

NOXAFIL® 100 mg

LPC-MK5592-T-052022a

MODIFIED RELEASE TABLET

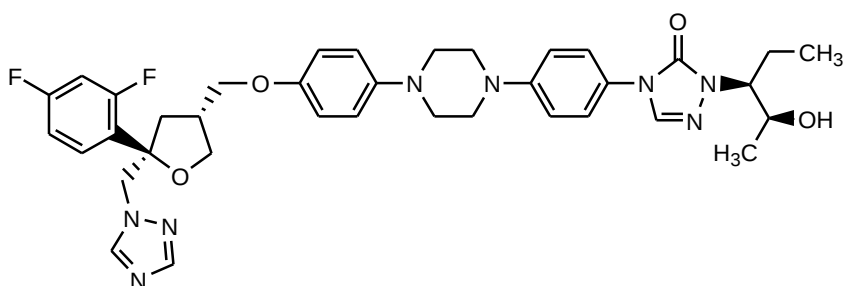
Product Information

NAME OF THE MEDICINE

Posaconazole

Posaconazole is a broad spectrum triazole antifungal compound with a molecular formula of $C_{37}H_{42}F_2N_8O_4$ yielding a molecular weight of 700.8.

The chemical structure, which possesses four chiral centres, two R and two S, and chemical name are illustrated below:



CAS INDEX NAME: D-threo-Pentitol, 2,5-anhydro-1,3,4-trideoxy-2-C-(2,4-difluorophenyl)-4-[[4-[4-[4-[1-[(1S,2S)-1-ethyl-2-hydroxypropyl]-1,5-dihydro-5-oxo-4H-1,2,4-triazol-4-yl]phenyl]-1-piperazinyl]phenoxy]methyl]-1-(1H-1,2,4-triazol-1-yl)]

CAS RN 171228-49-2.

IUPAC NAME: 4-4-[4-(4-[(3R, 5R)-5-(2,4-difluorophenyl)-5-(1H-1,2,4-triazol-1-yl)methyl]tetrahydro-3-furanyl]methoxyphenyl)piperazino]phenyl-1-[(1S,2S)-1-ethyl-2-hydroxypropyl]-4,5-dihydro-1H-1,2,4-triazol-5-one.

DESCRIPTION

Posaconazole is a white to off-white crystalline powder. It has a melting range of 164° – 165°C and is insoluble in water.

Noxafil® 100 mg modified release tablet is a yellow-coated, capsule-shaped tablet debossed with “100” on one side containing 100 mg of posaconazole.

List of excipients

Hypromellose acetate succinate, microcrystalline cellulose, hydroxypropylcellulose, silicon dioxide, croscarmellose sodium, magnesium stearate, and Opadry® II Yellow [consists of the following ingredients: polyvinyl alcohol partially hydrolyzed, Macrogol/PEG 3350 (polyethylene glycol 3350), titanium dioxide (E171), talc, and iron oxide yellow (E172)].

PHARMACOLOGY

Pharmacodynamic properties

Pharmacotherapeutic Group

Antiinfective for Systemic Use, Triazole derivative, J02AC04

Mechanism of action:

Posaconazole is a triazole antifungal agent. It is an inhibitor of the enzyme lanosterol 14 α -demethylase, which catalyses an essential step in ergosterol biosynthesis. Ergosterol depletion, coupled with the accumulation of methylated sterol precursors, is thought to impair membrane integrity and the function of some membrane-associated proteins. This results in the inhibition of cell growth and/or cell death.

Consequently, posaconazole exhibits broad-spectrum antifungal activity against a variety of yeasts and moulds including species of *Candida* (including *C. albicans* isolates resistant to fluconazole, voriconazole and itraconazole, *C. krusei* and *C. glabrata* which are inherently less susceptible to fluconazole, and *C. lusitaniae* which is inherently less susceptible to amphotericin B), *Aspergillus* (including isolates resistant to fluconazole, voriconazole, itraconazole and amphotericin B) and organisms not previously regarded as being susceptible to azoles such as the zygomycetes (e.g. species of *Absidia*, *Mucor*, *Rhizopus* and *Rhizomucor*).

In vitro posaconazole exhibited fungicidal activity against species of *Aspergillus*, dimorphic fungi (*Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Penicillium marneffe*, and *Coccidioides immitis*) and some species of *Candida*. In animal infection models posaconazole was active against a wide variety of fungal infections caused by moulds or yeasts. However, there was no consistent correlation between minimum inhibitory concentration and efficacy.

Microbiology:

Posaconazole has been shown *in vitro* and in clinical infections to be active against the following microorganisms: (See Indications): *Aspergillus* species (*Aspergillus fumigatus*, *A. flavus*, *A. terreus*, *A. nidulans*, *A. niger*, *A. ustus*, *A. ochraceus*), *Candida* species (*Candida albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis*), *Cryptococcus neoformans*, *Coccidioides immitis*, *Fonsecaea pedrosoi*, *Histoplasma capsulatum*, *Pseudallescheria boydii* and species of *Alternaria*, *Exophiala*, *Fusarium*, *Ramichloridium*, *Rhizomucor*, *Mucor*, and *Rhizopus*. While posaconazole has been used in a clinical setting against these microorganisms, sufficient evidence for efficacy has not been collected for all the listed microorganisms (see Clinical Trials).

Posaconazole also exhibits *in vitro* activity against the following yeasts and moulds: *Candida dubliniensis*, *C. famata*, *C. guilliermondii*, *C. lusitaniae*, *C. kefyr*, *C. rugosa*, *C. tropicalis*, *C. zeylanoides*, *C. inconspicua*, *C. lipolytica*, *C. norvegensis*, *C. pseudotropicalis*, *Cryptococcus laurentii*, *Kluyveromyces marxianus*, *Saccharomyces cerevisiae*, *Yarrowia lipolytica*, species of *Pichia*, and *Trichosporon*, *Aspergillus sydowii*, *Bjerkandera adusta*, *Blastomyces dermatitidis*, *Epidermophyton floccosum*, , *Paracoccidioides brasiliensis*, , *Scedosporium apiospermum*, *Sporothrix schenckii*, *Wangiella dermatitidis* and species of *Absidia*, *Apophysomyces*, *Bipolaris*, *Curvularia*, *Microsporum*, *Paecilomyces*, *Penicillium*, and *Trichophyton*. However, the safety and effectiveness of posaconazole in treating clinical infections due to these microorganisms have not been established in clinical trials.

The following *in vitro* data are available, but their clinical significance is unknown. In a surveillance study of > 3,000 clinical mould isolates from 2010-2018, 90 % of non-*Aspergillus* fungi exhibited the following *in vitro* minimum inhibitory concentration (MIC): *Mucorales* spp (n=81) of 2 mg/L; *Scedosporium apiospermum*/*S. boydii* (n=65) of 2 mg/L; *Exophiala dermatitidis* (n=15) of 0.5 mg/L, and *Purpureocillium lilacinum* (n=21) of 1 mg/L.

Posaconazole exhibits broad-spectrum antifungal activity against some yeasts and moulds not generally responsive to azoles, or resistant to other azoles:

- species of *Candida* (including *C. albicans* isolates resistant to fluconazole, voriconazole and itraconazole,
- *C. krusei* and *C. glabrata* which are inherently less susceptible to fluconazole,

- *C. lusitaniae* which is inherently less susceptible to amphotericin B),
- *Aspergillus* (including isolates resistant to fluconazole, voriconazole, itraconazole and amphotericin B)
- organisms not previously regarded as being susceptible to azoles such as the zygomycetes (e.g. species of *Absidia*, *Mucor*, *Rhizopus* and *Rhizomucor*).

In vitro posaconazole exhibited fungicidal activity against species of:

- *Aspergillus*,
- dimorphic fungi (*Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Penicillium marneffe*,
- *Coccidioides immitis*)
- some species of *Candida*.

In animal infection models posaconazole was active against a wide variety of fungal infections caused by moulds or yeasts. However, there was no consistent correlation between minimum inhibitory concentration and efficacy.

Specimens for fungal culture and other relevant laboratory studies (including histopathology) should be obtained prior to therapy to isolate and identify causative organism(s). Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

Drug Resistance:

C. albicans strains resistant to posaconazole could not be generated in the laboratory; spontaneous laboratory *Aspergillus fumigatus* mutants exhibiting a decrease in susceptibility to posaconazole arose at a frequency of 1×10^{-8} to 1×10^{-9} . Clinical isolates of *Candida albicans* and *Aspergillus fumigatus* exhibiting significant decreases in posaconazole susceptibility are rare. In those rare instances where decreased susceptibility was noted, there was no clear correlation between decreased susceptibility and clinical failure. Clinical success has been observed in patients infected with organisms resistant to other azoles; consistent with these observations posaconazole was active *in vitro* against many *Aspergillus* and *Candida* strains that developed resistance to other azoles and/or amphotericin B. Breakpoints for posaconazole have not been established for any fungi.

Antifungal drug combinations:

When combinations of posaconazole with either amphotericin B or caspofungin were tested *in vitro* and *in vivo* there was little or no antagonism and in some instances there was an additive effect. Clinical studies of posaconazole in combination with antifungal drugs including amphotericin B-based drugs and caspofungin have not been conducted.

Pharmacokinetic Properties

The general pharmacokinetic findings across the clinical program in both healthy volunteers and patients were consistent, in that posaconazole modified release was slowly absorbed and slowly eliminated with an extensive volume of distribution.

Exposure following multiple administration of posaconazole tablets (200 or 300 mg) QD was 1.3 times higher in healthy volunteers than in patients.

