PACKAGE INSERT

1. NAME OF THE MEDICINAL PRODUCT

Posatif Posaconazole gastro-resistant tablets, 100 mg

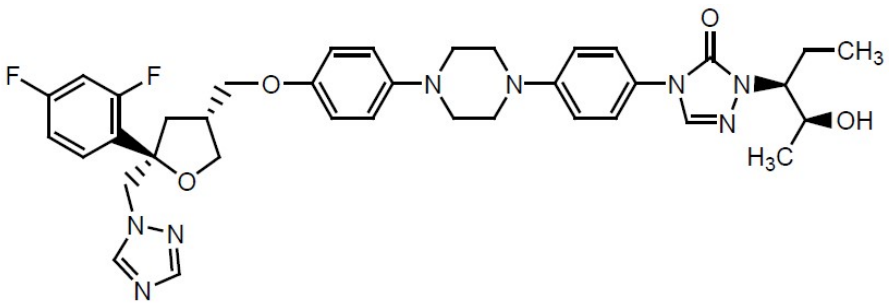
2. NAME AND STRENGTH OF ACTIVE SUBSTANCE(S)

Posatif Posaconazole gastro-resistant tablets contain 100 mg of posaconazole.

3. PRODUCT DESCRIPTION

Posaconazole is an azole antifungal agent. Posaconazole is available as delayed-release tablet intended for oral administration.

Posaconazole is designated chemically as 4-[4-[4-[4-[[(3*R*,5*R*)-5- (2,4-difluorophenyl)tetrahydro-5- (1*H*-1,2,4-triazol-1-ylmethyl)-3-furanyl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[(1*S*,2*S*)-1-ethyl-2- hydroxypropyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one with an empirical formula of $C_{37}H_{42}F_2N_8O_4$ and a molecular weight of 700.8. The chemical structure is:



Posaconazole is a white powder with a low aqueous solubility.

Approximately 17.5 x 6.7 mm, yellow coated, capsule shaped tablets, debossed with “100P” on one side and plain on the other side, containing 100 mg of posaconazole.

Each delayed-release tablet contains the inactive ingredients: partially neutralized methacrylic acid and ethyl acrylate copolymer, triethyl citrate, xylitol, hydroxypropyl cellulose, propyl gallate, cellulose, microcrystalline, silica, colloidal anhydrous, croscarmellose sodium, sodium stearyl fumarate and Opadry® II Yellow (consists of the following ingredients: polyvinyl alcohol partially hydrolyzed, macrogol, polyethylene glycol, titanium dioxide, talc, and iron oxide yellow).

4. PRECLINICAL INFORMATION

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.

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

5. PHARMACODYNAMICS/PHARMACOKINETICS

5.1 Pharmacokinetics

Absorption

Posaconazole delayed release tablets are absorbed with a median T_{max} of 4 to 5 hours and exhibit dose proportional pharmacokinetics after single and multiple dosing up to 300 mg.Following a single dose administration of 300 mg posaconazole tablet after a high fat meal to healthy volunteers, the AUC_{0-72} hours and C_{max} were higher compared to administration under fasted condition (51 % and 16 % for AUC_{0-72} hours and C_{max} respectively).
Posaconazole plasma concentrations following administration of posaconazole tablets may increase over time in some patients. The reason for this time-dependency is not completely understood.

The absolute availability of the oral tablet is approximately 54 %.

Posaconazole delayed release tablets can be given once daily after a BID dosing on Day 1.

Posaconazole oral suspension is absorbed with a median T_{max} of 3 hours (patients) and 5 hours (healthy volunteers). The pharmacokinetics of posaconazole oral suspension are linear following single and multiple dose administration of up to 800 mg. No further increases in exposure were observed when oral suspension doses above 800 mg daily were administered to patients and healthy volunteers. Dividing the total posaconazole oral suspension daily dose (800 mg) as 400 mg twice a day results in a 184 % higher exposurerelative to once-a-day administration in patients. Exposure further increased when posaconazole was given as 200 mg four times daily.

Effect of food on oral absorption in healthy volunteers

Posaconazole delayed release tablets can be taken without regard to food.
The AUC of posaconazole oral suspension 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 oral suspension should be administered with food or a nutritional supplement.

