

NEW ZEALAND DATA SHEET

NOXAFIL[®] ORAL SUSPENSION

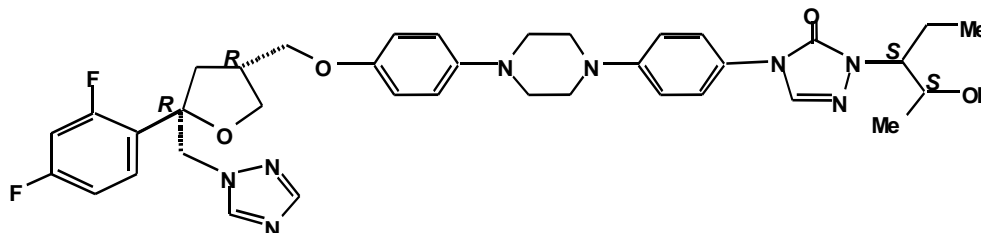
NAME OF THE MEDICINE

Posaconazole

Posaconazole is a broad spectrum triazole antifungal compound with a molecular formula of C₃₇H₄₂F₂N₈O₄ 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:

SCH 56592 (Posaconazole)



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 °C – 165 °C and is insoluble in water.

NOXAFIL ORAL SUSPENSION is a white, cherry flavoured immediate-release oral suspension containing 40 mg of posaconazole per mL and the following inactive ingredients: polysorbate 80, simethicone, sodium benzoate, sodium citrate dihydrate, citric acid monohydrate, glycerol, xanthan gum, liquid glucose, titanium dioxide, artificial cherry flavouring, and purified water.

PHARMACOLOGY

Pharmacodynamic properties

Antiinfective for systemic use, triazole derivative, J02AC04

Mechanism of action

Posaconazole is a triazole antifungal agent. It is a potent 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.

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*.

Posaconazole also exhibits *in vitro* activity against the following yeasts and moulds: *Candida dubliniensis*, *C. famata*, *C. guilliermondii*, *C. lusitaniae*, *C. kefir*, *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 micro-organisms have not been established in clinical trials.

NOXAFIL 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 NOXAFIL 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 NOXAFIL 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. The clinical significance of these results is unknown.

Pharmacokinetics

Absorption

Posaconazole is absorbed with a median T_{max} of 3 hours (patients) and ~ 5 hours (healthy volunteers). The pharmacokinetics of posaconazole are linear following single and multiple dose administration of up to 800 mg. No further increases in exposure are observed above 800 mg in patients and healthy volunteers. Dividing the total posaconazole daily dose (800 mg) as 400 mg twice a day results in a 184% higher exposure relative to once-a-day administration in patients.

Effect of food on oral absorption healthy volunteers

The AUC of posaconazole is about 2.6 times greater when administered with a nonfat meal or nutritional supplement (14 gm fat) and 4 times greater when administered with a high-fat meal (~ 50 gm fat) relative to the fasted state. Posaconazole should be administered with food or a nutritional supplement (See Dosage and Administration).

Distribution

Posaconazole has a large apparent volume of distribution (1774 L) suggesting extensive penetration into the peripheral tissues. 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 radiolabeled dose.

Excretion

Posaconazole is slowly eliminated with a mean half-life ($t_{1/2}$) of 35 hours (range 20 to 66 hours) and a total body clearance (Cl/F) of 32 L/hr. Posaconazole is predominantly excreted in the faeces (77 % of the radiolabeled dose) with the major component eliminated as parent drug (66 % of the radiolabeled dose). Renal clearance is a minor elimination pathway, with 14 % of the radiolabeled dose excreted in urine (<0.2 % of the radiolabeled dose is parent drug). Steady-state is attained following 7 to 10 days of multiple-dose administration.

Summary of the mean pharmacokinetic parameters in patients

The general pharmacokinetic findings across the clinical program in both healthy volunteers and patients were consistent, in that posaconazole was slowly absorbed and slowly eliminated with an extensive volume of distribution. In addition, the phenomenon of dose-limited absorption of posaconazole at 800 mg/day was observed both in healthy volunteers and patients. The mean pharmacokinetic parameters in patients and healthy volunteers following administration of posaconazole 400 mg twice a day for 7 days are displayed in Table 1.