Absorption:

When given orally in healthy volunteers, posaconazole modified release tablets are absorbed with a median T_{max} of 4 to 5 hours. Posaconazole modified release tablets exhibit dose proportional pharmacokinetics after single and multiple dosing up to 300 mg. Steady-state plasma concentrations are attained by Day 6 at the 300 mg dose (QD after BD loading dose at Day 1). The absolute bioavailability of the oral modified release tablet is approximately 54 %. Relative bioavailability was investigated between the 100 mg modified release tablet under fasted conditions and the 100 mg oral suspension under fed conditions in healthy adults. Under these conditions, plasma exposure to posaconazole for the two treatments was similar. Under fasted conditions, the exposure of posaconazole after single-dose modified release tablet administration was 3.7-fold higher than the oral suspension.

Effect of food on oral absorption healthy volunteers:

In a single dose study (P112) investigating the effect of a high fat meal on the bioavailability of posaconazole following administration of NOXAFIL modified release tablets 300 mg (3 x 100 mg) in healthy volunteers, the C_{max} was 16 % higher and the AUC₀₋₇₂ hours was 51 % higher with food relative to fasting. The results of the study are summarised below in Table 1. The effect of food on the absorption of NOXAFIL modified release tablets is not considered clinically meaningful. Food effect was taken into consideration at the time of

final dose selection of the 300 mg modified release tablet based on data from the pivotal clinical Phase 1b/Phase 3 pharmacokinetic/safety study P5615 in which patients took NOXAFIL modified release tablets without regard to food intake. NOXAFIL modified release tablets can therefore be administered with or without food. Posaconazole modified release tablets can be taken without regard to food.

TABLE 1: Statistical comparison of plasma pharmacokinetics of Posaconazole following single oral dose administration of 300 mg Posaconazole (as 3 tablets of 100 mg) to healthy subjects under fasting and fed conditions

	Fasting Conditions		Fed Conditions (High Fat Meal)*		Fed/Fasting
Pharmacokinetic Parameter	N	GM (95 % CI)	N	GM (95 % CI)	GMR (90 % CI)
C _{max} ⁺ (ng/mL)	14	893 (731, 1090)	16	1,040 (915, 1180)	1.16 (0.96, 1.41)
AUC _{0-last} [‡] hr• ng/mL	14	25600 (21500, 30400)	16	38700 (35000, 42700)	1.51 (1.33, 1.72)
T _{max} [§] (hr)	14	5.00 (3.00, 8.00)	16	6.0 (5.00, 24.00)	N/A

GM = Geometric least-squares mean; GMR = Geometric least-squares mean ratio;

CI = Confidence interval

* 48.5 g fat

⁺C_{max} = maximum observed concentration

[‡]AUC_{0-last} = AUC_{0-72hr}

[§]Median (Min, Max) reported for T_{max}

Distribution:

Posaconazole, after administration of the modified release tablet, has a mean apparent volume of distribution of 394 L (42 %), ranging between 294-583 L among the studies in healthy volunteers.

Posaconazole is highly protein bound (> 98.0 %), predominantly to serum albumin.

Metabolism:

Posaconazole does not have any major circulating metabolites and its concentrations are unlikely to be altered by inhibitors of CYP450 enzymes. Of the circulating metabolites, the majority are glucuronide conjugates of posaconazole with only minor amounts of oxidative (CYP450 mediated) metabolites observed. The excreted metabolites in urine and faeces account for approximately 17 % of the administered radio-labelled dose.

Excretion:

Posaconazole is predominantly excreted in the faeces (77 % of the radio-labelled dose) with the major component eliminated as parent drug (66 % of the radio-labelled dose). Renal clearance is a minor elimination pathway, with 14 % of the radio-labelled dose excreted in urine (< 0.2 % of the radio-labelled dose is parent drug).

Posaconazole modified release tablet is eliminated with a mean half-life ($t_{1/2}$) ranging between 26 and 31 hours and a mean apparent clearance ranging from 7.5 to 11 L/hr.

Summary of the mean pharmacokinetic parameters in patients:

The mean pharmacokinetic parameters in patients and healthy volunteers following administration of posaconazole modified release tablet 300 mg daily are displayed in Table 2a. Patients have approximately 25 % lower exposure as compared to healthy volunteers after multiple dosing of posaconazole modified release tablet. The differences in exposure between healthy volunteers and patients are much less than the exposure differences reported for posaconazole oral suspension.

TABLE 2a: Pharmacokinetics of posaconazole modified release tablets in patients and healthy volunteers

Population	Dose	Mean (%CV)		
		C _{max} (ng/mL)	T _{max} ^a (hr)	AUC(τ) (ng•hr/mL)
Healthy Volunteers	300 mg/day (n=12)	2764 (21)	3.98 (3 - 6)	51618 (25)
Patients	300 mg/day (n=50)	2090 (38)	4 (1.3 - 8.1)	37900 (42)

a: Median (range)

Simulation based on the population pharmacokinetic model was performed in patients receiving posaconazole modified release tablet 300 mg daily (following 300 mg BD on Day 1). Simulated pharmacokinetics in patients and subpopulations of AML/MDS and HSCT patients are displayed in Table 3b.

TABLE 2b: Simulated multiple dose pharmacokinetics of posaconazole modified release tablets by patient sub population

Patient sub population	Dose	Mean (%CV)	
		AUC(τ) (ng•hr/mL)	C _{avg} (ng/mL)
AML/MDS	300 mg/day (n=1000)	40031 (53)	1668 (53)
HSCT*	300 mg/day (n=1000)	47307 (53)	1971 (53)
Total	300 mg/day (n=2000)	43669 (54)	1820 (54)

n= number of simulated patients; AUC(τ): Area under the concentration versus time curve during a dosing interval τ

at steady state: C_{avg}: AUC(τ)/τ

*In the population PK model developed for POS modified release tablet, HSCT patients were considered not different from the healthy volunteer population.

Co-administration of food, or medications known to alter gastric pH (antacid, ranitidine, esomeprazole) or motility (metoclopramide) shows no clinically meaningful effect on the pharmacokinetics of posaconazole when administered as a modified release tablet.

In Table 3 a comparison is shown of exposure (C_{avg}) in patients after administration of posaconazole modified release tablet and posaconazole oral suspension at therapeutic doses.

TABLE 3: Mean C_{avg} exposure at steady state from pivotal patient studies with Posaconazole modified release tablet and Posaconazole oral suspension

	Posaconazole modified release tablet	Posaconazole oral suspension		
	Prophylaxis in AML and HSCT	Prophylaxis in GVHD	Prophylaxis in Neutropenia	Treatment - Invasive Aspergillosis
Study	P05615	C98-316	P01899	P00041
Dose	300 mg QD	200 mg TDS	200 mg TDS	POS 200 mg QID (hospitalized) then 400 mg BD
Mean C_{avg} (ng/mL) (%CV)	=1970 (56%)*	1122 (67%)	583 (65%)	841 (83%)
Quartile	pC_{avg} range (ng/mL)	C_{avg} range (ng/mL)	C_{avg} range (ng/mL)	C_{avg} range (ng/mL)
Q1	442-1223	22-557	90-332	55-277
Response	N/A	55.6%	45.3%	24%
Q2	1240-1710	557-915	322-490	290-544
Response	N/A	79.4%	63.0%	53%
Q3	1719-2291	915-1563	490-734	550-861

Response	N/A	82.5%	53.7%	53%
Q4	2304-9523	550-861	734-2200	877-2010
Response	N/A	53%	72.2%	71%

mean C_{avg} = the average concentration when measured at steady state

* pC_{avg} = predicted C_{avg}

Pharmacokinetics in Special Populations:

Paediatric (< 18 years)

There is limited paediatric experience for posaconazole tablets.

Following administration of 800 mg per day of posaconazole oral suspension as a divided dose for treatment of invasive fungal infections, mean trough plasma concentrations from 12 patients 8 - 17 years of age (776 ng/ml) were similar to concentrations from 194 patients 18 - 64 years of age (817 ng/ml). No pharmacokinetic data are available from paediatric patients less than 8 years of age. Similarly, in the prophylaxis studies, the mean steady-state posaconazole average concentration (C_{avg}) was comparable among ten adolescents (13-17 years of age) to C_{avg} achieved in adults (≥ 18 years of age).

In a study of 136 neutropenic paediatric patients 11 months – 17 years treated with posaconazole oral suspension, at doses up to 18 mg/kg/day divided TID, approximately 50 % met the prespecified target (Day 7 C_{avg} between 500 ng/mL-2500 ng/mL).

In general, exposures tended to be higher in the older patients (7 to <18 years) than in younger patients (2 to <7 years)

Gender

The pharmacokinetics of posaconazole are comparable in men and women. No adjustment in the dosage of NOXAFIL is necessary based on gender.

Geriatric

The pharmacokinetics of posaconazole modified release tablets are comparable in young and elderly subjects. No overall differences in safety were observed between the geriatric patients and younger patients; therefore, no dosage adjustment is recommended for geriatric patients.

Race

There is insufficient data among different races with posaconazole modified release tablets.

Weight

Pharmacokinetic modeling for posaconazole suggests that patients weighing greater than 120 kg may have lower posaconazole exposure. It is, therefore, suggested to closely monitor for breakthrough fungal infections in patients weighing more than 120 kg.

Renal insufficiency

Following single-dose administration, there was no effect of mild and moderate renal insufficiency ($n=18$, $Cl_{cr} \geq 20$ mL/min/1.73 m²) on posaconazole pharmacokinetics, therefore, no dose adjustment is required. In subjects with severe renal insufficiency ($n=6$, $Cl_{cr} < 20$ mL/min/1.73 m²), the exposure of posaconazole was highly variable (96 % CV) compared to the exposure in the other renal groups (40 % CV). However, as posaconazole is not significantly renally eliminated, an effect of severe renal insufficiency on the pharmacokinetics of posaconazole is not expected and no dose adjustment is recommended. Posaconazole is not removed by haemodialysis. Due to the variability in exposure, patients with severe renal impairment should be monitored closely for breakthrough fungal infections.

Similar recommendations apply to posaconazole modified release tablets; however, a specific study has not been conducted with posaconazole modified release tablets.