Distribution

Posaconazole delayed release tablets have a mean apparent volume of distribution of 394 L (42 %), ranging between 294-583 L among the studies in healthy volunteers.
Posaconazole oral suspension has a large apparent volume of distribution (1,774 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 feces account for approximately 17 % of the administered radiolabeled dose.

Excretion

Posaconazole is predominantly excreted in the feces (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).

Posaconazole delayed release tablet is eliminated with a mean half-life ($t_{½}$) ranging between 26 and 31 hours and a mean apparent clearance ranging from 7.5 to 11 L/hr.

Posaconazole oral suspension is slowly eliminated with a mean half-life ($t_{½}$) of 35 hours (range 20 to 66 hours) and apparent total body clearance (Cl/F) of 32 L/hr. 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.

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

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

Pharmacokinetics in Special Populations

Children (< 18 years)

Use of posaconazole delayed release tablets in patients 13 to 17 years of age is supported by evidence from adequate and well-controlled studies of posaconazole oral suspension.

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). Similarly, in the prophylaxis studies, the mean steady-state posaconazole average concentration (Cav) was comparable among ten children (13-17 years of age) to Cav achieved in adults (≥ 18 years of age).

In a study of 136 neutropenic pediatric patients 11 months – 17 years treated with posaconazole oral suspension, approximately 50 % met the prespecified target (Day 7 Cav 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 posaconazole is necessary based on gender.

Geriatric

Of the 230 patients treated with posaconazole delayed release tablets, 38 (17 %) were greater than 65 years of age. The pharmacokinetics of posaconazole delayed 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.

An increase in C_{max} (26 %) and AUC (29 %) was observed in elderly subjects (24 subjects ≥ 65 years of age) receiving posaconazole oral suspension relative to younger subjects (24 subjects 18 - 45 years of age). However, in a population pharmacokinetic analysis (Study 1899) age did not influence the pharmacokinetics of posaconazole oral suspension. Further, in clinical efficacy trials, the safety profile of posaconazole oral suspension between the young and elderly patients was similar. Therefore, no dose adjustment is required for age.

Race

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

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 oral suspension in Black subjects relative to Caucasian subjects, therefore, no dose adjustment for race is required.

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.

Patients, in particular those receiving Posaconazole after HSCT, who have a low body weight (< 60 kg) are more likely to experience higher plasma concentrations of posaconazole and should be closely monitored for adverse events.

Renal insufficiency

Following single dose administration, there was no effect of mild and moderate renal insufficiency (n=18, Cl_{cr} ≥ 20 ml/min/1.73 m^2) on posaconazole pharmacokinetics, therefore, no dose adjustment is required. In subjects with severe renal insufficiency (n=6, Cl_{cr} < 20 ml/min/1.73 m^2), 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. Due to the variability in exposure, patients with severe renal impairment should be monitored closely for breakthrough fungal infections.

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

5.2 Pharmacodynamics

ATC code: J02AC04

Mechanism of action

Posaconazole is a potent inhibitor of the enzyme lanosterol 14α-demethylase, which catalysesan essential step in ergosterol biosynthesis.

Microbiology

Posaconazole has been shown *in vitro* to be active against the following micro-organisms: *Aspergillus* species (*A. fumigatus*, *A. flavus*, *A. terreus*, *A. nidulans*, *A. niger*, *A. ustus, A.ochraceus*), *Candida* species (*C. 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. 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 dermatiditis* (n=15) of 0.5 mg/L, and *Purpureocillium lilacinum* (n=21) of 1 mg/L.

In vitro 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 marneffei, 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 $1x10^{-8}$ to $1x10^{-9}$. 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 medicinal product 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.

Clinical experience

Pharmacokinetics and Safety of Posaconazole Delayed Release Tablets in Patients

Study 5615 was a non-comparative multi-center study performed to evaluate thepharmacokinetic properties, safety, and tolerability of posaconazole 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 tablet in a more diverse patient population, and to confirm the exposure of posaconazole tablet in additional subjects at risk of a fungal infection. Posaconazole 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 andhad 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 Cav between 500- 2500 ng/mL. [Cav 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 Cav at steady state of 1580 ng/mL. The PK findings from the pivotal study (Study 5615) support a 300 mg daily dose of Posaconazole tablet for use in prophylaxis.