TABLE 1 - Pharmacokinetics of posaconazole in patients and healthy volunteers

Population	Dose	Mean (%CV)		
		C _{max} (ng/mL)	T _{max} ^a (hr)	AUC(τ) (ng·hr/mL)
Healthy Volunteers	400 mg twice a day (n=174)	2850 (36)	5 (0-12)	29453 (37)
Patients	400 mg twice a day (n=24)	851 (82)	3 (0-12.5)	8619 (86)

^a: Median (range)

The exposure to posaconazole following administration of 400 mg twice a day was ~ 3 times higher in healthy volunteers than in patients, without additional safety findings at the higher concentrations (Table 1).

Pharmacokinetics in Special Populations

Paediatric

Following administration of 800 mg per day of posaconazole as a divided dose for treatment of invasive fungal infections, mean trough plasma concentrations from 12 paediatric 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_{av}) was comparable among ten adolescents (13 - 17 years of age) to C_{av} achieved in adults (≥ 18 years of age).

Gender

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

Elderly

Results from a multiple dose study in healthy volunteers (n = 48) indicated that at steady state, there was an increase in C_{max} (26 %) and AUC (29 %) observed in elderly subjects (24 subjects \geq 65 years of age) relative to younger subjects (24 subjects 18 - 45 years of age). A similar trend was observed in the clinical program based on a small proportion of elderly subjects \geq 65 years of age (n=25 vs. 194 patients 18 – 64 years of age). However, in a population pharmacokinetic analysis (Study 1899) age did not influence the pharmacokinetics of posaconazole. The safety profile of posaconazole between the young and elderly patients was similar. Therefore no dose adjustment is required for age.

Race

Results from a multiple dose study in healthy volunteers (n = 56) indicated that there was only a slight decrease (16%) in the AUC and C_{max} of posaconazole in Black subjects relative to Caucasian subjects, therefore, no dose adjustment for race is required.

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 hemodialysis.

Hepatic insufficiency

In a study with small number of subjects (n=12) who had hepatic impairment, there was an increase in exposure associated with prolongation of half-life (26.6, 35.3, and 46.1 hours for the mild, moderate and severe groups, respectively compared to 22.1 hours in subjects with normal hepatic function). An approximately 2-fold increase in steady-state AUC is estimated in patients with severe hepatic impairment. Due to the limited pharmacokinetic data in patients with hepatic impairment, posaconazole should be used with caution in patients with severe hepatic impairment since the prolonged half-life that may occur will lead to increased exposure.

Electrocardiogram evaluation

Multiple, time-matched ECGs collected over a 12 hour period were recorded at baseline and steady-state from 173 healthy male and female volunteers (18 to 85 years of age) administered posaconazole 400 mg BID with a high-fat meal. In this pooled analysis, the mean QT_c (Fridericia) interval change was -5 msec following administration of the recommended clinical dose. A decrease in the QT_c (F) interval (- 3 msec) was also observed in a small number of subjects (n=16) administered placebo. The placebo-adjusted mean maximum QT_c (F) interval change from baseline was < 0 msec (- 8 msec). No subject administered posaconazole had a QT_c (F) interval of \geq 500 msec or an increase \geq 60 msec in their QT_c (F) interval from baseline.

CLINICAL TRIALS

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 voriconazole or in patients who were intolerant of these medicinal products, was demonstrated in 107 patients enrolled in a salvage therapy trial. Patients were administered posaconazole 800 mg/day in divided doses for up to 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 therapy 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 %). As shown in Table 2, 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).

At one year, the survival rate for posaconazole was 38 % compared to 22 % for the external control group. However, this was not a prospective, randomised controlled study and so all comparisons with the external control group must be viewed in this context.

TABLE 2 - Overall efficacy of posaconazole at the end of treatment for invasive aspergillosis in comparison to an external control group

	Posaconazole	External Control Group
Overall Response	45/107 (42 %)	22/86 (26 %)
	Odds Ratio 4.06 (95 % CI: 1.50, 11.04) P=0.006	
Survival at day 365	(38 %)	(22 %)
Success by Species		
All mycologically confirmed <i>Aspergillus</i> spp.*		
<i>A. fumigatus</i>	34/76 (45 %)	19/74 (26 %)
<i>A. flavus</i>	12/29 (41 %)	12/34 (35 %)
<i>A. terreus</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 %)

* includes other less common species or species unknown

Other Serious Fungal Pathogens

Posaconazole 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:

Candida: 11 of 23 (48 %) patients were successfully treated with posaconazole. Of the responders, 5 were HIV infected patients with oesophageal disease and 4 were patients with

candidemia. Furthermore, in fluconazole-resistant non *albicans* species a successful outcome was noted in 4/5 cases with *C. krusei* infection.