Hepatic insufficiency

In a small number of subjects ($n=12$) studied with hepatic insufficiency (Child-Pugh class A, B or C), C_{max} values generally decreased with the severity of hepatic dysfunction (545, 414 and 347 ng/mL for the mild, moderate, and severe groups, respectively), even though the C_{max} values (mean 508 ng/mL) for the normal subjects were consistent with

previous trials in healthy volunteers. In addition, an increase in half-life was also associated with a decrease in hepatic function (26.6, 35.3, and 46.1 hours for the mild, moderate, and severe groups, respectively), as all groups had longer half-life values than subjects with normal hepatic function (22.1 hours). Due to the limited pharmacokinetic data in patients with hepatic insufficiency; no recommendation for dose adjustment can be made.

Similar recommendations apply to posaconazole modified release tablets; however, a specific study has not been conducted with posaconazole modified release tablets.

CLINICAL TRIALS

Pharmacokinetics and Safety of Posaconazole Modified Release Tablets in Patients

Study 5615 was a non-comparative multi-center study performed to evaluate the pharmacokinetic properties, safety, and tolerability of posaconazole modified release tablet. Study 5615 was conducted in a similar patient population to that previously studied in the pivotal posaconazole oral suspension clinical program. The pharmacokinetics and safety data from Study 5615 were bridged to the existing data (including efficacy data) with the oral suspension.

Study 5615 enrolled a total of 230 subjects. Part 1 of the study was designed to select a dose for further study in Part 2, after first evaluating pharmacokinetics, safety, and tolerability in the neutropenic patient population at high risk of a fungal infection. Part 2 of the study was designed to evaluate posaconazole modified release tablet in a more diverse patient population, and to confirm the exposure of posaconazole modified release tablet in additional subjects at risk of a fungal infection. Posaconazole modified release tablet was administered without regard to food intake in both Part 1 and Part 2 of the study.

The subject population for Part 1 included subjects with acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS) who had recently received chemotherapy and had developed or were anticipated to develop significant neutropenia. Two different dosing groups were evaluated in Part 1: 200 mg BID on Day 1, followed by 200 mg QD thereafter (Part 1A) and 300 mg BID on Day 1, followed by 300 mg QD thereafter (Part 1B).

The subject population in Part 2 included: 1) patients with AML or MDS who had recently received chemotherapy and had developed or were anticipated to develop significant neutropenia, or 2) patients who had undergone a HSCT and were receiving immunosuppressive therapy for prevention or treatment of GVHD. These types of patients had been previously studied in a pivotal controlled trial of posaconazole oral suspension.

Based on the pharmacokinetics and safety results of Part 1, all subjects in Part 2 received 300 mg BID on Day 1, followed by 300 mg QD thereafter.

The total subject population had a mean age of 51 years (range = 19-78 years), 93 % were White, the major ethnicity was not Hispanic or Latino (84 %), and 62 % were male. The study treated 110 (48 %) subjects with AML (new diagnosis), 20 (9 %) subjects with AML (first relapse), 9 (4 %) subjects with MDS, and 91 (40 %) subjects with HSCT, as the primary diseases at study entry.

Serial PK samples were collected on Day 1 and at steady-state on Day 8 for all Part 1 subjects and a subset of Part 2 subjects. This serial PK analysis demonstrated that 90 % of the subjects treated with the 300 mg QD dose attained steady state C_{av} between 500-2500 ng/mL. [C_{av} was the average concentration of posaconazole at steady state, calculated as AUC/dosing interval (24 hours).] Subjects with AML/MDS with neutropenia following chemotherapy or HSCT subjects receiving immunosuppressive therapy to prevent or treat GVHD who received 300 mg QD achieved a mean C_{av} at steady state of 1580 ng/mL. The PK findings from the pivotal study (Study 5615) support a 300-mg daily dose of posaconazole modified release tablet for use in prophylaxis.

Pharmacokinetics and Safety of Posaconazole Oral Suspension in Patients

Invasive Aspergillosis:

Efficacy in patients with refractory disease or intolerance to prior therapy: The efficacy and survival benefit of oral posaconazole for the treatment of invasive aspergillosis in patients with disease refractory to amphotericin B (including liposomal formulations), itraconazole or, in a small number of cases, voriconazole or echinocandins, and/or with intolerance to amphotericin B (including liposomal formulations) or itraconazole was demonstrated in 107 patients enrolled in a salvage therapy trial. Patients were administered posaconazole oral suspension 800 mg/day in divided doses for up to 585 days. The median duration of posaconazole therapy was 56 days (1 – 585 days).

The majority of patients were severely immunocompromised with underlying conditions such as haematologic malignancies, including bone marrow transplantation; solid organ transplantation; solid tumours and/or AIDS. An independent expert panel reviewed all patient data, including diagnosis of invasive aspergillosis, refractoriness and intolerance to previous therapy, and clinical outcome in a parallel and blinded fashion with an external control group of 86 patients treated with standard salvage therapy (e.g. amphotericin B

including liposomal formulations, and/or itraconazole) mostly at the same time and at the same sites as the patients enrolled in the posaconazole trial.

A success was defined as either complete resolution (complete response) or a clinically meaningful improvement (partial response) of all signs, symptoms and radiographic findings attributable to the fungal infection. Stable, non-progressive disease and failure were considered to be a non-success. Most of the cases of aspergillosis were considered to be refractory in both the posaconazole group (88 %) and in the external control group (79 %) while the remaining patients were intolerant to prior antifungal therapy (12 %, posaconazole; 21 % external control group).

As shown in Table 4, a successful global response at end of treatment was seen in 42 % of posaconazole-treated patients compared to 26 % of the external group (P=0.006).

TABLE 4. Overall efficacy of posaconazole at the end of treatment* for invasive aspergillosis in comparison to an external control group

	Posaconazole oral suspension	External Control Group
Overall Response	45/107 (42 %)	22/86 (26 %)
	Adjusted Odds Ratio ** 4.06 (95 % CI: 1.50, 11.04) P=0.006	
	Unadjusted Odds ratio 2.11 (95 % CI: 1.14, 3.92) P=0.018	
Survival at day 365	(38 %)	(22 %)
Success by Species		
All mycologically confirmed <i>Aspergillus</i> spp.***	34/76 (45 %)	19/74 (26 %)
<i>A. fumigatus</i>	12/29 (41 %)	12/34 (35 %)
<i>A. flavus</i>	10/19 (53 %)	3/16 (19 %)
<i>A. terreus</i>	4/14 (29 %)	2/13 (15 %)
<i>A. niger</i>	3/5 (60 %)	2/7 (29 %)

* end of all study drug therapy plus 7 days within 372 days of the start of salvage therapy

** adjusted odds ratio was obtained using a logistic regression model adjusting for major covariates

*** includes other less common species or species unknown

Other Serious Fungal Pathogens

Posaconazole oral suspension has been shown to be effective against the following additional pathogens when other therapy had been ineffective or when the patient had developed intolerance of the prior therapy:

Zygomycosis: Successful responses to posaconazole oral suspension therapy were noted in 7/13 (54 %) of patients with zygomycete infections. Sites of infection included the sinuses, lung, and skin. Organisms included *Rhizopus*, *Mucor* and *Rhizomucor*. Most of the patients had underlying haematological malignancies, half of which required a bone marrow transplant. Half of the patients were enrolled with intolerance to previous therapy and the other half as a result of disease that was refractory to prior therapy. Three patients were noted to have disseminated disease, one of which had a successful outcome after failing amphotericin B therapy.

Fusarium spp.: Successful responses to posaconazole oral suspension therapy were seen in 11 of 24 (46%) of patients with fusariosis. Four of the responders had disseminated disease and one patient had disease localized to the eye; the remainder had a variety of sites of infection. Seven of 24 patients had profound neutropenia at baseline. In addition, 3/5 patients with infection due to *F. solani* which is typically resistant to most antifungal agents, were successfully treated.

Chromoblastomycosis/Mycetoma: Successful responses to posaconazole oral suspension therapy were seen in 9 of 11 (82 %) of patients with chromoblastomycosis or mycetoma. Five of these patients had chromoblastomycosis due to *Fonsecaea pedrosoi* and 4 had mycetoma, mostly due to *Madurella* species.

Coccidioidomycosis: The efficacy of posaconazole in the primary treatment of non-meningeal coccidioidomycosis was demonstrated in 15 clinically evaluable patients enrolled in an open-label, non-comparative trial to receive posaconazole 400 mg daily for 6 months. Most patients were otherwise healthy and had infections at a variety of sites. A satisfactory response (defined as an improvement of at least 50 % of the Cocci score as defined by the BAMSG Coccidioidomycosis trial group) was seen in 12 of 15 patients (80 %) after an average of 4 months of posaconazole treatment. In a separate open-label,

non-comparative trial, the safety and efficacy of posaconazole 400 mg twice a day was assessed in 16 patients with coccidioidomycosis infection refractory to standard treatment. Most had been treated with amphotericin B (including lipid formulations) and/or itraconazole or fluconazole for months to years prior to posaconazole treatment. At the end of treatment with posaconazole, a satisfactory response (complete or partial resolution of signs and symptoms present at baseline) as determined by an independent panel was achieved for 11/16 (69 %) of patients. One patient with CNS disease that had failed fluconazole therapy had a successful outcome following 12 months of posaconazole therapy.

Treatment of Azole-Susceptible Oropharyngeal Candidiasis (OPC) in HIV-infected patients

A randomised, double-blind, controlled study was completed in HIV-infected patients with azole-susceptible oropharyngeal candidiasis. The primary efficacy variable was the clinical success rate (defined as cure or improvement) after 14 days of treatment. Patients were treated with posaconazole or fluconazole oral suspension (both posaconazole and fluconazole were given as follows: 100 mg twice a day for 1 day followed by 100 mg once a day for 13 days).

The clinical and mycological response rates from the above study are shown in Table 5 below. Posaconazole and fluconazole demonstrated equivalent clinical success rates at Day 14 as well as 4 weeks after the end of treatment. However, posaconazole oral suspension demonstrated a significantly better mycological response rate than fluconazole 4 weeks after the end of treatment.