Pharmacokinetics and Safety of Posaconazole Oral Suspension in Patients

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 of patients with zygomycete infections. Sites of infection included the sinuses, lung, and skin. Most of the patients had underlying haematological malignancies, half of which required a bone marrow transplant. One-half of the patients were enrolled with intolerance to previous therapy and the other one-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.: 11 of 24 patients were successfully treated with posaconazole oral suspension. 4 of the responders had disseminated disease and one patient had disease localized to the eye; the remainder had a variety of sites of infection. 7 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: 15 of 31 patients were successfully treated with posaconazole oral suspension. Most of the patients were HIV infected with refractory cryptococcal meningitis.

Chromoblastomycosis/Mycetoma: 9 of 11 patients were successfully treated with posaconazole oral suspension. 5 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 the Table 1 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 sustained mycological response rate than fluconazole.

Table 1: Clinical Success Rates and Mycological Response Rates in Oropharyngeal Candidiasis.

Endpoint	**Posaconazole Oral Suspension**	**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 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*.

Of the total patients treated in this study, 43 had azole-refractory esophageal candidiasis, 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 oral suspension 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 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. 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 2 for results from both studies.

Table 2: 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
Proportion (%) of Patients with Proven/Probable Aspergillosis			
On-Treatment Period[b]			
1899[d]	2/304 (1)	20/298 (7)	0.0001
316[e]	3/291 (1)	17/288 (6)	0.0013
Fixed-Time Period[c]			
1899[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 itwas 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 periodfrom 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).

