

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use POSACONAZOLE INJECTION safely and effectively. See full prescribing information for POSACONAZOLE INJECTION

POSACONAZOLE injection, for intravenous use

Initial U.S. Approval: 2006

RECENT MAJOR CHANGES	
Warnings and Precautions, Pseudoaldosteronism (5.4)	10/2024

-- INDICATIONS AND USAGE-

Posaconazole is an azole antifungal indicated as follows:

- Posaconazole is indicated for the prophylaxis of invasive Aspergillus and Candida infections in patients who are at high risk of developing thes 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 as follows: (1.2) o Posaconazole injection: adults and pediatric patients 2 years of age and older
- ·····DOSAGE AND ADMINISTRATION
- Posaconazole injection must be administered through an in-line filter.
- Administer posaconazole injection by intravenous infusion over approximately 90 minutes via a central venous line. (2,1) Do NOT administer **posaconazole injection** as an intravenous bolus injection. (2.1)
- nded Dosane in Adult Pati Table 1: Rec

Tuble 1. Hecommended Dosage in Addit	
Indication	Dosage Form, Dose, and Duration of Therapy
Prophylaxis of	Posaconazole Injection:
invasive Aspergillus	Loading dose: 300 mg posaconazole injection intravenously twice a day on the first day.
and Candida infections	Maintenance dose: 300 mg posaconazole injection intravenously once a day thereafter. Duration of
	therapy is based on recovery from neutropenia or immunosuppression. (2.2, 2.3)

- For pediatric patients, see the Full Prescribing Information for dosing recommendations for posaconazole injection based on the age and indication associated with the dosage form. (1.2, 2.1, 2.3)
- --- DOSAGE FORMS AND STRENGTHS
- Posaconazole injection: 300 mg per vial (18 mg per mL) in a single dose vial (3)
- --- CONTRAINDICATIO
- Known hypersensitivity to posaconazole or other azole antifungal agents. (4.1)
- Coadministration of posaconazole with the following drugs is contraindicated; posaconazole increases concentrations and toxicities of Sirolimus (4.2, 5.1, 7.1)
- CYP3A4 substrates (pimozide, quinidine): can result in QTc interval prolo
- ation and cases of torsades de pointes (TdP) (4.3, 5.2, 7.2) HMG-CoA Reductase Inhibitors Primarily Metabolized through CYP3A4 (4.4, 7.3)
- Ergot alkaloids (4.5, 7.4)
- Venetoclax: In patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) at initiation and during the ramp-up phase (4.6, 5.11, 7.16)
- ····· WARNINGS AND PRECAUTIONS··· Calcineurin-Inhibitor Toxicity: Posaconazole increases concentrations of cyclosporine or tacrolimus; reduce dose of cyclosporine and tacrolimus and monitor concentrations frequently. (5.1)
- Arrhythmias and QTc Prolongation: Posaconazole has been shown to prolong the QTc interval and cause cases of TdP. Administer with caution to patients with potentially proarrhythmic conditions. Do not administer with drugs known to prolong QTc interval and metabolized through CYP3A4, (5.2)

FULL PRESCRIBING INFORMATION: CONTENTS*

INDICATIONS AND USAGE

- 1.2 Prophylaxis of Invasive Aspergillus and Candida Infections
- DOSAGE AND ADMINISTRATION 2
- Important Administration Instructions Dosing Regimen in Adult Patients
- Dosing Regimen in Pediatric Patients (ages 2 to less than 18 years of age) 2.3
- Preparation, Intravenous Line Compatibility, and Administration of Posaconazole Injection
 Dosage Adjustments in Patients with Renal Impairment
- 3 DOSAGE FORMS AND STRENGTHS
- CONTRAINDICATIONS 4
- Hypersensitivity
- Use with Sirolimus
- 4.3 OT Prolongation with Concomitant Use with CYP3A4 Substrates 4.4 HMG-CoA Reductase Inhibitors Primarily Metabolized Through CYP3A4
- Use with Ergot Alkaloids 4.5
- 4.6 Use with Venetoclax
- WARNINGS AND PRECAUTIONS Calcineurin-Inhibitor Toxicity
- 52 Arrhythmias and QT Prolonga
- 5.3 Electrolyte Disturbances
- 5.4 Pseudoaldosteronism
- 5.5 Hepatic Toxicity 5.6 Renal Impairment
- 5.7
- Midazolam Toxicity Vincristine Toxicity 5.11 Venetoclax Toxicity
- ADVERSE REACTIONS
- Clinical Trials Experience 6.2 Postmarketing Experience
- DRUG INTERACTIONS 7
- ants Metabolized by CYP3A4

- Electrolyte Disturbances: Monitor and correct, especially those involving potassium (K*), magnesium (Mg**), and calcium (Ca**), before and during posaconazole therapy. (5.3) Pseudoaldosteronism: Manifested by the onset or worsening of hypertension, and abnormal laboratory findings. Monitor blood pressure and .
- potassium levels, and manage as necessary. (5.4) Hepatic Toxicity: Elevations in liver tests may occur. Discontinuation should be considered in patients who develop abnormal liver tests or monitor
- liver tests during treatment. (5.5) Renal Impairment: Posaconazole injection should be avoided in patients with moderate or severe renal impairment (creatinine clearance <50
- nL/min), unless an assessment of the benefit/risk to the patient justifies the use of posaconazole injection. (5.6, 8.6) Concomitant Use with Midazolam: Posaconazole can prolong hypnotic/sedative effects. Monitor patients and benzodiazepine receptor antagonists
- hould be available. (5.7, 7.5) Vincristine Toxicity: Concomitant administration of azole antifungals, including posaconazole, with vincristine has been associated with
- neurotoxicity and other serious adverse reactions; reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options. (5.8, 7.10)
- Venetoclax Toxicity: Concomitant administration of posaconazole with venetoclax may increase venetoclax toxicities, including the risk of tumor lysis syndrome, neutropenia, and serious infections; monitor for toxicity and reduce venetoclax dose. (4.6, 5.11, 7.16)
 - ----- ADVERSE REACTIONS -
- Adult Patients: Common adverse reactions in studies with posaconazole in adults are diarrhea, nausea, fever, vomiting, headache, coughing, and • hypokalemia. (6.1
- Pediatric Patients: Common adverse reactions (incidence > 20% receiving 6 mg/kg posaconazole injection in a study in pediatric patients are pyrexia, febrile neutropenia, vomiting, mucosal inflammation, pruritus, hypertension, hypokalemia, and stomatitis. (6.1)
- To report SUSPECTED ADVERSE REACTIONS, contact Aspiro Pharma Limited at 1-866-495-1995, or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS		
Interaction Drug Interaction		
Rifabutin, phenytoin, efavirenz, cimetidine	Avoid coadministration unless the benefit outweighs the risks (7.6, 7.7, 7.8, 7.9)	
Other drugs metabolized by CYP3A4	Consider dosage adjustment and monitor for adverse effects and toxicity (7.1, 7.10, 7.11)	
Digoxin	Monitor digoxin plasma concentrations (7.12)	
Fosamprenavir	Monitor for breakthrough fungal infections (7.6)	

Pregnancy: Based on animal data, may cause fetal harm, (8,1)

received a single dose of 200 mg posaconazole injection, 21 patients verie = 00 years or age, and were 00 m white and 01 mspanic. Ten patients received 200 mg daily dose for a median of 14 days, and 237 patients received 300 mg daily dose for a median of 9 days.

