

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VORICONAZOLE FOR ORAL SUSPENSION safely and effectively. See full prescribing information for VORICONAZOLE FOR ORAL SUSPENSION ORAL SUSPENSION.

VORICONAZOLE for Oral Suspensio

Initial U.S. Approval: 2002

--RECENT MAJOR CHANGES-Warnings and Precautions, Photosensitivity (5.6)

10/2022 ----INDICATIONS AND USAGE-Voriconazole is an azole antifungal indicated for the treatment of adults and pediatric patients 2

years of age and older with:

Invasive aspergillosis (1.1)

 Candidemia in non-neutropenics and other deep tissue Candida infections (1.2) Esophageal candidiasis (1.3)

Serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* species including *Fusarium solani*, in patients intolerant of, or refractory to, other therapy (1.4)

--DOSAGE AND ADMINISTRATION-

• Dosage in Adults (2.3)

Infection Maintenance Dose Loading Dose Intravenous infusion Intravenous infusion Oral

Invasive Aspergillosis	6 mg/kg every	4 mg/kg every	200 mg every
	12 hours for the first	12 hours	12 hours
Candidemia in nonneutropenics and other deep tissue <i>Candida</i> infections	24 110015	3-4 mg/kg every 12 hours	200 mg every 12 hours
Scedosporiosis and		4 mg/kg every	200 mg every
Fusariosis		12 hours	12 hours
Esophageal Candidiasis	Not Evaluated	Not Evaluated	200 mg every 12 hours

o Adult patients weighing less than 40 kg: oral maintenance dose 100 mg or 150 mg every 12

hours o Hepatic Impairment: Use half the maintenance dose in adult patients with mild to moderate hepatic impairment (Child-Pugh Class A and B) (2.5) o Renal Impairment: Avoid intravenous administration in adult patients with moderate to severe renal impairment (creatinine clearance <50 mL/min) (2.6) Description: Dedicate Cleare of one and lader (2.4)

Dosage in Pediatric Patients 2 years of age and older (2.4)

FULL PRESCRIBING INFORMATION: CONTENTS*

DOSAGE FORMS AND STRENGTHS

Photosensitivity Renal Toxicity Adrenal Dysfunction Embryo-Fetal Toxicity Laboratory Tests Pancreatitis

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Invasive Aspergillosis

1.3 Esophageal Candidiasis

Skeletal Adverse Reaction

5.13 Clinically Significant Drug Interactions

Hepatic Toxicity Arrhythmias and QT Prolongation Infusion Related Reactions

Visual Disturbances Severe Cutaneous Adverse Reactions Photosensitivity

CONTRAINDICATIONS

o For pediatric patients 2 to less than 12 years of age and 12 to 14 years of age weighing less

Infection	Loading dose	Maintenan	nce Dose	
	Intravenous infusion	Intravenous infusion	Oral	
Invasive Aspergillosis	9 mg/kg every	8 mg/kg every	9 mg/kg every	
Candidemia in nonneutropenics and other deep tissue <i>Candida</i> infections	24 hours	first 24 hours	(maximum dose of 350 mg every 12 hours)	
Scedosporiosis and Fusariosis				
Esophageal Candidiasis	Not Evaluated	4 mg/kg every 12 hours	9 mg/kg every 12 hours (maximum dose of 350 mg every 12 hours)	

suspension and important administration instructions (2.1, 2.6, 2.7) ODSAGE FORMS AND STRENGTHS
 For Oral Suspension: 49 grams of powder; after reconstitution 40 mg/mL (3)

-----CONTRAINDICATIONS--Hypersensitivity to voriconazole or its excipients (4)

· Coadministration with pimozide, quinidine, sirolimus or ivabradine due to risk of serious adverse eactions (4, 7)

 Coadministration with rifampin, carbamazepine, long-acting barbiturates, efavirenz, ritonavir rifabutin, ergot alkaloids, and St. John's Word due to risk of loss of efficacy (4, 7) • Coadministration with naloxegol, tolvaptan, and lurasidone due to risk of adverse reactions (4, 7) • Coadministration of voriconazole with venetoclax at initiation and during the ramp-up phase in patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) due to increased risk of adverse reactions (4, 7)

-----WARNINGS AND PRECAUTIONS--• Hepatic Toxicity: Serious hepatic reactions reported. Evaluate liver function tests at start of and

Arrhythmias and QT Prolongation: Correct potassium, magnesium and calcium prior to use;
 caution patients with proarrhythmic conditions (5.2)

Influsion Related Reactions (including anaphylaxis) Stop the influsion (5.3)
 Visual Disturbances (including optic neuritis and papilledema): Monitor visual function if

treatment continues beyond 28 days (5.4)

 Severe Cutaneous Adverse Reactions: Discontinue for exfoliative cutaneous reactions (5.5)
 Photosensitivity: Avoid sunlight due to risk of photosensitivity (5.6)
 Adrenal Dysfunction: Carefully monitor patients receiving voriconazole and corticosteroids (via all routes of administration) for adrenal dysfunction both during and after voriconazole treatment. Instruct patients to seek immediate medical care if they develop signs and symptoms of Cushing's syndrome or adrenal insufficiency (5.8)

Embryo-Fetal Toxicity: Voriconazole can cause fetal harm when administered to a pregnant woman. Inform pregnant patients of the potential hazard to the fetus. Advise females of reproductive potential to use effective contraception during treatment with voriconazole (5.9, 8.1, 8.3)

Skeletal Adverse Reactions: Fluorosis and periositits with long-term voriconazole therapy. Discontinue if these adverse reactions occur (5.12)
 Clinically Significant Drug Interactions: Review patient's concomitant medications (5.13, 7)

-----ADVERSE REACTIONS-----Adult Patients: The most common adverse reactions (incidence $\geq 2\%$) were visual disturbances fever, nausea, rash, vomiting, chills, headache, liver function test abnormal, tachycardia, hallucinations (6)

 Pediatric Patients: The most common adverse reactions (incidence ≥5%) were visual disturbances, pyrexia, vomiting, epistaxis, nausea, rash, abdominal pain, diarrhea, hypertension hypokalemia, cough, headache, thrombocytopenia, ALT abnormal, hypotension, periphera edema, hyperglycemia, tachycardia, dyspnea, hypocalcemia, hypophosphatemia, LFT abnormal, nucosal inflammation, photophobia, abdominal distention, constipation, dizziness, hallucinations, hemoptysis, hypoalbuminemia, hypomagnesemia, renal impairment, upper respiratory tract infection (6)

report SUSPECTED ADVERSE REACTIONS, contact Lupin Pharmaceuticals Inc. at 1-866-403-7592 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

-----DRUG INTERACTIONS--CYP3A4, CYP2C9, and CYP2C19 inhibitors and inducers: Adjust voriconazole dosage and

monitor for adverse reactions or lack of efficacy (4, 7) Vorionazole may increase the concentrations and activity of drugs that are CYP3A4, CYP2C9 and CYP2C19 substrates. Reduce dosage of these other drugs and monitor for adverse reactions (4, 7) Phenytoin or Efavirenz: With co-administration, increase maintenance oral and intravenous dosage

of voriconazole (2.3, 2.7, 7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling Rev. 11/2022

 LINICAL STUDIES

 14.1
 Invasive Aspergillosis (IA)

 14.2
 Candidemia in Non-neutropenic Patients and Other Deep Tissue Candida Infections

 14.3
 Esophageal Candidiasis (EC)

 14.4
 Other Serious Fungal Pathogens

 14.5
 Pediatric Studies

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

In patients with moderate or severe renal impairment (creatinine clearance <50 mL/min) who are In patients with moderate or severe renal impairment (creatinine clearance <00 mL/min) who are receiving an intravenous infusion of voriconazole, accumulation of the intravenous vehicle, SBECD, occurs. Oral voriconazole should be administered to these patients, unless an assessment of the benefit/risk to the patient justifies the use of intravenous voriconazole. Serum creatinine levels should be closely monitored in these patients, and, if increases occur, consideration should be given to changing to oral voriconazole therapy [see Warnings and Precautions (5.7)].

conazole and the intravenous vehicle, SBECD, are dialyzable. A 4-hour hemodialysis session is not remove a sufficient amount of voriconazole to warrant dose adjustment [see Clinical rmacology (12.3)].

Dosage adjustment of voriconazole in pediatric patients with renal impairment has not been established [see Use in Specific Populations (8.4)].

INSE REACTIONS Clinical Trials Experience Postmarketing Experience in Adult and Pediatric Patients

Pregnancy Lactation Females and Males of Reproductive Potential Pediatric Use Geriatric Use

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility 14 CLINICAL STUDIES

HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

ADVERSE REACTIONS

BUG INTERACTIONS USE IN SPECIFIC POPULATIONS

Mechanism of Actio Pharmacodynamics Pharmacokinetics

Microbiology

NONCLINICAL TOXICOLOGY

OVERDOSAGE

13

16

Pediatric Patients

DESCRIPTION CLINICAL PHARMACOLOGY

o For pediatric patients aged 12 to 14 years weighing greater than or equal to 50 kg and those aged 15 years and older regardless of body weight use adult dosage. (2.4)
 o Dosage adjustment of voriconazole in pediatric patients with renal or hepatic impairment has not been established (2.5, 2.6)
 o. See full prescribing information for instructions on reconstitution of voriconazole oral

PHESCRIBING INFORMATION: CUNTENTS*
INDICATIONS AND USAGE
1.1 Invasive Aspergillosis
1.2 Candidemia in Non-neutropenic Patients and Other Deep Tissue Candida Infections
1.3 Esophageal Candidiasis
1.4 Scedosporiosis and Fusariosis
1.5 Ulsage

1.5 Usage
 1.5 Usage

5.9 Embryo-Fetal Toxicity

Voriconazole can cause fetal harm when administered to a pregnant woman In animals, voriconazole administration was associated with fetal malformations, embryotoxicity, increased gestational length, dystocia and embryomortality [see Use in Specific Populations (8.1)]. If voriconazole is used during pregnancy, or if the patient becomes pregnant while taking voriconazole inform the patient of the potential hazard to the fetus. Advise females of reproductive potential to use effective contraception during treatment with voriconazole [see Use in Specific Populations (8.3)].

5.10 Laboratory Tests

Electrolyte disturbances such as hypokalemia, hypomagnesemia and hypocalcemia should be Patient management should include laboratory evaluation of renal (particularly serum creatinine) and hepatic function (particularly liver function tests and bilirubin). 5.11 Pancreatitis

Pancreatitis has been observed in patients undergoing treatment with voriconazole [see Adverse Reactions (6.1, 6.2)] Patients with risk factors for acute pancreatitis (e.g., recent chemotherapy hematopoietic stem cell transplantation [HSCT]) should be monitored for the development of pancreatitis during voriconazole treatment.

5.12 Skeletal Adverse Reactions

Fluorosis and periostitis have been reported during long-term voriconazole therapy. If a patient develops skeletal pain and radiologic findings compatible with fluorosis or periostitis, voriconazole should be discontinued [see Adverse Reactions (6.2)]. 5.13 Clinically Significant Drug Interactions

See Table 10 for a listing of drugs that may significantly alter voriconazole concentrations. Also, see Table 11 for a listing of drugs that may interact with voriconazole resulting in altered pharmacokinetics or pharmacodynamics of the other drug [see Contraindications (4) and Drug Interactions (7)]. 6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling: Hepatic Toxicity [see Warnings and Precautions (5.1)]

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

Infusion Related Reactions [see Warnings and Precautions (5.3)] Visual Disturbances [see Warnings and Precautions (5.4)]

Severe Cutaneous Adverse Reactions [see Warnings and Precautions (5.5)] Photosensitivity [see Warnings and Precautions (5.6)]

Renal Toxicity [see Warnings and Precautions (5.7)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Clinical Trials Experience in Adults

Overview

The most frequently reported adverse reactions (see Table 4) in the adult therapeutic trials were visual disturbances (18.7%), fever (5.7%), nausea (5.4%), rash (5.3%), vomiting (4.4%), chills (3.7%), headache (3.0%), liver function test increased (2.7%), tachycardia (2.4%), hallucinations (2.4%). The adverse reactions which most often led to discontinuation of vorconazole therapy were elevated liver function tests, rash, and visual disturbances [see Warning and Precautions (5.1, 5.4) and Adverse Reactions (6.1)].

