 8 weeks of age), an increase in the incidence of brain ventricle enlargement was observed in treated animals as compared with concurrent control animals. No difference in the incidence of brain ventricle enlargement between control and treated animals was observed following the subsequent 5-month treatment-free period. There were no neurologic, behavioral or developmental abnormalities in the dogs with this finding, and a similar brain finding was not seen with oral posaconazole administration to juvenile dogs (4 days to 9 months of age). There were no drug-related increases in the incidence of brain ventricle enlargement when treated and control animals were compared in a separate study of 10-week old dogs dosed with intravenous posaconazole for 13 weeks with a 9-week recovery period or a follow-up study of 31-week old dogs dosed for 3 months.

14 CLINICAL STUDIES

14.1 Treatment of Invasive Aspergillosis with Noxafil Injection and Noxafil Delayed-Release Tablets

Aspergillosis Treatment Study (NCT01782131) was a randomized, double-blind, controlled trial which evaluated the safety and efficacy of Noxafil injection and Noxafil delayed-release tablets versus voriconazole for primary treatment of invasive fungal disease caused by *Aspergillus* species. Eligible patients had proven, probable, or possible invasive fungal infections per the European Organization for Research and Treatment of Cancer/Mycoses Study Group, EORTC/MSG criteria. Patients were stratified by risk for mortality or poor outcome where high risk included a history of allogeneic bone marrow transplant, liver transplant, or relapsed leukemia undergoing salvage chemotherapy. The median age of patients was

57 years (range 14-91 years), with 27.8% of patients aged ≥65 years; 5 patients were pediatric patients 14-16 years of age, of whom 3 were treated with Noxafil and 2 with voriconazole. The majority of patients were male (59.8%) and white (67.1%). With regard to risk factors for invasive aspergillosis, approximately two-thirds of the patients in the study had a recent history of neutropenia, while approximately 20% with a history of an allogeneic stem cell transplant. Over 80% of subjects in each treatment group had infection limited to the lower respiratory tract (primarily lung), while approximately 11% to 13% also had infection in another organ. Invasive aspergillosis was proven or probable in 58.1% of patients as classified by independent adjudicators blinded to study treatment assignment. At least one *Aspergillus* species was identified in 21% of the patients; *A. fumigatus* and *A. flavus* were the most common pathogens identified.

Patients randomized to receive Noxafil were given a dose of 300 mg once daily (twice daily on Day 1) IV or tablet. Patients randomized to receive voriconazole were given a dose of 6 mg/kg twice daily Day 1 followed by 4 mg/kg twice daily IV, or oral 300 mg twice daily Day 1 followed by 200 mg twice daily. The recommended initial route of administration was IV; however, patients could begin oral therapy if clinically stable and able to tolerate oral dosing. The transition from IV to oral therapy occurred when the patient was clinically stable. The protocol recommended duration of therapy was 84 days with a maximum allowed duration of 98 days. Median treatment duration was 67 days for Noxafil patients and 64 days for voriconazole patients. Overall, 55% to 60% of patients began treatment with the IV formulation with a median duration of 9 days for the initial IV dosing.

The Intent to Treat (ITT) population included all patients randomized and receiving at least one dose of study treatment. All-cause mortality through Day 42 in the overall population (ITT) was 15.3% for Noxafil patients compared to 20.6% for voriconazole patients for an adjusted treatment difference of -5.3% with a 95% confidence interval of -11.6 to 1.0%. Consistent results were seen in patients with proven or probable invasive aspergillosis per EORTC criteria (see **Table 30**).

Table 30: Noxafil Injection and Noxafil Delayed-Release Tablets Invasive Aspergillosis Treatment Study: All-Cause Mortality Through Day 42

	Noxafil Injection and Delayed-Release Tablets		Voriconazole		
Population	N	n (%)	N	n (%)	Difference* (95% CI)
Intent to Treat	288	44 (15.3)	287	59 (20.6)	-5.3 (-11.6, 1.0)
Proven/Probable Invasive Aspergillosis	163	31 (19.0)	171	32 (18.7)	0.3 (-8.2, 8.8)
* Adjusted treatment difference based on Miettinen and Nurminen's method stratified by randomization factor (risk for mortality/poor outcome), using Cochran-Mantel-Haenszel weighting scheme.					