Zygomycosis: Successful responses to posaconazole 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 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.

***Cryptococcus*:** Successful responses to posaconazole therapy were seen in 15 of 31 (48 %) of patients with cryptococcus. Most of the patients were HIV infected with refractory cryptococcal meningitis.

Chromoblastomycosis/Mycetoma: Successful responses to posaconazole 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):

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 3 below. Posaconazole and fluconazole demonstrated equivalent clinical success rates at Day 14 as well as 4 weeks after the end of treatment. However, posaconazole demonstrated a significantly better sustained mycological response rate than fluconazole.

TABLE 3 - 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 Azole-refractory Oropharyngeal Candidiasis (rOPC) (Studies 330 and 298)

The primary efficacy parameter in Study 330 was the clinical success rate (cure or improvement) after 4 weeks of treatment. HIV-infected patients were treated with posaconazole 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*.

Of the total patients treated in this study, 43 had azole-refractory oesophageal candidiasis (EC), either alone or in combination with OPC. All patients with azole-refractory EC had endoscopically confirmed EC at baseline. The clinical success rate after 4 weeks was 74.4 %.

In Study 298 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.

Of the patients treated in Study 298, 15 with azole-refractory EC had been previously treated in Study 330. Sixty-seven percent (67 %, 10/15) were considered cured by the end of treatment and 33 % (5/15) were considered improved. For those patients, treatment durations ranged from 81 to 651 days.

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

Two large, randomised, controlled studies were conducted using posaconazole as prophylaxis for the prevention of IFIs among patients at high risk.

Study 316 was a randomised, double-blind trial that compared posaconazole oral suspension (200 mg three times a day) with fluconazole capsules (400 mg once daily) as prophylaxis against invasive fungal infections in allogeneic HSCT 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 medication + 7 days). The mean duration of therapy was comparable between the two treatment groups (80 days, posaconazole; 77 days, fluconazole).

Study 1899 was a randomised, evaluator-blinded study that compared posaconazole oral suspension (200 mg three 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 acute myelogenous leukaemia 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. The mean duration of therapy was comparable between the two treatment groups (29 days, posaconazole; 25 days, fluconazole/itraconazole).

In both prophylaxis studies, aspergillosis was the most common breakthrough infection. There were significantly fewer breakthrough *Aspergillus* infections in patients receiving posaconazole prophylaxis when compared to control patients receiving fluconazole or itraconazole. See Table 4 for results from both studies.

TABLE 4 - Results from Clinical Studies in Prophylaxis of Invasive Fungal Infections.

Study	Posaconazole	Control ^a	p-Value
Proportion (%) of Patients With Proven/Probable IFIs			
On-Treatment Period^b			
1,899 ^d	7/304 (2)	25/298 (8)	0.0009
316 ^e	7/291 (2)	22/288 (8)	0.0038
Fixed-Time Period^c			
1,899 ^d	14/304 (5)	33/298 (11)	0.0031
316 ^d	16/301 (5)	27/299 (9)	0.0740
Proportion (%) of Patients With Proven/Probable Aspergillosis			
On-Treatment Period^b			
1,899 ^d	2/304 (1)	20/298 (7)	0.0001
316 ^e	3/291 (1)	17/288 (6)	0.0013
Fixed-Time Period^c			
1,899 ^d	4 /304 (1)	26 /298 (9)	< 0.0001
316 ^d	7/301 (2)	21/299 (7)	0.0059

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 medication plus 7 days; in 316 it was the period from first dose to last dose of study medication 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 ($p = 0.0354$) (Figure 1) as well as IFI-related deaths ($p = 0.0209$).

