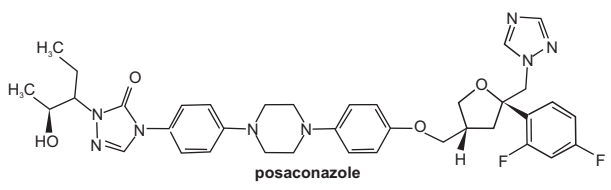
Posaconazole Injection 300 mg/16.7 ml

Posaone पोसावन

Composition:
Each mL Contains:
Posaconazole.....18 mg

DESCRIPTION
Posaconazole is an azole antifungal agent available as concentrated solution to be diluted before intravenous administration. Posaconazole is designated chemically as 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

Posaconazole is a white powder with a low aqueous solubility. Posaconazole injection is available as a clear colorless to yellow, sterile liquid essentially free of foreign matter. Each vial contains 300 mg of posaconazole and the following inactive ingredients: Betadex Sulfobutyl ether solution, Edetate disodium, Hydrochloric acid and Sodium hydroxide.

DOSAGE FORMS AND STRENGTHS
Injection; 300 mg/16.7 ml

PHARMACODYNAMICS AND PHARMACOKINETICS
Pharmacodynamics.
Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02A C04.

Mechanism of Action:
Posaconazole inhibits the enzyme lanosterol 14α-demethylase (CYP51), which catalyses an essential step in ergosterol biosynthesis.

Microbiology
Posaconazole has been shown in vitro to be active against the following microorganisms: *Aspergillus* species (*Aspergillus fumigatus*, A. *flavus, A. terreus, A. nidulans, A. niger, A. ustus*), *Candida* species (*Candida albicans, C. glabrata, C. krusei, C. parapsilosis, C. tropicalis, C. dubliniensis, C. famata, C. inconspicua, C. lipolytica, C. norvegensis, C. pseudotropicalis*), *Coccidioides immitis, Fonsecaea pedrosoi*, and species of *Fusarium, Rhizomucor, Mucor*, and *Rhizopus*. The microbiological data suggest that posaconazole is active against *Rhizomucor, Mucor*, and *Rhizopus*; however the clinical data are currently too limited to assess the efficacy of posaconazole against these causative agents.

Resistance
Clinical isolates with decreased susceptibility to posaconazole have been identified. The principle mechanism of resistance is the acquisition of substitutions in the target protein, CYP51.

Epidemiological Cut-off (ECOFF) values for Aspergillus spp.
The ECOFF values for posaconazole, which distinguish the wild type population from isolates with acquired resistance, have been determined by EUCAST methodology.

EUCAST ECOFF values:
- *Aspergillus flavus*: 0.5 mg/L
- *Aspergillus fumigatus*: 0.25 mg/L
- *Aspergillus nidulans*: 0.5 mg/L
- *Aspergillus niger*: 0.5 mg/L
- *Aspergillus terreus*: 0.25 mg/L

There are currently insufficient data to set clinical breakpoints for *Aspergillus spp*. ECOFF values do not equate to clinical breakpoints.

Breakpoints
EUCAST MIC breakpoints for posaconazole [susceptible (S); resistant (R)]:
• *Candida albicans:* S ≤0.06 mg/L, R >0.06 mg/L
• *Candida tropicalis*: S ≤0.06 mg/L, R >0.06 mg/L
• *Candida parapsilosis*: S ≤0.06 mg/L, R >0.06 mg/L
There are currently insufficient data to set clinical breakpoints for other Candida species.

Combination with other antifungal agents
The use of combination antifungal therapies should not decrease the efficacy of either posaconazole or the other therapies; however, there is currently no clinical evidence that combination therapy will provide an added benefit.

Pharmacokinetics
Pharmacokinetic / Pharmacodynamic relationships
A correlation between total medicinal product exposure divided by MIC (AUC/MIC) and clinical outcome was observed. The critical ratio for subjects with Aspergillus infections was ~200. It is particularly important to try to ensure that maximal plasma levels are achieved in patients infected with Aspergillus.