	Soo ng dany dose for a median of 9 days.
DRUG INTERACTIONS	Table 8 presents adverse reactions observed in patients treated with posaconazole injection 300 mg daily dose in the Posaconazole Injection Study. Each patient received a loading dose, 300 mg twice on Day 1. Following posaconazole intravenous therapy, patients received Noxafil oral suspension to
Interaction	Later parent receive a rotating cose, soo ing twice on pay 1.1 moving posedinacity intervention therapy, patients received rotating assessment of complete 28 days of total posedinacity for any .
Avoid coadministration unless the benefit outweighs the risks (7.6, 7.7, 7.8, 7.9)	Table 8: Posaconazole Injection Study: Adverse Reactions in at Least 10% of Subjects Treated with Posaconazole Injection 300 mg Daily
Consider decade adjustment and meniter for adjusted affects and toxisity (7.1. 7.10, 7.11)	Dose

Issued: 01/2025

	USE IN SPECIFIC POPULATIONS	
prenavir	Monitor for breakthrough fungal infections (7.6)	
1	Monitor digoxin plasma concentrations (7.12)	
4		

- Pediatrics: Safety and effectiveness in patients younger than 2 years of age have not been established. (8.4) Severe Renal Impairment: Monitor closely for breakthrough fungal infections. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

7.8 Phenytoi

- 7.10 Vinca Alkaloid 7.11 Calcium Channel Blockers Metabolized by CYP3A4
- 7.12 Digoxin
- 7.14 Glipizide
- 7.16 Venetoclax
- USE IN SPECIFIC POPULATIONS
- Pregnancy 8.1
- 8.2 Lactation 8.4 Pediatric Use
- 8.5 Geriatric Use
- Renal Impai 8.6
- 8.7 Hepatic Impairment 8.8 Gender
- 8.9 Race
- 8.10 Weight
- 10 OVERDOSAGE
- 11 DESCRIPTION
- 12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action 12.2 Pharmacodyna
- 12.3 Pharmacokinetics
- 12.4 Microbiology
- 13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinonenesis Mutanenesis Imnairment of Fertility 13.2 Animal Toxicology and/or Pharmacology
- 14 CLINICAL STUDIES
- 4.2 Prophylaxis of Aspergillus and Candida Infections with Noxafil Oral Suspension
- 16 HOW SUPPLIED/STORAGE AND HANDLING How Supplied
- 16.2 Storage and Handling

Administration:

- CYP3A4 Substrates
- HMG-CoA Reductase Inhibitors (Statins) Primarily Metabolized Through CYP3A4 7.3
- 74 Ergot Alkaloids
- Benzodiazepines Metabolized by CYP3A4 7.5
- 7.6 Anti-HIV Drugs
- 77 Rifabuti

FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

1.2 Prophylaxis of Invasive Aspergillus and Candida Infections

Posaconazole is indicated for the prophylaxis of invasive Asperaillus and Candida infections in patients who are at high risk of developing these rosolutazie is molecter in the propryskis of invasive Aspergimus and Canuara intections in patients who are at myr his of developing t infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host dis (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy *[see Clinical Studies (14.1)]* as follows:

- Posaconazole injection: adults and pediatric patients 2 years of age and older.
- 2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

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 minutes [see Dosage and Administration (2.4]]. 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
- Do NOT administer posaconazole injection as an intravenous bolus injection.
- 2.2 Dosing Regimen in Adult Patients

Table 1: Dosing Regimens in Adult Patients

Indication	Dose and Frequency	Duration of Therapy
	Posaconazole Injection:	
	Loading dose:	Loading dose:
	300 mg Posaconazole injection intravenously	1 day
Prophylaxis of invasive	twice a day on the first day.	Maintenance dose:
Aspergillus and Candida	Maintenance dose:	Duration of therapy is based on recovery from
infections	300 mg posaconazole injection intravenously	neutropenia or immunosuppression.
	once a day, thereafter.	

2.3 Dosing Regimen in Pediatric Patients (ages 2 to less than 18 years of age)

The recommended dosing regimen of posaconazole injection for pediatric patients 2 to less than 18 years of age is shown in Table 2 /see Clinical Pharmacology (12.3)]. No Injection Desing Pagimone for Padiatric Patients (ages 2 to less than 19

Table 2: Pos	Table 2: Posaconazole Injection Dosing Regimens for Pediatric Patients (ages 2 to less than 18 years of age)		
		Recommended Pediatric Dosage and Formulation	
Indication	Weight/Age	Injection	Duration of therapy
Prophylaxis of invasive	Less than or equal to 40 kg	Loading dose:	Duration of therapy is based
Aspergillus and Candida	(2 to less than 18 years of	6 mg/kg up to a maximum of 300 mg twice	on recovery from neutropenia
infections	age)	daily on the first day	or immunosuppression.
	Greater than 40 kg (2 to	Maintenance dose:	
	less than 18 years of age)	6 mg/kg up to a maximum of 300 mg once	
		daily	

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

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 (containing 300 mg of posaconazole in solution) to an intravenous bag (or bottle) of a compatible admixture diluent (as described in **Table 5**), 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. Discard any unused portion from the vial.
- Once admixed, the diluted solution of posaconazole in the intravenous bag (or bottle) should be used immediately. If not used immediately, the solution can be stored up to 24 hours refrigerated 2 to 8°C (36 to 46°F). Discard any unused portion.
- Parenteral drug products should be inspected visually for particulate matter prior to administration, whenever solution and container permit. Once admixed, the solution of posaconazole ranges from colorless to yellow. Variations of color within this range do not affect the quality of the product

Intravenous Line Compatibility:

A study was conducted to evaluate physical compatibility of posaconazole injection with injectable drug products and commonly used intravenous diluents during simulated Y-site infusion. Compatibility was determined through visual observations, measurement of particulate matter and turbidity. Compatible diluents and drug products are listed in Tables 5 and 6 below. Any diluents or drug products not listed in the tables below should not be conistered 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 5: 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 mEg 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

Table 6: Compatible Drugs

Amikacin sulfate
Caspofungin
Ciprofloxacin
Daptomycin
Dobutamine hydrochloride
Famotidine
Filgrastim
Gentamicin sulfate
Hydromorphone hydrochloride
Levofloxacin
Lorazepam
Meropenem
Micafungin
Morphine sufate
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

PATIENT COUNSELING

injection is not for holus administration

DOSAGE FORMS AND STRENGTHS

Posaconazole injection

4.1 Hypersensitivity

4.2 Use with Sirolimus

4 CONTRAINDICATIONS

2.9 Dosage Adjustments in Patients with Renal Impairment

benefit/risk to the patient justifies the use of posaconazole injection.

*Sections or subsections omitted from the full prescribing information are not listed.

Clinical Trial Experience in Pediatric Patients (2 to less than 18 Years of Age)

Immune system disorders: allergic reaction [see Contraindications (4.1)]

Cardiac disorders: torsades de pointes (see Warnings and Precautions (5.2))

The safety of posaconazole injection and Noxafil PowderMix for delayed-release or al suspension for prophylaxis of invasive fungal infections has been assessed in an open label uncontrolled dose-ranging PK and safety study (Posaconazole injection) Noxafil PowderMix for delayed-release or al suspension Pediatric Study 1, NCT02452034); hereinafter referred to as Posaconazole Pediatric Study) in 115 immunocompromised pediatric patients 2 to less than 18 years of age with known or expected neutropenia. Posaconazole injection and Noxafil PowderMix for delayed-release oral suspension was administered at daily doses of up to 6 mg/kg (twice daily on day 1) in three dose cohorts. All 115 subjects initially received posaconazole injection for at least 7 days, and 63 subjects were transitioned to Noxafil PowderMix for delayed-release oral suspension. The mean overall treatment duration for all treated subjects was 20.6 days with 14.3 days (range: 1 to 28 days) on posaconazole injection and 11.6 days (range: 2 to 18 days) on Noxafil PowderMix for delayed-release oral suspension /see Clinical Pharmacology (12.3).

For patients with acute myeloid leukemia (AML), dose reduction and safety monitoring are recommended across all dosing phases when coadmin posaconazole with venetoclax (see Drug Interactions (7.16)). Refer to the venetoclax prescribing information for dosing instructions

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of posaconazole cannot be directly

Multiple doses of posaconazole injection administered via a peripheral venous catheter were associated with thrombophlebitis (60% incidence). Therefore, in subsequent studies, posaconazole injection was administered via central venous catheter.