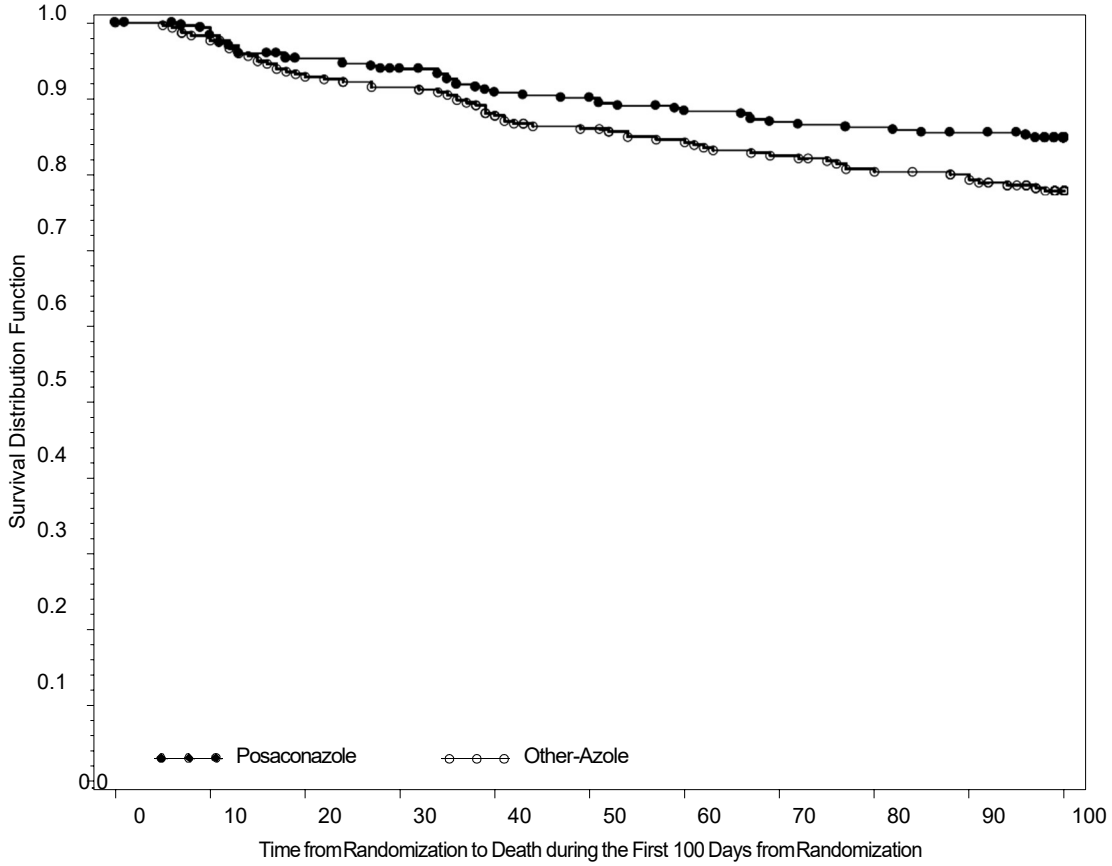


Figure 1: All cause mortality in Study 1899 (POS vs FLU/ITZ; P= 0.0354)

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).

6. INDICATIONS AND USAGE

Posaconazole delayed release tablets are indicated for the prophylaxis of invasive *Aspergillus* and *Candida* infections, including both yeasts and molds, in patients 13 years of age and older, who are at high risk of developing these infections, such as patients with prolonged neutropenia or hematopoietic stem cell transplant (HSCT) recipients.

Posaconazole delayed release tablets are indicated for use in the treatment of the following fungal infections in patients 13 years of age or older:

- Refractory Invasive Fungal infections (IFI) /Intolerant Patients with IFI: Fusariosis, zygomycosis, cryptococcosis, coccidioidomycosis, chromoblastomycosis, and mycetoma in patients with disease 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.

7. DOSAGE AND ADMINISTRATION

Important Administration Instructions

Non-Interchangeability between Posaconazole Delayed Release Tablets and Posaconazole Oral Suspension

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

Posatif Posaconazole gastro-resistant tablets

- Tablets should not be administered together with alcohol.
- Swallow tablets whole. Do not divide, crush, or chew.
- Tablets may be taken without regard to food intake.

Indication	Dose and Duration of therapy
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. Each dose may be taken without regard to food intake. Duration of therapy is based on recovery from neutropenia or immunosuppression. For patients with acute myelogenous leukemia or myelodysplastic syndromes, prophylaxis with posaconazole should start several days before the anticipated onset of neutropenia and continue for 7days after the neutrophil count rises above 500 cells per mm^3.
Refractory Invasive Fungal Infections (IFI)/Patients with IFI Intolerant to 1^{st} Line Therapy	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 severityof the underlying disease, recovery from immunosuppression, and clinical response.

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.

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 inhalf-life with a decrease in hepatic function.

Use in children: Safety and efficacy in children below the age of 13 years have not been established.

8. MODE/ROUTE OF ADMINISTRATION

Oral route of administration.

9. CONTRAINDICATIONS

Posaconazole is contraindicated in patients with known hypersensitivity to posaconazole or any component of the product.

Although not studied *in vitro* or *in vivo*, coadministration of the CYP3A4 substrates terfenadine, astemizole, cisapride, pimozide, or quinidine with posaconazole are contraindicated since increased plasma concentrations of these drugs can lead to QT prolongation and rare occurrences of torsade de pointes.

Coadministration with the HMG-CoA reductase inhibitors that are primarily metabolized through CYP3A4 is contraindicated since increased plasma concentration of these drugscan lead to rhabdomyolysis.

Although not studied *in vitro* or *in vivo*, posaconazole may increase the plasma concentrationsof ergot alkaloids which may lead to ergotism. Coadministration of posaconazole and ergot alkaloids is contraindicated.

10. WARNINGS AND 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). The elevations in liver function tests were generally reversible on discontinuation of therapy, and in some instances these tests normalized without drug interruption and rarely required drug discontinuation. Rarely, more severe hepatic reactions including cholestasis or hepatic failure were reported in patients with serious underlying medical conditions (e.g., hematologic malignancy) during treatment with posaconazole. Posaconazole should be used with caution in patient with severe hepatic impairment. In these patients, the prolonged elimination half-life may lead to increased exposure.