Distribution
Following administration of 300 mg posaconazole concentrate for solution for infusion over 90 minutes, mean peak plasma concentration at the end of infusion was 3280 ng/mL (74 % CV). Posaconazole exhibits dose proportional pharmacokinetics after single and multiple dosing in the therapeutic dose range (200-300 mg). Posaconazole has a distribution volume of 261 L, indicating extravascular distribution. Posaconazole is highly protein bound (> 98 %), predominantly to serum albumin.

Biotransformation
Posaconazole does not have any major circulating metabolites. 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 radiolabelled dose of posaconazole oral suspension.

Elimination
Posaconazole, after administration of 300 mg of posaconazole concentrate for solution for infusion, is slowly eliminated with a mean half-life (t½) of 27 hours and a mean clearance of 7.3 L/hr. After administration of 14Cposaconazole as oral suspension, radioactivity was predominantly recovered in the faeces (77 % of the radiolabelled dose) with the major component being parent compound (66 % of the radiolabelled dose). Renal clearance is a minor elimination pathway, with 14 % of the radiolabelled dose excreted in urine (< 0.2 % of the radiolabelled dose is parent compound). Steady-state plasma concentrations are attained by Day 6 at the 300 mg dose (once daily after twice daily loading dose at Day 1).

Posaconazole plasma concentrations following administration of posaconazole concentrate for solution for infusion single dose increased in a greater than dose proportional manner over the range of 50-200 mg; by comparison, dosedependent increases were observed over a range of 200-300 mg.

INDICATIONS
Prophylaxis of Invasive *Aspergillus* and *Candida* Infections
Posaconazole injection is indicated for prophylaxis of invasive *Aspergillus* and *Candida* infections in patients who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy.

Posaconazole injection is indicated in patients 18 years of age and older.

DOSAGE AND ADMINISTRATION
Posaconazole injection
- Administer via a central venous line, including a central venous catheter or peripherally inserted central catheter (PICC), by slow intravenous infusion over approximately 90 min utes.
- If a central venous catheter is not available, Posaconazole injection may be administered through a peripheral venous catheter by slow intravenous infusion over 30 minutes only as a single dose in advance of central venous line placement or to bridge the period during which a central venous line is replaced or is in use for other intravenous treatment.
- When multiple dosing is required, the infusion should be done via a central venous line.
- Never administer Posaconazole injection as an intravenous bolus injection.

Dosage, Preparation, Intravenous Line Compatibility and Administration of Posaconazole Injection

Dosage:

Table 1: Dosage for Posaconazole Injection

Indication	Dose and Duration of Therapy
Prophylaxis of invasive *Aspergillus* and *Candida* infections	Loading dose: 300 mg Posaconazole injection intravenously twice a day on the first day. Maintenance dose: 300 mg Posaconazole injection intravenously once a day, starting on the second day. Duration of therapy is based on recovery from neutropenia or immunosuppression.

Preparation:

- Equilibrate the refrigerated vial of Posaconazole injection to room temperature.
- To prepare the required dose, aseptically transfer one vial (16.7 mL) of Posaconazole injection) to an intravenous bag (or bottle) of a compatible admixture diluent (as described in Table 2), to achieve a final concentration of posaconazole that is between 1 mg/mL and 2 mg/mL. Use of other diluents is not recommended because they may result in particulate formation.
- Posaconazole injection is a single dose sterile solution without preservatives. Once ad mixed, the product should be used immediately. If not used immediately, the solution can be stored up to 24 hours refrigerated 2-8°C (36-46°F). Posaconazole injection is for single use only and any unused solution should be discarded.
- Parenteral drug products should be inspected visually for particulate matter prior to ad ministration, whenever solution and container permit. Once admixed, the solution of Po saconazole ranges from colorless to yellow. Variations of color within this range do not affect the quality of the product.

Intravenous Line Compatibility:
- Compatible diluents and drug products are listed in **Tables 2 and 3** below. Any diluents or drug products not listed in the tables below should not be co-administered through the same intravenous line (or cannula).
- Posaconazole injection can be infused at the same time through the same intravenous line (or cannula) with the following compatible diluents:

Table 2: Compatible Diluents

0.45% sodium chloride
0.9% sodium chloride
5% dextrose in water
5% dextrose and 0.45% sodium chloride
5% dextrose and 0.9% sodium chloride
5% dextrose and 20 mEq potassium chloride

- Posaconazole injection can be infused at the same time through the same intravenous line (or cannula) with the following drug products prepared in 5% dextrose in water or sodium chloride 0.9%. Coadministration of drug products prepared in other diluents may result in particulate formation.