The safety of posaconazole injection has been assessed in 268 patients in a clinical trial. Patients were enrolled in a non-comparative pharmacokinetic

and safety trial of posaconazole injection when given as antifungal prophylaxis (Posaconazole Injection Study). Patients were immunocompromised with

male, had a mean age of 51 years (range 18 to 82 years, 19% of patients were \geq 65 years of age), and were 95% white and 8% His,

underlying conditions including hematological malignancy, neutropenia post-chemotherapy, GVHD, and post HSCT. This patient population was 55%

220

16

30

18

46

29

19

28

28

49

23

51

25

33

21

16

34

35

*Adverse reactions reported in patients with an onset during the posaconazole intravenous dosing phase of the study

Other clinically significant adverse reactions reported in less than 5% of patients in clinical trials of posaconazole are listed below

20

¹Adverse reactions reported with an onset at any time during the study in patients who were treated for up to 28 days of posaconazole therap

The most frequently reported adverse reactions with an onset during the posaconazole intravenous phase of dosing with 300 mg once daily were

diarrhea (32%), hypokalemia (22%), pyrexia (21%), and nausea (19%). These adverse reactions were consistent with those seen in studies with Noxafi

Blood and lymphatic system disorders: hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, neutropenia aggravated

Liver and Biliary System Disorders: hepatic enzymes increased, hepatic function abnormal, hepatitis, hepatomegaly, jaundice Renal & Urinary System Disorders: renal failure acute

Posaconazole Iniectio

Treatment Phase

n=237 (%)

(93)

(7)

(13)

(8)

(32)

(19)

(12)

(12)

(12)

(21)

(10)

(22)

(11)

(14)

(14)

(15)

(8)

panic. Ten patients

Posaconazole Injection Treatment Phase

or

Suspension Treatment Phase

n=237 (%) *

ent Noxafil Oral

(99)

(10)

(11)

(11)

(17)

(13)

(39)

(30)

(19)

(10)

(16)

(15)

(31)

(12)

(28)

(13)

(21)

(13)

(10)

(17)

(10)

(24)

(11)

Subsea

235

23

41

45

38

73

29

67

30

49

31

24

40

56

26

The following serious and otherwise important adverse reactions are discussed in detail in another section of the labeling:

compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6 ADVERSE REACTIONS

6 1 Clinical Trials Experience

Clinical Trial Experience in Adults

Hypersensitivity /see Contraindications (4.1)

Arrhythmias and QT Prolongation (see Warnings and Precautions (5.2))

Clinical Trial Experience with Posaconazole Injection for Prophylaxis

Hepatic Toxicity [see Warnings and Precautions (5.5)]

Body Systen

Subjects Reporting any Adverse

Blood and Lymphatic System Disorder

General Disorders and Administration Site Cond

Respiratory, Thoracic and Mediastinal Disorde

Endocrine disorders: adrenal insufficiency

Nervous system disorders: paresthesia

Vascular disorders: pulmonary embolism

Gastrointestinal disorders: pancreatitis

Clinical Trial Experience in Pediatrics

Skin and Subcutaneous Tissue Disorders

Reaction

Anemia

Thrombocytopenia

Abdominal Pain

Constipation

Diarrhea

Nausea

Vomiting

Fatigue

Chills

Edema Peripheral

Decreased appetite

Hypomagnesemia

Nervous System Disorde

Hypokalemia

Headache

Cough

Dyspnea

Epistaxis

Petechiae

Vascular Disorders

Hypertension

Rash

oral suspension

Pyrexia Metabolism and Nutrition Disorders

Gastrointestinal Disorders

Abdominal Pain Upper

Table 15 presents adverse reactions observed in greater than or equal to 10% of pediatric patients treated with posaconazole in the Posaconazole

Reported adverse reaction profile of posaconazole in pediatric patients was consistent with the safety profile of posaconazole in adults. The most common adverse reactions (occurring in greater than 20% of pediatric patients receiving 6 mg/kg posaconazole injection and Noxafil PowderMix for delayed-release oral suspension daily dose) were pyrexia, febrile neutropenia, vomiting, mucosal inflammation, pruritus, hypertension, hypokalemia, and

Table 15: Adverse Reactions in at Least 10% of Pediatric Patients Treated with Posaconazole Injection and Noxafil PowderMix for

Adverse Reaction	Posaconazole Injection and Noxafil PowderMix for Delayed-Release Oral Suspension & mg/kg Dose Cohort n=49 (%)	Posaconazole Injection and Noxafil PowderMix for Delayed-Releas Oral Suspension All Dose Cohorts n=115 (%)
Pyrexia	16 (33)	50 (43)
Febrile neutropenia	15 (31)	25 (22)
Vomiting	12 (24)	30 (26)
Mucosal inflammation	11 (22)	32 (28)
Pruritus	11 (22)	18 (16)
Hypertension	10 (20)	20 (17)
Hypokalemia	10 (20)	16 (14)
Stomatitis	10 (20)	13 (11)
Diarrhea	9 (18)	25 (22)
Nausea	9 (18)	18 (16)
Abdominal pain	8 (16)	20 (17)
Decreased appetite	7 (14)	17 (15)
Rash	7 (14)	18 (16)
Alanine aminotransferase increased	6 (12)	8 (7)
Headache	6 (12)	16 (14)
Aspartate aminotransferase increased	5 (10)	8 (7)

The number of patients receiving posaconazole in the Posaconazole Pediatric Study who had changes in liver tests from Grade 0, 1, or 2 at baseline to Grade 3 or 4 is presented in Table 16.

Table 16: Posaconazole Pediatric Study: Changes in Liver Tests from CTC Grade 0, 1, or 2 at Baseline to Grade 3 or 4

Number (%) of Patients with Change* Pediatric Study 1			
Laboratory Parameter Posaconazole Injection and Noxafil PowderMix for Release Oral Suspension (6 mg/kg daily) n=49 (%)			
AST	2/49 (4)		
ALT	3/49 (6)		
Bilirubin	0/48 (0)		
Alkaline Phosphatase	0/48 (0)		

Change from Grade 0 to 2 at baseline to Grade 3 or 4 during the study. These data are presented in the form X/Y, where X represents the umber of patients who met the criterion as indicated, and Y represents the number of patients who had a baseline observation and at least one post-baseline observation.

CTC = Common Toxicity Criteria; AST = Aspartate Aminotransferase;

ALT - Alanine Aminotransferase Postmarketing Experience 6.2

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: Pseudoaldo

7 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 concentration of postcontrace postcontrace postcontrace postcontractor because of the second of a log that can be be a second of the postcontractor because of the second of the postcontractor because of the postcontr

Posaconazole is also a strong inhibitor of CYP3A4. Therefore, plasma concentrations of drugs predominantly metabolized by CYP3A4 may be increased by posaconazole [see Clinical Pharmacology (12.3)]

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

7.1 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 /see Contraindications (4.2) and Clinical Pharmacology (12.3)].

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 (see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)].

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 [see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)].

7.2 CYP3A4 Substrates

Concomitant administration of posaconazole with CYP3A4 substrates such as pimozide and quinidine may result in increased plasma concentrations of these drugs, leading to UTC profongation and cases of torsades de pointes. Therefore, posaconazole is contraindicated with these drugs *[see Contraindications (4.3) and Warnings and Precautions (5.2)]*.

7.3 HMG-CoA Reductase Inhibitors (Statins) Primarily Metabolized Through CYP3A4

Concomitant administration of posaconazole with simvastatin increases the simvastatin plasma concentrations by approximately 10-fold. Therefore, posaconazole is contraindicated with HMG-CoA reductase inhibitors primarily metabolized through CYP3A4 *(see Contraindications (4.4) and Clinical* Pharmacology (12.3)].

7.4 Ergot Alkaloid

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 [see Cont

7.5 Benzodiazenines 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 benzodiazepin receptor antagonists must be available to reverse these effects [see Warnings and Precautions (5.7) and Clinical Pharmacology (12.3)].

7.6 Anti-HIV Drugs

Efavirenz: Efavirenz induces UDP-glucuronidase and significantly decreases posaconazole plasma concentrations /see Clinical Pharmacology (12.3)]. 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 /see Clinical Pharmacology (12.3)]. 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 /see Clinical Pharmacology (12.3)].