Global clinical response at Week 6 was assessed by a blinded, independent adjudication committee based upon prespecified clinical, radiologic, and mycologic criteria. In the subgroup of patients with proven or probable invasive aspergillosis per EORTC criteria, the global clinical response of success (complete or partial response) at Week 6 was seen in 44.8% for Noxafil-treated patients compared to 45.6% for voriconazole-treated patients (see **Table 31**).

Table 31: Noxafil Injection and Noxafil Delayed-Release Tablets Invasive Aspergillosis Treatment Study: Successful Global Clinical Response* at Week 6

	Posaconazole		Voriconazole		
Population	N	Success	N	Success	Difference† (95% CI)
Proven/Probable Invasive Aspergillosis	163	73 (44.8)	171	78 (45.6)	-0.6 (-11.2, 10.1)
* Successful Global Clinical Response was defined as survival with a partial or complete response. † Adjusted treatment difference based on Miettinen and Nurminen's method stratified by randomization factor (risk for mortality/poor outcome), using Cochran-Mantel-Haenszel weighting scheme.					

14.2 Prophylaxis of *Aspergillus* and *Candida* Infections with Noxafil Oral Suspension

Two randomized, controlled studies were conducted using Noxafil as prophylaxis for the prevention of invasive fungal infections (IFIs) among patients at high risk due to severely compromised immune systems.

The first study (Noxafil Oral Suspension Study 1) was a randomized, double-blind trial that compared Noxafil oral suspension (200 mg three times a day) with fluconazole capsules (400 mg once daily) as prophylaxis against invasive fungal infections in allogeneic hematopoietic stem cell transplant (HSCT) recipients with Graft versus Host Disease (GVHD). Efficacy of prophylaxis was evaluated using a composite endpoint of proven/probable IFIs, death, or treatment with systemic antifungal therapy (patients may have met more than one of these criteria). This assessed all patients while on study therapy plus 7 days and at 16 weeks post-randomization. The mean duration of therapy was comparable between the 2 treatment groups (80 days, Noxafil oral suspension; 77 days, fluconazole). **Table 32** contains the results from Noxafil Oral Suspension Study 1.

Table 32: Results from Blinded Clinical Study in Prophylaxis of IFI in All Randomized Patients with Hematopoietic Stem Cell Transplant (HSCT) and Graft-vs.-Host Disease (GVHD): Noxafil Oral Suspension Study 1

	Posaconazole n=301	**Fluconazole n=299**
On therapy plus 7 days		
Clinical Failure*	50 (17%)	55 (18%)
Failure due to:		
Proven/Probable IFI	7 (2%)	22 (7%)
(*Aspergillus*)	3 (1%)	17 (6%)
(*Candida*)	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†	27 (9%)	25 (8%)
Through 16 weeks		
Clinical Failure*,‡	99 (33%)	110 (37%)
Failure due to:		
Proven/Probable IFI	16 (5%)	27 (9%)
(*Aspergillus*)	7 (2%)	21 (7%)
(*Candida*)	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†	26 (9%)	30 (10%)
Event free lost to follow-up§	24 (8%)	30 (10%)

* Patients may have met more than one criterion defining failure.
† Use of systemic antifungal therapy (SAF) criterion is based on protocol definitions (empiric/IFI usage >4 consecutive days).
‡ 95% confidence interval (posaconazole-fluconazole) = (-11.5%, +3.7%).
§ 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.

The second study (Noxafil Oral Suspension Study 2) was a randomized, open-label study that compared Noxafil oral suspension (200 mg 3 times a day) with fluconazole suspension (400 mg once daily) or itraconazole oral solution (200 mg twice a day) as prophylaxis against IFIs in neutropenic patients who were receiving cytotoxic chemotherapy for AML or MDS. As in Noxafil Oral Suspension Study 1, efficacy of prophylaxis was evaluated using a composite endpoint of proven/probable IFIs, death, or treatment with systemic antifungal therapy (Patients might have met more than one of these criteria). This study assessed patients while on treatment plus 7 days and 100 days postrandomization. The mean duration of therapy was comparable between the 2 treatment groups (29 days, posaconazole; 25 days, fluconazole or itraconazole). **Table 33** contains the results from Noxafil Oral Suspension Study 2.