Table 3: Compatible Drugs

Amikacin sulfate
Caspofungin
Ciprofloxacin
Daptomycin
Dobutamine hydrochloride
Famotidine
Filgrastim
Gentamicin sulfate
Hydromorphone hydrochloride
Levofloxacin
Lorazepam
Meropenem
Micafungin
Morphine sulfate
Norepinephrine bitartrate
Potassium chloride
Vancomycin hydrochloride

Incompatible Diluents:
Posaconazole injection must not be diluted with the following diluents:
Lactated Ringer's solution 5% dextrose with Lactated Ringer's solution 4.2% sodium bicarbonate.

Administration:
- Posaconazole injection must be administered through a 0.22 micron polyethersulfone (PES) or polyvinylidene difluoride (PVDF) filter.
- Administer via a central venous line, including a central venous catheter or PICC by slow infusion over approximately 90 minutes. Posaconazole injection is not for bolus adminis tration.
- If a central venous catheter is not available, Posaconazole injection may be administered through a peripheral venous catheter only as a single dose in advance of central venous line placement or to bridge the period during which a central venous line is replaced or is in use for other treatment.
- When multiple dosing is required, the infusion should be done via a central venous line. When administered through a peripheral venous catheter, the infusion should be admin istered over approximately 30 minutes.

USE IN SPECIAL POPULATIONS
Pregnancy
Category C
There are no adequate and well-controlled studies in pregnant women. Posaconazole should be used in pregnancy only if the potential benefit outweighs the potential risk to the fetus. Posaconazole has been shown to cause skeletal malformations (cranial malformations and missing ribs) in rats when given in doses ≥27 mg/kg (≥1.4 times the 400-mg BID oral suspension regimen based on steady-state plasma concentrations of drug in healthy volunteers). The no-effect dose for malformations in rats was 9 mg/kg, which is 0.7 times the exposure achieved with the 400-mg BID oral suspension regimen. No malformations were seen in rabbits at doses up to 80 mg/kg. In the rabbit, the no-effect dose was 20 mg/kg, while high doses of 40 mg/kg and 80 mg/kg, 2.9 or 5.2 times the exposure achieved with the 400-mg BID oral suspension regimen, caused an increase in resorptions. In rabbits dosed at 80 mg/kg, a reduction in body weight gain of females and a reduction in litter size were seen.

Nursing Mothers
Posaconazole is excreted in milk of lactating rats. It is not known whether Posaconazole is excreted in human milk. Because of the potential for serious adverse reactions from Posaconazole in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
The safety and effectiveness of Posaconazole injection in pediatric patients below the age of 18 years of age has not been established.

Geriatric Use
The pharmacokinetics of posaconazole injection are comparable in young and elderly. No overall differences in safety were observed between the geriatric patients and younger patients; therefore, no dosage adjustment is recommended for Posaconazole injection in geriatric patients.

Renal Impairment
Posaconazole injection should be avoided in patients with moderate or severe renal impairment (eGFR <50 mL/min), unless an assessment of the benefit/risk to the patient justifies the use of Posaconazole injection. In patients with moderate or severe renal impairment (eGFR <50 mL/min), receiving the Posaconazole injection, accumulation of the intravenous vehicle, SBECD, is expected to occur. Serum creatinine levels should be closely monitored in these patients, and, if increases occur, consideration should be given to changing to oral Posaconazole therapy.

Hepatic Impairment
Limited data on the effect of hepatic impairment (including Child-Pugh C classification of chronic liver disease) on the pharmacokinetics of posaconazole demonstrate an increase in plasma exposure compared to subjects with normal hepatic function, but do not suggest that dose adjustment is necessary. It is recommended to exercise caution due to the potential for higher plasma exposure.

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

Race
The pharmacokinetic profile of posaconazole is not significantly affected by race. No adjustment in the dosage of Posaconazole is necessary based on race.

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

CONTRAINDICATIONS
Hypersensitivity
Posaconazole is contraindicated in persons with known hypersensitivity to posaconazole or other azole antifungal agents.