TABLE 5. Clinical Success Rates and Mycological Response Rates in Oropharyngeal Candidiasis

Endpoint	Posaconazole	Fluconazole
Clinical Success Rate at Day 14	91.7 % (155/169)	92.5 % (148/160)
Clinical Success Rate 4 Weeks After End of Treatment	68.5 % (98/143)	61.8 % (84/136)
Mycological Response Rate 4 Weeks After End of Treatment*	40.6 % (41/101)	26.4 % (24/91)

*Statistically significant (P=0.0376)

Clinical success rate was defined as the number of cases assessed as having a clinical response (cure or improvement) divided by the total number of cases eligible for analysis. Mycological response rate was defined as mycological success (≤ 20 CFU/ml) divided by the total number of cases eligible for analysis.

Treatment of Oropharyngeal Candidiasis refractory to itraconazole and fluconazole (rOPC) in HIV-infected patients

The primary efficacy parameter in the short-term treatment study was the clinical success rate (cure or improvement) after 4 weeks of treatment. HIV-infected patients were treated with posaconazole oral suspension 400 mg twice a day with an option for further treatment during a 3-month maintenance period. A 75 % (132/176) clinical success rate and a 36.5 % (46/126) mycological response rate (≤ 20 CFU/ml) were achieved after 4 weeks of posaconazole treatment. Clinical success rates ranged from 71 % to 100 %, inclusive, for all azole-resistant *Candida* species identified at baseline, including *C. glabrata* and *C. krusei*.

In the long-term treatment study the primary efficacy endpoint was the clinical success rate (cure or improvement) after 3 months of treatment. A total of 100 HIV-infected patients with OPC and/or EC were treated with posaconazole 400 mg twice a day for up to 15 months. Sixty of these patients had been previously treated in Study 330. An 85.6 % (77/90) clinical success rate overall (cure or improvement) was achieved after 3 months of posaconazole treatment; 80.6 % (25/31) for previously untreated subjects.

The mean exposure to posaconazole based on the actual days dosed was 102 days (range: 1-544 days). Sixty-seven percent (67 %, 10/15) of patients treated with posaconazole for at least 12 months had continued clinical success at the last assessment.

Prophylaxis of Invasive Fungal Infections (IFIs) (Studies 316 and 1899):

Two randomised, controlled prophylaxis studies were conducted using posaconazole oral suspension as prophylaxis for the prevention of IFIs among patients at high risk for developing invasive fungal infections.

Study 316 was a randomised, double-blind trial of posaconazole oral suspension (200 mg three times a day) versus fluconazole capsules (400 mg once daily) in allogeneic hematopoietic stem cell transplant recipients with graft-versus-host disease (GVHD). The primary efficacy endpoint was the incidence of proven/probable IFIs at 16 weeks post-randomization as determined by an independent, blinded external expert panel. A key

secondary endpoint was the incidence of proven/probable IFIs during the on-treatment period (first dose to last dose of study medicinal product + 7 days). The majority (377/600, [63 %]) of patients included had Acute Grade 2 or 3 or chronic extensive (195/600, [32.5 %]) GVHD at study start. The mean duration of therapy was 80 days for posaconazole and 77 days for fluconazole.

Study 1899 was a randomised, evaluator-blinded study of posaconazole oral suspension (200 mg three times a day) versus fluconazole suspension (400 mg once daily) or itraconazole oral solution (200 mg twice a day) in neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukemia or myelodysplastic syndromes. The primary efficacy endpoint was the incidence of proven/probable IFIs as determined by an independent, blinded external expert panel during the on-treatment period. A key secondary endpoint was the incidence of proven/probable IFIs at 100 days post-randomization. New diagnosis of acute myelogenous leukemia was the most common underlying condition (435/602, [72 %]). The mean duration of therapy was 29 days for posaconazole and 25 days for fluconazole/itraconazole.

In both prophylaxis studies, aspergillosis was the most common breakthrough infection. See Table 6 and 7 for results from both studies. There were fewer breakthrough *Aspergillus* infections in patients receiving posaconazole prophylaxis when compared to control patients.

TABLE 6. Results from clinical studies in prophylaxis of Invasive Fungal Infections.

Study	Posaconazole Oral Suspension	Control ^a	P-Value
Proportion (%) of patients with proven/probable IFIs			
On-treatment period^b			
1899 ^d	7/304 (2)	25/298 (8)	0.0009
316 ^e	7/291 (2)	22/288 (8)	0.0038
Fixed-time period^c			
1899 ^d	14/304 (5)	33/298 (11)	0.0031
316 ^d	16/301 (5)	27/299 (9)	0.0740

FLU = fluconazole; ITZ = itraconazole; POS = posaconazole.

a: FLU/ITZ (1899); FLU (316).

- b: In 1899 this was the period from randomization to last dose of study medicinal product plus 7 days; in 316 it was the period from first dose to last dose of study medicinal product plus 7 days.
- c: In 1899, this was the period from randomization to 100 days post-randomization; in 316 it was the period from the baseline day to 111 days post-baseline.
- d: All randomized
- e: All treated

TABLE 7. Results from clinical studies in prophylaxis of Invasive Fungal Infections.

Study	Posaconazole	Control ^a
Proportion (%) of patients with proven/probable Aspergillosis		
On-treatment period^b		
1899 ^d	2/304 (1)	20/298 (7)
316 ^e	3/291 (1)	17/288 (6)
Fixed-time period^c		
1899 ^d	4/304 (1)	26/298 (9)
316 ^d	7/301 (2)	21/299 (7)

FLU = fluconazole; ITZ = itraconazole; POS = posaconazole.

- a: FLU/ITZ (1899); FLU (316).
- b: In 1899 this was the period from randomization to last dose of study medicinal product plus 7 days; in 316 it was the period from first dose to last dose of study medicinal product plus 7 days.
- c: In 1899, this was the period from randomization to 100 days post-randomization; in 316 it was the period from the baseline day to 111 days post-baseline.
- d: All randomized
- e: All treated

In Study 1899, a significant decrease in all cause mortality in favour of posaconazole was observed [POS 49/304 (16 %) vs. FLU/ITZ 67/298 (22 %) p= 0.048]. Based on Kaplan-Meier estimates, the probability of survival up to day 100 after randomization, was significantly higher for posaconazole recipients; this survival benefit was demonstrated when the analysis considered all causes of death (P= 0.0354) as well as IFI-related deaths (P = 0.0209).

In Study 316, overall mortality was similar (POS, 25 %; FLU, 28 %); however, the proportion of IFI-related deaths was significantly lower in the POS group (4/301) compared with the FLU group (12/299; $P=0.0413$).

Use in paediatric patients

Sixteen patients 8-17 years of age were treated with up to 800 mg/day in a study for invasive fungal infections. Based on the available data in 16 of these paediatric patients, the safety profile appears to be similar to patients ≥ 18 years of age.

Additionally, twelve patients 13-17 years of age received 600 mg/day for prophylaxis of invasive fungal infections (Studies 316 and 1899). The safety profile in these patients < 18 years of age appears similar to the safety profile observed in adults. Based on pharmacokinetic data in 10 of these paediatric patients, the pharmacokinetic profile appears to be similar to patients ≥ 18 years of age.

Safety and efficacy in paediatric patients below the age of 18 years have not been established.

Electrocardiogram evaluation

Multiple, time-matched ECGs collected over a 12 hour period were obtained before and during administration of posaconazole oral suspension (400 mg twice daily with high fat meals) from 173 healthy male and female volunteers aged 18 to 85 years. No clinically relevant changes in the mean QTc (Fridericia) interval from baseline were observed.

INDICATIONS

NOXAFIL (posaconazole) modified release tablet is indicated for use in the treatment of the following fungal infections in adults:

- Invasive aspergillosis in patients with disease that is refractory to amphotericin B or itraconazole or in patients who are intolerant of these medicinal products;
- Fusariosis, zygomycosis, coccidioidomycosis, chromoblastomycosis, and mycetoma in patients with disease that is refractory to other therapy or patients who are intolerant of other therapy.

Refractoriness is defined as progression of infection or failure to improve after a minimum of 7 days of prior therapeutic doses of effective antifungal therapy.

NOXAFIL modified release tablet is also indicated for prophylaxis of invasive fungal infections in the following adult patients:

- Patients receiving remission-induction chemotherapy for acute myelogenous leukaemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia and who are at high-risk of developing invasive fungal infections.
- Haematopoietic stem cell transplant (HSCT) recipients who are undergoing high-dose immunosuppressive therapy for graft versus host disease and who are at high risk of developing invasive fungal infections.

Noxafil modified release tablets are not indicated for the treatment of oropharyngeal candidiasis. Please refer to the package insert of Noxafil oral suspension for use in oropharyngeal candidiasis.

DOSAGE AND ADMINISTRATION

Non-Interchangeability between Noxafil Modified Release Tablets and Noxafil Oral Suspension

Noxafil modified release tablets and oral suspension are not to be used interchangeably due to the differences in the dosing of each formulation. Therefore, follow the specific dosage recommendations for each of the formulations.

Noxafil modified release tablets may be taken without regard to food intake.

Noxafil modified release tablets are intended for oral administration only.

Noxafil modified release tablets should be swallowed whole, and not be divided, crushed, or chewed.

Important Administration Instructions for Noxafil Modified Release Tablet and Noxafil Oral Suspension

The prescriber should follow the specific dosing instructions for each formulation. The modified release tablet and oral suspension are not to be used interchangeably due to the differences in the dosing of each formulation.

Co-administration of drugs that can decrease the plasma concentrations of posaconazole should generally be avoided unless the benefit outweighs the risk. If such drugs are necessary, patients should be monitored closely for breakthrough fungal infections (see Interactions with other medicines).

Refractory Invasive Fungal Infections (IFI) / Intolerant Patients with IFI: Loading dose of 300 mg (three 100 mg tablets) twice a day on the first day, then 300 mg (three 100 mg tablets) once a day thereafter.

Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response.

Prophylaxis of Invasive Fungal Infections: Loading dose of 300 mg (three 100 mg tablets) twice a day on the first day, then 300 mg (three 100 mg tablets) once a day thereafter.

Duration of therapy is based on recovery from neutropenia or immunosuppression. For patients with acute myelogenous leukemia or myelodysplastic syndromes, prophylaxis with Noxafil should start several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 500 cells per mm³.

Use in renal impairment: No dose adjustment is required for renal dysfunction and posaconazole is not significantly renally eliminated, an effect of severe renal insufficiency on the pharmacokinetics of posaconazole is not expected and no dose adjustment is recommended.

Due to variability in exposure, patients with severe renal impairment should be monitored closely for breakthrough fungal infections.

Use in hepatic impairment: There are limited pharmacokinetic data in patients with hepatic insufficiency; therefore, no recommendation for dose adjustment can be made. In the small number of subjects studied who had hepatic insufficiency, there was an increase in half-life with a decrease in hepatic function.

Use in paediatrics: Safety and efficacy in children and adolescents below the age of 18 years have not been established. Therefore, posaconazole is not recommended for use in patients below 18 years of age.

Use in the Elderly: No dosage adjustment is recommended for elderly patients.

CONTRAINDICATIONS

NOXAFIL is contraindicated in patients with known hypersensitivity to posaconazole or to any of the excipients.

Co-administration of posaconazole and ergot alkaloids (ergotamine, dihydroergotamine) is contraindicated as posaconazole may increase the plasma concentration of ergot alkaloids, which may lead to ergotism (See Interactions with other medicines).

Co-administration with the HMG-CoA reductase inhibitors that are primarily metabolised through CYP3A4 is contraindicated since increased plasma concentration of these drugs can lead to rhabdomyolysis.

Although not studied *in vitro* or *in vivo*, co-administration of posaconazole and certain drugs metabolised through the CYP3A4 system: terfenadine, astemizole, cisapride, pimozide, and quinidine may result in increased plasma concentrations of those drugs, leading to potentially serious and/or life threatening adverse events, such as QT prolongation and rare occurrences of torsade de pointes (See Interactions with other medicines).

PRECAUTIONS

Hypersensitivity:

There is no information regarding cross-sensitivity between posaconazole and other azole antifungal agents. Caution should be used when prescribing posaconazole to patients with hypersensitivity to other azoles. Subjects with severe or serious reactions to azoles were excluded from key studies of posaconazole.

Hepatic toxicity:

Hepatic reactions (e.g., mild to moderate elevations in ALT, AST, alkaline phosphatase, total bilirubin, and/or clinical hepatitis) have been reported during treatment with posaconazole. Elevated liver function tests were generally reversible on discontinuation of therapy and in some instances these tests normalized without interruption of therapy. Rarely, more severe hepatic reactions with fatal outcomes have been reported. Posaconazole should be used with caution in patients with severe hepatic impairment. In these patients, the prolonged elimination half-life may lead to increased exposure.

QT prolongation:

Some azoles have been associated with prolongation of the QT_C interval. Posaconazole

must not be administered with medicines that are substrates for CYP3A4 and are known to prolong the QTc interval (See Contraindications, Interactions, Clinical Trials – Electrocardiogram Evaluation). Noxafil should be administered with caution to patients with pro-arrhythmic conditions such as:

- Congenital or acquired QTc prolongation
- Cardiomyopathy, especially in the presence of cardiac failure
- Sinus bradycardia
- Existing symptomatic arrhythmias
- Concomitant use with medicinal products known to prolong the QTc interval

Electrolyte disturbances, especially those involving potassium, magnesium or calcium levels, should be monitored and corrected as necessary before and during posaconazole therapy.

Vincristine Toxicity: Concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with neurotoxicity and other serious adverse reactions, including seizures, peripheral neuropathy, syndrome of inappropriate antidiuretic hormone secretion, and paralytic ileus. Reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options (see Interactions with other medicines).

Venetoclax Toxicity: Concomitant administration of posaconazole with venetoclax (a CYP3A4 substrate) may increase venetoclax toxicities, including the risk of tumor lysis syndrome (TLS) and neutropenia (see Interactions with other medicines under Effects of Posaconazole on Other Drugs). Refer to the venetoclax prescribing information for detailed guidance.

Effects on Fertility:

Posaconazole had no effect on the fertility of male rats at doses up to 180 mg/kg/day (1.6 times the maximum recommended clinical dose (RCD) based on AUC at steady state in healthy volunteers fed a high fat meal). Like other azoles, male dogs administered oral posaconazole had findings consistent with reduced plasma testosterone levels, including spermatogenic giant cells (relative exposure 4.2).

Posaconazole administered to female rats at doses up to 45 mg/kg/day (relative exposure 2.0) for 2 weeks prior to mating did not affect fertility, but disruption of oestrus cycling was seen in female rats treated for 4 weeks.

Use in Pregnancy:

Pregnancy Category B3 – There are no adequate studies in pregnant women. A total of three pregnancies have been reported in female subjects treated with posaconazole. Two pregnancies were electively terminated; no examination was reported on the fetuses. Another pregnancy was diagnosed at a follow-up visit approximately 1 month after the completion of a full 16-week prophylactic treatment with POS oral 200 mg TID in a patient who had received an allogeneic haematopoietic stem cell transplant. The subject delivered a healthy full-term male infant via caesarean section.

Studies in rats have shown reproductive toxicity including post implantation loss, increased skeletal variations, teratogenicity (craniofacial malformations), increased gestation length, dystocia, and reduced postnatal viability at exposure levels lower than those expected at the recommended doses in humans. An increase in post implantation loss and increased skeletal variations were seen in rabbits at plasma exposure levels greater than those of humans receiving therapeutic doses of posaconazole.

NOXAFIL must not be used during pregnancy unless the benefit to the mother clearly outweighs the risk to the foetus. Women of childbearing potential must be advised to always use effective contraceptive measure during treatment and for at least 2 weeks after completing therapy.

Use in Lactation:

Posaconazole is excreted in milk of lactating rats. The excretion of posaconazole in human breast milk has not been investigated. Women taking posaconazole should not breastfeed.

Use in the Elderly:

No dosage adjustment is recommended for geriatric patients (See Clinical Pharmacology – Pharmacokinetics in special populations – Elderly).

Effects on Adrenal Steroid Hormones:

As observed with other azole antifungal agents, effects related to inhibition of adrenal steroid hormone synthesis were seen in repeat-dose toxicity studies with posaconazole. Adrenal suppressive effects were observed in toxicity studies in rats and dogs at exposures equal to or greater than those obtained at therapeutic doses in humans.

Carcinogenicity:

Posaconazole caused an increase in hepatocellular adenomas in mice at plasma exposure levels ~7-times higher than anticipated in humans at the maximum recommended clinical dose. This finding is considered to have occurred secondary to liver toxicity in the species, and mice are known to be particularly susceptible to this neoplastic change.

Rats treated with posaconazole at exposure levels ≥ 2.4 -times that of humans developed adrenal cortical cell adenomas and/or carcinomas and pheochromocytomas. The cortical tumours are consistent with endocrinological disruption following chronic impairment of adrenal steroidogenesis. The increase in pheochromocytomas is considered to be a rat-specific phenomenon that follows changes in calcium homeostasis. Altered calcium homeostasis has not been observed in humans receiving posaconazole. The results of animal studies indicate little carcinogenic risk for posaconazole in clinical use.

Genotoxicity:

Posaconazole has been tested for genotoxicity in a series of *in vitro* assays (bacterial mutation, mammalian mutation and human lymphocyte chromosomal aberration) and an *in vivo* mouse micronucleus test. Under the conditions of these assays, posaconazole did not cause genetic damage.

Interactions with other medicines:

Summary of Drug Interactions

Contraindicated	Avoid concomitant use unless the benefit outweighs the risk	Dose adjustment of other medications and/or monitoring of adverse events	No dose adjustment required
Ergotamine or dihydroergotamine	Rifabutin	Rifabutin	Antacids

Terfenadine, astemizole	Phenytoin	Cyclosporine	Zidovudine, ritonavir, lamivudine, indinavir
Cisapride	Cimetidine	Tacrolimus	Glipizide
Pimozide	Efavirenz	Sirolimus	
Quinidine		Vinca alkaloids	
Halofantrine		Midazolam	
HMG-CoA reductase inhibitors primarily metabolised through CYP3A4		Atazanavir/ritonavir Fosamprenavir	
		Calcium channel blockers metabolized through CYP3A4	
		Sulfonylureas	
		Digoxin	

Note that the majority of the interaction studies were carried out in healthy volunteers with a repeat dose regimens of posaconazole 400 mg (suspension) twice daily administered with a meal or nutritional supplement. See below for further information.

Effect of Other Drugs on Posaconazole

Posaconazole is 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.

Rifabutin (300 mg once a day) decreased the C_{max} (maximum plasma concentration) and AUC (area under the plasma concentration time curve) of posaconazole by 43 % and 49 %, respectively. Concomitant use of posaconazole and rifabutin should be avoided unless the benefit to the patient outweighs the risk.

Phenytoin (200 mg once a day) decreased the C_{max} and AUC of posaconazole by 41 % and 50 %, respectively. Concomitant use of posaconazole and phenytoin should be avoided unless the benefit to the patient outweighs the risk.

Cimetidine (400 mg twice a day) decreased the C_{max} and AUC of posaconazole 200 mg once a day each by 39 %. Concomitant use of posaconazole and cimetidine should be avoided unless the benefit outweighs the risk. No clinically relevant effects were observed when posaconazole modified release tablets are concomitantly used with antacids, H_2 -receptor antagonists and proton pump inhibitors. No dosage adjustment of posaconazole modified release tablets is required when posaconazole modified release tablets are concomitantly used with antacids, H_2 -receptor antagonists and proton pump inhibitors.