Patient Information Posaconazole (poe" sa kon' a zole) injection	 What is posaconazole injection? Posaconazole is a prescription medicine used in adults and children to help prevent fungal infections that can spread throughout your body (invasive fungal infections). These infections are caused by fungi called <i>Aspergillus</i> or <i>Candida</i>. Posaconazole injection is used in people who have an increased chance of getting these infections due to a weak immune system. These include people who have had a hematopoietic stem cell transplantation (bone marrow transplant) with graft versus host disease or those with a low white blood cell count due to chemotherapy for blood cancers (hematologic malignancies). Posaconazole injection is used for: prevention of fungal infections in adults and children 2 years of age and older. 	 Who should not take posaconazole? Do not take posaconazole if you: are allergic to posaconazole, any of the ingredients in posaconazole or other azole antifungal medicines. See the end of this leaflet for a complete list of ingredients in posaconazole. are taking any of the following medicines: are taking any of the following medicines: are taking any of the following medicines: c sirolimus pimozide o quinidine o certain statin medicines that lower cholesterol (atorvastatin, lovastatin, simvastatin) e ertain statin medicines that lower cholesterol (atorvastatin, lovastatin, simvastatin) o ergot alkaloids (ergotamine) have chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) and you have just started taking venetoclax or your venetoclax dose is being slowly increased. Ask your healthcare provider or pharmacist if you are not sure if you are taking any of these medicines. 	 What should I tell my healthcare provider before taking posaconazole? What should I tell my healthcare provider taking posaconazole? Before you take posaconazole, tell your healthcare provider if you: are taking certain medicines that lower your immune system like cyclosporine or tacrolimus. are taking certain drugs for HIV infection, such as ritonavir, atazanavir, efavirenz, or fosamprenavir. Efavirenz and fosamprenavir can cause a decrease in the posaconazole levels in your body. Efavirenz and fosamprenavir should not be taken with posaconazole. are taking windzolam, a hypnotic and sedative medicine. are taking vincristine, vinblastine and other "vinca alkaloids" (medicines used to treat cancer). are taking venetoclax, a medicine used to treat cancer. have or had liver problems. have or had liver problems. have or had an abnormal heart rate or rhythm, heart problems, or blood circulation problems. have or had an abnormal heart rate or rhythm, heart problems, or blood circulation problems. are breastfeeding or plan to become pregnant. It is not known if posaconazole passes into your unborn baby. are breastfeeding or plan to breastfeed. It is not known if posaconazole or breastfeed. You should not do both. 	Len your nearmeare provider about all the medicines you take, including prescription and over-me-counter medicines, vitamins, and herbal supplements. Posaconazole can affect the way other medicines work, and other medicines can affect the way other medicines work, and other medicines can affect the way to a supplements. Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure. Know the medicines you take. Keep a list of them with you to show your healthcare provider or pharmacist for a list of these medicines if you are not sure. Know the medicines you take. Keep a list of them with you to show your healthcare provider or pharmacist when you get a new medicine.	 How will I take posaconazole? Take posaconazole exactly as your healthcare provider tells you to take it. Your healthcare provider will tell you how much posaconazole to take and when to take it. Take posaconazole for as long as your healthcare provider tells you to take it. If you take too much posaconazole, call your healthcare provider or go to the nearest hospital emergency room right away. Posaconazole injection is usually given over 30 to 90 minutes through a plastic tube placed in your vein. Follow the instructions from your healthcare provider on how much posaconazole you should take and when to take it. 	 What are the possible side effects of posaconazole? Posaconazole may cause serious side effects, including: drug interactions with cyclosporine or tacrolimus. If you take posaconazole with cyclosporine or tacrolimus, your blood levels of cyclosporine or tacrolimus in your blood. Your healthcare provider should do blood tests to check your levels of cyclosporine or tacrolimus if you are taking these medicines while taking posaconazole. Tell your healthcare provider right away if you have swelling in your are nor leg or shortness of breath. problems with the electrical system of your heart (arrhythmias and OTc prolongation). Certain medicines used to treat fungus called azoles, including posaconazole, the active ingredient in posaconazole, may cause heart rhythm problems. People who have certain heart problems or who take certain medicines
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5.5 Hepatic Toxicity atic reactions (e.g., mild to moderate elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total

bilirubin, and/or clinical hepatitis) have been reported in clinical trials. The elevations in liver tests were generally reversible on discontinuation of therapy, and in some instances these tests normalized without drug interruption. Cases of more severe hepatic reactions including cholestasis or hepatic failure including deaths have been reported in patients with serious underlying medical conditions (e.g., hematologic malignancy) during treatment with posaconazole. These severe hepatic reactions were seen primarily in subjects receiving the Noxafil oral suspension 800 mg daily (400 mg twice daily or 200 mg four times a day) in clinical trials.

Liver tests should be evaluated at the start of and during the course of posaconazole therapy. Patients who develop abnormal liver tests during posaconazole therapy should be monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver 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

5.6 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 postcontrol barries to the postcontrol and the control of the postcontrol and the postcontro Administration (2.9) and Use in Specific Populations (8.6)].

5.7 Midazolam Toxicity

Concomitant administration of posaconazole with midazolam increases the midazolam plasma concentrations by approximately 5-fold. Increased plasma with high plasma concentrations could potentiate and prolong hyponotic 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 *[see Drug Interactions*] (7.5) and Clinical Pharmacology (12.3)

5.8 Vincristine Toxicity

Concomitant administration of arole antifunnals, including nosaconazole, with vincristine has been associated with neurotoxicity and other serious concommant autimistration of acure antitringias, including posaconazole, with vincistine has been associated with neurotoxicity and unlet serious adverse reactions, including seizures, peripheral neuropathy, syndrome of inappropriate antidiuretic hormone secretion, and paralytic ileus. Reserve azole antifungals, including posaconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options [see Drug Interactions (7,10)].

5.11 Venetoclax Toxicity

Concomitant administration of posaconazole, a strong CYP3A4 inhibitor, with venetoclax may increase venetoclax toxicities, including the risk of tumor lysis syndrome (TLS), neutropenia, and serious infections. In patients with CLL/SLL, administration of posaconazole during initiation and the ramp-up phase of venetoclax is contraindicated *(see Contraindications (4.6))*. Refer to the venetoclax labeling for safety monitoring and dose reduction in the steady daily dosing phase in CLL/SLL patients

by approximately 9-fold and can result in sirolimus toxicity [see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]. 4.3 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 (see Warnings and Precautions (5.2) and Drug Interactions (7.2)).

4.4 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 (see Drug Interactions (7.3) and Clinical Pharmacology (12.3)].

Posaconazole is contraindicated with sirolimus. Concomitant administration of posaconazole with sirolimus increases the sirolimus blood concentrations

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

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

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 administered over approximately 30 minutes. Note: In clinical trials, multiple peripheral infusions given through the same vein resulted in infusion site reactions *(see Adverse Reactions (6.1))*.

Posaconazole injection should be avoided in patients with moderate or severe renal impairment (eGFR < 50 mL/min), unless an assessment of the

In patients with moderate or severe renal impairment (estimated glomerular filtration rate (eGFR) < 50 mL/min), receiving the posaconazole injection, accumulation of the intravenous vehicle, Betadex Sulfobutyl Ether Sodium (SBECD), is expected to occur. Serum creatinine levels should

closely monitored in these patients, and, if increases occur, consideration should be given to changing to oral posaconazole therapy

Posaconazole injection (300 mg per vial) is available as a clear, colorless to yellow sterile liquid in a single-dose vial.

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

4.5 Use with Ergot Alkaloids

Posaconazole may increase the plasma concentrations of ergot alkaloids (ergotamine and dihydroergotamine) which may lead to ergotism /see Drug Interactions (7.4)].

4.6 Use with Venetoclax

Coadministration of posaconazole with venetoclax at initiation and during the ramp-up phase is contraindicated in patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) due to the potential for increased risk of tumor lysis syndrome *[see Warnings and Precautions*] (5.11) and Drug Interactions (7.16)].

Concomitant administration of posaconazole with cyclosporine or tacrolimus increases the whole blood trough concentrations of these calcineurin inhibitors (see Drug Interactions (7.1) and Clinical Pharmacology (12.3)). 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

Some azoles, including posaconazole, have been associated with prolongation of the QT interval on the electrocardiogram. In addition, cases of torsades

Results from a multiple time-matched ECG analysis in healthy volunteers did not show any increase in the mean of the QTc interval. Multiple, time-matched ECGs collected over a 12-hour period were recorded at baseline and steady-state from 173 healthy male and female volunteers (18 to 85 years

of age) administered Noxafil oral suspension 400 mg twice daily with a high-fat meal. In this pooled analysis, the mean QTc (Fridericia) interval change from baseline was -5 msec following administration of the recommended clinical dose. A decrease in the QTc(F) interval ($\cdot3$ msec) was also observed in a small number of subjects (n = 16) administered placebo. The placebo-adjusted mean maximum QTc(F) interval change from baseline was < 0 msec ($\cdot8$

Posaconazole should be administered with caution to patients with potentially proarrhythmic conditions. Do not administer with drugs that are known to

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

renin and aldosterone, and elevated 11-deoxycortisol), has been reported with posaconazole use in the postmarket setting. Monitor blood pressure and

potassium levels and manage as necessary. Management of pseudoaldosteronism may include discontinuation of Noxafil, substitution with an appropriate antifungal drug that is not associated with pseudoaldosteronism, or use of aldosterone receptor antagonists.

steronism, manifested by the onset of hypertension or worsening of hypertension, and abnormal laboratory findings (hypokalemia, low serum

prolong the QTc interval and are metabolized through CYP3A4 [see Contraindications (4.3) and Drug Interactions (7.2)].

5 WARNINGS AND PRECAUTIONS

5.1 Calcineurin-Inhibitor Toxicity

5.2 Arrhythmias and QT Prolongation

5.3 Electrolyte Disturbances

during posaconazole therapy.