Monitoring of hepatic function: Liver function tests should be evaluated at the start and during the course of posaconazole therapy. Patients who develop abnormal liver function test during posaconazole therapy should be monitored for the development of more severe hepaticfunction (particularly liver function tests and bilirubin). Discontinuation of posaconazole must be considered if clinical signs and symptoms consistent with liver disease develop that may be attributable to posaconazole.

QT Prolongation: Some azoles have been associated with prolongation of the QT interval. Results from a multiple time-matched ECG analysis in healthy volunteers did not show any increase in the mean of the QTc interval. Nevertheless, posaconazole should not be administered with drugs that are known to prolong the QTc interval and are metabolized through CYP3A4. Posaconazole should be administered with caution to patient with potentially proarrhythmic conditions and should not be administered with medicines that are known to prolong QTc interval and are metabolized through CYP3A4.

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 treatmentoptions (see DRUG INTERACTIONS).

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 DRUG INTERACTIONS). Refer to the venetoclax prescribing information for detailed guidance.

Gastrointestinal dysfunction: There are limited pharmacokinetic data in patients with severe gastrointestinal dysfunction (such as severe diarrhoea). Patients who have severe diarrhoea or vomiting should be monitored closely for breakthrough fungal infections.

Plasma exposure: Posaconazole plasma concentrations following administration of posaconazole tablets are generally higher than those obtained with posaconazole oral suspension. Posaconazole plasma concentrations following administration of posaconazole tablets may increase over time in some patients. Safety data at higher exposure levels achieved with posaconazole tablets are at present limited.

11. USAGE DURING PREGNANCY AND LACTATION

There is insufficient information on the use of posaconazole in pregnant women. Studies in animals have shown reproductive toxicity. 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 for humans is unknown. Posaconazole should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus. Women of childbearing potential must be advised to always use effective contraceptive measure during treatment and for at least 2 weeks after completing therapy.

Posaconazole is excreted into the 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 clearly outweighs the risk to the infant.

12. DRUG INTERACTIONS

The interactions described in the following subsections apply to posaconazole delayed release tablets and oral suspension unless otherwise specified.

Effects of other medicinal products on Posaconazole Delayed Release Tablets and oral suspension:

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.

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.

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.

H_2 Receptor Antagonists, Proton Pump Inhibitors (PPIs) and Antacids:

Posaconazole Delayed Release Tablets:

No clinically relevant effects were observed when posaconazole delayed release tablets are concomitantly used with antacids, H_2-receptor antagonists and proton pump inhibitors. No dosage adjustment of posaconazole delayed release tablets is required when posaconazole delayed release tablets are concomitantly used with antacids, H2-receptor antagonists and proton pump inhibitors.

Posaconazole Oral Suspension:

Posaconazole plasma concentrations (C_{max} and AUC) were reduced by 39 % when posaconazole oral suspension was administered with cimetidine (400 mg twice a day) due to reduced absorption possibly secondary to a decrease in gastric acid production. Co- administration of posaconazole oral suspension with H_2 receptor antagonists should be avoided if possible.

Similarly, administration of 400 mg posaconazole oral suspension with esomeprazole (40 mg daily) decreased mean C_{max} and AUC by 46 % and 32 %, respectively, compared to dosing with 400 mg posaconazole alone. Co-administration of posaconazole oral suspension with proton pump inhibitors should be avoided if possible.

Gastrointestinal Motility Agents:

Posaconazole Delayed Release Tablets:

No clinically meaningful effect on the pharmacokinetics of posaconazole was observed when posaconazole delayed release tablets were concomitantly administered with metoclopramide. No dosage adjustment of posaconazole delayed release tablets is required when given concomitantly with metoclopramide.

Posaconazole Oral Suspension:

Metoclopramide, when given with posaconazole oral suspension, decreases posaconazole plasma concentrations. If metoclopramide is concomitantly administered with posaconazole oral suspension, it is recommended to closely monitor for breakthrough fungal infections.

Loperamide does not affect posaconazole plasma concentrations. No dosage adjustment of posaconazole is required when loperamide and posaconazole are used concomitantly.

Glipizide: (10 mg single dose) had no clinically significant effect on posaconazole C_{max} and AUC.