Antacids (20 mL single dose of liquid antacid equivalent to 25.4 mEq acid neutralizing capacity/5 mL) had no clinically significant effect on posaconazole C_{max} and AUC. No posaconazole dosage adjustments are required.

Glipizide (10 mg single dose) had no clinically significant effect on posaconazole C_{max} and AUC. No posaconazole dosage adjustments are required.

Ritonavir (600 mg twice a day) had no clinically significant effect on posaconazole C_{max} and AUC. No posaconazole dosage adjustments are required.

Efavirenz (400 mg once a day) decreased the C_{max} and AUC of posaconazole by 45 % and 50 %, respectively. Concomitant use of posaconazole and efavirenz should be avoided unless the benefit to the patient outweighs the risk.

Fosamprenavir: Combining fosamprenavir with posaconazole may lead to decreased posaconazole plasma concentrations. If concomitant administration is required, close monitoring for breakthrough fungal infections is recommended.

Repeat dose administration of fosamprenavir (700 mg BID x 10 days) decreased the C_{max} and AUC of posaconazole (200 mg QD on the 1st day, 200 mg BID on the 2nd days, then 400 mg BID x 8 Days) by 21 % and 23 % respectively.

Effects of Posaconazole on Other Drugs

Posaconazole is not metabolized to a clinically significant extent through the cytochrome P450 system. However, posaconazole is an inhibitor of CYP3A4 and thus the plasma levels of drugs that are metabolized through this enzyme pathway may increase when administered with posaconazole.

Terfenadine, astemizole, cisapride, pimozone, and quinidine: Although not studied *in vitro* or *in vivo*, co-administration of posaconazole and certain drugs such as terfenadine, astemizole, cisapride, pimozone, and quinidine, metabolized through the CYP3A4 system may result in increased plasma concentrations of these drugs, leading to potentially serious and/or life threatening adverse events (QTc prolongation and rare occurrences of torsade de pointes). Therefore, co-administration of these drugs with posaconazole is contraindicated (See Contraindications).

Ergot alkaloids: Although not studied *in vitro* or *in vivo*, posaconazole may increase the plasma concentration of ergot alkaloids (ergotamine and dihydroergotamine), which may lead to ergotism. Co-administration of posaconazole and ergot alkaloids is contraindicated (See Contraindications).

Vinca alkaloids: Most of the vinca alkaloids (e.g., vincristine and vinblastine) are substrates of CYP3A4. Concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with serious adverse reactions (see Precautions). Posaconazole may increase the plasma concentrations of vinca alkaloids which may lead to neurotoxicity and other serious adverse reactions. Therefore, reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options.

Cyclosporine: In heart transplant patients on stable doses of cyclosporine, posaconazole 200 mg once daily increased cyclosporine concentrations requiring dose reductions. Cases of elevated cyclosporine levels resulting in serious adverse events, including nephrotoxicity and one fatal case of leukoencephalopathy, were reported in clinical efficacy studies. When initiating treatment with posaconazole in patients already receiving cyclosporine, the dose of cyclosporine should be reduced (e.g. to about three quarters of the current dose). Thereafter blood levels of cyclosporine should be monitored carefully during co-administration, and upon discontinuation of posaconazole treatment, and the dose of cyclosporine should be adjusted as necessary.

Tacrolimus: Posaconazole increased C_{max} and AUC of tacrolimus (0.05 mg/kg single dose) by 121 % and 358 %, respectively. Clinically significant interactions resulting in hospitalisation and/or posaconazole discontinuation were reported in clinical efficacy studies. When initiating posaconazole treatment in patients already receiving tacrolimus, the dose of tacrolimus should be reduced (e.g. to about one third of the current dose). Thereafter blood levels of tacrolimus should be monitored carefully during

co-administration, and upon discontinuation of posaconazole, and the dose of tacrolimus should be adjusted as necessary.

Sirolimus: Repeat dose administration of oral posaconazole (400 mg twice daily for 16 days) increased the C_{max} and AUC of sirolimus (2 mg single dose) an average of 6.7-fold and 8.9 fold, respectively, in healthy subjects. When initiating therapy in patients already taking sirolimus, the dose of sirolimus should be reduced (e.g., to about 1/10 of the current dose) with frequent monitoring of sirolimus whole blood trough concentrations. Sirolimus concentrations should be performed upon initiation, during co-administration, and at discontinuation of posaconazole treatment, with sirolimus doses adjusted accordingly.

Rifabutin: Posaconazole increased the C_{max} and AUC of rifabutin by 31 % and 72 %, respectively. Concomitant use of posaconazole and rifabutin should be avoided unless the benefit to the patient outweighs the risk. If the drugs are co-administered, careful monitoring of full blood counts and adverse effects related to increased rifabutin levels (e.g., uveitis) is recommended.

Midazolam: Repeat dose administration of oral posaconazole 200 mg or 400 mg twice daily with a high fat meal, significantly increased the midazolam C_{max} by 2.2 fold (~7.03 to 15.4 ng/mL); AUC by approximately 5 fold (~31.9 to 159 h.ng/mL); and prolonged the mean terminal half-life of midazolam 8 to 10 hours in healthy subjects. It is recommended that dose adjustments of benzodiazepines, including midazolam metabolised by CYP3A4, be considered during co-administration with posaconazole.

Zidovudine (AZT), lamivudine (3TC), indinavir: In HIV infected patients on stable doses of zidovudine (300 mg twice a day or 200 mg every 8 hours), lamivudine (150 mg twice a day), and/or indinavir (800 mg every 8 hours), posaconazole had no clinically significant effect on the C_{max} and AUC of these medicinal products.

HMG-CoA reductase inhibitors primarily metabolized through CYP3A4: Repeat dose administration of oral posaconazole (50, 100 and 200 mg once daily for 13 days) increased the C_{max} and AUC of simvastatin (40 mg single dose) an average of 7.4- to 11.4-fold, and 5.7- to 10.6-fold, respectively. Increased HMG-CoA reductase inhibitor concentrations in plasma can be associated with rhabdomyolysis. Co-administration of

posaconazole and HMG-CoA reductase inhibitors primarily metabolized through CYP3A4 is contraindicated.

Calcium channel blockers metabolized through CYP3A4: Although not studied *in vitro* or *in vivo*, frequent monitoring for adverse effects and toxicity related to calcium channel blockers is recommended during co-administration with posaconazole. Dose adjustment of calcium channel blockers may be required.

Digoxin: Administration of other azoles has been associated with increases in digoxin levels. Therefore, posaconazole may increase plasma concentration of digoxin and digoxin levels need to be monitored when initiating or discontinuing posaconazole treatment.

Sulfonylureas: Glucose concentrations decreased in some healthy volunteers when glipizide was co-administered with posaconazole. Monitoring of glucose concentrations is recommended in diabetic patients.

HIV Protease Inhibitors: As HIV protease inhibitors are CYP3A4 substrates, it is expected that posaconazole will increase plasma levels of these antiretroviral agents. Repeat dose administration of oral posaconazole (400 mg twice daily for 7 days) increased the C_{max} and AUC of atazanavir (300 mg once a day for 7 days) an average of 2.6-fold and 3.7-fold, respectively, in healthy subjects. Repeat dose administration of oral posaconazole (400 mg twice daily for 7 days) increased the C_{max} and AUC of atazanavir to a lesser extent when administered as a boosted regimen with ritonavir (300 mg atazanavir plus ritonavir 100 mg once a day for 7 days) with an average of 1.5-fold and 2.5-fold, respectively, in healthy subjects. Frequent monitoring for adverse events and toxicity related to antiretroviral agents that are substrates of CYP3A4 is recommended during co-administration with posaconazole.

Venetoclax: Concomitant use of venetoclax (a CYP3A4 substrate) with posaconazole increases venetoclax C_{max} and AUC_{0-INF} , which may increase venetoclax toxicities (see PRECAUTIONS).

ADVERSE EFFECTS

Posaconazole Oral Suspension

Drug-related adverse reactions observed in 2 400 subjects dosed with posaconazole oral suspension are shown in Table 10. 172 patients received posaconazole oral suspension therapy for ≥ 6 months; 58 of these received posaconazole oral suspension therapy for ≥ 12 months.

The most frequently reported adverse reactions reported across the whole population of healthy volunteers and patients were nausea (6 %) and headache (6 %).

TABLE 8: Treatment-related adverse reactions reported in posaconazole oral suspension dosed subjects by body system and frequency N=2400

Common ($>1/100$, $<1/10$); uncommon ($>1/1,000$, $<1/100$); rare ($>1/10,000$, $<1/1,000$)

Infections and infestations	
<i>Uncommon:</i>	oral candidiasis, sinusitis
<i>Rare:</i>	catheter related infection, non herpetic cold sores, oesophageal candidiasis, pneumonia, upper respiratory tract infection, urinary tract infection
Blood and lymphatic system disorders	
<i>Common:</i>	neutropenia
<i>Uncommon:</i>	anaemia, thrombocytopenia, leukopenia, eosinophilia, lymphadenopathy
<i>Rare:</i>	abnormal blood gases, haemolytic uraemic syndrome, neutrophilia, pancytopenia, coagulation disorder, haemorrhage NOS, platelet count increased, prothrombin decreased, prothrombin time prolonged, purpura, thrombotic thrombocytopenic purpura
Immune system disorders	
<i>Uncommon:</i>	allergic reaction
<i>Rare:</i>	hypersensitivity reaction, Stevens Johnson syndrome
Endocrine disorders	
<i>Rare:</i>	adrenal insufficiency, gonadotropins decreased
Metabolism and nutrition disorders	
<i>Common:</i>	anorexia, electrolyte imbalance