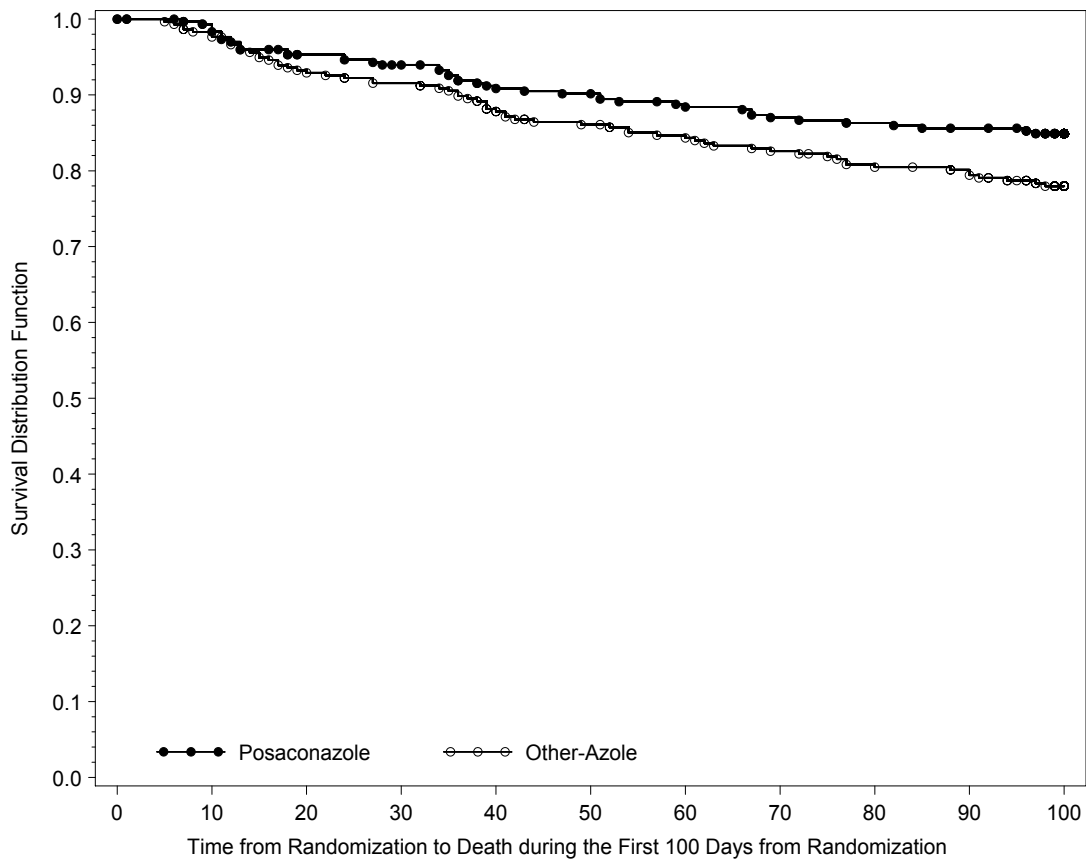


FIGURE 1 - All cause mortality in Study 1899 (POS vs FLU/ITZ; $p = 0.0354$)

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

A total of 16 patients aged 8 to 17 years were included in the therapeutic trials of invasive fungal infections. Five patients were < 13 years of age and 11 were 13-17 years old. Infections included aspergillosis, candidiasis and fusariosis. Successful response after treatment with posaconazole at divided doses up to 800 mg/day was seen in 50 % (8/16) of patients. Pharmacokinetic parameters obtained from 12 of these patients were not different

from those obtained from the patients in the 18 - 65 year age group, and the safety profile appeared similar.

Additionally, 12 patients aged 13 to 17 years 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 \geq 18 years of age.

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

INDICATIONS

NOXAFIL (posaconazole) is indicated for use in the treatment of the following invasive fungal infections in patients 18 years of age or older:

- Invasive aspergillosis in patients with disease that is refractory to, or are intolerant of, amphotericin B, itraconazole or voriconazole.
- Oesophageal candidiasis or candidemia in patients with disease that is refractory to, or who are intolerant of, amphotericin B, fluconazole or itraconazole.
- Fusariosis, zygomycosis, cryptococcosis, chromoblastomycosis, and mycetoma in patients with disease refractory to other therapy, or patients who are intolerant of other therapy.
- Coccidioidomycosis.

NOXAFIL is also indicated for the:

- Treatment of oropharyngeal candidiasis in immunocompromised adults, including patients with disease that is refractory to itraconazole and fluconazole.
- Prophylaxis of invasive fungal infections, including both yeasts and moulds, in patients 13 years of age and older who are at high risk of developing these infections, such as patients with prolonged neutropenia or haematopoietic stem cell transplant (HSCT) recipients.

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).

Although not studied *in vitro* or *in vivo*, co-administration of posaconazole and certain drugs metabolized through the CYP3A4 system: terfenadine, astemizole, cisapride, pimozone, 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).

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.