5.4 Pseudoaldosteronism

de pointes have been reported in patients taking posaconazole

msec). No healthy subject administered posaconazole had a QTc(F)

interval \geq 500 msec or an increase \geq 60 msec in their QTc(F) interval from baseline.

adjusted accordingly.



Table 27: Summary of the Effect of Coadministered Drugs on Posaconazole in Healthy Volunteers

Dose/Sche

400 mg (oral susp

twice daily x 10 and 20 days

200 mg once daily

on the 1st day, 200 mg twic

daily on the 2nd day, then

400 mg twice daily x 8 Day

200 mg (tablets) once

daily × 10 days[†]

daily × 10 days[†]

nazole alone for Cmax or AUC

200 mg (t

In vitro studies with human hepatic microsomes and clinical studies indicate that posaconazole is an inhibitor primarily of CYP3A4. A clinical study in

healthy volunteers also indicates that posaconazole is a strong CYP3A4 inhibitor as evidenced by a >5-fold increase in midazolam AUC. Therefore plasma concentrations were affected by poseconazole, is provided in **Table 28** (see Contraindications (4) and Drug Interactions (7.1) including

Table 28: Summary of the Effect of Posaconazole on Coadministered Drugs in Healthy Adult Volunteers and Patients

Posaconazoli

Dose/Schedul

400 mg (oral su:

twice daily x 16 days

200 mg (tablets) once

x 10 days

twice daily \times 7 days

once daily x 13 days

200 mg (oral suspension

once daily x 13 days

200 mg (oral suspens

twice daily x 7 days

400 mg (oral suspension

twice daily x 7 days

once daily x 7 days

twice daily x 7 days

200 mg (tablets) once

× 10 days¹

200 mg (tablets) once

daily

x 10 days[†]

twice daily x 7 days

twice daily x 7 days

twice daily x 7 days

400 mg (oral sus

400 mg (oral sus

400 mg (oral su

Ratio Estimate is the ratio of coadministered drug plus posaconazole to coadministered drug alone for Cmax or AUC.

200 mg (oral suspe

400 mg (oral sus

400 mg (oral susp

100 mg (oral sus

Coadministered

Drug Dose/Schedule

400 mg once daily

x 10 and 20 days

700 mg twice

daily x 10 days

300 mg once dail

x 17 days

200 mg once daily

The tablet refers to a non-commercial tablet formulation without polymer.

Coadministered

Dose/Schedule

2 mg single oral dose

Stable maintenance dose in heart transplan

recipients

0.05 mg/kg single oral

40 mg single oral dose

0.4 mg single

0.4 mg single

intravenous dose

2 mg single oral dose

2 mg single oral dose

300 mg once daily x 17 days

200 mg once daily PO x 10

days

100 mg once daily x 14 days

300 mg once daily

x 14 days

300 mg/100 mg once daily x

14 days

Drug

10 days

tered drug plus posa

Drug (Postulated Mechanism of

Interaction

(UDP-G Induction

(UDP-G Induction)

UDP-G Induction)

Drug Postulated

Achanism of

iteraction is

nhibition of

YP3A4 by

osaconazole

Sirolimu

Cyclosporine

Tacrolimus

Simvastatin

Midazolam

Rifabutin

Phenytoin

Ritonavir

Atazanavir

Atazanavir

ritonavir boosted

regimen

Ratio Estimate is the ratio of co

Effect on Bioavailahili

Change in Mea

Cmax (ratio estimate*

90% CI of the ratio

estimate)

1 45%

(0.55; 0.47 to 0.66)

1 21%

0.79 (0.71 to

0.89)

/12%

of Posaconazole

(0.57; 0.43 to 0.75) (0.51; 0.37 to 0.71)

↓ 41% ↓ 50% (0.59; 0.44 to 0.79) (0.50; 0.36 to 0.71)

Effect on

Bioavailability of Coadministered Drug

↑ cyclosporine whole blood trough

concentrations

Cyclosporine dose reductions of up to 29%

were required

Change in Mean

max (ratio estimate*

90% CI of the ratio

estimate)

↑ **572%**

(6.72; 5.62 to 8.03)

↑ 121%

(2.21; 2.01 to 2.42)

↑ 841%

(9.41, 7.13 to 12.44)

Simvastatin Acid

↑ 817%

(9.17, 7.36 to 11.43)

↑ 1041%

(11.41, 7.99 to 16.29)

↑851% (9.51, 8.15 to

11 10)

↑ 30%

(1.3; 1.13 to 1.48)

↑62%

(1.62; 1.41 to 1.86)

↑ 169%

(2.69; 2.46 to 2.93)

↑ 138%

(2.38; 2.13 to 2.66)

↑ 31%

(1.31; 1.10 to 1.57)

(1.16; 0.85 to 1.57)

↑ 49%

(1.49; 1.04 to 2.15)

↑ 155%

(2.55; 1.89 to 3.45)

↑ 53%

(1.53: 1.13 to 2.07)

tatin Acid

Simvastatin

Change in Mean AUC

(ratio estimate*;

90% Cl of the ratio

estimate)

1.50%

(0.50; 0.43 to 0.60)

23%

0.77 (0.68 to

0.87)

499

Change in Mean AUC

90% CI of the ratio

estimate)

↑ 788%

(8.88; 7.26 to 10.9)

↑ 358%

(4.58; 4.03 to 5.19)

Simvasta

↑ 9319

(10.31, 8.40 to 12.67)

Simvastatin Acid

1634%

(7.34, 5.82 to 9.25)

Simvastatin

(10.60, 8.63 to 13.02)

Simvastatin Acid

↑ 748% (8.48, 7.04 to

10.23)

↑ 362%

(4.62; 4.02 to 5.3)

(6.24; 5.43 to 7.16)

↑ 470%

(5.70; 4.82 to 6.74)

↑ 397%

(4.97; 4.46 to 5.54)

↑ 72%

(1.72;1.51 to 1.95)

(1.16: 0.84 to 1.59)

↑ 80%

(1.8;1.39 to 2.31)

1 268%

(3.68; 2.89 to 4.70)

↑ 146%

(2.46: 1.93 to 3.13)

7.7 Rifabutin

Bifabutin induces UDP-olucuronidase and decreases nosaconazole plasma concentrations. Bifabutin is also metabolized by CYP3A4. Therefore, coadministration of rifabutin with possconazole increases rifabutin plasma concentrations *[see Clinical Pharmacology (12.3)]*. 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.

7.8 Phenvtoin

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 [see Clinical Pharmacology (12.3)]. 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.

7.10 Vinca Alkaloids

Most of the vinca alkaloids (e.g., vincristine and vinblastine) are substrates of CYP3A4. Concomitant administration of azole antifungals, including posaconazole injection, with vincristine has been associated with serious adverse reactions [see Warnings and Precautions (5.8)]. 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 injection, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatmen

7 11 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

7.12 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

7.14 Glipizide

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

7.16 Venetocla

Concomitant use of venetoclax (a CYP3A4 substrate) with posaconazole increases venetoclax C__ and AUC_nuer which may increase venetoclax toxicities [see Contraindications (4.6), Warnings and Precautions (5.11)]. Refer to the venetoclax prescribing information for more information on the dosing instructions and the extent of increase in venetoclax exposure

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary Based on findings from animal data, posaconazole may cause fetal harm when administered to pregnant women. Available data for use of posaconazole in pregnant women are insufficient to establish a drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In in program to the matrix of external and and any dispersion take the original to the correct, including of a constraint of the original to the correct of t twice daily or al suspension regimen based on steady-state plasma concentrations of posacnazole in healthy volunteers. In pregnant rabbits doed or ally during organogenesis, increased resorptions, reduced litter size, and reduced body weight gain of females were seen at doses 5 times the exposure achieved with the 400 mg twice daily oral suspension regimen. Doses of \geq 3 times the clinical exposure caused an increase in resorptions in these rabbits (see Data). Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data Animal Data

Posaconazole resulted in maternal toxicity (reduced food consumption and reduced body weight gain) and skeletal malformations (cranial malformations and missing ribs) when given orally to pregnant rats during organogenesis (Gestational Days 6 through 15) at doses \geq 27 mg/kg (\geq 1.4 times the 400 ma twice daily oral suspension regimen based on steady-state plasma concentrations of drug in healthy volunteers). The no-effect dose for ing twice daily oral suspension regimen based on steady-state plasma concentrations of orug in nearitry volunteers). The no-effect dose for malformations and maternal toxicity in rats was 9 mg/kg, which is 0.7 times the exposure achieved with the 400 mg twice daily oral suspension regimen. No malformations were seen in rabbits dosed during organogenesis (Gestational Days 7 through 19) at doses up to 80 mg/kg (5 times the exposure achieved with the 400 mg twice daily oral suspension regimen). In the rabbit, the no-effect dose was 20 mg/kg, while high doses of 40 mg/kg and 80 mg/kg (3 or 5 times the clinical exposure) 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.