Table 33: Results from Open-Label Clinical Study 2 in Prophylaxis of IFI in All Randomized Patients with Hematologic Malignancy and Prolonged Neutropenia: Noxafil Oral Suspension Study 2

	Posaconazole	**Fluconazole/Itraconazole**

	n=304	n=298
On therapy plus 7 days		
Clinical Failure*,†	82 (27%)	126 (42%)
Failure due to:		
Proven/Probable IFI	7 (2%)	25 (8%)
(*Aspergillus*)	2 (1%)	20 (7%)
(*Candida*)	3 (1%)	2 (1%)
(Other)	2 (1%)	3 (1%)
All Deaths	17 (6%)	25 (8%)
Proven/probable fungal infection prior to death	1 (<1%)	2 (1%)
SAF‡	67 (22%)	98 (33%)
Through 100 days postrandomization		
Clinical Failure†	158 (52%)	191 (64%)
Failure due to:		
Proven/Probable IFI	14 (5%)	33 (11%)
(*Aspergillus*)	2 (1%)	26 (9%)
(*Candida*)	10 (3%)	4 (1%)
(Other)	2 (1%)	3 (1%)
All Deaths	44 (14%)	64 (21%)
Proven/probable fungal infection prior to death	2 (1%)	16 (5%)
SAF‡	98 (32%)	125 (42%)
Event free lost to follow-up§	34 (11%)	24 (8%)

* 95% confidence interval (posaconazole-fluconazole/itraconazole) = (-22.9%, -7.8%).
† Patients may have met more than one criterion defining failure.
‡ Use of systemic antifungal therapy (SAF) criterion is based on protocol definitions (empiric/IFI usage >3 consecutive days).
§ 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.

In summary, 2 clinical studies of prophylaxis were conducted with the Noxafil oral suspension. As seen in the accompanying tables (**Tables 32 and 33**), clinical failure represented a composite endpoint of breakthrough IFI, mortality and use of systemic antifungal therapy. In Noxafil Oral Suspension Study 1 (**Table 32**), the clinical failure rate of posaconazole (33%) was similar to fluconazole (37%), (95% CI for the difference posaconazole–comparator -11.5% to 3.7%) while in Noxafil Oral Suspension Study 2 (**Table 33**) clinical failure was lower for patients treated with posaconazole (27%) when compared to patients treated with fluconazole or itraconazole (42%), (95% CI for the difference posaconazole–comparator -22.9% to -7.8%).

All-cause mortality was similar at 16 weeks for both treatment arms in Noxafil Oral Suspension Study 1 [POS 58/301 (19%) vs. FLU 59/299 (20%)]; all-cause mortality was lower at 100 days for Noxafil-treated patients in Noxafil Oral Suspension Study 2 [POS 44/304 (14%) vs. FLU/ITZ 64/298 (21%)]. Both studies demonstrated fewer breakthrough infections caused by *Aspergillus* species in patients receiving Noxafil prophylaxis when compared to patients receiving fluconazole or itraconazole.

14.3 Treatment of Oropharyngeal Candidiasis with Noxafil Oral Suspension

Noxafil Oral Suspension Study 3 was a randomized, controlled, evaluator-blinded study in HIV-infected patients with oropharyngeal candidiasis. Patients were treated with Noxafil or fluconazole oral suspension (both Noxafil and fluconazole were given as follows: 100 mg twice a day for 1 day followed by 100 mg once a day for 13 days).

Clinical and mycological outcomes were assessed after 14 days of treatment and at 4 weeks after the end of treatment. Patients who received at least 1 dose of study medication and had a positive oral swish culture of *Candida* species at baseline were included in the analyses (see **Table 34**). The majority of the subjects had *C. albicans* as the baseline pathogen.

Clinical success at Day 14 (complete or partial resolution of all ulcers and/or plaques and symptoms) and clinical relapse rates (recurrence of signs or symptoms after initial cure or improvement) 4 weeks after the end of treatment were similar between the treatment arms (see **Table 34**).