(5.1, 5.4) and Adverse Reactions (6.1)]. The data described in Table 4 reflect exposure to voriconazole in 1655 patients in nine therapeutic studies. This represents a heterogeneous population, including immunocompromised patients, e.g., patients with hematological malignancy or HIV and non-neutropenic patients. This subgroup does not include healthy subjects and patients treated in the compassionate use and non-therapeutic studies. This patient population was 62% male, had a mean age of 46 years (range 11-90, including 51 patients aged 12-18 years), and was 78% White and 10% Black Five hundred sixty one patients had a duration of voriconazole therapy of greater than 12 weeks, with 136 patients receiving voriconazole for over six months. Table 4 includes all adverse reactions which were reported at an incidence of ≥2% during voriconazole therapy in the all therapeutic studies population, studies 307/602 and 608 combined, or study 305, as well as events of concern which occurred at an incidence of <2%.</p>

occurred at an incidence of <2%. In study 307/602, 381 patients (196 on voriconazole, 185 on amphotericin B) were treated to compare voriconazole to amphotericin B followed by other licensed antifungal therapy (OLAT) in the primary treatment of patients with acute IA. The rate of discontinuation from voriconazole study medication due to adverse reactions was 21.4% (42/196 patients). In study 608, 403 patients with candidemia were treated to compare voriconazole (272 patients) to the regimen of amphotericin B followed by fluconazole (131 patients). The rate of discontinuation from voriconazole study medication due to adverse reactions was 19.5% out of 272 patients. Study 305 evaluated the effects of oral voriconazole (200 patients) and oral fluconazole (191 patients) in the treatment of EC. The rate of discontinuation from voriconazole study medication in Study 305 due to adverse reactions was 7% (14/200 patients). Laboratory test abnormalities for these studies are discussed under Clinical Laboratory Values below. Table 4:

Table 4:

Adverse Reactions Rate ≥ 2% on Voriconazole or Adverse Reactions of Concern in Therapeutic Studies Population, Studies 307/602-608 Combined, or Study 305. Possibly Related to Therapeutic Studies and the study an

	Related	to Therapy of	or Causaii	ty Unknown ¹		
	Therapeutic Studies*	Studies 307/602 and 608 (IV/ oral therapy)			Stud (oral ti	/ 305 herapy)
	Voriconazole N=1655	Voriconazole N=468	Ampho B** N=185	Ampho B → Fluconazole N=131	Voriconazole N=200	Fluconazole N=191
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Special Senses***						
Abnormal vision	310 (18.7)	63 (13.5)	1 (0.5)	0	31 (15.5)	8 (4.2)
Photophobia	37 (2.2)	8 (1.7)	0	0	5 (2.5)	2 (1.0)
Chromatopsia	20 (1.2)	2 (0.4)	0	0	2 (1.0)	0
Body as a Whole						
ever	94 (5.7)	8 (1.7)	25 (13.5)	5 (3.8)	0	0
Chills	61 (3.7)	1 (0.2)	36 (19.5)	8 (6.1)	1 (0.5)	0
Headache	49 (3.0)	9 (1.9)	8 (4.3)	1 (0.8)	0	1 (0.5)
Condiana contex Custom						
Laruiovascular System	00 (0 4)	0 (1 0)	F (0 7)	0	0	0
lacnycardia	39 (2.4)	6(1.3)	5 (2.7)	U	U	U
Digestive System						
Vausea	89 (5.4)	18 (3.8)	29 (15.7)	2 (1.5)	2 (1.0)	3 (1.6)
/omitina	72 (4.4)	15 (3.2)	18 (9.7)	1 (0.8)	2 (1.0)	1 (0.5)
Liver function	45 (2.7)	15 (3.2)	4 (2.2)	1 (0.8)	6 (3.0)	2 (1.0)
ests abnormal	```	. ,	, í	. ,	, ,	. ,
Cholestatic jaundice	17 (1.0)	8 (1.7)	0	1 (0.8)	3 (1.5)	0
Metabolic and						
Nutritional Systems						
Alkaline phosphatase ncreased	59 (3.6)	19 (4.1)	4 (2.2)	3 (2.3)	10 (5.0)	3 (1.6)
Hepatic enzymes	30 (1.8)	11 (2.4)	5 (2.7)	1 (0.8)	3 (1.5)	0

*Without regard to baseline value n = number of patients with a clinically significant abnormality while on study therapy N = total number of patients with at least one observation of the given lab test while on study therapy AST = Aspartate aminotransferase; ALT = alanine aminotransferase

ULN = upper limit of normal LLN = lower limit of normal Clinical Trials Experience in Pediatric Patients

The safety of voriconazole was investigated in 105 pediatric patients aged 2 to less than 18 years, including 52 pediatric patients less than 18 years of age who were enrolled in the adult therapeutic crudios.

Serious Adverse Reactions and Adverse Reactions Leading to Discontinuation In clinical studies, serious adverse reactions occurred in 46% (48/105) of voriconazole treated pediatric patients. Treatment discontinuations due to adverse reactions occurred in 12/105 (11%) of all patients. Hepatic adverse reactions (i.e. ALT increased; liver function test adnormal; jaundice) 6% (6/105) accounted for the majority of voriconazole treatment discontinuations. Most Common Adverse Reactions

The most common adverse reactions occurring in ≥5% of pediatric patients receiving voriconazole in the pooled pediatric clinical trials are displayed by body system, in Table 8. Table 8: Adverse Reactions Occurring in ≥5% of Pediatric Patients Receiving Voriconazole in the Pooled Pediatric Clinical Trials

Body System Adverse Reaction Pooled Pediatric Data^a N=105 n (%) Blood and Lymphatic Systems 10 (10) Thrombocytopenia Tachycardia Visual Disturbances Photophobia Cardiac Disorders Eye Disorders Vomiting Nausea Abdominal pain^c Diarrhea Abdominal distention Gastrointestinal Disorders

General Disorders and Administration Site Conditions Upper respiratory tract infection 5 Infections and Infestatio Investigations Metabolism and Nutrition Disorders Hypokalemi Hyperglycen Hypophosphote nagnesemia Nervous System Disorders Psychiatric Disorder

Renal and Urinary Disorders Respiratory Disorders Renal impairmer Skin and Subcutaneous Tissue Rash^g 14 (13)

Disorders Vascular Disorders Hyperten Hypotension a Reflects all adverse reactions and not treatment-related only

^a Reflects all adverse reactions and not treatment-related only.
 ^b Poolet reports include such terms as: amaurosis (partial or total blindness without visible change in the eye); asthenopia (eye strain); chromatopsia (abnormally colored vision); color blindness; diplopia; photopsia; retinal disorder, vision blurred, visual acuity decreased, visual brightness; visual impairment. Several patients had more than one visual disturbance.
 ^c Pooled reports include such terms as: AldTabornal and ALT increased.
 ^e Pooled reports include such terms as: ALT abnormal and ALT increased.
 ^e Pooled reports include such terms as: ALT abnormal and ALT increased.
 ^e Pooled reports include such terms as; hallourination; hallucination, auditory; hallucination, visual. Several patients had both visual and auditory hallucination.
 ^e Pooled reports include such terms as; hard nemarized; rash macular, rash maculopapular, rash pruritic. Abbreviations: ALT = alanine aminotransferase; LFT = liver function test
 The following adverse reactions with incidence less than 5% were reported in 105 pediatric patients treated with voriconazole:

The following duvise reactions with induction too that a second the treated with voriconazole: Blood and Lymphatic System Disorders: anemia, leukopenia, pancytopenia Cardiac Disorders: bradycardia, palpitations, supraventricular tachycardia Eye Disorders: dry eye, keratilis Ear and Labyrinth Disorders: tinnitus, vertigo

Ear and Labyrinin Disorders, unimus, veringo Gastrointestinal Disorders: abdominal tenderness, dyspepsia General Disorders and Administration Site Conditions: asthenia, catheter site pain, chills,

Hepatobiliary Disorders: cholestasis, hyperbilirubinemia, jaundice Immune System Disorders: hypersensitivity, urticaria

I*nfections and Infestations:* conjunctivitis Laboratory Investigations: AST increased, blood creatinine increased, gamma-glutamyl transferase

increased Metabolism and Nutrition Disorders: hypercalcemia, hypermagnesemia, hyperphosphatemia,

hypoglycemia Musculoskel

hypoglycemia Musculoskeletal and Connective Tissue Disorders: arthralgia, myalgia Nervous System Disorders: attaxia, convulsion, dizziness, nystagmus, paresthesia, syncope Psychiatric Disorders: attect lability, agitation, anxiety, depression, insomnia Respiratory Disorders: tonchospasm, nasal congestion, respiratory failure, tachypnea Skin and Subcutaneous Tissue Disorders: alopecia, dermatitis (allergic, contact, and extoliative), pruritus Versultz Disorders: function, oblebitic

Vascular Disorders: flushing, phlebitis

Hepatic-Related Adverse Reactions in Pediatric Patients The frequency of hepatic-related adverse reactions in pediatric patients exposed to voric in therapeutic studies was numerically higher than that of adults (28.6% compared to 24.1%, respectively). The higher frequency of hepatic adverse reactions in the pediatric population was mainly due to an increased frequency of liver enzyme elevations (21.9% in pediatric patients compared to 16.1% in adults), including transaminase elevations (ALT and AST combined) 7.6% in the pediatric patients compared to 5.1% in adults.

Clinical Laboratory Values in Pediatric Patients

The overall incidence of transaminase increases >3x upper limit of normal was 27.2% (28/103) in pediatric and 17.7% (268/1514) in adult patients treated with voriconazole in pooled clinical trials. The majority of abnormal liver function tests either resolved on treatment with or without dose adjustment or after voriconazole discontinuation.

A higher frequency of clinically significant liver laboratory abnormalities, irrespective of baseline laboratory values (>3x ULN ALT or AST), was consistently observed in the combined therapeutic pediatric population (15.5% AST and 22.5% ALT) when compared to adults (12.9% AST and 11.6% ALT). The incidence of bilirubin elevation was comparable between adult and pediatric patients. The incidence of hepatic abnormalities in pediatric patients is shown in Table 9.

Table 9: Incidence of Hepatic Abnormalities in pediatric patients is shown in Table 9. Table 9: Incidence of Hepatic Abnormalities among Pediatric Subjects						
	Criteria	n/N (%)				
Total bilirubin	>1.5x ULN	19/102 (19)				
AST	>3.0x ULN	16/103 (16)				
ALT	>3.0x ULN	23/102 (23)				
Alkaline Phosphatase >3.0x ULN 8/97 (8)						
n = number of patients with a clinically significant abnormality while on study therapy						

N = total number of patients with at least one observation of the given lab test while on study therapy

The following adverse reactions have been identified during post-approval use of voriconazole Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure

Increased risk of skin taxicity with concomitant use of methotrexate, a drug associated with UV reactivation, was observed in postmarketing reports [see Warnings and Precautions (5.6) and Adverse Reactions (6.1)].

Skeletal: fluorosis and periostitis have been reported during long-term voriconazole therapy [see Warnings and Precautions (5.12)].

Eye disorders: prolonged visual adverse reactions, including optic neuritis and papilledema [see Warnings and Precautions (5.4)].

Skin and Appendages: trug reaction with eosinophilia and systemic symptoms (DRESS) has been reported [see Warnings and Precautions (5.5) and Adverse Reactions (6.1)].

Endocrine disorders: adrenal insufficiency, Cushing's syndrome (when voriconazole has been used concomitantly with corticosteroids) [see Warnings and Precautions (5.8)].

riconazole is metabolized by cytochrome P450 isoenzymes, CYP2C19, CYP2C9, and CYP3A4 Voriconazole is metabolized by cytochrome P450 Isoenzymes, CTP2C19, CTP2C9, and CTP3C9. Therefore, inhibitors or inducers of these isoenzymes may increase or decrease voriconazole plasma concentrations, respectively. Voriconazole is a strong inhibitor of CVP3A4, and also inhibits CYP2C19 and CYP2C9. Therefore, voriconazole may increase the plasma concentrations of substances metabolized by these CVP450 isoenzymes.