8.2 Lactation **Risk Summary**

There are no data on the presence of posaconazole in human milk, the effects on the breastfed infant, or the effects on milk production. Posaconazole is excreted in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for posaconazole and any potential adverse effects on the breastfed child from posaconazole or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of **posaconazole injection** for the prophylaxis of invasive Aspergillus and Candida infections have been established in nts aged 2 and older who are at high risk of developing these infections due to being severely immunocompromised, such as HSCT recipients with GVHD or those with hematologic malignancies with prolonged neutropenia from chemotherapy.

Use of posaconazole in these age groups is supported by evidence from adequate and well-controlled studies of posaconazole in adult and pediatric okinetic and safety data in pediatric patients 2 years of age and older [see Adverse Reactions (6.1), Clinical patients and additional pharmac Pharmacology (12.3) and Clinical Studies (14)].

The safety and effectiveness of posaconazole have not been established in pediatric patients younger than 2 years of age

8.5 Geriatric Use

No overall differences in the safety of posaconazole injection was observed between geriatric patients and younger adult patients in the clinical trials; therefore, no dosage adjustment is recommended for any formulation of posaconazole in geriatric patients. No clinically meaningful differences in the pharmacokinetics of posaconazole were observed in geriatric patients compared to younger adult patients during clinical trials [see Clinical] Pharmacology (12.3)].

Of the 279 patients treated with posaconazole injection in the Posaconazole Injection Study, 52 (19%) were greater than 65 years of age No overall differences in the pharmacokinetics and safety were observed between elderly and young subjects during clinical trials, but greater sensitivity

The tablet refers to a non-commercial tablet formulation without polyme The mean terminal half-life of midazolam was increased from 3 hours to 7 to 11 hours during coadministration with posaconazole.

were observed when

	1111	ouyn To weeks		
Clinical Failure ^{*, ‡}		99 (33%)	110 (37%)	
Failure due to:				
Proven/Probable IFI		16 (5%)		27 (9%)
	(Aspergillus)		7 (2%)	21 (7%)
	(Candida)		4 (1%)	4 (1%)
	(Other)		5 (2%)	2 (1%)
All Deaths		58 (19%)		59 (20%)
	Proven/probable fungal		10 (3%)	16 (5%)
	infection prior to death			
SAF [†]		26 (9%)		30 (10%)
	Event free lost to follow-up ^s	24 (8%)		30 (10%)

Event free lost to follow-up[§] 24 (8%) Patients may have met more than one criterion defining failure.

Use of systemic antifungal therapy (SAF) criterion is based on protocol definitions (empiric/IFI usage >4 consecutive days).

95% confidence interval (posaconazole-fluconazole) = (-11.5%, +3.7%).

Patients who are lost to follow-up (not observed for 112 days), and who did not meet another clinical failure endpoint. These patients were considered failures.

The second study (Noxafil Oral Suspension Study 2) was a randomized, open-label study that compared Noxafil oral suspension (200 mg 3 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 AML or MDS. As in Noxafil Oral Suspension Study 1, efficacy of prophylaxis was evaluated using a composite endpoint of proven/probable IFIs, death, or treatment with systemic antifungal therapy (Patients might have met more than one of these criteria). This study assessed patients while on treatment plus 7 days and 100 days postrandomization. The mean duration of therapy was comparable between the 2 treatment groups (29 days, posaconazole; 25 days, fluconazole or itraconazole). Table 33 contains the results from Noxafil Oral Suspension Study 2.

Table 33: Results from Open-Label Clinical Study 2 in Prophylaxis of IFI in All Randomized Patients with Hematologic Malignancy and

	Posaconazole	Fluconazole/Itraconazole
	n=304	n=298
	On therapy plus 7 days	
Clinical Failure ^{*,†}	82 (27%)	126 (42%)
Failure due to:		
Proven/Probable IFI	7 (2%)	25 (8%)
(Aspergillus)	2 (1%)	20 (7
(Candida)	3 (1%)	2 (1
(Other)	2 (1%)	3 (1
All Deaths	17 (6%)	25 (8%)
Proven/probable fungal	1 (<1%)	2 (1
infection prior to death		
SAF [‡]	67 (22%)	98 (33%)
	Through 100 days postrandomization	
Clinical Failure [†]	158 (52%)	191 (64%)
Failure due to:		
Proven/Probable IFI	14 (5%)	33 (11%)
(Aspergillus)	2 (1%)	26 (9
(Candida)	10 (3%)	4 (1
(Other)	2 (1%)	3 (1
All Deaths	44 (14%)	64 (21%)
Proven/probable fungal	2 (1%)	16 (5
infection prior to death		
SAF [‡]	98 (32%)	125 (42%)
Event free lost to follow-up ⁶	34 (11%)	24 (8%)

[†] Use of systemic antifungal therapy (SAF) criterion is based on protocol definitions (empiric/IFI usage > 3 consecutive days).

⁶ Patients who are lost to follow-up (not observed for 100 days), and who did not meet another clinical failure endpoint. These patients were considered failures.

In summary, 2 clinical studies of prophylaxis were conducted with the Noxafil oral suspension. As seen in the accompanying tables (Tables 32 and 33), clinical failure represented a composite endpoint of breakthrough IFI, mortality and use of systemic antifungal therapy. In Noxafil Oral Suspension Study 1 (Table 32), the clinical failure rate of posaconazole (33%) was similar to fluconazole (37%), (95% CI for the difference posaconazole-comparator 11.5% to 3.7%) while in Noxafil Oral Suspension Study 2 (**Table 33**) clinical failure was lower for patients treated with posaconazole (27%) when compared to patients treated with fluconazole or itraconazole (42%), (95% CI for the difference posaconazole-comparator ·22.9% to ·7.8%).

All-cause mortality was similar at 16 weeks for both treatment arms in Noxafil Oral Suspension Study 1 (POS 58/301 (19%) vs. FLU 59/299 (20%)): allcause mortality was lower at 100 days for posaconazole-treated patients in Noxafil Oral Suspension Study 2 (POS 44/304 (14%) vs. FLU/ITZ 64/298 (21%)]. Both studies demonstrated fewer breakthrough infections caused by Aspergillus species in patients receiving posaconazole prophylaxis when compared to patients receiving fluconazole or itraconazol

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Posaconazole Injection

ion is available as a clear, colorless to yellow sterile liquid in single-dose Type I glass vials closed with serum rubber stopper and flip Posaconazole injection is available as a clear, countess to yenow scence inquire in angle clear, the square of off seal (NDC 31722-370-31) containing 300 mg of posaconazole in 16.7 mL of solution (18 mg of posaconazole per mL).

16.2 Storage and Handling

Posaconazole Injection

Posaconazole injection vial should be stored refrigerated at 2° to 8°C (36° to 46°F). Storage conditions for the diluted solution are presented in another section of the prescribing information [see Dosage and Admin inistration (2.4))

are currently taking a cyclosponie or tacrolimus, or they notice swelling in a arr or leg or shortness of breath. are taking a cyclosponie or tacrolimus, or they notice swelling in an arm or leg or shortness of breath.

notice a change in heart rate or heart rhythm or have a heart condition or circulatory disease. Posaconazole can be administered with caution to

are pregnant, plan to become pregnant, or are nursing. have liver disease or develop itching, nausea or vomiting, their eyes or skin turn yellow, they feel more tired than usual or feel like they have the

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have a higher chance for this problem. Tell your healthcare provider right away if your heartbeat becomes

have ever had an alleroic reaction to other antifundal medicines such as ketoconazole, fluconazole, itraconazole, or voriconazole

17 PATIENT COUNSELING INFORMATION

e the patient to read the FDA-approved patient labeling (Patient Information)

are currently taking drugs that are known to prolong the QTc interval and are metabolized through CYP3A4.

Drug Interactions

Serious and Potentially Serious Adverse Reactions

Advise patients to inform their physician immediately if they:

patients with potentially proarrhythmic conditions.

Advise patients to inform their physician immediately if they: develop severe diarrhea or vomiting.

on should be avoided in ents with moderate or severe renal impairment (eGFR $\,<$ 50 mL/min), unless an 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 (see Dosage and Administration (2.9) and Warnings and Precautions (5.6)].