Mycologic eradication rates (absence of colony forming units in quantitative culture at the end of therapy, Day 14), as well as mycologic relapse rates (4 weeks after the end of treatment) were also similar between the treatment arms (see **Table 34**).

Table 34: Noxafil Oral Suspension Clinical Success, Mycological Eradication, and Relapse Rates in Oropharyngeal Candidiasis

	Noxafil	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 posttreatment quantitative culture with ≤20 colony forming units (CFU/mL) were also similar between the two groups (Noxafil 68.0%, fluconazole 68.1%). The clinical significance of this finding is unknown.

14.4 Noxafil Oral Suspension Treatment of Oropharyngeal Candidiasis Refractory to Treatment with Fluconazole or Itraconazole

Noxafil Oral Suspension Study 4 was a noncomparative study of Noxafil oral suspension in HIV-infected subjects with OPC that was refractory to treatment with fluconazole or itraconazole. An episode of OPC was considered refractory if there was failure to improve or worsening of OPC after a standard course of therapy with fluconazole greater than or equal to 100 mg/day for at least 10 consecutive days or itraconazole 200 mg/day for at least 10 consecutive days and treatment with either fluconazole or itraconazole had not been discontinued for more than 14 days prior to treatment with Noxafil. Of the 199 subjects enrolled in this study, 89 subjects met these strict criteria for refractory infection.

Forty-five subjects with refractory OPC were treated with Noxafil oral suspension 400 mg twice daily for 3 days, followed by 400 mg once daily for 25 days with an option for further treatment during a 3-month maintenance period. Following a dosing amendment, a further 44 subjects were treated with posaconazole 400 mg twice daily for 28 days. The efficacy of Noxafil was assessed by the clinical success (cure or improvement) rate after 4 weeks of treatment. The clinical success rate was 74.2% (66/89). The clinical success rates for both the original and the amended dosing regimens were similar (73.3% and 75.0%, respectively).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Noxafil Injection

Noxafil injection is available as a clear, colorless to yellow sterile liquid in single-dose Type I glass vials closed with bromobutyl rubber stopper and aluminum seal (NDC 0085-4331-01) containing 300 mg of posaconazole in 16.7 mL of solution (18 mg of posaconazole per mL).

Noxafil Delayed-Release Tablets

Noxafil delayed-release tablets are available as yellow, coated, oblong, debossed with "100" on one side containing 100 mg of posaconazole. Bottles with child-resistant closures of 60 delayed-release tablets (NDC 0085-4324-02).

Noxafil Oral Suspension

Noxafil oral suspension is available as a white, cherry-flavored suspension in 4-ounce (123 mL) amber glass bottles with child-resistant closures (NDC 0085-1328-01) containing 105 mL of suspension (40 mg of posaconazole per mL).

Supplied with each oral suspension bottle is a plastic dosing spoon calibrated for measuring 2.5-mL and 5-mL doses.

Noxafil PowderMix for Delayed-Release Oral Suspension

Noxafil PowderMix for delayed-release oral suspension is supplied as:

- Package A: a kit with 8 child-resistant single-use packets of Noxafil PowderMix for delayed-release oral suspension 300 mg, two 3 mL (green) notched tip syringes, two 10 mL (blue) notched tip syringes, two mixing cups, one mixing liquid bottle, and one bottle adapter for the mixing liquid bottle.
- Package B: a box of six 3 mL (green) and six 10 mL (blue) notched tip syringes.

- Packages A and B are supplied separately.

NDC 0085-2224-02 unit of use carton with 8 packets.
NDC 0085-2224-01 individual packet.

16.2 Storage and Handling

Noxafil Injection

Noxafil injection vial should be stored refrigerated at 2 to 8°C (36 to 46°F). Storage conditions for the diluted solution are presented in another section of the prescribing information *[see Dosage and Administration (2.4)].*

Noxafil Delayed-Release Tablets

Store at 20 to 25°C (68 to 77°F), excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

Noxafil Oral Suspension

Store at 25°C (77°F); excursions permitted to 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature]. **DO NOT FREEZE.**

Noxafil PowderMix for Delayed-Release Oral Suspension

Store the entire kit at 20 to 25°C (68 to 77°F), excursions permitted to 15 to 30°C (59 to 86°F) in a clean, dry place. Do not open foil packet containing Noxafil PowderMix for delayed-release oral suspension until ready for use. Storage conditions for the reconstituted solution are presented in another section of the prescribing information *[see Dosage and Administration (2.8)].*

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Important Administration Instructions

Noxafil Delayed-Release Tablets

Advise patients that Noxafil delayed-release tablets must be swallowed whole and not divided, crushed, or chewed.