Use with Sirolimus
Posaconazole is contraindicated with sirolimus. Concomitant administration of Posaconazole with sirolimus increases the sirolimus blood concentrations by approximately 9-fold and can result in sirolimus toxicity.

QT Prolongation with Concomitant Use with CYP3A4 Substrates
Posaconazole is contraindicated with CYP3A4 substrates that prolong the QT interval. Concomitant administration of Posaconazole with the CYP3A4 substrates, pimozide and quinidine may result in increased plasma concentrations of these drugs, leading to QTc prolongation and cases of torsades de pointes.

HMG-CoA Reductase Inhibitors Primarily Metabolized Through CYP3A4
Coadministration with the HMG-CoA reductase inhibitors that are primarily metabolized through CYP3A4 (e.g., atorvastatin, lovastatin, and simvastatin) is contraindicated since increased plasma concentration of these drugs can lead to rhabdomyolysis.

Use with Ergot Alkaloids
Posaconazole may increase the plasma concentrations of ergot alkaloids (ergotamine and dihydroergotamine) which may lead to ergotism.

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.

Arrhythmias and QT Prolongation
Some azoles have been associated with prolongation of the QTc interval. Posaconazole must not be administered with medicinal products that are substrates for CYP3A4 and are known to prolong the QTc interval. Posaconazole should be administered with caution to patients with pro-arrhythmic conditions such as:

- Congenital or acquired QTc prolongation
- Cardiomyopathy, especially in the presence of cardiac failure
- Sinus bradycardia
- Existing symptomatic arrhythmias
- Concomitant use with medicinal products known to prolong the QTc interval (other than those mentioned in section CONTRAINDICATIONS).

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

In patients, mean maximum plasma concentrations (C_{max}) after posaconazole concentrate for solution for infusion are 4-fold increase compared to administration of oral suspension. An increased effect on the QTc interval cannot be ruled out. Particular caution is advised in such cases where posaconazole is administered peripherally, as the recommended infusion time of 30 minutes may further increase C_{max}.

Hepatic Toxicity
Hepatic reactions (e.g. elevations in ALT, AST, alkaline phosphatase, total bilirubin and/or clinical hepatitis) have been reported during treatment with posaconazole. Elevated liver function tests were generally reversible on discontinuation of therapy and in some instances these tests normalised without interruption of therapy. Rarely, more severe hepatic reactions with fatal outcomes have been reported.

Posaconazole should be used with caution in patients with hepatic impairment due to limited clinical experience and the possibility that posaconazole plasma levels may be higher in these patients.

Monitoring of hepatic function
Liver function tests should be evaluated at the start of and during the course of posaconazole therapy. Patients who develop abnormal liver function tests during Posaconazole therapy must be routinely monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of Posaconazole should be considered if clinical signs and symptoms are consistent with development of liver disease.

Calcineurin-Inhibitor Drug Interactions
Concomitant administration of Posaconazole with cyclosporine or tacrolimus increases the whole blood trough concentrations of these calcineurin-inhibitors. Nephrotoxicity and leukoencephalopathy (including deaths) have been reported in clinical efficacy studies in patients with elevated cyclosporine or tacrolimus concentrations. Frequent monitoring of tacrolimus or cyclosporine whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the tacrolimus or cyclosporine dose adjusted accordingly.

Use with Midazolam other benzodiazepines
Concomitant administration of Posaconazole with midazolam increases the midazolam plasma concentrations by approximately 5-fold. Increased plasma midazolam concentrations could potentiate and prolong hypnotic and sedative effects. Patients must be monitored closely for adverse effects associated with high plasma concentrations of midazolam and benzodiazepine receptor antagonists must be available to reverse these effects.

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

Rifamycin antibacterials (rifampicin, rifabutin), certain anticonvulsants (phenytoin, carbamazepine, phenobarbital, primidone), and efavirenz
Posaconazole concentrations may be significantly lowered in combination; therefore, concomitant use with posaconazole should be avoided unless the benefit to the patient outweighs the risk.

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

Thromboembolic events
Caution is warranted on any sign or symptom of thromboembolic events.