8.7 Hepatic Impairmer

8.6 Renal Impairment

It is recommended that no dose adjustment of posaconazole injection is needed in patients with mild to severe hepatic impairment (Child-Pugh Class A, B, or C) (see Dosage and Administration (2) and Warnings and Precautions (5.5)). However, a specific study has not been conducted with posacona

8.8 Gende

of some older individuals cannot be ruled out.

The pharmacokinetics of posaconazole are comparable in males and females. No adjustment in the dosage of posaconazole is necessary based on gender

8.9 Race

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

8.10 Weight tic 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 [see Clinical Pharmacology (12.3)].

10 OVERDOSAGE

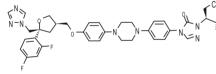
There is no experience with overdosage of posaconazole injection.

During the clinical trials, some patients received Noxafil oral suspension up to 1,600 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 1,200 mp twice daily Noxafil oral suspension for 3 days. No related adverse reactions were noted by the investigator.

Posaconazole is not removed by hemodialysis.

11 DESCRIPTION

Posaconazole is an azole antifungal agent. Posaconazole is available as an injection solution to be diluted before intravenous administration Posaconazole is designated chemically as 4-[4-[4-[4-[(3R, 5R)-5-(2,4-difluoro phenyl) tetrahydro-5-(1H-1,2,4-triazol-1-ylmethyl)-3furanyl]methoxy]phenyl]-1-piperazinyl]phenyl] -2-[(1\$,2\$)-1-ethyl-2-hydroxypropyl]-2,4-dihydro-3#-1,2,4-triazol-3-one with an molecular formula of $C_{22}H_{42}F_2N_aO_4$ and a molecular weight of 700.79. The chemical structure is:



Posaconazole is an off-white to white powder, slightly soluble in methanol and sparingly soluble in dimethyl sulfoxide.

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: 6.68 g betadex sulfobutyl ether sodium (SBECD), 0.0033 g edetate disodium, hydrochloric acid and sodium hydroxide to adjust the pH to 2.6, and water for injection

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Posaconazole is an azole antifungal agent [see Clinical Pharmacology (12.4)].

12.2 Pharmacodynamics

Exposure Response Relationship Prophylaxis: In clinical studies of neutropenic patients who were receiving cytotoxic chemotherapy for acute myelogenous leukemia (AML) or myelodysplastic syndromes (MDS) or hematopoietic stem cell transplant (HSCT) recipients with Graft versus Host Disease (GVHD), a wide range of plasma exposures to posaconazole was noted following administration of Noxafil oral suspension. A pharmacokinetic pharmacohymaic analysis of patient data revealed an apparent association between average posaconazole concentrations (Cavg) and prophylactic efficacy (Table 17). A lower Cavg may be associated with an increased risk of treatment failure, defined as treatment discontinuation, use of empiric systemic antifungal therapy (SAF), or occurrence of breakthrough invasive fungal infections

Table 17: Noxafil Oral Suspension Exposure Analysis (Cavg) in Prophylaxis Trials

······································							
	Prophylaxis	in AML/MDS [*]	Prophylaxis in GVHD [†]				
	Cavg Range (ng/mL)	Treatment Failure [‡] (%)	Cavg Range (ng/mL)	Treatment Failure [‡] (%)			
Quartile 1	90 to 322	54.7	22 to 557	44.4			
Quartile 2	322 to 490	37	557 to 915	20.6			
Quartile 3	490 to 734	46.8	915 to 1,563	17.5			
Quartile 4	734 to 2,200	27.8	1,563 to 3,650	17.5			

Cavg = the average posaconazole concentration when measured at steady state

tropenic patients who were receiving cytotoxic chemotherapy for AML or MDS [†] HSCT recipients with GVHD

[‡] Defined as treatment discontinuation, use of empiric systemic antifungal therapy (SAF), or occurrence of

breakthrough invasive fungal infections

12.3 Pharmacokinetics

General Pharmacokinetic Characteristic

aconazole Injectio

Posaconazole injection exhibits dose proportional pharmacokinetics after single doses between 200 and 300 mg in healthy volunteers and patients. The mean pharmacokinetic parameters after single doses with posaconazole injection in healthy volunteers and patients are shown in Table 18.

Table 18: Summary of Mean Pharmacokinetic Parameters (%CV) in Healthy Volunteers (30-minute infusion via peripheral venous line) and

Patients (90 minute infusion via central venous line) after Dosing with Posaconazole Injection on Day 1							
	Dose (mg)	Dose (mg) n		AUC ₀₋₁₂	AUC ₀₋₁₂ C _{max}	t 1/2	CL
			(ng∙hr/mL)	(ng·hr/mL)	(ng/mL)	(hr)	(L/hr)
Healthy	200	9	35,400 (50)	8,840 (20)	2,250 (29)	23.6 (23)	6.5 (32)
Volunteers	300	9	46,400 (26)	13,000 (13)	2,840 (30)	24.6 (20)	6.9 (27)
Patients	200	30	N/D	5,570 (32)	954 (44)	N/D	N/D
	000	00	NUD	0.040 (00)	1 500 (00)	NU/D	NUD.

 300
 22
 N/D
 8,240 (26)
 1,590 (62)
 N/D
 N/D

 AUCo... – Area under the plasma concentration-time curve from time zero to infinity; AUCo... – Area under the plasma concentration-time
 N/D
 N/D
 N/D
 curve from time zero to 12 hr after the first dose on Day 1: C max = maximum observed concentration; t y = terminal phase half-life; CL total body clearance; N/D = Not Determined

Table 19 displays the pharmacokinetic parameters of posaconazole in patients following administration of posaconazole injection 300 mg taken once a

day for 10 or 14 days following twice daily dosing on Day 1.

Table 19: Arithmetic Mean (%CV) of PK Parameters in Serial PK-Evaluable Patients Following Dosing of Posaco zole Injection (300 mg) Tmax[†] AUCn.24 Day Cmax Cav Cmin (hr) (ng/mL) (ng*hr/mL) (ng/mL) (ng/mL) 1,500 (35) 10/14 49 3,280 (74) 1.5 (0.98 to 4.0) 36,100 (35) 1,090 (44) AUCo24 = area under the concentration time curve over the dosing interval (i.e. 24 hours); Cav = timeaveraged concentrations (i.e., AUCo24/24h Cmin = POS trough level immediately before a subject received the dose of POS on the day specified in the protocol; Cmax = observed maximum eraged concentrations (i.e., AUC0-24h/24hr) plasma concentration: CV = coefficient of variation, expressed as a percent (%); Day = study day on treatment; Tmax = time of observed maxi

300 mg dose administered over 90 minutes once a day following twice daily dosing on Day 1 Median (minimum-maximum)

Distribution

The mean volume of distribution of posaconazole after intravenous solution administration was 261 L and ranged from 226 to 295 L between studies and dose levels.

Posaconazole is highly bound to human plasma proteins (>98%), predominantly to albumin

Metabolism

Posaconazole primarily circulates as the parent compound in plasma. Of the circulating metabolites, the majority are glucuronide conjugates formed via UDP glucuronidation (phase 2 enzymes). Posaconazole does not have any major circulating oxidative (CYP450 mediated) metabolites. The excreted metabolites in urine and feces account for ~17% of the administered radiolabeled dose.

Posaconazole is primarily 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. A summary of drugs studied clinically with the oral suspension or an early tablet formulation, which affect posaconazole concentrations, is provided in Table 27.

administered with posaconazole 200 mg once daily; therefore, no dose adjustments are required for these coadministered drugs when coadminist with posaconazole 200 mg once daily

Excretion:

Following administration of Noxafil oral suspension, posaconazole is predominantly eliminated in the feces (71% of the radiolabeled dose up to 120 hours) with the major component eliminated as parent drug (66% of the radiolabeled dose). Renal clearance is a minor elimination pathway, with 13% of the radiolabeled dose excreted in urine up to 120 hours (< 0.2% of the radiolabeled dose is parent drup)

Posaconazole injection is eliminated with a mean terminal half-life (1%) of 27 hours and a total holy clearance (CI) of 7.3 L/h

Specific Populations

No clinically significant differences in the pharmacokinetics of posaconazole were observed based on age, sex, renal impairment, and indication (prophylaxis or treatment

Race/Ethnicity:

In a population pharmacokinetic analysis of posaconazole, AUC was found to be 25% higher in Chinese patients relative to patients from other ies. This higher exposure is not expected to be clinically relevant given the expected variability in posaconazole exposur

Patients Weighing More Than 120 kg:

Weight has a clinically significant effect on posaconazole clearance. Relative to 70 kg patients, the Cavg is decreased by 25% in patients greater than 120 kg. Patients administered posaconazole weighing more than 120 kg may be at higher risk for lower posaconazole plasma concentrations compared to lower weight patients [see Use in Specific Populations (8 10)]

Pediatric Patients

redunatic narameters after multiple dose administration of nosaconazole injection in neutronomic padiatric nations 2 to less than 18 years of age are shown in Table 29. Patients were enrolled into 2 age groups and received posaconazole injection doses at 6 mg/kg (0.6 to 1 times the recommended dose) with a maximum 300 mg dose once daily (twice daily on Day 1) /see Adverse Reactions (6.1)].