Instruct patients that if they miss a dose, they should take it as soon as they remember. If they do not remember until it is within 12 hours of the next dose, they should be instructed to skip the missed dose and go back to the regular schedule. Patients should not double their next dose or take more than the prescribed dose.

Noxafil Oral Suspension

Advise patients to take each dose of Noxafil oral suspension during or immediately (i.e., within 20 minutes) following a full meal. In patients who cannot eat a full meal, each dose of Noxafil oral suspension should be administered with a liquid nutritional supplement or an acidic carbonated beverage (e.g., ginger ale) in order to enhance absorption.

Instruct patients that if they miss a dose, they should take it as soon as they remember. However, if it is almost time for the next dose, they should be instructed to skip the missed dose and go back to the regular schedule. Patients should not double their next dose or take more than the prescribed dose.

Noxafil PowderMix for Delayed-Release Oral Suspension

Instruct parents and/or caregivers that ONLY the provided notched tip syringes can be used to administer Noxafil PowderMix for delayed-release oral suspension to pediatric patients.

Advise patients to take Noxafil PowderMix for delayed-release oral suspension with food.

Drug Interactions

Advise patients to inform their physician immediately if they:

- develop severe diarrhea or vomiting.
- are currently taking drugs that are known to prolong the QTc interval and are metabolized through CYP3A4.
- are currently taking a cyclosporine or tacrolimus, or they notice swelling in an arm or leg or shortness of breath.

- are taking other drugs or before they begin taking other drugs as certain drugs can decrease or increase the plasma concentrations of posaconazole.

Serious and Potentially Serious Adverse Reactions

Advise patients to inform their physician immediately if they:

- notice a change in heart rate or heart rhythm or have a heart condition or circulatory disease. Noxafil can be administered with caution to patients with potentially proarrhythmic conditions.
- are pregnant, plan to become pregnant, or are nursing.
- have liver disease or develop itching, nausea or vomiting, their eyes or skin turn yellow, they feel more tired than usual or feel like they have the flu.
- have ever had an allergic reaction to other antifungal medicines such as ketoconazole, fluconazole, itraconazole, or voriconazole.

Hereditary Fructose Intolerance (HFI)

Inform patients and caregivers that Noxafil PowderMix for delayed-release oral suspension contains sorbitol and can be life-threatening when administered to patients with hereditary fructose intolerance (HFI) *[see Warnings and Precautions (5.8)]*. Inquire for symptoms of sorbitol/fructose and/or sucrose intolerance before administration.

Manuf. for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

For patent information: www.merck.com/product/patent/home.html

uspi-mk5592-mf-2112r047

Patient Information

Noxafil® (**NOX**-a-fil)
(posaconazole) injection
Noxafil® (**NOX**-a-fil)
(posaconazole) delayed-release tablets
Noxafil® (**NOX**-a-fil)
(posaconazole) oral suspension
Noxafil® (**NOX**-a-fil) PowderMix
(posaconazole) for delayed-release oral suspension

What is Noxafil and Noxafil PowderMix?

Noxafil (which refers to injection, delayed-release tablets, and oral suspension) and Noxafil PowderMix (for delayed-release oral suspension) are prescription medicines used in adults and children to help prevent or treat fungal infections that can spread throughout your body (invasive fungal infections). These infections are caused by fungi called *Aspergillus* or *Candida*. Noxafil and Noxafil PowderMix are used in people who have an increased chance of getting these infections due to a weak immune system. These include people who have had a hematopoietic stem cell transplantation (bone marrow transplant) with graft versus host disease or those with a low white blood cell count due to chemotherapy for blood cancers (hematologic malignancies).

Noxafil injection is used for:

- prevention of fungal infections in adults and children 2 years of age and older.
- treatment of fungal infections in adults and children 13 years of age and older.