Tables 10 and 11 provide the clinically significant interactions between voriconazole and other

Voriconazole Plasma Exposure

(Cmax and AUC₊ after

200 mg every 12 hours)

Significantly Reduced

Significantly Reduced

Slight Decrease in AUC_T

Significantly Reduced

Reduced

ot Studied In Vivo or In Vitro

Significant Reduction

but Likely to Result in

but Likely to Result in Significant Reductio

Significantly Reduced

Reduced

Significantly Reduced

Significantly Increased

gnificant Effects of Indinavir of

riconazole Exposure

In Vitro Studies Demonstrate

Voriconazole

Metabolism (Increased Plasma

Exposure) In Vitro Studies Demonstrated

Potential for Inhibition of Voriconazole Metabolism by Delavirdine and Other NNRTIs (Increased Plasma Exposure)

A Voriconazole-Efavirenz Drug

Interaction Study Demonstrated the Potential for the Metabolism

f Voriconazole to be Induced by Efavirenz and Other NNRTIS

1 day, then 200 mg every 12 hours for at least 2 days voriconazole to healthy subject

⁷ Results based on *in vivo* clinical study following repeat oral dosing with 400 mg every 12 hours fo

Table 11:

Effect of Voriconazole on Pharmacokinetics of Other Drugs [see Clinical Pharmacology (12.3)]

Drug Plasma Exposure

 $(C_{max} and AUC_{T})$

Significantly Increased

Significantly Increased

Significantly Increased

Slight Increase in AUC_T

No Significant Effect of

Slight Decrease in Ritonav C_{max} and AUC_{τ}

Not Studied In Vivo or In Vitro.

oriconazole on Rito C_{max} or AUC_τ

nical studies generally following repeat oral dosing with 200 mg every 12

Potential for Inhibition of

inetics [see Clinical Pharmacology (12.3)]

Becommendations for

Voriconazole Dosage

Adjustment/Comments

Contraindicated

Contraindicated

When voriconazole is

dose should be increased t

400 mg every 12 hours and hould be decre

to 300 mg every 24 hours.

Coadministration of

itonavir (100 mg every 12 hou should be avoided, unless ar

o the patient justifies the use

of voriconazole.

Contraindicated

Contraindicated

Increase voriconazole

maintenance dose from maintenance dose from mg/kg to 5 mg/kg IV even 12 hours or from 200 mg to

400 mg orally every 12 hours 100 mg to 200 mg orally ever 12 hours in patients weighing

less than 40 kg). If concomitant administration

of voriconazole with letermu annot be avoided, monitor f reduced effectiveness of voriconazole.

Contraindicated

nitoring for adverse reactions

and toxicity related to priconazole is recommended nen coadministered with oral

contraceptives. Avoid concomitant

nd fluconazole. Monitoring f adverse reactions and toxici

last dose of fluconazole. No dosage adjustment in the

oriconazole dosage needed when coadministered with indinavir.

Frequent monitoring for

lverse reactions and toxicity elated to voriconazole when

quent monitoring for adverse

reactions and toxicity

related to voriconazole

Careful assessment of

Recommendations for

Drug Dosage

Contraindicated

Contraindicated

Contraindicated

When voriconazole is

oriconazole oral maintenan

dose should be increased to 400 mg every 12 hours and

)0 mg every 12 hours an /irenz should be decreased

300 mg every 24 hours. Contraindicated because of

priconazole Cmax and AUCT

Coadministration of

voriconazole and low-dose tonavir (100 mg every 12 hou should be avoided (due to the

and ALIC_T) unless ar

to the patient justifies the use

Contraindicated because of

stered with efavi

Adjustment/Comments

priconazole effectiveness.

tered with other

related to voriconazole is arted within 24 hours after the

/hen coad

azole and low-o

nt of the benefit/ris

conazole oral ma

red with efay

There have been postmarketing reports of pancreatitis in pediatric patients.

Table 10: Effect of Other Drugs on Voriconazole Pharmacoki

AST = Aspartate aminotransferase; ALT = alanine aminotransferase ULN = upper limit of normal

6.2 Postmarketing Experience in Adult and Pediatric Patients

Dermatological Reactions

Adults

Pediatric Patients

DRUG INTERACTIONS

Drug/Drug Class

(Mechanism of Interaction

by the Drug)

Rifabutin* (CYP450 Inductio

Efavirenz (400 mg every 24

urs)**(CYP450 Induc

Efavirénz (300 mg every 24 hours)** (CYP450 Inductior

High-dose Ritonavir (400 me every 12 hours)** (CYP450

Low-dose Ritonavir (100 m every 12 hours)**

(CYP450 Induction)

(CYP450 Induction)

CYP450 Induction)

Long Acting Barbiturates (e.g

nenobarbital, mephobarbita YP450 Induction)

P2C9/2C19 Induction)

St. John's Wort (CYP450

inducer; P-gp inducer) Oral Contraceptives**

ontaining ethinyl estradio

ibition) conazole** (CYP2C9,

CYP2C19 and CYP3A

Other HIV Proteas Inhibitors (CYP3A

CYP3A4 Inhibition or CYP450 Induction)

Results based on in vivi

Drug/Drug Class (Mechanism

of Interaction by Voriconazo

CYP3A4 Inhibition) favirenz (400 mg very 24 hours)** (CYP3A4

Efavirenz (300 mg every 24 hours)** (CYP3A4

CYP3A4 Inhibition)

h-dose Ritona

400 mg every 12 hours)* CYP3A4 Inhibition)

w-dose Ritonavir 00 mg every 12 hours)*

hours voriconazole to healthy subjects

Non-Nucleoside Reverse Transcriptase Inhit

indrone (CYP2C19

PATIENT INFORMATION

Voriconazole (vor" i kon' a zole) for Oral Suspension Read the Patient Information that comes with voriconazole before you start taking it and each time you get a refill There may be new information. This information does not take the place of talking with your healthcare provider about your condition or treatment.

What is voriconazole?

Do not take voriconazole if you:

of ingredients in voriconazole.

pimozide

quinidine

sirolimus

• rifampin

• efavirenz

ritonavir

rifabutin

tolvaptan

naloxegol

• lurasidone

ivabradine

voriconazole

voriconazole.

be right for you.

medicine.

if you take voriconazole.

How should I take voriconazole?

Voriconazole for oral suspension

before or at least 1 hour after meals.

medicine, flavored liquid, or syrup.

blurring or sensitivity to light.

provider if you get sunburn.

• yellowing of your eyes

• changes in the way you see colors

other medicines like methotrexate.

• faster skin aging from the sun

skin rash or your skin rash gets worse.

heart stopping (cardiac arrest).

feeling very tired

blurred vision

skin cancer

may include:

chest tightness

trouble breathing

fever

sweating

feel faint

nausea

skin rash

voriconazole

reactions may include:

rash or hives

itching

flu-like symptoms

nausea or vomiting

itchy skin

healthcare provider tells you to.

if you:

venetoclax

carbamazepine

Voriconazole is a prescription medicine used to treat certain serious fungal infections in your blood and body. These infections are called "aspergillosis," "esophageal candidiasis," "*Scedosporium,*" "*Fusarium,*" and "candidemia".

It is not known if voriconazole is safe and effective in children younger than 2 years old.

are allergic to voriconazole or any of the ingredients in

voriconazole. See the end of this leaflet for a complete list

are taking any of the following medicines:

long-acting barbiturates like phenobarbital

• St. John's Wort (herbal supplement)

healthcare provider or pharmacist.

• ergotamine, dihydroergotamine (ergot alkaloids)

Ask your healthcare provider or pharmacist if you are not

Do not start taking a new medicine without talking to your

Before you take voriconazole, tell your healthcare

provider about all of your medical conditions, including

• have or ever had heart disease, or an abnormal heart rate

or rhythm. Your healthcare provider may order a test to

have low potassium levels, low magnesium levels, and

low calcium levels. Your healthcare provider may do

blood tests before starting and during treatment with

have liver or kidney problems. Your healthcare provider

may do blood tests to make sure you can take

have trouble digesting dairy products, lactose (milk

sugar), or regular table sugar. Voriconazole for oral

are pregnant or plan to become pregnant. Voriconazole

can harm your unborn baby. Talk to your healthcare

provider if you are pregnant or plan to become pregnant.

Women who can become pregnant should use effective

birth control while taking voriconazole. Talk to your healthcare provider about birth control methods that may

• are breastfeeding or plan to breastfeed. It is not known if

voriconazole passes into breast milk. Talk to your

healthcare provider about the best way to feed your baby

Tell your healthcare provider about all the medicines you

take, including prescription and over-the-counter

Voriconazole may affect the way other medicines work, and

Know what medicines you take. Keep a list of them to show

vour healthcare provider or pharmacist when you get a new

Take voriconazole for oral suspension exactly as your

Take voriconazole for oral suspension at least 1 hour

Voriconazole oral suspension will be mixed for you by

your pharmacist. Shake the bottle of voriconazole oral

suspension for 10 seconds each time before you use it.

Only use the oral dispenser that comes with your

voriconazole oral suspension to administer your medicine.

Do not mix voriconazole oral suspension with any other

• If you take too much voriconazole, call your healthcare

provider or go to the nearest hospital emergency room.

You should not drive at night while taking voriconazole.

Voriconazole can cause changes in your vision such as

Do not drive or operate machinery, or do other dangerous

Avoid direct sunlight. Voriconazole can make your skin

sensitive to the sun and the light from sunlamps and

tanning beds. You could get a severe sunburn. Use

sunscreen and wear a hat and clothes that cover your

skin if you have to be in sunlight. Talk to your healthcare

Voriconazole may cause serious side effects including:

liver problems. Symptoms of liver problems may include:

vision changes. Symptoms of vision changes may include:

sensitivity to light or sun (photosensitivity)

Photosensitivity reactions may also increase your risk of:

Call your healthcare provider right away if you get a new

• serious heart problems. Voriconazole may cause

allergic reactions. Symptoms of an allergic reaction

kidney problems. Voriconazole may cause new or worse

problems with kidney function, including kidney failure.

Your healthcare provider should check your kidney

function while you are taking voriconazole. Your

healthcare provider will decide if you can keep taking

serious skin reactions. Symptoms of serious skin

feels like your heart is beating fast (tachycardia)

changes in your heart rate or rhythm, including your

voriconazole can cause serious photosensitivity. There

is an increased chance of skin toxicity while taking

voriconazole. This can happen with or without taking

What are possible side effects of voriconazole?

activities until you know how voriconazole affects you.

What should I avoid while taking voriconazole?

other medicines may affect how voriconazole works.

medicines, vitamins and herbal supplements.

Voriconazole may be prescribed to you as:

suspension contains sucrose (table sugar).

check your heart (EKG) before starting voriconazole.

sure if you are taking any of the medicines listed above.

foriconazole is indicated in adults and pediatric patients (2 years of age and older) for the treatmen f esophageal candidiasis (EC) in adults and pediatric patients 2 years of age and older [see Clinica studies (14.3, 14.5) and Microbiology (12.4)]. 1.4 Scedosporiosis and Fusariosis

Voriconazole is indicated for the treatment of serious fungal infections caused by *Scedosporium* apiospermum (asexual form of *Pseudallescheria boydii*) and *Fusarium spo*. including *Fusarium* solani, in adults and pediatric patients (2 years of age and older) intolerant of, or refractory to, other therapy (see Clinical Studies (14.4) and Microbiology (12.4)]. 1.5 Usage

Voriconazole is indicated in adults and pediatric patients (2 years of age and older) for the treatment of invasive aspergillosis (IA). In clinical trials, the majority of isolates recovered were Aspergillus fumigatus. There was a small number of cases of culture-proven disease due to species of Aspergillus other than A. fumigatus [see Clinical Studies (14.1, 14.5) and Microbiology (12.4)].