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 oral suspension QD on the 1st day, 200 mg oral suspension BID on the 2nd day, then 400 mg oral suspension BID x 8 days) by 21 % and 23 %, respectively.

Terfenadine, astemizole, cisapride, pimozole and quinidine: Although not studied *in vitro* or *in vivo*, co-administration of posaconazole and certain drugs such as terfenadine, astemizole, cisapride, pimozole and quinidine, metabolizes 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.

Effects of Posaconazole Delayed Release Tablets and oral suspension on other medicinal products:

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.

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. Coadministration of posaconazole and ergot alkaloids is contraindicated.

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 WARNINGS AND 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 oral suspension 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-fourths of the current dose). Thereafter blood levels of cyclosporine should be monitored carefully during coadministration and upon discontinuation of posaconazole treatment, 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 oral suspension 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 coadministration, 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 coadministered, careful monitoring of full blood counts and adverse effects related to increased rifabutin levels (e.g., uveitis) is recommended.

Midazolam: In a study in healthy volunteers, posaconazole (200 mg once daily for 10 days) increased the exposure (AUC) of IV midazolam (0.05 mg/kg) by 83 %. In another study in healthy volunteers, repeat dose administration of oral posaconazole (200 mg oral suspension 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 oral suspension 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 oral suspension) prolonged the mean terminal half-life of midazolam from approximately 3-4 hours to 8-10 hours during coadministration.
Due to the risk of prolonged sedation, it is recommended that dose adjustments of benzodiazepines, metabolized by CYP3A4, be considered during coadministration with posaconazole.

Zidovudine (AZT), lamivudine (3TC), ritonavir, indinavir: Clinical studies demonstrated that no clinically significant effects on zidovudine, lamivudine, ritonavir, indinavir were observed when administered with posaconazole; therefore, no dose adjustments are required for these co-administered drugs. Although not considered clinically significant, ritonavir exposure was increased by 30 % with the addition of posaconazole.

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 posaconazole (400 mg oral suspension 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 posaconazole (400 mg oral suspension 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.

HMG-CoA reductase inhibitors primarily metabolized through CYP3A4: Repeat dose administration of oral posaconazole (50, 100, and 200 mg oral suspension 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. Coadministration 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 coadministration 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.

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

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

13. ADVERSE EFFECTS:

Posaconazole Delayed 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 delayed release tablets has been assessed in 230 patients enrolled in the pivotal clinical study. Patients were enrolled in a non-comparative pharmacokinetic and safety trial of posaconazole delayed release tablets when given as antifungal prophylaxis. Patients were immunocompromised with underlying conditions including hematological malignancy, neutropenia post-chemotherapy, Graft versus Host. Disease (GVHD), and post HSCT. 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 BID dosing on Day 1 in each cohort).

The most frequently reported treatment-related adverse reactions (≥ 5 %) with posaconazole delayed release tablets (300 mg once daily) were nausea and diarrhea.

The most frequently reported adverse reaction leading to discontinuation of posaconazole delayed release tablets 300 mg once daily was nausea.

Table 3 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 3: 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 delayed release tablets (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 Disorders		
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)

Postmarketing Experience

The following adverse reaction has been identified during the post-approval use of posaconazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Endocrine Disorders: Pseudoaldosteronism

14. OVERDOSAGE

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

During the clinical trials, some patients received posaconazole oral suspension up to 1600 mg/day with no adverse reactions noted that were different from the lower doses. In addition, accidental overdose was noted in one patient who took 1200 mg twice daily posaconazole oral suspension for 3 days. No related adverse reactions were noted by the investigator. Posaconazole is not removed by hemodialysis.

15. INCOMPATIBILITIES

Not applicable.

16. STORAGE CONDITION

Store under 30ºC.

17. SHELF LIFE

36 months

18. DOSAGE FORM OR PRESENTATION

Posaconazole gastro-resistant tablets are packaged in a Alu-Alu blisters in cartons of 24 (2x12) tablets.

19. Name and Address of Manufacturer / Product owner:

AET Laboratories Pvt. Ltd.
Survey No.42, Gaddapotharam village,
Kazipally Industrial Area,
Sangareddy District,
Telangana state, 502319
India.