<i>Uncommon:</i>	hyperglycaemia, hypertriglyceridaemia, hyperuricaemia, weight decrease, LDH increased, dehydration
<i>Rare:</i>	amylase increased, hypercholesterolemia, hyperlipaemia, hyperproteinaemia, hypoalbuminaemia, lipase increased, metabolic acidosis, renal tubular acidosis, vitamin K deficiency, weight increase
Psychiatric disorders	
<i>Uncommon:</i>	altered mental status, anxiety, confusion, insomnia
<i>Rare:</i>	amnesia, depression, abnormal dreaming, emotional lability, libido decreased, paroniria, psychosis
Nervous system disorders	
<i>Common:</i>	dizziness, headache, paresthesia, somnolence
<i>Uncommon:</i>	neuropathy, hypoesthesia, convulsions, tremor
<i>Rare:</i>	peripheral neuropathy, areflexia, ataxia, cognition impaired, delirium, dysphonia, dystonia, encephalopathy, hemiparesis, hyperkinesia, hyperreflexia, hyporeflexia, hypotonia, impaired concentration, memory impairment, meningism, mononeuritis, restless leg syndrome, sciatica, syncope
Eye disorders	
<i>Uncommon:</i>	conjunctivitis, blurred vision
<i>Rare:</i>	eye pain, eyes dry, periorbital oedema, diplopia, photophobia, scotoma
Ear and labyrinth disorder	
<i>Uncommon:</i>	earache, vertigo
<i>Rare:</i>	hearing impairment, tinnitus
Cardiac disorders	
<i>Uncommon:</i>	abnormal ECG, QTc/QT prolongation, atrial flutter, atrial fibrillation, bundle branch block, tachycardia, extrasystoles, palpitation, ventricular hypertrophy
<i>Rare:</i>	bradycardia, cardiac failure, cardio-respiratory arrest, sudden death, ventricular tachycardia, aortic valve sclerosis, cardiomegaly, ejection fraction decreased, mitral valve disease NOS, myocardial infarction, supraventricular tachycardia, premature atrial contractions, premature ventricular contractions, AV block, torsades de pointes
Vascular disorders	

<i>Uncommon:</i>	flushing, hot flushes, hypertension, hypotension
<i>Rare:</i>	atherosclerosis, cerebrovascular accident, deep venous thrombosis NOS, pulmonary embolism, ischemia, haematoma
Respiratory, thoracic and mediastinal disorders	
<i>Uncommon:</i>	chest pain, coughing, dyspnoea, epistaxis, pharyngitis, nasal congestion
<i>Rare:</i>	atelectasis, dry throat, pulmonary hypertension, interstitial pneumonia, nasal irritation, pneumonitis, postnasal drip, pulmonary infiltration, rales, rhinitis, rhinorrhoea
Gastrointestinal disorders	
<i>Common:</i>	abdominal pain, diarrhoea, dyspepsia, flatulence, dry mouth, nausea, vomiting
<i>Uncommon:</i>	taste perversion, constipation, loose stools, abdominal distention, dysphagia, ascites, eructation, thirst, gastritis, gastroesophageal reflux, mucositis NOS, oesophagitis, pancreatitis, tongue discolouration
<i>Rare:</i>	gastrointestinal tract haemorrhage, ileus, abdominal tenderness, cheilitis, haemorrhagic diarrhoea, oesophagus ulceration, haemorrhagic gastritis, odynophagia, pancreatic enzymes NOS increased, proctalgia, retching, aphthous stomatitis, tenesmus, melena, gingivitis, glossitis
Hepatobiliary disorders	
<i>Common:</i>	elevated liver function tests (including AST, ALT, alkaline phosphatase, GGT, bilirubin)
<i>Uncommon:</i>	hepatitis, hepatocellular damage, hepatomegaly, jaundice
<i>Rare:</i>	asterixis, cholestasis, hepatic failure, hepatitis cholestatic, hepatosplenomegaly, liver tenderness, splenomegaly
Skin and subcutaneous tissue disorders	
<i>Common:</i>	rash
<i>Uncommon:</i>	alopecia, dry skin, maculopapular rash, urticaria, furunculosis, acne, mouth ulceration, pruritus, pruritic rash
<i>Rare:</i>	stomatitis, dermatitis, erythema, erythematous rash, follicular rash, macular rash, night sweats, seborrhoea, skin nodule, vesicular rash
Musculoskeletal and connective tissue disorders	
<i>Uncommon:</i>	myalgia, arthralgia, back pain, musculoskeletal pain, flank pain, muscle

	weakness
<i>Rare:</i>	bone pain, chest wall pain, fasciitis, neck stiffness, cramps extremities, muscle cramps
Renal and urinary disorders	
<i>Uncommon:</i>	albuminuria, altered micturition frequency, dysuria, increased blood creatinine, acute renal failure, renal failure, haematuria, renal impairment, nocturia
<i>Rare:</i>	increased BUN, interstitial nephritis, micturition disorder, renal calculus, urinary tract obstruction NOS
Reproductive system and breast disorders	
<i>Uncommon:</i>	menstrual disorder
<i>Rare:</i>	leukorrhoea, breast pain
General disorders and administration site conditions	
<i>Common:</i>	asthenia, fatigue, fever
<i>Uncommon:</i>	increased sweating, pain, rigors, malaise, weakness, oedema, tooth discolouration
<i>Rare:</i>	face oedema, tongue oedema
Investigations	
<i>Uncommon:</i>	altered drug levels
Injury, poisoning and procedural complications	
<i>Uncommon:</i>	drug toxicity (NOS)
<i>Rare:</i>	ecchymoses

Serious adverse events that were considered treatment related were reported in 8 % (35/428) of patients in the refractory invasive fungal infection pool. Most individual treatment related serious adverse events were reported by <1 % of patients and are largely reflective of the serious underlying conditions that predisposed to the development of the invasive fungal infection. Treatment related serious adverse events reported in 1 % of subjects (3 or 4 subjects each) included altered concentration of other medicinal products, increased hepatic enzymes, nausea, rash, and vomiting. Treatment-related serious adverse events reported in 605 patients treated with posaconazole oral suspension for prophylaxis (1 % each) included bilirubinaemia, increased hepatic enzymes, hepatocellular damage, nausea, and vomiting.

Uncommon and rare treatment related medically significant adverse events reported during clinical trials with posaconazole oral suspension have included adrenal insufficiency, pancreatitis, allergic and/or hypersensitivity reactions.

Some azoles have been associated with prolongation of the QT interval on the electrocardiogram. A pooled analysis of 173 posaconazole oral suspension-dosed healthy volunteers utilizing time matched ECGs did not show a potential to prolong the QT interval. In addition, rare cases of torsade de pointes have been reported in patients taking posaconazole oral suspension.

In addition, rare cases of haemolytic uremic syndrome and thrombotic thrombocytopenic purpura have been reported primarily among patients who had been receiving concomitant cyclosporine or tacrolimus for management of transplant rejection or graft vs. host disease.

TABLE 9: Treatment-related adverse events reported in $\geq 1\%$ of patients treated for invasive fungal infections with posaconazole oral suspension (Severity as classified by the investigator)

Disorder	Total (All) n=330 Number (%)	Total (Mild/Moderate) n=330 Number (%)	Total (Severe/Life- Threatening) n=330 Number (%)
Body as a Whole-General			
anorexia	8 (2)	8 (2)	0
asthenia	4 (1)	4 (1)	0
chest pain	2 (1)	2 (1)	0
dizziness	7 (2)	6 (2)	1 (<1)
drug level altered	7 (2)	4 (1)	3 (1)
fatigue	7 (2)	6 (2)	1 (<1)
fever	3 (1)	3 (1)	0
headache	15 (5)	13 (4)	2 (1)

weakness	2 (1)	2 (1)	0
Cardiovascular, general			
cardio-respiratory arrest	2 (1)	0	2 (1)
ventricular hypertrophy	2 (1)	1 (<1)	1 (<1)
Central and Peripheral Nervous System			
confusion	3 (1)	3 (1)	0
convulsions	2 (1)	0	2 (1)
hyperreflexia	2 (1)	2 (1)	0
hypoesthesia	2 (1)	2 (1)	0
mental status, altered	2 (1)	2 (1)	0
paresthesia	6 (2)	6 (2)	0
somnolence	3 (1)	3 (1)	0
tremor	2 (1)	2 (1)	0
Blood and lymphatic system	6 (2)	4 (1)	2 (1)
anaemia	4 (1)	3 (1)	1 (<1)
Eye	4 (1)	3 (1)	1 (<1)
vision blurred	2 (1)	2 (1)	0
Reproductive system and breast			
breast pain	1 (<1)	1 (<1)	0
menstrual disorder (based on females only)	2 (2)	2 (2)	0
Gastro-intestinal system			
abdominal distension	2 (1)	2 (1)	0
abdominal pain	16 (5)	13 (4)	3 (1)
constipation	2 (1)	2 (1)	0
diarrhoea	11 (3)	10 (3)	1 (<1)
dyspepsia	2 (1)	2 (1)	0
flatulence	3 (1)	3 (1)	0
mouth dry	5 (2)	5 (2)	0
nausea	31 (9)	2 (1)	29 (9)

vomiting	19 (6)	18 (5)	1 (<1)
Heart Rate and Rhythm			
atrial flutter	2 (1)	1 (<1)	1 (<1)
ECG abnormal specific	2 (1)	2 (1)	0
extrasystoles	2 (1)	1 (<1)	1 (<1)
fibrillation atrial	3 (1)	2 (1)	1 (<1)
QTc/QT prolongation	6 (2)	6 (2)	0
tachycardia	2 (1)	2 (1)	0
tachycardia supraventricular	2 (1)	1 (<1)	1 (<1)
Injury and poisoning			
drug toxicity (NOS)	2 (1)	0	2 (1)
Liver and biliary system			
bilirubinemia	4 (1)	3 (1)	1 (<1)
gamma-GT increased	2 (1)	0	2 (2)
hepatic enzymes increased	7 (2)	6 (2)	1 (<1)
hepatic function abnormal	2 (1)	2 (1)	0
jaundice	2 (1)	1 (<1)	1 (<1)
AST increased	9 (3)	6 (2)	3 (1)
ALT increased	11 (3)	9 (3)	2 (1)
Metabolic and nutritional			
phosphatase alkaline increased	6 (2)	5 (2)	1 (<1)
thirst	2 (1)	2 (1)	0
Musculo-skeletal system			
musculo-skeletal pain	2 (1)	2 (1)	0
Platelet, bleeding and clotting			
thrombocytopenia	2 (1)	2 (1)	0
Renal & Urinary System			
blood creatinine	5 (2)	4 (2)	1 (<1)

decreased			
nocturia	2 (1)	2 (1)	0
renal failure	2 (1)	1 (<1)	1 (<1)
renal failure acute	2 (1)	0	2 (1)
Skin/ subcutaneous tissue			
alopecia	4 (1)	4 (1)	0
dry skin	3 (1)	3 (1)	0
pruritus	3 (1)	3 (1)	0
rash	9 (3)	7 (2)	2 (1)
rash maculopapular	4 (1)	3 (1)	1 (<1)
rash vesicular	2 (1)	2 (1)	0