Voriconazole is indicated in adults and pediatric patients (2 years of age and older) for the treatment of candidemia in non-neutropenic patients and the following *Candida* infections: disseminated infections in skin and infections in abdomen, kidney, bladder wall, and wounds *[see Clinical Studies* (14.2, 14.5) and *Microbiology* (12.4)].

1.2 Candidemia in Non-neutropenic Patients and Other Deep Tissue Candida Infections

Specimens for fungal culture and other relevant laboratory studies (including histopathology) should be obtained prior to therapy to isolate and identify causative organism(s). Therapy may be instituted before the results of the cultures and other laboratory studies are known. However, once these results become available, antifungal therapy should be adjusted accordingly. DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions for Use in All Patients

Administer Voriconazole Oral Suspension at least one hour before or after a meal

2.3 Recommended Dosing Regimen in Adults Invasive aspergillosis and serious fungal infections due to Fusarium spp. and Scedosporium

See Table 1. Therapy must be initiated with the specified loading dose regimen of intravenou Voriconazole on Day 1 followed by the recommended maintenance dose (RMD) regimer See Table 1. Therapy must be initiated with the specified loading dose regimen of initravehous Voriconazole on Day 1 followed by the recommended maintenance dose (RMD) regimen. Intravenous treatment should be continued for at least 7 days. Once the patient has clinically improved and can tolerate medication given by mouth, the oral tablet form or oral suspension form of Voriconazole may be utilized. The recommended maintenance dose of 200 mg achieves a voriconazole exposure similar to 3 mg/kg intravenously; a 300 mg oral dose achieves an exposure similar to 4 mg/kg intravenously [see Clinical Pharmacology (12.3)].

Candidemia in non-neutropenic patients and other deep tissue Candida infections

See Table 1. Patients should be treated for at least 14 days following resolution of symptoms or t positive culture, whichever is lo

Esophageal Candidiasis See Table 1. Patients should be treated for a minimum of 14 days and for at least 7 days following

Table 1: Recommended Dosing Regimen (Adults)

Infection	Loading Dose	Maintenanc	ance Dose ^{a,b}	
	Intravenous infusion	Intravenous infusion	0ral ^c	
Invasive Aspergillosis ^d	6 mg/kg every 12 hours for the first 24 hours	4 mg/kg every 12 hours	200 mg every 12 hours	
Candidemia in nonneutropenic patients and other deep tissue <i>Candida</i> infections	6 mg/kg every 12 hours for the first 24 hours	3-4 mg/kg every 12 hours ^e	200 mg every 12 hours	
Esophageal Candidiasis	Not Evaluated ^r	Not Evaluated ^r	200 mg every 12 hours	
Scedosporiosis and Fusariosis	6 mg/kg every 12 hours for the first 24 hours	4 mg/kg every 12 hours	200 mg every 12 hours	

^a Increase dose when voriconazole is co-administered with phenytoin or efavirenz (7); Decrease dose ir patients with hepatic impairment (2.5)

In healthy volunteer studies, the 200 mg oral every 12 hours dose provided an exposure (AUC_T) similar to a 3 mg/kg intravenous infusion every 12 hours dose; the 300 mg oral every 12 hours dose provided an exposure (AUC_T) similar to a 4 mg/kg intravenous infusion every 12 hours dose (12).

Adult patients who weigh less than 40 kg should receive half of the oral maintenance dose Adding patients who weigh less than 40 kg should receive that on the oral millentance does. In a clinical study of IA, the median duration of intravenous voriconazole therapy was 10 days (range 2 to 85 days). The median duration of oral voriconazole therapy was 76 days (range 2 to 232 days) (14.1). In clinical trials, patients with candidemia received 3 mg/kg intravenous infusion every 12 hours as primary therapy, while patients with other deep tissue Candida infections received 4 mg/kg every 12 hours as salvage therapy. Appropriate dose should be based on the severity and nature of the infection.

Not evaluated in patients with EC.

Method for Adjusting the Dosing Regimen in Adults

If patient's response is inadequate, the oral maintenance dose may be increased from 200 mg In patients response is induceduate, the oran inflamination busiser how the interaced interaced interaction 200 imig every 12 hours (similar to 3 mg/kg intravenously every 12 hours) to 300 mg every 12 hours. (Similar to 4 mg/kg intravenously every 12 hours). For adult patients weighing less than 40 kg, the oral maintenance dose may be increased from 100 mg every 12 hours to 150 mg every 12 hours. If patient is unable to tolerate 300 mg orally every 12 hours, reduce the oral maintenance dose by 50 mg steps to a minimum of 200 mg every 12 hours, reduce the oral maintenance dose by 50 mg steps to a minimum of 200 mg every 12 hours (or to 100 mg every 12 hours for adult patients weighing less than 40 kg).

If patient is unable to tolerate 4 mg/kg intravenously every 12 hours, reduce the intravenous maintenance dose to 3 mg/kg every 12 hours.

2.4 Recommended Dosing Regimen in Pediatric Patients

The recommended dosing regimen in reutaric ratients The recommended dosing regimen for pediatric patients 2 to less than 12 years of age and 12 to 14 years of age with body weight less than 50 kg is shown in Table 2. For pediatric patients 12 to 14 years of age with a body weight greater than or equal to 50 kg and those 15 years of age and above regardless of body weight, administer the adult dosing regimen of voriconazole [see Dosage and Administration (2.3)].

Table 2: Recommended Dosing Regimen for Pediatric Patients 2 to less than 12 years of age and 12 to 14 years of age with body weight less than 50 kg $^\circ$

	Loading Dose	Maintenan	ce Dose
	Intravenous infusion	Intravenous infusion	Oral
Invasive Aspergillosis*	9 mg/kg every	8 mg/kg every	9 mg/kg every
Candidemia in nonneutropenics and other deep tissue <i>Candida</i> infections [†]	24 hours	first 24 hours	(maximum dose of 350 mg every 12 hours)
Scedosporiosis and Fusariosis			
Esophageal Candidiasis†	Not Evaluated	4 mg/kg every 12 hours	9 mg/kg every 12 hours (maximum dose of 350 mg every 12 hours)

*Based on a population pharmacokinetic analysis in 112 immunocompromised pediatric patients age 2 to less than12 years of age and 26 immunocompromised pediatric patients aged 12 to less than 1 years of age.

* In the Phase 3 clinical trials, patients with IA received intravenous (IV) treatment for at least 6 weeks and up to a maximum of 12 weeks. Patients received IV treatment for at least the first 7 days of therapy and then could be switched to oral voriconazole therapy.

The there could be switched to do a working the other applies the start of the star

Initiate therapy with an intravenous infusion regimen. Consider an oral regimen only after there is a significant clinical improvement. Note that an 8 mg/kg intravenous dose will provide voriconazole exposure approximately 2-fold higher than a 9 mg/kg oral dose. The oral dose recommendation for children is based on studies in which voriconazole was administered as the powder for oral suspension formulation. Bioequivalence between the voriconazole powder for oral suspension and voriconazole tablets has not been investigated in a nerdiatric ponulation pediatric population

Oral bioavailability may be limited in pediatric patients 2 to 12 years with malabsorption and very low body weight for age. In that case, intravenous voriconazole administration is recommended Method for Adjusting the Dosing Regimen in Pediatric Patients

Pediatric Patients 2 to less than 12 years of age and 12 to 14 years of age with body weight less than 50 kg

If patient response is inadequate and the patient is able to tolerate the initial intravenous In patient response is indiceduate and in patient is patient of the data the initiate fuel in the patient response is inadequate and the patient is able to tolerate the oral maintenance dose, the dose may be increased by 1 mg/kg steps or 50 mg steps to a maximum of 350 mg every 12 hours. If patients are unable to tolerate the initial intravenous maintenance dose, reduce the dose by 1 mg/kg steps. If patients are unable to tolerate the initial intravenous maintenance dose, reduce the dose by 1 mg/kg steps. Pediatric patients 12 to 14 years of age weighing greater than or equal to 50 kg and 15 years of age and older regardless of body weight:

Use the optimal method for titrating dosage recommended for adults [see Dosage and Administration

2.5 Dosage Modifications in Patients With Hepatic Impairment Adults

The maintenance dose of voriconazole should be reduced in adult patients with mild to moderate hepatic impairment, Child-Pugh Class A and B. There are no PK data to allow for dosage adjustment recommendations in patients with severe hepatic impairment (Child-Pugh Class C). Duration of therapy should be based on the severity of the patient's underlying disease, recovery

from immunosuppression, and clinical response

Adult patients with baseline liver function tests (ALT, AST) of up to 5 times the upper limit of normal (ULN) were included in the clinical program. Dose adjustments are not necessary for adult patients with this degree of abnormal liver function, but continued monitoring of liver function tests for further elevations is recommended [see Warnings and Precautions (5.1)]. 5.7 Renal Toxicity

The maintenance dose of voriconazole should be increased when co-administered with phenytoin or efavirenz. Use the optimal method for titrating dosage [see Drug Interactions (7) and Dosage and Administration (2) use 2.9 Preparation and Administration of Voriconazole Oral Suspension

2.7 Dosage Adjustment When Co-Administered With Phenytoin or Efavirenz

Tap the bottle to release the powder. Add 46 mL of water to the bottle. Shake the closed bottle tap the bottle characteristic persons reader that whether and the bottle. Leads the characteristic objects update vigorously for about 1 minute. Remove child-resistant cap and push bottle adaptor into the neck of the bottle. Replace the cap. Write the date of expiration of the reconstituted suspension on the bottle label (the shelf-life of the reconstituted suspension is 14 days at controlled room temperature 15°C to 30°C [59°F to 86°F]) Instructions for use

Shake the closed bottle of reconstituted suspension for approximately 10 seconds before each use. The reconstituted oral suspension should only be administered using the oral dispenser supplied with each pack. Incompatibilities

Voriconazole for Oral Suspension and the 40 mg/mL reconstituted oral suspension should not be ixed with any other medication or additional flavoring agent. It is not intended that the suspension be further diluted with water or other vehicles.

DOSAGE FORMS AND STRENGTHS

Powder for Oral Suspension

Voriconazole for oral suspension is supplied in 100 mL high density polyethylene (HDPE) bottles. Each bottle contains 49 g of powder for oral suspension. Following reconstitution, the volume of the suspension is 75 mL, providing a usable volume of 70 mL (40 mg voriconazole/mL). A 5 mL oral dispenser and a press-in bottle adaptor are also provided. 4 CONTRAINDICATIONS

Voriconazole is contraindicated in patients with known hypersensitivity to voriconazole or its excipients. There is no information regarding cross-sensitivity between voriconazole and other azole antifungal agents. Caution should be used when prescribing voriconazole to patients with hypersensitivit to other cache. hypersensitivity to other azoles.

Coadministration of pimozide, quinidine or ivabradine with voriconazole is contraindicated because increased plasma concentrations of these drugs can lead to QT prolongation and rare occurrences of *torsade de pointes* [see Drug Interactions (7)]. Coadministration of voriconazole with sirolimus is contraindicated because voriconazole significantly increases sirolimus concentrations [see Drug Interactions (7) and Clinical Pharmacology (12.3)].

Coadministration of voriconazole with rifampin, carbamazepine, and long-acting barbiturate and St John's Wort is contraindicated because these drugs are likely to decrease plasma voriconazole concentrations significantly [see Drug Interactions (7) and Clinical Pharmacology (12.3)].

Coadministration of standard doses of voriconazole with efavirenz doses of 400 mg every 24 hours or higher is contraindicated, because efavirenz significantly decreases plasma voriconazole concentrations in healthy subjects at these doses. Voriconazole also significantly increases efavirenz plasma concentrations [see Drug Interactions (7) and Clinical Pharmacology (12.3)].

 Coadministration of voriconazole with high-dose ritonavir (400 mg every 12 hours) is contraindicated because ritonavir (400 mg every 12 hours) significantly decreases plasma voriconazole concentrations. Coadministration of voriconazole and low-dose ritonavir (100 mg every 12 hours) should be avoided, unless an assessment of the benefitrisk to the patient justifies the use of voriconazole [see Drug Interactions (7) and Clinical Pharmacology (12.3)]. Coadministration of voriconazole with rifabutin is contraindicated since voriconazole significantly increases rifabutin plasma concentrations and rifabutin also significantly decreases voriconazole plasma concentrations [see Drug Interactions (7) and Clinical Pharmacology (12.3)].