Noxafil delayed-release tablets are used for:

- prevention of fungal infections in adults and children 2 years of age and older who weigh greater than 88 lbs (40 kg).
- treatment of fungal infections in adults and children 13 years of age and older.

Noxafil oral suspension is used for:

- prevention of fungal infections in adults and children 13 years of age and older.

Noxafil PowderMix for delayed-release oral suspension is used for:

- prevention of fungal infections in children 2 years of age and older who weigh 88 lbs (40 kg) or less.

Noxafil oral suspension is also used to treat a fungal infection called “thrush” caused by *Candida* in your mouth or throat area. **Noxafil oral suspension** can be used as the first treatment for thrush, or as another treatment for thrush after itraconazole or fluconazole treatment has not worked.

Noxafil oral suspension is for adults and children 13 years of age and older.

It is not known if Noxafil or Noxafil PowderMix is safe and effective in children under 2 years of age.

Who should not take Noxafil or Noxafil PowderMix?

Do not take Noxafil or Noxafil PowderMix if you:

- are allergic to posaconazole, any of the ingredients in Noxafil or Noxafil PowderMix, or other azole antifungal medicines. See the end of this leaflet for a complete list of ingredients in Noxafil and Noxafil PowderMix.
- are taking any of the following medicines:
  - sirolimus
  - pimozide
  - quinidine
  - certain statin medicines that lower cholesterol (atorvastatin, lovastatin, simvastatin)
  - ergot alkaloids (ergotamine, dihydroergotamine)
- have chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) and you have just started taking venetoclax or your venetoclax dose is being slowly increased.
- are taking **Noxafil PowderMix for delayed-release oral suspension** and have hereditary fructose intolerance.

Ask your healthcare provider or pharmacist if you are not sure if you are taking any of these medicines.
Do not start taking a new medicine without talking to your healthcare provider or pharmacist.

What should I tell my healthcare provider before taking Noxafil or Noxafil PowderMix?

Before you take Noxafil or Noxafil PowderMix, tell your healthcare provider if you:

- are taking certain medicines that lower your immune system like cyclosporine or tacrolimus.

- are taking certain drugs for HIV infection, such as ritonavir, atazanavir, efavirenz, or fosamprenavir. Efavirenz and fosamprenavir can cause a decrease in the Noxafil levels in your body. Efavirenz and fosamprenavir should not be taken with Noxafil or Noxafil PowderMix.
- are taking midazolam, a hypnotic and sedative medicine.
- are taking vincristine, vinblastine and other "vinca alkaloids" (medicines used to treat cancer).
- are taking venetoclax, a medicine used to treat cancer.
- have or had liver problems.
- have or had kidney problems.
- have or had an abnormal heart rate or rhythm, heart problems, or blood circulation problems.
- are pregnant or plan to become pregnant. It is not known if Noxafil will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if Noxafil passes into your breast milk. You and your healthcare provider should decide if you will take Noxafil or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Noxafil and Noxafil PowderMix can affect the way other medicines work, and other medicines can affect the way Noxafil and Noxafil PowderMix work, and can cause serious side effects.

Especially tell your healthcare provider if you take:

- rifabutin or phenytoin. If you are taking these medicines, you should not take **Noxafil delayed-release tablets**, **Noxafil oral suspension**, or **Noxafil PowderMix for delayed-release oral suspension**.
- cimetidine or esomeprazole. If you are taking these medicines, you should not take **Noxafil oral suspension**.

Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure.

Know the medicines you take. Keep a list of them with you to show your healthcare provider or pharmacist when you get a new medicine.

How will I take Noxafil or Noxafil PowderMix?