Sodium content
Each vial of Posaconazole contains 462 mg (20 mmol) of sodium. This should be taken into consideration for patients on a controlled sodium diet.

DRUG INTERACTIONS
Posaconazole is primarily metabolized via UDP glucuronosyltransferase and is a substrate of p-glycoprotein (P-gp) efflux. Therefore, inhibitors or inducers of these clearance pathways may affect posaconazole plasma concentrations.

Coadministration of drugs that can decrease the plasma concentrations of posaconazole should generally be avoided unless the benefit outweighs the risk. If such drugs are necessary, patients should be monitored closely for breakthrough fungal infections. Posaconazole is also a strong inhibitor of CYP3A4. Therefore, plasma concentrations of drugs predominantly metabolized by CYP3A4 may be increased by posaconazole.

The following information was derived from data with posaconazole oral suspension or early tablet formulation.. All drug interactions with posaconazole oral suspension, except for those that affect the absorption of posaconazole (via gastric pH and motility) are considered.

Immunosuppressants Metabolized by CYP3A4*:*
Sirolimus: Concomitant administration of posaconazole with sirolimus increases the sirolimus blood concentrations by approximately 9-fold and can result in sirolimus toxicity. Therefore, posaconazole is contraindicated with sirolimus.

Tacrolimus: Posaconazole has been shown to significantly increase the C_{max} and AUC of tacrolimus. At initiation of posaconazole treatment, reduce the tacrolimus dose to approximately one-third of the original dose. Frequent monitoring of tacrolimus whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the tacrolimus dose adjusted accordingly.

Cyclosporine: Posaconazole has been shown to increase cyclosporine whole blood concentrations in heart transplant patients upon initiation of posaconazole treatment. It is recommended to reduce cyclosporine dose to approximately three-fourths of the original dose upon initiation of posaconazole treatment. Frequent monitoring of cyclosporine whole blood trough concentrations should be performed during and at discontinuation of posaconazole treatment and the cyclosporine dose adjusted accordingly.

CYP3A4 Substrates:
Co-administration of posaconazole and terfenadine, astemizole, cisapride, pimozide, halofantrine or quinidine is contraindicated. Co-administration may result in increased plasma concentrations of these medicinal products, leading to QTc prolongation and rare occurrences of torsades de pointes

HMG-CoA Reductase Inhibitors (Statins. *e.g. simvastatin, lovastatin, and atorvastatin)* Primarily Metabolized through CYP3A4:
Posaconazole may substantially increase plasma levels of HMG-CoA reductase inhibitors that are metabolised by CYP3A4. Treatment with these HMG-CoA reductase inhibitors should be discontinued during treatment with posaconazole as increased levels have been associated with rhabdomyolysis.

Ergot Alkaloids
Most of the ergot alkaloids are substrates of CYP3A4. Posaconazole may increase the plasma concentrations of ergot alkaloids (ergotamine and dihydroergotamine) which may lead to ergotism. Therefore, posaconazole is contraindicated with ergot alkaloids.

Benzodiazepines Metabolized by CYP3A4
Concomitant administration of posaconazole with midazolam increases the midazolam plasma concentrations by approximately 5-fold. Increased plasma midazolam concentrations could potentiate and prolong hypnotic and sedative effects. Concomitant use of posaconazole and other benzodiazepines metabolized by CYP3A4 (e.g., alprazolam, triazolam) could result in increased plasma concentrations of these benzodiazepines. Patients must be monitored closely for adverse effects associated with high plasma concentrations of benzodiazepines metabolized by CYP3A4 and benzodiazepine receptor antagonists must be available to reverse these effects.

Anti-HIV Drugs
Efavirenz: Efavirenz induces UDP-glucuronidase and significantly decreases posaconazole plasma concentrations. It is recommended to avoid concomitant use of efavirenz with posaconazole unless the benefit outweighs the risks.

Ritonavir and Atazanavir: Ritonavir and atazanavir are metabolized by CYP3A4 and posaconazole increases plasma concentrations of these drugs. Frequent monitoring of adverse effects and toxicity of ritonavir and atazanavir should be performed during coadministration with posaconazole.

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.