Coadministration of voriconazole with ergot alkaloids (ergotamine and dihydroergotamine) is contraindicated because voriconazole may increase the plasma concentration of ergot alkaloids, which may lead to ergotism [see Drug Interactions (7)].

Coadministration of voriconazole with naloxeool is contraindicated because voriconazole may ncrease plasma concentrations of naloxegol which may precipitate opioid withdrawal symptoms [see Drug Interactions (7)]

Coadministration of voriconazole with tolvaptan is contraindicated because voriconazole may increase tolvaptan plasma concentrations and increase risk of adverse reactions Isee Druc Interactions (7)

Coadministration of voriconazole 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 Drug Interactions (7)].

 Coadministration of voriconazole with lurasidone is contraindicated since it may result in ignificant increases in lurasidone exposure and the potential for serious adverse reactions [see Drug Interactions (7)

WARNINGS AND PRECAUTIONS

5.1 Hepatic Toxicity

In clinical trials, there have been uncommon cases of serious hepatic reactions during treatment with voriconazole (including clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities). Instances of hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly hematological malignancy). Hepatic reactions, including hepatitis and jaundice, have occurred among patients with no other identifiable risk factors. Liver dysfunction has usually been reversible on discontinuation of therapy [see Adverse Reactions (6 11) Reactions (6.1)].

A higher frequency of liver enzyme elevations was observed in the pediatric population (see A higher frequency of liver enzyme elevations was observed in the pediatric population *[see Adverse Reactions (6.1)]*. Hepatic function should be monitored in both adult and pediatric patients. Measure serum transaminase levels and bilrubin at the initiation of voriconazole therapy and monitor at least weekly for the first month of treatment. Monitoring frequency can be reduced to monthly during continued use if no clinically significant changes are noted. If liver function tests become markedly elevated compared to baseline, voriconazole should be discontinued unless the medical judgment of the benefit/risk of the treatment for the patient justifies continued use *[see Dosage and Administration (2.5) and Adverse Reactions (6.1)]*.

5.2 Arrhythmias and QT Prolongation

5.2 Armyninias and of Prolongation Some azoles, including voriconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During clinical development and post-marketing surveillance, there have been rare cases of arrhythmias, (including ventricular arrhythmias such as torsade de pointes), cardiac arrests and sudden deaths in patients taking voriconazole. These cases usually involved seriously ill patients with multiple confounding risk factors, such as history of cardiotoxic chemotherapy, cardiomyopathy, hypokalemia and concomitant medications that may have been contributory. Voriconazole should be administered with caution to patients with potentially proarrhythmic onditions, such as:

Congenital or acquired QT prolongation

 Cardiomyopathy, in particular when heart failure is present Sinus bradycardia

• Existing symptomatic arrhythmias

Concomitant medicinal product that is known to prolong QT interval [see Contraindications (4), Drug Interactions (7), and Clinical Pharmacology (12.3)] Rigorous attempts to correct potassium, magnesium and calcium should be made before starting and during voriconazole therapy [see Clinical Pharmacology (12.3)].

5.3 Infusion Related Reactions

During infusion of the intravenous formulation of voriconazole in healthy subjects, anaphylactoid-type

reactions, including flushing, fever, sweating, tachycardia, chest tightness, dyspnea, faintness, nausea, pruritus and rash, have occurred uncommonly. Symptoms appeared immediately upon initiating the infusion. Consideration should be given to stopping the infusion should these reactions occur. 5.4 Visual Disturbances

The effect of voriconazole on visual function is not known if treatment continues beyond 28 days. There have been post-marketing reports of prolonged visual adverse reactions, including optic neuritis and papilledema. If treatment continues beyond 28 days, visual function including visual acuity, visual field, and color perception should be monitored [see Adverse Reactions (6.2]). 5.5 Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCARs), such as Stevens-Johnson syndrome (SJS)

pidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), hich can be life-threatening or fatal, have been reported during treatment with voriconazole. If a natient develops a severe cutaneous adverse reaction, voriconazole should be discontinued [see Adverse Reactions (6.1, 6.2)].

5.6 Photosensitivity

Voriconazole has been associated with photosensitivity skin reaction. Patients, including pediatric patients, should avoid exposure to direct sunlight during voriconazole treatment and should use measures such as protective clothing and sunscreen with high sun protection factor (SPF). If phototoxic reactions occur, the patient should be referred to a dermatologist and voriconazole discontinuation should be considered. If voriconazole is continued despite the occurrence of phototoxicity-related lesions, dermatologic evaluation should be performed on a systematic and regular basis to allow early detection and management of premalignant lesions. Squamous cell carcinoma of the skin (including cutaneous SCC *in situ*, or Bowen's disease) and melanoma have been reported during long-term voriconazole therapy in patients with photosensitivity skin reactions. If a patient develops a skin lesion consistent with premalignant skin lesions, squamous cell cell carcinoma or melanoma, voriconazole should be discontinued. In addition, voriconazole has been associated with photosensitivity related skin reactions such as pseudoporphyria, chellitis, and cutaneous lupus erythematosus, as well as increased risk or skin toxicity with concomitant use of methotrexate, a drug associated with ultraviolet (UV) reactivation. There is the potential for this risk to be observed with other drugs associated with UV reactivation. Patients should avoid strong, direct sunlight during voriconazole has p. Voriconazole has been associated with photosensitivity skin reaction. Patients, including pediatric strong, direct sunlight during voriconazole therapy.

Ing. uncet sumption during voirconazore merapy. Frequency of phototoxicity reactions is higher in the pediatric population. Because squamous I carcinoma has been reported in patients who experience photosensitivity reactions, stringent asures for photoprotection are warranted in children. In children experiencing photoaging rises such as lentigines or ephelides, sun avoidance and dermatologic follow-up are ommended even after treatment discontinuation.

1 (0.8) 3 (1.5) 88 (5.3) 20 (4.3) 7 (3.8) 1 (0.5) 10 (0.6) 6 (1.3) 40 (21.6) 9 (6.9) 1 (0.5) 1 (0.5) ute kidney failure 7 (0.4) 2 (0.4) 11 (5.9) 7 (5.3) Study 307/602: IA; Study 608: candidemia; Study 30 Studies 303, 304, 305, 307, 309, 602, 603, 604, 608 v 305: EC

39 (2.4) 13 (2.8) 1 (0.5)

ifungal therapy

4 (0.2)

cin B followed by other lice ings and Precautions (5.4)

increased SGOT increased

lervous System

Skin and Appendages

nine increasec

Vis<u>ual Disturbances</u> onazole treatment-related visual disturbances are common. In therapeutic trials, approxir 21% of patients experienced abnormal vision, color vision change and/or photophobia. Visual disturbances may be associated with higher plasma concentrations and/or doses. The mechanism of action of the visual disturbance is unknown, although the site of action is most likely to be within the retina. In a study in healthy subjects investigating the effect of 28-day treatment with voriconazole on retinal function, voriconazole caused a decrease in the electroretinogram (ERG) waveform amplitude, a decrease in the visual field, and an alteration in color perception. The ERG measures electrical currents in the retina. These effects were noted early in administration of voriconazole and continued through the course of study drug treatment.

early in administration of vorticonazole and continued through the course of study drug treatment. Fourteen days after the end of dosing, ERG, visual fields and color perception returned to normal [see Warnings and Precautions (5.4)]. Dermatological Reactions

Dermatological reactions were common in patients treated with voriconazole. The mechanism underlying these dermatologic adverse reactions remains unknown.

Underlying these dermatologic adverse reactions remains unknown. Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported during treatment with voriconazole. Erythema multiforme has also been reported during treatment with voriconazole (see Warnings and Precautions (5.5) and Adverse Reactions (6.2)). Voriconazole has also been associated with additional photosensitivity related skin reactions such as pseudoporphyria, chellitis, and cutaneous lupus crythematosus [see Warnings and Precautions (5.6) and Adverse Reactions (6.2)]. Less Common Adverse Reactions

Less Common Adverse Reactions The following adverse reactions occurred in <2% of all voriconazole-treated patients in all therapeutic studies (N=1655). This listing includes events where a causal relationship to voriconazole cannot be ruled out or those which may help the physician in managing the risks to the patients. The list does not include events included in Table 4 above and does not include every event reported in the voriconazole clinical program. Body as a Whole: abdominal pain, abdomen enlarged, allergic reaction, anaphylactoid reaction [see Warnings and Precautions (5.3)], ascites, asthenia, back pain, chest pain, cellulitis, edema, tace edema, flank pain, flu syndrome, graft versus host reaction, granuloma, infection, bacterial infection, fungal infection, injection site pain, injection site infection/inflammation, muccus membrane disorder, multi-organ failure, pain, pelvic pain, peritonitis, sepsis, substernal chest pain, chest pain (actriovascular, atiai a trivthythmia, atrial fibrillation. AV block complete, bioeminy, bradvcardia.

Cardiovascular: atrial arrhythmia, atria fibrillation, AV block complete, bigeminy, bradycardia, bundle branch block, cardiomegaly, cardiomyopathy, cerebral hemorrhage, cerebral acchemia, cerebrovascular accident, congestive heart failure, deep thrombophebitis, endocarditis, extrasystoles, heart arrest, hypertension, hypotension, myocardial infarction, noda arrhythmia, appliptation, philebitis, postural hypotension, pulmonary embolus, DT interval prolonged, supraventricular extrasystoles, supraventricular tachycardia, syncope, thrombophebitis, extrasystole, the supraventice of the supraventicular tachycardia, syncope, thrombophebitis, supraventricular, extrasystoles, supraventricular tachycardia, syncope, thrombophebitis, provident and the supraventice of vasodilatation, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia (including torsade de pointes) [see Warnings and Precautions (5.2)].

Digestive: anorexia, cheilitis, cholecystitis, cholelithiasis, constipation, diarrhea, duodenal ulcer perforation, duodentiis, dyspepsia, dysphagia, dry mouth, esophageal ulcer, esophagits, flatulence, gastroenteritis, gastrointestinal hemorrhage, GGT/LDH elevated, gingivitis, glossitis, gum hemorrhage, gum hyperplasia, hematemesis, hepatic coma, hepatic failure, hepatitis, intestinal perforation intestinal ulcer, jaundice, enlarged liver, melena, mouth ulceration, pancreatitis, parotid gland integrated under sensitive and the sensitive meteric and the sensitive contest in a perforation integrated under and the sensitive and the sensitive sensitive contest in a performance integrated under and the sensitive and the sensitive sensitive contest in a performance integrated and the sensitive sensitive sensitive sensitive sensitive integrated and the sensitive sensitive sensitive sensitive integrated and the sensitive sensitive sensitive sensitive integrated and the sensitive sensitive sensitive integrated and the sensitive sensitive sensitive integrated and the sensitive sensitive integrated and the sensitive sensitive sensitive integrated and the sensitive sensitive integrated and the sensitive sensitive sensitive integrated and the sensitive sensitive sensitive sensitive integrated and the sensitive sensitive sensitive integrated and the sensitive sensitive sensitive sensitive sensitive sensitive sensitive sensitive integrated and the sensitive se enlargement, periodontitis, proctitis, pseudomembranous colitis, rectal disorder, rectal hemorrhage, stomach ulcer, stomatitis, tongue edema.