Table 29: Summary of Steady-State Geometric Mean Pharmacokinetic Parameters (% Geometric CV) After Multiple Dosing with Posaconazole Iniection 6 malka' in Pediatric Patients with Neutropenia or Expected Neutropenia

Age Group	Dose Type	N	AUC®-24 hr (ng·hr/mL)	Cav† (ng/mL)	C _{max} (ng/mL)	C _{min} (ng/mL)	T _{max} ‡ (hr)	CL ^s (L/hr)
2 to <7 years	IV	17	31100 (48.9)	1300 (48.9)	3060 (54.1)	626 (104.8)	1.75 (1.57 to 1.83)	3.27 (49.3)
7 to 17 years	IV	24	44200 (41.5)	1840 (41.5)	3340 (39.4)	1160 (60.4)	1.77 (1.33 to 6.00)	4.76 (55.7)

V = Posaconazole injection; AUC 0.24 = Area under the plasma concentration time curve from time zero to 24 hr; C max = maximum observed concentration in = minimum observed plasma concentration: Tmax = time of maximum observed concentration: CL /F = apparent total body clearance

0.6 to 1 times the recommended dose Cav = time-averaged concentrations (i.e., AUC_{0-24 tr}/24hr)

⁵ Clearance (CL for IV)

Based on a population pharmacokinetic model evaluating posaconazole pharmacokinetics and predicting exposures in pediatric patients, the exposure of steady-state posaconazole average concentration greater than or equal to 700 ng/mL in approximately 90% of patients is attained with the recommended dose of posaconazole injection.

The population pharmacokinetic analysis of posaconazole in pediatric patients suggests that age, sex, renal impairment and ethnicity have no clinically meaningful effect on the pharmaco

12.4 Microhiology

lechanism of Action

Posaconazole blocks the synthesis of ergosterol, a key component of the fungal cell membrane, through the inhibition of cytochrome P-450 dependent regression and the syntaxia of regression a key component of the initial can memory in a manufact, more syntaxia of or promotion - 150 opponent of the initial can memory in a manufact in the fungal call memory in a manufact in the syntaxia of the syntaxia of the syntaxia of the initial call memory in a source of the syntaxia of the fungal cell membrane. This may be responsible for the antifungal activity of posaconazole

Resistance:

Clinical isolates of Candida albicans and Candida glabrata with decreased susceptibility to posaconazole were observed in oral swish samples taken Connect sources of compared and can be allowed grant of white decreases asceptioning to postcontactor where operation in order switch astrong and the control of the state of

Antimicrobial Activity:

Posaconazole has been shown to be active against most isolates of the following microorganisms, both in vitro and in clinical infections [see Indications and Usage (1)].

Microorganisms

Aspergillus spp. and Candida spp.

Susceptibility Testing:

For specific information regarding susceptibility test interpretive criteria and associated test methods and guality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No drug-related neoplasms were recorded in rats or mice treated with posaconazole for 2 years at doses higher than the clinical dose. In a 2-year carcinogenicity study, rats were given posaconazole orally at doses up to 20 mg/kg (females), or 30 mg/kg (males). These doses are equivalent to 3.9- or 3.5.times the exposure achieved with a 400 mg twice daily oral suspension regimen. In the mouse study, mice were treated at oral doses up to 60 mg/kg/day or 4.8-times the exposure achieved with a 400 mg twice daily oral suspension regimen.

Mutagenesis

Posaconazole was not genotoxic or clastogenic when evaluated in bacterial mutagenicity (Ames), a chromosome aberration study in human periphera blood lymphocytes, a Chinese hamster ovary cell mutagenicity study, and a mouse bone marrow micronucleus study Impairment of Fertility

Posaconazole had no effect on fertility of male rats at a dose up to 180 mg/kg (1.7 x the 400 mg twice daily oral suspension regimen based on steady state plasma concentrations in healthy volunteers) or female rats at a dose up to 45 mg/kg (2.2 x the 400 mg twice daily oral suspension regimen).

13.2 Animal Toxicology and/or Pharmacology

In a nonclinical study using intravenous administration of posaconazole in very young dogs (dosed from 2 to 8 weeks of age), an increase in the in a momenta study dang interenous bummisterior of postcollador in very young dog (boost of 100 2 00 weeks of 196), an increase in the incidence of brain ventricle anargement was observed in treated animals as compared with concurrent control animals. No difference in the incidence of brain ventricle enlargement between control and treated animals was observed following the subsequent 5-month treatment-free period. There were no neurologic, behavioral or developmental abnormalities in the dogs with this finding, and a similar brain finding was not seen with oral posaconazole administration to give an end of the second administration of the second with the second many was not seen with one possible administration administration to give an edge of the second with a second recovery period or a follow-up study of 31-week-old doos dosed for 3 months

14 CLINICAL STUDIES

14.2 Prophylaxis of Aspergillus and Candida Infections with Noxafil Oral Suspension Two randomized, controlled studies were conducted using posaconazole as prophylaxis for the prevention of invasive fungal infections (IFIs) among patients at high risk due to severely compromised immune systems

The first study (Noxafil Oral Suspension Study 1) was a randomized, double-blind trial that compared Noxafil oral suspension (200 mg three times a day with fluconazole capsules (400 mg once daily) as prophylaxis against invasive fungal infections in allogeneic hematopoietic stem cell transplant (HSCT) recipients with Graft versus Host Disease (GVHD). Efficacy of prophylaxis was evaluated using a composite endpoint of proven/probable IFIs, death, or treatment with systemic antifungal therapy (patients may have met more than one of these criteria). This assessed all patients while on study therapy plus 7 days and at 16 weeks post-randomization. The mean duration of therapy was comparable between the 2 treatment groups (80 days, Noxafil ora sion; 77 days, fluconazole). Table 32 contains the results from Noxafil Oral Suspension Study 1

Table 32: Results from Blinded Clinical Study in Prophylaxis of IFI in All Randomized Patients with Hematopoietic Stem Cell Transplant (HSCT) and Graft.vs -Host Disease (GVHD): Novafil Oral Suspension Study 1

		Posaconazole n=301	Fluconazole n=299		
	On the	rapy plus 7 days			
Clinical Failure*		50 (17%)		55 (18%)	
Failure due to:					
Proven/Probable IFI		7 (2%)		22 (7%)	
	(Aspergillus)		3 (1%)		17 (6%)
	(Candida)		1 (<1%)		3 (1%)
	(Other)		3 (1%)		2 (1%)
All Deaths		22 (7%)		24 (8%)	
	Proven/probable fungal infection prior to death		2 (<1%)		6 (2%)
SAF [†]		27 (9%)		25 (8%)	

Manufactured for: Camber Pharmaceuticals, Inc. Piscataway, NJ 08854

Manufactured by

Aspiro Pharma Limited Survey No. 321, Biotech Park, Phase - III Karkapatla Village, Markook (Mandal

Siddipet, Telangana-502281, India

Issued: 01/2025

Orgenoving of your eyes or shin
Increases the amount of midzalam in your blood. If you take paraenazable with midzalam, paraenazable in adults include:

Increase
Incre • • liver problems. Some people who also have other serious medical problems may have severe liver problems that may lead to death, especially if you take certain doses of posaconazole. Your healthcare provider should do blood tests to check your liver while you are taking posaconazole. Call your healthcare provider right away if you have any of the following symptoms of liver problems: fast or irregular. **changes in body salt (electrolytes) levels in your blood.** Your healthcare provider should check your new or worsening high blood pressure and low potassium levels in your blood (pseudoaldosteronism). Your healthcare provider should check your blood pressure and potassium levels. o nausea or vomiting o itchy skin o flu-like symptoms o feeling very tired

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Levent Administration has been approved by the U.S. Food and Drug Administration.

ied: 01/2025