TABLE 10: Treatment-related, treatment-emergent adverse events (any grade): $\geq 2\%$ of subjects (OPC) with posaconazole oral suspension

Adverse event	Number (%) of subjects		
	Controlled OPC pool		Refractory OPC pool
	POS n = 557	FLU n = 262	POS n = 239
Subjects reporting any adverse event^a	150 (27)	70 (27)	135 (56)
Body as a whole – general disorders			
Anorexia	6 (1)	1 (< 1)	7 (3)
Asthenia	4 (1)	2 (1)	6 (3)
Dizziness	9 (2)	5 (2)	8 (3)
Fatigue	8 (1)	5 (2)	7 (3)
Fever	10 (2)	1 (<1)	6 (3)
Headache	16 (3)	5 (2)	18 (8)
Central and peripheral nervous system disorders			
Somnolence	4(1)	5 (2)	3 (1)
Disorders of blood and lymphatic system			

Anaemia	2 (< 1)	0 (0)	6 (3)
Neutropenia	10 (2)	4 (2)	20 (8)
Gastro-intestinal system disorders			
Abdominal pain	10 (2)	8 (3)	12 (5)
Diarrhoea	19 (3)	13 (5)	26 (11)
Flatulence	6 (1)	0 (0)	11 (5)
Mouth dry	7 (1)	6 (2)	5 (2)
Nausea	27 (5)	18 (7)	20 (8)
Vomiting	20 (4)	4 (2)	16 (7)
Liver and biliary system disorders			
Hepatic enzymes increased	1 (< 1)	0 (0)	5 (2)
Hepatic function abnormal	3 (1)	4 (2)	0 (0)
Metabolic and nutritional disorders			
Phosphatase alkaline increased	3 (1)	3 (1)	5 (2)
Musculo-skeletal system disorders			
Myalgia	1 (<1)	0 (0)	4 (2)
Platelet, bleeding and clotting disorders			
Thrombocytopenia	3 (1)	0 (0)	4 (2)
Psychiatric disorders			
Insomnia	3 (1)	0 (0)	6 (3)
Skin and subcutaneous tissue disorders			
Pruritus	6 (1)	2 (1)	5 (2)
Rash	8 (1)	4 (2)	10 (4)

a number of subjects reporting treatment-emergent adverse events at least once during the study. Subjects may have reported more than one event.

TABLE 11: Studies 316 and 1899, Treatment-related, treatment-emergent adverse events: All ($\geq 2\%$ incidence) and Severe/Life Threatening Number (%) of Subjects (Prophylaxis) in the Posaconazole oral suspension or Fluconazole treatment groups

[illegible]

Hypokalemia	11 (2)	2 (<1)	6 (1)	1 (<1)	1 (2)	1 (2)
Skin and Subcutaneous Tissue Disorders						
Rash	12 (2)	1 (<1)	10 (2)	0	1 (2)	0

GGT = gamma glutamyl transpeptidase; ALT = serum glutamic oxaloacetic transaminase; ALT = serum glutamic pyruvic transaminase

^a number of subjects reporting treatment-emergent adverse events at least once during the study. Subjects may have reported more than one event.

Posaconazole Modified Release Tablets

In clinical trials, the type and frequency of adverse effects reported for posaconazole modified release tablets were generally similar to that reported in trials of posaconazole oral suspension.

The safety of posaconazole modified release tablets has been assessed in 230 patients in clinical trials. Patients were enrolled in a non-comparative pharmacokinetic and safety trial of posaconazole modified release tablets when given as antifungal prophylaxis (P05615). Patients were immunocompromised with underlying conditions including haematological malignancy, neutropenia post- chemotherapy, GVHD, and post HSCT. This patient population was 62% male, had a mean age of 51 years (range 19-78 years, 17 % of patients were ≥65 years of age), and were 93 % white and 16 % Hispanic. Posaconazole therapy was given for a median duration of 28 days. Twenty patients received 200 mg daily dose and 210 patients received 300 mg daily dose (following BD dosing on Day 1 in each cohort).

The most frequently reported treatment-related adverse reactions (≥5 %) with posaconazole modified release tablets (300 mg once daily) were nausea and diarrhoea. The most frequently reported adverse reaction leading to discontinuation of posaconazole modified release tablets 300 mg once daily was nausea.

Table 12 presents treatment-emergent adverse reactions observed in patients treated with 300 mg daily dose at an incidence of ≥10 % in posaconazole modified release tablet study.

TABLE 12: Posaconazole Study 5615: Number (%) of Subjects Treated with 300 mg Daily Dose Reporting Treatment-Emergent Adverse Reactions: Frequency of at Least 10%

Body System Preferred Term	Posaconazole Tablet (300 mg) (n=210)	
Subjects Reporting any Adverse Reaction	201	(99)
Blood and Lymphatic System Disorder		
Anemia	22	(10)
Febrile Neutropenia	42	(20)
Thrombocytopenia	29	(14)
Gastrointestinal Disorder		
Abdominal Pain	23	(11)
Constipation	20	(10)
Diarrhea	61	(29)
Nausea	56	(27)
Vomiting	28	(13)
General Disorders and Administration Site Conditions		
Asthenia	20	(10)
Catheter Site erythema	20	(10)
Chills	22	(10)
Mucosal inflammation	29	(14)
Edema Peripheral	33	(16)
Pyrexia	59	(28)
Metabolism and Nutrition Disorders		
Hypokalemia	46	(22)
Hypomagnesemia	20	(10)
Nervous System Disorders		
Headache	30	(14)
Respiratory, Thoracic and Mediastinal Disorders		
Cough	35	(17)
Epistaxis	30	(14)
Skin and Subcutaneous Tissue Disorders		

Rash	34	(16)
Vascular Disorders		
Hypertension	23	(11)

Clinical Laboratory Values

In (uncontrolled) trials of patients with invasive fungal infections treated with NOXAFIL oral suspension doses of 800 mg/day, the incidence of clinically significant liver function test abnormalities was: ALT and AST ($> 3 \times$ Upper Limit Normal {ULN}) 11 % and 10 %, respectively; total bilirubin ($> 1.5 \times$ ULN) 22 %; and alkaline phosphatase ($> 3 \times$ ULN) 14 %. In healthy volunteers, elevation of hepatic enzymes did not appear to be associated with higher plasma concentrations of posaconazole. In patients, the majority of abnormal liver function tests results showed minor and transient changes and rarely led to discontinuation of therapy.

In the comparative trials of patients infected with HIV treated with NOXAFIL at doses up to 400 mg, the incidence of clinically significant liver function test abnormalities was as follows: ALT and AST ($> 3 \times$ ULN) 3 % and 6 %, respectively; total bilirubin ($> 1.5 \times$ ULN) 3 %; and alkaline phosphatase ($> 3 \times$ ULN) 3 %.

The number of patients with changes in liver function tests from Common Toxicity Criteria (CTC) Grade 0, 1, or 2 at baseline to Grade 3 or 4 during the study are presented in Table 13 for the prophylaxis studies 316 and 1899.

TABLE 13: Studies: Posaconazole oral suspension studies 316 and 1899, Changes in Liver Function Test Results from CTC Grade 0, 1 or 2 at baseline to Grade 3 or 4.

	Number (%) of Patients With Change ^a	
Oral suspension Study 316		
Laboratory Parameter	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)
Oral suspension Study 1899		
	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.

Post-marketing Experience

The following post-marketing adverse experience has been reported:

Endocrine Disorders: pseudoaldosteronism

OVERDOSAGE

During clinical trials, patients who received posaconazole oral suspension doses up to 1600 mg/day had no noted adverse reactions different from those reported with patients at the lower doses. In addition, accidental overdose was noted in one patient who took 1200 mg posaconazole oral suspension twice a day for 3 days. No adverse reactions were noted by the investigator.

In a trial of patients with severe haemodialysis-dependent renal dysfunction ($Cl_{cr} < 20$ mL/min), posaconazole was not removed by haemodialysis. Thus, haemodialysis is unlikely to be effective in removing posaconazole from the systemic circulation.

There is no experience with overdosage of posaconazole modified release tablets.

PRESENTATION AND STORAGE CONDITIONS

Store below 30°C in the original packaging.

Noxafil 100 mg modified release tablets are packaged in a PVC/ Aclar laminate blister with push-through aluminium lidding.

Noxafil 100 mg modified release tablets are packaged in a blister in cartons of 24 (2x12) or 96 (8x12) tablets.

Not all pack sizes may be marketed.

MANUFACTURER

Manufactured by:

N. V. Organon

Kloosterstraat 6

5349 AB Oss

Netherlands

Packed by:

Organon Heist bv

Industriepark 30

2220 Heist-op-den-Berg

Belgium

PRODUCT REGISTRATION HOLDER

Merck Sharp & Dohme (Malaysia) Sdn. Bhd.

Lot No. B-22-1 & B-22-2, Level 22

The Ascent, Paradigm No.1

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