Hepatic toxicity

In clinical trials, there were infrequent cases of hepatic reactions (e.g., mild to moderate elevations in ALT, AST, alkaline phosphatase, total bilirubin, and/or clinical hepatitis) 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 and rarely required drug discontinuation. Rarely, more severe hepatic reactions including (cases that have progressed to fatal outcomes) were reported in patients with serious underlying medical conditions (e.g. haematologic malignancy) during treatment with posaconazole.

QT prolongation

Some azoles have been associated with prolongation of the QT_c interval on the electrocardiogram (ECG). Results from a multiple time-matched ECG analysis in healthy volunteers did not show an increase in the mean QT_c interval. Nevertheless, posaconazole should not be administered with medications that are known to prolong the QT_c interval and are metabolized through the CYP3A4 system (see Contraindications, Interactions, Clinical Trials – Electrocardiogram Evaluation).

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

Effects on Fertility

Posaconazole had no effect on fertility of male and female rats.

Women of Childbearing Potential

Women of childbearing potential must always use effective contraceptive measures during treatment with posaconazole.

Use in Pregnancy

Category B3. There is insufficient information on the use of NOXAFIL in pregnant women. Studies in animals have shown reproductive toxicity (See PRECLINICAL TOXICOLOGY). Posaconazole has been shown to cause skeletal malformations in rats at exposures lower than those obtained at therapeutic doses in humans. In rabbits, posaconazole was embryotoxic at exposures greater than those obtained at therapeutic doses. The potential risk to humans is unknown. Posaconazole must not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus.

Pregnancy categorisation definition:

Category B3: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

Use in Lactation

Posaconazole is excreted in milk of lactating rats. The excretion of posaconazole in human breast milk has not been investigated. Posaconazole should not be used by nursing mothers unless the benefit to the mother clearly outweighs the potential risk to the infant.

Paediatric Use

(See Clinical Pharmacology – Pharmacokinetics in special populations, Paediatric). Safety and effectiveness in paediatric patients below the age of 18 years have not been established.

Use in the Elderly

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

Preclinical safety

As observed with other azole antifungal agents, effects related to inhibition of steroid hormone synthesis were seen in repeated-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.

Reproduction, peri- and postnatal development studies were conducted in rats. At exposures lower than those obtained at therapeutic doses in humans, posaconazole caused skeletal variations and malformations, dystocia, increased length of gestation, reduced mean litter size and postnatal viability. In rabbits, posaconazole was embryotoxic at exposures greater than those obtained at therapeutic doses. As observed with other azole antifungal agents, these effects on reproduction were considered related to a treatment-related effect on steroidogenesis.

Carcinogenicity/Genotoxicity

Posaconazole was not genotoxic in *in vitro* and *in vivo* studies. Carcinogenicity studies did not reveal special hazards for humans.

Interactions with other medicines

Effect of Other Drugs on Posaconazole

Posaconazole is metabolised 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.

Antacids (20 mL single dose of liquid antacid equivalent to 25.4 mEq acid neutralizing capacity/5mL) 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.

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 (QT 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: Although not studied *in vitro* or *in vivo*, posaconazole may increase the plasma concentration of vinca alkaloids (e.g., vincristine and vinblastine), which may lead to neurotoxicity. Therefore, it is recommended that dose adjustment of vinca alkaloids be considered.

Cyclosporine: In heart transplant patients on stable doses of cyclosporine, posaconazole 200 mg once daily increased cyclosporine concentrations requiring dose reductions. 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. 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 twice daily for 7 days) increased the C_{max} and AUC of IV midazolam (0.4 mg single dose) an average of 1.3- and 4.6-fold, respectively. Posaconazole 400 mg twice daily for 7 days increased the IV midazolam C_{max} and AUC by 1.6- and 6.2-fold, respectively. Both doses of posaconazole increased C_{max} and AUC of oral midazolam (2 mg single oral dose) by 2.2- and 4.5-fold, respectively. In addition, oral posaconazole (200 mg or 400 mg) prolonged the mean terminal half-life of midazolam from approximately 3-4 hours to 8-10 hours during co-administration. It is recommended that dose adjustments of benzodiazepines, metabolised by CYP3A4, be considered during co-administration with posaconazole.

Zidovudine (AZT), lamivudine (3TC), ritonavir, 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), ritonavir (600 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 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. It is recommended that dose adjustment of HMG-CoA reductase inhibitors be considered during coadministration. Frequent monitoring for adverse events and toxicity related to statins may be needed.