Rifabutin
Rifabutin induces UDP-glucuronidase and decreases posaconazole plasma concentrations. Rifabutin is also metabolized by CYP3A4. Therefore, coadministration of rifabutin with posaconazole increases rifabutin plasma. Concomitant use of posaconazole and rifabutin should be avoided unless the benefit to the patient outweighs the risk. However, if concomitant administration is required, close monitoring for breakthrough fungal infections as well as frequent monitoring of full blood counts and adverse reactions due to increased rifabutin plasma concentrations (e.g., uveitis, leukopenia) are recommended.

Phenytoin
Phenytoin induces UDP-glucuronidase and decreases posaconazole plasma concentrations. Phenytoin is also metabolized by CYP3A4. Therefore, coadministration of phenytoin with posaconazole increases phenytoin plasma concentrations. Concomitant use of posaconazole and phenytoin should be avoided unless the benefit to the patient outweighs the risk. However, if concomitant administration is required, close monitoring for breakthrough fungal infections is recommended and frequent monitoring of phenytoin concentrations should be performed while coadministered with posaconazole and dose reduction of phenytoin should be considered.

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. 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.

Calcium Channel Blockers Metabolized by CYP3A4
Posaconazole may increase the plasma concentrations of calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, diltiazem, nifedipine, nicardipine, felodipine). Frequent monitoring for adverse reactions and toxicity related to calcium channel blockers is recommended during coadministration. Dose reduction of calcium channel blockers may be needed.

Digoxin
Increased plasma concentrations of digoxin have been reported in patients receiving digoxin and posaconazole. Therefore, monitoring of digoxin plasma concentrations is recommended during coadministration.

Glipizide
Although no dosage adjustment of glipizide is required, it is recommended to monitor glucose concentrations when posaconazole and glipizide are concomitantly used.

UNDESIRABLE EFFECTS
Posaconazole concentrate for solution for infusion safety
In initial studies of healthy volunteers, administration of a single dose of posaconazole infused over 30 minutes via a peripheral venous catheter was associated with a 12 % incidence of infusion site reactions (4 % incidence of thrombophlebitis). Multiple doses of posaconazole administered via a peripheral venous catheter were associated with thrombophlebitis (60 % incidence). Therefore, in subsequent studies posaconazole was administered via central venous catheter. If a central venous catheter was not readily available, patients could receive a single infusion over 30 minutes via a peripheral venous catheter. Peripheral infusion time longer than 30 minutes, leads to a higher incidence of infusion site reactions and thrombophlebitis.

The most frequently reported adverse reaction (>25 %) with an onset during the posaconazole intravenous phase of dosing with 300 mg once daily was diarrhoea (32 %).

The most common adverse reaction (>1 %) leading to discontinuation of posaconazole concentrate for solution for infusion 300 mg once daily was Acute Myelogenous Leukemia AML (1 %).

Tabulated list of adverse reactions
Within the organ system classes, adverse reactions are listed under headings of frequency using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥ 1/10,000 to <1/1,000); very rare (<1/10,000); not known.