- **Do not switch between Noxafil oral suspension and Noxafil delayed-release tablets or Noxafil PowderMix for delayed-release oral suspension**.
- Take Noxafil or Noxafil PowderMix exactly as your healthcare provider tells you to take it.
- Your healthcare provider will tell you how much Noxafil or Noxafil PowderMix to take and when to take it.
- Take Noxafil or Noxafil PowderMix for as long as your healthcare provider tells you to take it.
- If you take too much Noxafil or Noxafil PowderMix, call your healthcare provider or go to the nearest hospital emergency room right away.
- Noxafil injection is usually given over 30 to 90 minutes through a plastic tube placed in your vein.
- **Noxafil delayed-release tablets:**
  - Take Noxafil delayed-release tablets with or without food.
  - Take Noxafil delayed-release tablets whole. Do not break, crush, or chew Noxafil delayed-release tablets before swallowing. If you cannot swallow Noxafil delayed-release tablets whole, tell your healthcare provider. You may need a different medicine.
  - If you miss a dose, take it as soon as you remember and then take your next scheduled dose at its regular time. If it is within 12 hours of your next dose, do not take the missed dose. Skip the missed dose and go back to your regular schedule. Do not double your next dose or take more than your prescribed dose.
- **Noxafil oral suspension:**
  - Shake Noxafil oral suspension well before use.
  - Take each dose of Noxafil oral suspension during or within 20 minutes after a full meal. If you cannot eat a full meal, take each dose of Noxafil oral suspension with a liquid nutritional supplement or an acidic carbonated beverage, like ginger ale.
  - A measured dosing spoon comes with your Noxafil oral suspension and is marked for doses of **2.5 mL** and **5 mL**. **See Figure A.**

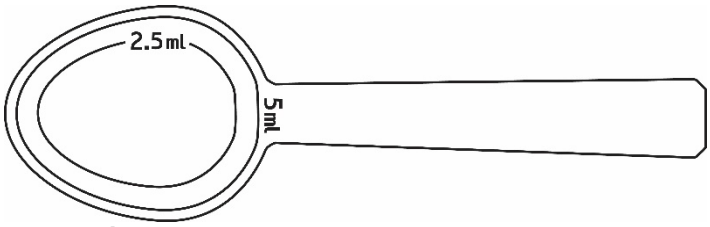

Figure A

  - Rinse the spoon with water after each dose of Noxafil oral suspension and before you store it away.

- If you miss a dose, take it as soon as you remember. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not take a double dose to make up for the missed dose.

- **Noxafil PowderMix for delayed-release oral suspension:**
  - Before giving the first dose of Noxafil PowderMix for delayed-release oral suspension, **read the Instructions for Use booklet that comes with Noxafil PowderMix for delayed-release oral suspension** for information about the correct way to mix and give a dose of Noxafil PowderMix for delayed-release oral suspension to your child. **Keep the booklet and follow it each time you prepare the medicine. Bring this booklet to your child's appointments.**
  - If you have questions about how to mix or give Noxafil PowderMix, talk with your healthcare provider or pharmacist.
  - Only use the mixing liquid that comes with the kit to prepare Noxafil PowderMix.
  - Once mixed, measure the prescribed dose with notched tip syringe provided with the kit. **Only use the notched tip syringes that come with the kit to prepare and administer the medicine.**
  - **Give the dose within 1 hour of mixing the suspension. Give with food.**
  - **If your child does not take all of the prescribed dose or spits some of it out, call your healthcare provider to find out what to do.**

Follow the instructions from your healthcare provider on how much Noxafil or Noxafil PowderMix you should take and when to take it.

What are the possible side effects of Noxafil or Noxafil PowderMix?

Noxafil or Noxafil PowderMix may cause serious side effects, including:

- **drug interactions with cyclosporine or tacrolimus.** If you take Noxafil or Noxafil PowderMix with cyclosporine or tacrolimus, your blood levels of cyclosporine or tacrolimus may increase. Serious side effects can happen in your kidney or brain if you have high levels of cyclosporine or tacrolimus in your blood. Your healthcare provider should do blood tests to check your levels of cyclosporine or tacrolimus if you are taking these medicines while taking Noxafil or Noxafil PowderMix. Tell your healthcare provider right away if you have swelling in your arm or leg or shortness of breath.

- **problems with the electrical system of your heart (arrhythmias and QTc prolongation).** Certain medicines used to treat fungus called azoles, including posaconazole, the active ingredient in Noxafil and Noxafil PowderMix, may cause heart rhythm problems. People who have certain heart problems or who take certain medicines have a higher chance for this problem. Tell your healthcare provider right away if your heartbeat becomes fast or irregular.

- **changes in body salt (electrolytes) levels in your blood.** Your healthcare provider should check your electrolytes while you are taking Noxafil or Noxafil PowderMix.