Endocrine: adrenal cortex insufficiency, diabetes insipidus, hyperthyroidism, hypothyroidism. Hemic and Lymphatic: agranulocytosis, anemia (macrocytic, megaloblastic, microcytic, normocytic), aplastic anemia, hemolytic anemia, bleeding time increased, cyanosis, DIC, ecchymosis, eosinophilia, hypervolemia, leukopenia, lymphadenopathy, lymphangitis, marrow depression, pancytopenia, petechia, purpura, enlarged spleen, thrombocytopenia, thrombotic thrombocytopenic purpura. Metabolic and Nutritional: albuminuria, BUN increased, creatine phosphokinase increased, edema ose tolerance decreased, hypercalcemia, hypercholesteremia, hyperglycemia, hyperkalemia, rmagnesemia, hypernatremia, hyperuricemia, hypocalcemia, hypoglycemia, hypomagnesemia, natremia, hypophosphatemia, peripheral edema, uremia. glucose tolerance decreased, hypercalcemia, hyperchol

Musculoskeletal: arthralgia, arthritis, bone necrosis, bone pain, leg cramps, myalgia, myasthenia

Nervous System: abnormal dreams, acute brain syndrome, agitation, akathisia, amnesia, anxiety Nervous System, antonna dreams, acute trian syndrome, agriculton, akalinsta, annesa, ankery, ataxia, brain edema, coma, confusion, convulsion, delirium, dementia, depersonalization, depression, diplopia, dizziness, encephalitis, encephalopathy, euphoria, Extrapyramidal Syndrome, grand mal convulsion, Guillain-Barré syndrome, hypertonia, hypesthesia, insomnia, intracranial hypertension, libido decreased, neuralgia, neuropathy, nystagmus, oculogyric crisis, paresthesia, psychosis, somolence, suicidal ideation, tremor, vertigo.

Respiratory System: cough increased, dyspnea, epistaxis, hemoptysis, hypoxia, lung edema, pharyngitis, pleural effusion, pneumonia, respiratory disorder, respiratory distress syndrome, respiratory tract infection, rhinitis, sinusitis, voice alteration.

Skin and Appendages: alopecia, angioedema, contact dermatitis, discoid lupus erythematosis, eczema, erythema multiforme, exfoliative dermatitis, fixed drug eruption, furunculosis, herpes simplex, maculopapular rash, melanoma, melanosis, photosensitivity skin reaction, pruritus, pseudoporphyria, psoriasis, skin discoloration, skin disorder, skin dry, Stevens-Johnson syndrome, squamous cell carcinoma (including cutaneous SCC *in situ*, or Bowen's disease), sweating, toxic rmal necrolysis, urticaria.

Special Senses: abnormality of accommodation, blepharitis, color blindness, conjunctivitis, corneal opacity, deafness, ear pain, eye pain, eye hemorrhage, dry eyes, hypoacusis, keratitos, keratoconjunctivitis, mydriasis, night blindness, optic atrophy, optic neuritis, otitis externa, papilledema, retinal hemorrhage, retinitis, scleritis, taste loss, taste perversion, tinnitus, uveitis, visual field refert. visual field defec

Urogenital: anuria, blighted ovum, creatinine clearance decreased, dysmenorrhea, dysuria eriddymitis, glycosuria, hemorrhagic cystitis, hematuria, hydronephrosis, impotence, kidney kidney tubular necrosis, metrorrhagia, nephritis, nephrosis, oliguria, scrotal edema, ur incontinence, urinary retention, urinary tract infection, uterine hemorrhage, vaginal hemorrh Clinical Laboratory Values in Adults

The overall incidence of transaminase increases >3x upper limit of normal (not necessarily comprising an adverse reaction) was 17.7% (268/1514) in adult subjects treated with voriconazole for therapeutic use in pooled clinical trials. Increased incidence of liver function test abnormalities may be associated with higher plasma concentrations and/or doses. The majority of abnormal liver function tests either resolved during treatment without dose adjustment or resolved following dose adjustment, including discontinuation of therapy.

Voriconazole has been infrequently associated with cases of serious hepatic toxicity including cases of jaundice and rare cases of hepatitis and hepatic failure leading to death. Most of these reliests here determine underking randitions.

patients had other serious underlying conditions. Liver function tests should be evaluated at the start of and during the course of voriconazole therapy. Patients who develop abnormal liver function tests during vorticonazole therapy should be monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of vorticonazole must be considered if clinical signs and symptoms consistent with liver disease develop that may be attributable to voriconazole (*see Warnings and Precautions (5.1*)]. Acute real failure has been observed in severely ill patients undergoing treatment with voriconazole. Patients being treated with voriconazole are likely to be treated concomitantly with nephrotoxic medications and may have concurrent conditions that can result in decreased renal function. It is recommended that patients are monitored for the development of abnormal renal function. This should include laboratory evaluation of serum creatinine.

Tunction. This should include laboratory evaluation of serum creatinine. Tables 5 to 7 show the number of patients with hypokalemia and clinically significant changes in renal and liver function tests in three randomized, comparative multicenter studies. In study 305, patients with EC were randomized to either oral voriconazole or oral fluconazole. In study 307/602, patients with definite or probable IA were randomized to either voriconazole or amphotericin B therapy. In study 608, patients with candidemia were randomized to either voriconazole or the regimen of amphotericin B followed by fluconazole.

Criteria*

Criteria*

 AST
 >3.0x ULN

 ALT
 >3.0x ULN

 Alkaline Phosphatase
 >3.0x ULN

*Without regard to baseline value

III N – upper limit of normal

>1.5x ULN

Table 5: Protocol 305 – Patients with Esophageal Candidiasis Clinically Significant Laboratory Test Abnormalities Voriconazole

n/N (%)

8/185 (4.3)

<u>38/187 (20.3)</u> 20/187 (10.7) 19/187 (10.2)

Fluconazole

n /N (%)

7/186 (3.

15/186 (8.1 12/186 (6.5 14/186 (7.5

Amphotericin B**

It is recommended that the recommended voriconazole loading dose regimens be used, but that the maintenance dose be halved in adult patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B) [see Clinical Pharmacology (12.3)].

Voicionazole has not been studied in adult patients with severe hepatic cirrhosis (Child-Pugh Class C) or in patients with chronic hepatitis B or chronic hepatitis C disease. Voriconazole has been associated with elevations in liver function tests and with clinical signs of liver damage, such as jaundice. Voriconazole should only be used in patients with severe hepatic impairment if the benefit outweights the potential risk. Patients with hepatic impairment must be carefully monitored for drug toxicity.

Pediatric Patients

Dosage adjustment of vorionazole in pediatric patients with hepatic impairment has not been established [see Use in Specific Populations (8.4)].
 2.6 Dosage Modifications in Patients With Renal Impairment

Adult Patients

The pharmacokinetics of orally administered voriconazole are not significantly affected by renal impairment. Therefore, no adjustment is necessary for <u>oral</u> dosing in patients with mild to severe renal impairment [see Clinical Pharmacology (12.3)].

Acute renal failure has been observed in patients undergoing treatment with voriconazole. Patients being treated with voriconazole are likely to be treated concomitantly with nephrotoxic medications and may have concurrent conditions that may result in decreased renal function.

Patients should be monitored for the development of abnormal renal function. This should include laboratory evaluation of serum creatinine [see Clinical Pharmacology (12.3) and Dosage and Administration (2.6)].

5.8 Adrenal Dysfunction

5.6 Aurenal Dystanticum Reversible cases of azole-induced adrenal insufficiency have been reported in patients receiving azoles, including voriconazole. Adrenal insufficiency has been reported in patients receiving azoles with or without concomitant corticosteroids. In patients receiving azoles without corticosteroids adrenal insufficiency is related to direct inhibition of steroidogenesis by azoles. In patients taking corticosteroids, voriconazole associated CYP3A4 inhibition of their metabolism may lead to corticosteroid excess and adrenal suppression [see Drug Interactions (7) and Clinical Pharmacology (12.3)]. Cushing's syndrome with and without subsequent adrenal insufficiency has also been reported in patients receiving voriconazole concomitantly with corticosteroids.

Patients receiving voriconazole and corticosteroids (via all routes of administration) should be carefully monitored for adrenal dysfunction both during and after voriconazole treatment. Patients should be instructed to seek immediate medical care if they develop signs and symptoms of Cushing's syndrome or adrenal insufficiency.

	ontona	001001102010	Amphotoriom D
		n/N (%)	n/N (%)
T. Bilirubin	>1.5x ULN	35/180 (19.4)	46/173 (26.6)
AST	>3.0x ULN	21/180 (11.7)	18/174 (10.3)
ALT	>3.0x ULN	34/180 (18.9)	40/173 (23.1)
Alkaline Phosphatase	>3.0x ULN	29/181 (16.0)	38/173 (22.0)
Creatinine	>1.3x ULN	39/182 (21.4)	102/177 (57.6)
Potassium	<0.9x LLN	30/181 (16.6)	70/178 (39.3)

Norman regard to assemble value n = number of patients with at clinically significant abnormality while on study therapy N = total number of patients with at least one observation of the given lab test while on study therapy AST = Aspartate aminotransferase; ALT= alanine aminotransferase IUN = uncertimit of exercise

Table 6: Protocol 307/602 - Primary Treatment of Invasive Aspergillosis Clinically Significant

Laboratory Test Abnormalities

Voriconazole

*Without regard to baseline value

Bilirubin

Amphotericin B followed by other licensed antifungal therapy = number of patients with a clinically significant abnormality while on study therapy = total number of patients with a tleast one observation of the given lab test while on study therapy = Aspartate aminotransferase; ALT = alanine aminotransferase AST = Aspartate an ULN = upper limit of normal LLN = lower limit of normal

Table 7: Protocol 608 – Treatment of Candidemia Clinically Significant Laboratory Test Abnormalities

	Criteria*	Voriconazole	Amphotericin B followed by Fluconazole
Biliruhin	>1.5x III N	<u> </u>	<u>n/N (%)</u> 31/115 (27 0)
ST	>3.0x ULN	40/261 (15.3)	16/116 (13.8)
LT	>3.0x ULN	22/261 (8.4)	15/116 (12.9)
Ikaline Phosphatase	>3.0x ULN	59/261 (22.6)	26/115 (22.6)
reatinine	>1.3x ULN	39/260 (15.0)	32/118 (27.1)
otassium	<0.9x LLN	43/258 (16.7)	35/118 (29.7)

Quinidine, Ivabradine (CYP3A4 Inhibition)	but Drug Plasma Exposure Likely to be Increased	potential for QT prolongation and rare occurrence of <i>torsade</i> <i>de pointes</i> .
Ergot Alkaloids (CYP450 Inhibition)	Not Studied <i>In Vivo</i> or <i>In Vitro</i> , but Drug Plasma Exposure Likely to be Increased	Contraindicated
Naloxegol (CYP3A4 Inhibition)	Not Studied <i>In Vivo</i> or <i>In Vitro</i> , but Drug Plasma Exposure Likely to be Increased which may Increase the Risk of Adverse Reactions	Contraindicated
Tolvaptan (CYP3A4 Inhibition)	Although Not Studied Clinically, Voriconazole is Likely to Significantly Increase the Plasma Concentrations of Tolvaptan	Contraindicated
Venetoclax (CYP3A4 Inhibition)	Not Studied <i>In Vivo</i> or <i>In Vitro</i> , but Venetoclax Plasma Exposure Likely to be Significantly Increased	Coadministration of voriconazole is contraindicated at initiation and during the ramp-up phase in patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). Refer to the venetoclax labeling for safety monitoring and dose reduction in the steady daily dosing phase in CLL/SLL patients.

mouth sores • blistering or peeling of your skin trouble swallowing or breathing • adrenal gland problems: • Voriconazole may cause reduced adrenal function (adrenal insufficiency). • Voriconazole may cause overactive adrenal function (Cushing's syndrome) when voriconazole is used at the same time with corticosteroids. Symptoms of adrenal insufficiency include: o feeling tired o lack of energy o nausea and vomiting o weakness o feeling dizzy or lightheaded o weight loss

o abdominal pain

11/17/2022 03:54 PM / NP Item# NOVE-NP 750293 / page 1 of 2

	РАК			
IT'S OUR NATURE TO 500 Walnut Street Norwoo	PROTECT ™ d NJ 07648	Proof Date: 11/17/2022	Proof Time: 03:54 PM	Prepared by: jeanb
NP Item#: NOVE-NP_750293		Size: 17 x 26.375 (folded: 1.562 x 1.75)		<i>Type size</i> : 6pt/10 pt
PO No.:		Item Iss./Rev. Date: Rev. 11/2022		Cust. Part No.: 271523
Customer: Novel	F L	Private Label:	Lupin Description: Voriconazole Tabs for C	
Bar code details: Type: UPC-A	Code: 43386-03	38-60		
Notes:				
_ Approved				
Resubmit	Signature:		Da	te:

Symptoms of Cushing's syndrome include: o fatty hump between the o weight gain shoulders (buffalo hump) and a rounded face (moon face) o darkening of the skin o thinning skin on the stomach, thighs, breasts, and arms o bruising easily o high blood sugar o excessive hair growth o excessive sweating bone problems. Voriconazole may cause weakening of bones and bone pain. Tell your healthcare provider if you have bone pain. Call your healthcare provider or go to the nearest hospital emergency room right away if you have any of the symptoms listed above. The most common side effects of voriconazole in adults include: • vision changes rash vomiting • nausea headache • fast heart beat (tachycardia) hallucinations (seeing • abnormal liver function tests or hearing things that • fever chills are not there) The most common side effects of voriconazole in children include: fever stomach pain nose bleeds diarrhea high blood pressure • low blood potassium levels low platelet counts cough Inflammation of mucous
 abnormal liver function tests membranes low blood pressure • low blood calcium levels constipation • high blood sugar levels • low blood magnesium levels vision changes low blood phosphate levels rash headache • fast heart beat (tachycardia) • Fullness of the stomach • vomiting area nausea • swelling in the arms and legs • hallucinations (seeing or hearing things that are not there) coughing up blood upper respiratory tract infection Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of voriconazole. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. How should I store voriconazole? Store voriconazole oral suspension at room temperature, 59°F to 86°F (15°C to 30°C). Do not refrigerate or freeze. · Voriconazole suspension should be thrown away (discarded) after 14 days. Keep voriconazole for oral suspension in a tightly closed container. • Safely throw away medicine that is out of date or no longer needed. • Keep voriconazole, as well as all other medicines, out of the reach of children. General information about the safe and effective use of voriconazole Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use voriconazole for a condition for which it was not prescribed. Do not give voriconazole to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about voriconazole that is written for health professionals.