Table 4. Adverse reactions by body system and frequency*

Blood and lymphatic system disorders	
Common:	neutropenia
Uncommon:	thrombocytopenia, leukopenia, anaemia, eosinophilia, lymphadenopathy, splenic infarction
Rare:	haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura, pancytopenia, coagulopathy, haemorrhage
Immune system disorders	
Uncommon:	allergic reaction
Rare:	hypersensitivity reaction
Endocrine disorders	
Rare:	adrenal insufficiency, blood gonadotropin decreased
Metabolism and nutrition disorders	
Common:	electrolyte imbalance, anorexia, decreased appetite, hypokalaemia, hypomagnesaemia
Uncommon:	Hyperglycaemia, hypoglycaemia
Psychiatric disorders	
Uncommon:	abnormal dreams, confusional state, sleep disorder
Rare:	psychotic disorder, depression
Nervous system disorders	
Common:	paresthesia, dizziness, somnolence, headache, dysgeusia
Uncommon:	convulsions, neuropathy, hypoaesthesia, tremor, aphasia, insomnia
Rare:	cerebrovascular accident, encephalopathy, peripheral neuropathy, syncope
Eye disorders	
Uncommon:	blurred vision, photophobia, visual acuity reduced
Rare:	diplopia, scotoma
Ear and labyrinth disorder	
Rare:	hearing impairment
Cardiac disorders	
Uncommon:	long QT syndrome§, electrocardiogram abnormal§, palpitations, bradycardia, supraventricular extrasystoles, tachycardia
Rare:	torsade de pointes, sudden death, ventricular tachycardia, cardio-respiratory arrest, cardiac failure, myocardial infarction
Vascular disorders	
Common:	hypertension
Uncommon:	hypotension, thrombophlebitis, vasculitis
Rare:	pulmonary embolism, deep vein thrombosis
Respiratory, thoracic and mediastinal disorders	
Uncommon:	cough, epistaxis, hiccups, nasal congestion, pleuritic pain, tachypnoea
Rare:	pulmonary hypertension, interstitial pneumonia, pneumonitis
Gastrointestinal disorders	
Very Common	nausea
Common:	vomiting, abdominal pain, diarrhoea, dyspepsia, dry mouth, flatulence, constipation, anorectal discomfort
Uncommon:	pancreatitis, abdominal distension, enteritis, epigastric discomfort, eructation, gastrooesophageal reflux disease, oedema mouth
Rare:	gastrointestinal haemorrhage, ileus
Hepatobiliary disorders	
Common:	liver function tests raised (ALT increased, AST increased, bilirubin increased, alkaline phosphatase increased, GGT increased)
Uncommon:	hepatocellular damage, hepatitis, jaundice, hepatomegaly, cholestasis, hepatic toxicity, hepatic function abnormal
Rare:	hepatic failure, hepatitis cholestatic, hepatosplenomegaly, liver tenderness, asterixis
Skin and subcutaneous tissue disorders	
Common:	rash, pruritis
Uncommon:	mouth ulceration, alopecia, dermatitis, erythema, petechiae
Rare:	Stevens Johnson syndrome, vesicular rash
Musculoskeletal and connective tissue disorders	
Uncommon:	back pain, neck pain, musculoskeletal pain, pain in extremity
Renal and urinary disorders	
Uncommon:	acute renal failure, renal failure, blood creatinine increased
Rare:	renal tubular acidosis, interstitial nephritis
Reproductive system and breast disorders	
Uncommon:	menstrual disorder
Rare:	breast pain
General disorders and administration site conditions	
Common:	pyrexia (fever), asthenia, fatigue
Uncommon:	oedema, pain, chills, malaise, chest discomfort, drug intolerance, feeling jittery, infusion site pain, infusion site phlebitis, infusion site thrombosis, mucosal inflammation
Rare:	tongue oedema, face oedema
Investigations	
Uncommon:	altered medicine levels, blood phosphorus decreased, chest x-ray abnormal

* Based on adverse reactions observed with the oral suspension, gastro-resistant tablets, and concentrate for solution for infusion.

§ See **WARNINGS AND PRECAUTIONS**

Description of selected adverse reactions

Hepatobiliary disorders

During post-marketing surveillance severe hepatic injury with fatal outcome has been reported (see section **WARNINGS AND PRECAUTIONS**).

OVERDOSAGE
There is no experience with overdose of posaconazole concentrate for solution for infusion.

During clinical trials, patients who received posaconazole oral suspension doses up to 1,600 mg/day experienced no different adverse reactions from those reported with patients at the lower doses. Accidental overdose was noted in one patient who took posaconazole oral suspension 1,200 mg twice a day for 3 days. No adverse reactions were noted by the investigator.

Posaconazole is not removed by haemodialysis. There is no special treatment available in the case of overdose with posaconazole. Supportive care may be considered.

PACKAGING INFORMATION
20Ml Tubular Vial with 20mm Bromobutyl stopper with 20mm with aluminum flip-off seals.

STORAGE AND HANDLING INSTRUCTIONS
Storage: Store refrigerated at 2 to 8°C (36 to 46°F).

After dilution if not used immediately,
the solution can be stored up to 24 hours refrigerated 2 to 8°C (36 to 46°F)

KEEP OUT OF REACH OF CHILDREN
Keep away from infants and small children

Manufactured by:
MSN Laboratories Private Limited
(Formulations Division),
Plot No. 42, Anrich Industrial Estate,
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B32919-00