- **liver problems.** Some people who also have other serious medical problems may have severe liver problems that may lead to death, especially if you take certain doses of Noxafil or Noxafil PowderMix. Your healthcare provider should do blood tests to check your liver while you are taking Noxafil or Noxafil PowderMix. Call your healthcare provider right away if you have any of the following symptoms of liver problems:
  - itchy skin
  - nausea or vomiting
  - yellowing of your eyes or skin
  - feeling very tired
  - flu-like symptoms

- **increased amounts of midazolam in your blood.** If you take Noxafil or Noxafil PowderMix with midazolam, Noxafil or Noxafil PowderMix increases the amount of midazolam in your blood. This can make your sleepiness last longer. Your healthcare provider should check you closely for side effects if you take midazolam with Noxafil or Noxafil PowderMix.

The most common side effects of Noxafil in adults include:

- diarrhea
- nausea
- fever
- vomiting
- headache
- coughing
- low potassium levels in the blood

The most common side effects of Noxafil injection and Noxafil PowderMix in children include:

- fever
- itching
- high blood pressure

- fever with low white blood cell count (febrile neutropenia)
- vomiting
- redness and sores of the lining of the mouth, lips, throat, stomach, and genitals (mucositis or stomatitis)
- low potassium levels in the blood

If you take Noxafil delayed-release tablets, Noxafil oral suspension, or Noxafil PowderMix for delayed-release oral suspension, tell your healthcare provider right away if you have diarrhea or vomiting.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of Noxafil or Noxafil PowderMix. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Noxafil or Noxafil PowderMix?

Noxafil injection

- Store Noxafil injection refrigerated at 36°F to 46°F (2°C to 8°C).

Noxafil delayed-release tablets

- Store Noxafil delayed-release tablets at room temperature between 68°F to 77°F (20°C to 25°C).

Noxafil oral suspension

- Store Noxafil oral suspension at room temperature between 68°F to 77°F (20°C to 25°C).
- Do **not** freeze Noxafil oral suspension.

Noxafil PowderMix for delayed-release oral suspension

- Store the entire kit at room temperature between 68°F to 77°F (20°C to 25°C) in a clean, dry place.
- Do not open the foil packet until ready for use.

Safely throw away medicine that is out of date or no longer needed.

Keep Noxafil and Noxafil PowderMix and all medicines out of the reach of children.

General information about the safe and effective use of Noxafil and Noxafil PowderMix.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use Noxafil or Noxafil PowderMix for a condition for which it was not prescribed. Do not give Noxafil or Noxafil PowderMix to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about Noxafil or Noxafil PowderMix that is written for health professionals.

What are the ingredients in Noxafil and Noxafil PowderMix?

Active ingredient: posaconazole

Inactive ingredients:

Noxafil injection: Betadex Sulfobutyl Ether Sodium (SBECD), edetate sodium, hydrochloric acid, sodium hydroxide, and water for injection.

Noxafil delayed-release tablets: croscarmellose sodium, hydroxypropylcellulose, hypromellose acetate succinate, iron oxide yellow, Macrogol/PEG 3350, magnesium stearate, microcrystalline cellulose, polyvinyl alcohol partially hydrolyzed, silicon dioxide, talc, and titanium dioxide.

Noxafil oral suspension: artificial cherry flavor, citric acid monohydrate, glycerin, liquid glucose, polysorbate 80, purified water, simethicone, sodium benzoate, sodium citrate dihydrate, titanium dioxide, and xanthan gum.

Noxafil PowderMix for delayed-release oral suspension: hypromellose acetate succinate. The mixing liquid contains: anhydrous citric acid, antifoam Af emulsion, berry citrus sweet flavor, carboxymethylcellulose sodium, carrageenan calcium sulfate trisodium phosphate, glycerin, methylparaben, microcrystalline cellulose, potassium sorbate, propylparaben, purified water, sodium citrate, sodium phosphate monobasic monohydrate, sodium saccharin, sorbitol solution, and xanthan gum.

Manuf. for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

usppi-mk5592-mf-2112r021

For more information, go to www.noxafil.com or call 1-800-672-6372.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 1/2022