



#### 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<sub>max</sub> 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, hypoesthesia, 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 <sup>†</sup> , electrocardiogram abnormal <sup>†</sup> , 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, gastroesophageal 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:

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