Calcium channel blockers metabolised 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.

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.

ADVERSE EFFECTS

Drug-related, adverse reactions observed in 2,400 subjects dosed with posaconazole are shown in Table 5. One hundred and seventy-two patients received posaconazole therapy for ≥ 6 months; 58 of these received posaconazole 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 (8 %).

TABLE 5 - Treatment-related adverse reactions reported in posaconazole dosed subjects by body system n=2,400 Common (>1/100, <1/10)

Blood and lymphatic system disorders	
Common	Neutropenia
Metabolism and nutrition disorders	
Common	Anorexia
Nervous system disorders	
Common	Dizziness, headache, paresthesia, somnolence
Gastrointestinal disorders	
Common	Abdominal pain, diarrhoea, dyspepsia, flatulence, dry mouth, nausea, vomiting
Hepatobiliary disorders	
Common	Elevated liver function tests (including AST, ALT, alkaline phosphatase, GGT, bilirubin)
Skin and subcutaneous tissue disorders	
Common	Rash

General disorders and administration site conditions Common	Asthenia, fatigue, pyrexia (fever)
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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 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 have included adrenal insufficiency, 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-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.

In addition, rare cases of haemolytic uraemic 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.

Clinical Laboratory Values

In (uncontrolled) trials of patients with invasive fungal infections treated with NOXAFIL doses of 800 mg/day, the incidence of clinically significant liver function test abnormalities was ; ALT and AST (> 3 X Upper Limit Normal {ULN}) 11 % and 10 %, respectively; total bilirubin (> 1.5 X ULN) 22 %; and alkaline phosphatase (> 3 X 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 (or another indication) 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 X ULN), 3 % and 6 %, respectively; total bilirubin (> 1.5 X ULN), 3 %; and alkaline phosphatase (> 3 X ULN), 3 %.

DOSAGE AND ADMINISTRATION

NOXAFIL should be administered with a meal, or with 240 mL of a nutritional supplement. Shake well before use.

TABLE 6 - Recommended Dose According to Indication

Indication	Dose and Duration of Therapy
Refractory Invasive Fungal infections (IFI)/Intolerant Patients with IFI	400 mg (10 mL) twice a day with food or a nutritional supplement. Dividing the dose further to 200 mg (5 mL) four times a day has been shown to enhance exposure to posaconazole, particularly in patients who have limited oral intake. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response.
Coccidioidomycosis	NOXAFIL should be administered at a dose of 400 mg (10 mL) twice a day with food or a nutritional supplement. Dividing the dose further to 200 mg (5 mL) four times a day has been shown to enhance exposure to posaconazole, particularly in patients who have limited oral intake. Duration of therapy should be based on the severity of the underlying disease, recovery from immunosuppression, and clinical response.
Oropharyngeal Candidiasis	Loading dose of 200 mg (5 mL) once a day on the first day, then 100 mg (2.5 mL) once a day for 13 days.
Refractory Oropharyngeal or Oesophageal Candidiasis	400 mg (10 mL) twice a day. Duration of therapy should be based on the severity of the patient's underlying disease and clinical response.
Prophylaxis of Invasive Fungal Infections	200 mg (5 mL) three times a day. The duration of therapy is based on recovery from neutropenia or immunosuppression.

Increasing the total daily dose above 800 mg does not further enhance the exposure to posaconazole (see Pharmacology).

Use in renal impairment: No dose adjustment is required for renal dysfunction and 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 (see Pharmacology).

Use in hepatic impairment: There is 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 (see Pharmacology).

Use in Paediatrics: Safety and efficacy in adolescents and children below the age of 18 years have not been established.

Use in the Elderly: No dosage adjustment is recommended for elderly patients (See Pharmacology).

OVERDOSAGE

During clinical trials, patients who received posaconazole 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 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.

PRESENTATION AND STORAGE CONDITIONS

NOXAFIL oral suspension contains 40 mg posaconazole per mL of suspension.

NOXAFIL oral suspension 105 mL is packaged in a 123 mL amber Ph.Eur. Type IV glass bottle, closed with a plastic child-resistant closure. A measuring spoon, composed of clear polystyrene and graduated to measure 2.5 mL or 5 mL of the suspension, is provided with each bottle.

Shake well before use. Store below 25 °C. Do not freeze.

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MEDICINE CLASSIFICATION

Prescription Medicine

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