ug/Drug Class (Mechanism Interaction by Voriconazole)	Drug Plasma Exposure	Recommendations for	aged 2 to less than 12 [N=26] and aged 12 to less than 18 [N=79] from two, non-comparative Phase 3 pediatric studies and eight adult therapeutic trials provided safety information for
		Adjustment/Comments For patients with acute myeloid leukemia (AML), dose reduction	Indee to pound should also and a start of the population (see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies in population (see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and clinical Studies in pediatric nations, below the are of 2 years has not been established.
		and safety monitoring are recommended across all dosing phases when coadministering	Therefore, voriconazole is not recommended for pediatric patients less than 2 years of age. A higher frequency of liver enzyme elevations was observed in the pediatric patients <i>[see Dosage</i> and Administration (2.5). Warrings and Precautions (5.1). and Adverse Reactions (6.1).
		voriconazole with venetoclax. Refer to the venetoclax prescribing information for dosing instructions.	The frequency of phototoxicity reactions is higher in the pediatric population. Squamous cell carcinoma has been reported in patients who experience photosensitivity reactions. Stringent measures for photoprotection are warranted. Sun avoidance and dermatologic follow-up are
nborexant (CYP3A4 libition)	Not Studied <i>In Vivo</i> or <i>In Vitro</i> , but Drug Plasma Exposure Likely to be Increased	Avoid concomitant use of Voriconazole with lemborexant.	recommended in pédiatric patients experiencing photoaging injuries, such as lentigines or ephelides, even after treatment discontinuation <i>(see Warnings and Precautions (s.6))</i> . Voriconazole has not been studied in pediatric patients with hepatic or renal impairment <i>[see</i>
isdegib (CYP3A4 iibition)	Not Studied <i>In Vivo</i> or <i>In Vitro</i> , but Drug Plasma Exposure Likely to be Increased	Consider alternative therapies. If concomitant use cannot be avoided, monitor patients for	Dosage and Administration (2.5, 2.6)]. Hepatic function and serum creatinine levels should be closely monitored in pediatric patients [see Dosage and Administration (2.6) and Warnings and Precautions (5.1, 5.10)].
raging kingga inhihitara	Not Studied In Vive or In Vite	increased risk of adverse reactions including QTc interval prolongation.	8.5 Geriatric Use In multiple dose therapeutic trials of voriconazole, 9.2% of patients were ≥65 years of age and 1.8% of patients were ≥75 years of age. In a study in healthy subjects, the systemic exposure
cluding but not limited to tinib, bosutinib,	but Drug Plasma Exposure Likely to be Increased	Voriconazole. If concomitant use cannot be avoided, dose reduction of the tyrosine kinase	(AUC) and peak plasma concentrations (C _{max}) were increased in elderly males compared to young males. Pharmacokinetic data obtained from 552 patients from 10 voriconazole thrapeutic trials showed that voriconazole plasma concentrations in the elderly patients were approximately 80%
bimetinib, dabrafenib, satinib, nilotinib, nitinib, ibrutinib,		inhibitor is recommended. Refer to the prescribing information for the relevant product.	to 90% higher than those in younger patients after either IV or oral administration. However, the overall safety profile of the elderly patients was similar to that of the young so no dosage adjustment is recommended [see <i>Clinical Pharmacology</i> (12.3)].
ociclib) /P3A4 Inhibition)	Not Ctudied In Vive or In Vitro	Controindicated	10 OVERDOSAGE In clinical trials, there were three cases of accidental overdose. All occurred in pediatric patients who received up to five times the recommended intravenous dose of voriconazole. A single adverse
ibition)	but Voriconazole is Likely to Significantly Increase the Plasma Concentrations of	Contramuicateu	reaction of photophobia of 10 minutes duration was reported. There is no known antidote to voriconazole. Voriconazole is hemodialyzed with clearance of 121 ml /min. The intravenous vehicle. SBECD is
closporine* (P3A4 Inhibition)	AUC _T Significantly Increased;	When initiating therapy with voriconazole in patients already	For the interview of
,	No Significant Effect on C _{max}	receiving cyclosporine, reduce the cyclosporine dose to one-half of the starting dose and follow	Voriconzole, an azole antifungal agent is available as a lyophilized powder for oral suspension. The structural formula is:
		cyclosporine blood levels. Increased cyclosporine levels have been associated with	N CH- F
		nephrotoxicity. When voriconazole is discontinued, cyclosporine concentrations	
thadana***		must be frequently monitored and the dose increased as necessary.	
(P3A4 Inhibition)	Increased	concentrations of methadone have been associated with toxicity including QT	I F Voriconazole is designated chemically as (2R,3S)-2-(2,4-diffuorophenyl)-3-(5-fluoro-4- pyrimidinyl)-
		prolongation. Frequent monitoring for adverse reactions and toxicity related to mothedana is recommended	1-(1H-1,2,4 triazol-1-yl)-2-butanol with an empirical formula of C1 ₆ H1 ₄ F ₃ N ₅ O and a molecular weight of 349.3. Voriconazole drug substance is a white to almost white powder.
		during coadministration. Dose reduction of methadone may be needed.	Voriconazole for oral suspension is a white to off-white powder providing a white to off-white orange-flavored suspension when reconstituted. Bottles containing 49 g powder for oral suspension are intended for reconstitution with water to produce a suspension containing 40 mo/mL
ntanyl (CYP3A4 libition)	Increased	Reduction in the dose of fentanyl and other long-acting opiates metabolized by	voriconazole. The inactive ingredients include colloidal silicon dioxide, titanium dioxide, xanthan gum, sodium citrate dihydrate, sodium benzoate, anhydrous citric acid, natural and artificial orange flavor, and sucrose.
		CYP3A4 should be considered when coadministered with voriconazole. Extended and frequent monitoring for opiate-	12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action Vericeographic is an actifunged drug <i>(and Missobiology (12.4)</i>)
entanil (CYP3A4	Significantly Increased	associated adverse reactions may be necessary. An increase in the incidence	12.2 Pharmacodynamics Exposure-Response Relationship For Efficacy and Safety
ibition)	Significantly increased	of delayed and persistent alfentanil-associated nausea and vomiting were observed when	In 10 clinical trials (N=1121), the median values for the average and maximum voriconacle plasma concentrations in individual patients across these studies was 2.51 µg/mL (inter-quartile range 1.21 to 4.44 µg/mL) and 3.79 µg/mL (inter-quartile range 2.06 to 6.31 µg/mL), respectively. A
		voriconazole. Reduction in the dose of alfentanil and other opiates metabolized by CYP3A4	pharmacokinetic-pharmacodynamic analysis of patient data from 6 of these 10 clinical trails (N=280) could not detect a positive association between mean, maximum or minimum plasma vorisonazole concentration and efficacy. However, pharmacokinetic/pharmacodynamic analyses of the date for out 4 mini ad using data trained and the second second and the second second and the second s
		(e.g., sufentanil) should be considered when coadministered with voriconazole. A longer period	or the data from all to clinical transition interfunction between plasma vonconazole concentrations and rate of both liver function test abnormalities and visual disturbances [see Adverse Reactions (6)].
(0)/0044		for monitoring respiratory and other opiate-associated adverse reactions may be necessary.	<u>Cardiac Electrophysiology</u> A placebo-controlled, randomized, crossover study to evaluate the effect on the QT interval of healthy male and female subjects was conducted with three single oral doses of voriconazole and
vcodone (CYP3A4 iibition)	Significantly Increased	Increased visual effects (heterophoria and miosis) of oxycodone were observed when coadministered with voriconazole	ketoconazole. Serial EUGs and plasma samples were obtained at specified intervals over a 24-hour post dose observation period. The placebo-adjusted mean maximum increases in QTc from baseline after 800, 1200, and 1600 mg of voriconazole and after ketoconazole 800 mg were all
		Reduction in the dose of oxycodone and other long- acting opiates metabolized by	<10 msec. Females exhibited a greater increase in QIC than males, although all mean changes were <10 msec. Age was not found to affect the magnitude of increase in QIC. No subject in any group had an increase in QIC of ≥60 msec from baseline. No subject experienced an interval to be an interval to be baddet 6.000 msec. Age was not found to be baddet 6.000 msec. Age was not been approximately a subject experienced an interval to be baddet 6.000 msec. Age was not been approximately a subject experienced an interval to be baddet 6.000 msec. Age was not been approximately a subject experienced an interval subject experienced an interval subject experienced an interval subject experience and an interval subject experience an interval subject
		CYP3A4 should be considered when coadministered with voriconazole. Extended and	vorconazole combined with drugs known to prolong the QT interval is unknown [see Contraindications (4) and Drug Interactions (7)].
		frequent monitoring for opiate- associated adverse reactions may be necessary.	The pharmacokinetics of voriconazole have been characterized in healthy subjects, special populations and patients.
profen and diclofenac (P2C9 Inhibition)	Increased	adverse reactions and toxicity related to NSAIDs. Dose reduction of NSAIDs may be	The pharmacokinetics of voriconazole are non-linear due to saturation of its metabolism. The interindividual variability of voriconazole pharmacokinetics is high. Greater than proportional increase in exposure is observed with increasing dose. It is estimated that, on average, increasing
crolimus* (CYP3A4 iibition)	Significantly Increased	needed. When initiating therapy with voriconazole in patients	the oral dose from 200 mg every 12 hours to 300 mg every 12 hours leads to an approximately 2.5-fold increase in exposure (AUC-); similarly, increasing the intravenous dose from 3 mg/kg every 12 hours to 4 mg/kg every 12 hours produces an approximately 2.5-fold increase in exposure (Tobia 1)
		already receiving tacrolimus, reduce the tacrolimus dose to one-third of the starting dose	(1400e 12). Table 12: Geometric Mean (%CV) Plasma Voriconazole Pharmacokinetic Parameters in Adults Receiving Different Design Regimens
		monitoring of tacrolimus blood levels. Increased tacrolimus	6 mg/kg 3 mg/kg 4 mg/kg 400 mg 200 mg 300 mg IV (loading IV every IV every Oral loading Oral every Oral every
		with nephrotoxicity. When voriconazole is discontinued, tacrolimus concentrations must	dose) 12 hours 12 hours dose) 12 hours 12 hours N 35 23 40 17 48 16 AUC ₁₂ 13,9 (32) 13,7 (53) 33,9 (54) 9,31 (38) 12,4 (78) 34,0 (53)
		be frequently monitored and the dose increased as necessary.	(µg•h/mL) Cmax (µg/mL) 3.13 (20) 3.03 (25) 4.77 (36) 2.30 (19) 2.31 (48) 4.74 (35) Cmax (µg/mL) 0.46 (92) 1.72 (74) 0.46 (120) 1.62 (70)
enytoin* (P2C9 Inhibition)	Significantly Increased	Frequent monitoring of phenytoin plasma concentrations and frequent monitoring of adverse effects	Note: Parameters were estimated based on non-compartmental analysis from 5 pharmacokinetic studies. AUC12 = area under the curve over 12 hour dosing interval, C _{max} = maximum plasma concentration,
al Contraceptives containing inyl estradiol and	Increased	related to phenytoin. Monitoring for adverse reactions related to oral contraceptives	Cmin = minimum plasma concentration. CV = coefficient of variation When the recommended intravenous loading dose regimen is administered to healthy subjects, plasma concentrations close to steady state are achieved within the first 24 hours of dosing (e.g.,
rethindrone (CYP3A4 iibition)** ednisolone and other	In Vivo Studies Showed No	is recommended during coadministration. No dosage adjustment for for production	6 mg/kg (V every 12 hours on day 1 followed by 3 mg/kg (V every 12 hours). Without the loading dose, accumulation occurs during twice daily multiple dosing with steady state plasma voriconazole concentrations being achieved by day 6 in the majority of subjects.
(P3A4 Inhibition)	voriconazole on Prednisolone Exposure	coadministered with voriconazole [see Clinical Pharmacology (12,3)].	Absorption The pharmacokinetic properties of voriconazole are similar following administration by the intravenous and oral routes. Based on a population pharmacokinetic analysis of pooled data in
	Not Studied <i>In Vivo</i> or <i>In Vitro</i> , for Other Corticosteroids, but Drug Exposure Likely	Monitor for potential adrenal dysfunction when voriconazole is administered with other	nearmy subjects (m=207), the oral bloavailability of voriconazole is estimated to be 95% (VO 13%). Bioequivalence was established between the 200 mg tablet and the 40 mg/mL oral suspension when administered as a 400 mg every 12 hours loading dose followed by a 200 mg every 12 hours maintanene does
ırfarin*	to be Increased Prothrombin Time	corticosteroids [See Warnings and Precautions (5.8)]. If patients receiving coumarin	Maximum plasma concentrations (C_{max}) are achieved 1-2 hours after dosing. When multiple doses of voriconazole are administered with high-fat meals, the mean C_{max} and AUC _T are reduced by $M_{\rm const}^{\rm MO}$ and $M_{\rm const}^{\rm T}$ are reduced by
er Oral Coumarin	Significantly Increased Not Studied <i>In Vivo</i> or <i>In Vitro</i>	preparations are treated simultaneously with voriconazole, the prothrombin time or other suitable apticeagulation	c) And and 2-M, isoboration when administration as a water and by done and of its responsibility with administered as the oral suspension (see Dosage and Administration (2)). In healthy subjects, the absorption of voriconazole is not affected by coadministration of oral ranking and administration administration and administration a
P2C9/3A4 Inhibition)	Anticoagulants, but Drug Plasma Exposure Likely to be Increased	tests should be monitored at close intervals and the dosage of anticoagulants	Distribution Distribution The volume of distribution at steady state for voriconazole is estimated to be 4.6 L/kg, suggesting
caftor P3A4 Inhibition)	Not Studied <i>In Vivo</i> or <i>In Vitro</i> , but Drug Plasma Exposure	adjusted accordingly. Dose reduction of ivacaftor is recommended. Refer to the	extensive distribution into tissues. Plasma protein binoing is estimated to be 50% and was shown to be independent of plasma concentrations achieved following single and multiple oral doses of 200 mg or 300 mg (approximate range: 0.9-15 μ g/mL). Varying degrees of hepatic and renal important date not affed the arcteric bigding of warenamaple.
zoniclone	Likely to be increased which may increase the Risk of Adverse Reactions Not Studied In Vivo or In Vitro	prescribing information for ivacaftor	Elimination Metabolism
(P3A4 Inhibition)	but Drug Plasma Exposure Likely to be Increased which may Increase the Sedative Effect	recommended. Refer to the prescribing information for eszopiclone.	In vitro studies showed that voriconazole is metabolized by the human hepatic cytochrome P450 enzymes, CYP2C19, CYP2C9 and CYP3A4 [see Drug Interactions (7)]. In vivo studies indicated that CYP2C19 is significantly involved in the metabolism of voriconazole.
neprazole* (P2C19/3A4	of Eszopiclone Significantly Increased	When initiating therapy with voriconazole in patients	This enzyme exhibits genetic polymorphism [see Clinical Pharmacology (12.5)]. The major metabolite of voriconazole is the N-oxide, which accounts for 72% of the circulating radiolabelled metabolities in plasma. Since this metabolite has minimal antifungal activity, it does
nonion)		doses of 40 mg or greater, reduce the omeprazole dose by one-half. The metabolism of	not contribute to the overall efficacy of voriconazole. Excretion Voriconazole is eliminated via benatic metabolism with less than 2% of the dose excreted
		other proton pump inhibitors that are CYP2C19 substrates may also be inhibited by	unchanged in the unite. After administration of a single radiolabelled dose of either oral or IV voriconazole, preceded by multiple oral or IV dosing, approximately 80% to 83% of the radioactivity is recovered in the unite. The majority (>94%) of the total radioactivity is excreted in the first 96
		voriconazole and may result in increased plasma concentrations of other proton	hours after both oral and intravenous dosing. As a result of non-linear pharmacokinetics, the terminal half-life of voriconazole is dose dependent and therefore not useful in prediction the accumulation or elimination of voriconazole.
ner HIV Protease ibitors (CYP3A4 ibition)	In Vivo Studies Showed No Significant Effects on Indinavir Exposure	No dosage adjustment for indinavir when coadministered with	Specific Populations Male and Female Patients
,	In Vitro Studies Demonstrated Potential for Voriconazole to	voriconazole Frequent monitoring for	In a multiple oral dose study, the mean G_{max} and AUC _T for healthy young females were 83% and 113% higher, respectively, than in healthy young males (18-45 years), after tablet dosing. In the same study, no significant differences in the mean G_{max} and AUC _T were observed between healthy
ner NNRTIe****	Inhibit Métabolism (Increased Plasma Exposure)	adverse reactions and toxicity related to other HIV protease inhibitors.	enterly mates and nearly enterly remarks (sob years). In a similar study, and rousing winning of a suspension, the mean AUC for healthy young females was 45% higher than in healthy young males whereas the mean C _{max} was comparable between genders. The steady state trough voriconazole concentrations (C _{max}) seen in females were 100%, and 91% higher than in males receiving the
(P3A4 Inhibition)	Drug Interaction Study Demonstrated the Potential for Voriconazole to Inhibit	adverse reactions and toxicity related to NNRTI	tablet and the oral suspension, respectively. In the clinical program, no dosage adjustment was made on the basis of gender. The safety profile and plasma concentrations observed in male and female subjects wars similar. Therefore, no
tinoin (CYP3A4 Inhibition)	Metabolism of Other NNRTIs (Increased Plasma Exposure) Although Not Studied,	Frequent monitoring for	dio spasific concentrations observed in male and remain subjects were similar. Therefore, no dosage adjustment based on gender is necessary. Geriatric Patients
	Tretinoin Concentrations and Increase the Risk of Adverse Beactions	signs and symptoms of pseudotumor cerebri or hypercalcemia.	in an oral multiple dose study the mean U _{max} and AUU _T in healthy elderly males (≥b years) were 61% and 86% higher, respectively. Ithan in young males (18-45 years). No significant differences in the mean G _{max} and AUG _T were observed between healthy elderly females (≥65 years) and healthy young nearby (18-45 years)
dazolam (P3A4 Inhibition)	Significantly Increased	Increased plasma exposures may increase the risk of adverse reactions and toxicities related	In the clinical program, no dosage adjustment was made on the basis of age. An analysis of pharmacokinetic data obtained from 552 patients from 10 voriconazole clinical trials showed that
ner benzodiazepines luding triazolam and razolam	In Vitro Studies Demonstrated Potential for Voriconazole to Inhibit Metabolism	to benzodiazepines.	the median vonconazole plasma concentrations in the elderly platents (>oo years) were approximately 80% to 90% higher than those in the younger patients (<65 years) after either IV or oral administration. However, the safety profile of voriconazole in young and elderly subjects was cimilar and therefore, no decage adjustment ic necessarili, for the default, <i>Lese Usa in Sacial</i>
(P3A4 Inhibition) IG-CoA Reductase	(Increased Plasma Exposure)	Refer to drug-specific labeling for details. Frequent monitoring for	Populations (8.5), Pediatric Patients
(P3A4 Inhibition)	Inhibit Metabolism (Increased Plasma Exposure)	related to statins. Increased statin concentrations in plasma have been associated with	ine recommended doses in pediatric patients were based on a population pnarmacokinetic analysis of data obtained from 112 immunocompromised pediatric patients aged 2 to less than 12 years and 26 immunocompromised pediatric patients aged 12 to less than 17 years.
		rhabdomyolysis. Adjustment of the statin dosage may be needed.	A comparison of the pediatric and adult population pharmacokinetic data indicated that the predicted total exposure (AUC ₁₂) in pediatric patients aged 2 to less than 12 years following administration of a 9 mg/kg intravenous loading dose was comparable to that in adults following double to the second sec
annel Blockers (P3A4 Inhibition)	In vitro Studies Demonstrated Potential for Voriconazole to Inhibit Metabolism (Increased Plasma Exposure)	adverse reactions and toxicity related to calcium channel	a origing intervendes loading does. The produced occurs exposites in potiant exposites the stand and the stand and the standard standard and the standard st
		Adjustment of calcium channel blocker dosage may be needed.	dose of 9 mg/kg (maximum of 350 mg) twice daily was comparable to that in adults following 200 mg oral twice daily. An 8 mg/kg intravenous dose will provide voriconazole exposure approximately 2-fold higher than a 9 mg/kg oral dose in pediatric patients aged 2 to less than 12 years.
lfonylurea Oral poglycemics /P2C9 Inhibition)	Not Studied <i>In Vivo</i> or <i>In Vitro</i> , but Drug Plasma Exposure Likely to be Increased	Frequent monitoring of blood glucose and for signs and symptoms of hypoglycemia.	Voriconazole exposures in the majority of pediatric patients aged 12 to less than 17 years were comparable to those in adults receiving the same dosing regimens. However, lower voriconazole exoosure was observed in some cediatric patients aged 12 to less than 17 years with low body
uca Alkaloide	Not Studied In Vive or In Vitro	Adjustment of oral hypoglycemic drug dosage may be needed.	weight compared to adults [see Dosage and Administration (2.4)]. Limited voriconazole trough plasma samples were collected in pediatric patients aged 2 to less than 18 wares with La cripyesive candidises includion candidemia and E to huo prospective
(P3A4 Inhibition)	but Drug Plasma Exposure Likely to be Increased	adverse reactions and toxicity (i.e., neurotoxicity) related to vinca alkaloids. Reserve azole	open-label, non-comparative, multicenter clinical studies. In eleven pediatric patients aged 2 to less than 12 years and aged 12 to 14 years, with body weight less than 50 kg, who received 9 mg/kg intravenously every 12 hours as a loading does on the first day of treatment followed by 8
		antifungals, including voriconazole, for patients receiving a vinca alkaloid who have no alternative	mg/kg every 12 hours as an intravenous maintenance dose, or 9 mg/kg every 12 hours as an oral maintenance dose, the mean trough concentration of voriconazole was 3.6 mcg/mL (range 0.3 to 10.7 mcg/mL). In four pediatric patients aged 2 to less than 12 vears and aner 12 to 14 vears
erolimus (P3A4 Inhibition)	Not Studied In Vivo or In Vitro, but Drug Plasma Exposure	antifungal treatment options. Concomitant administration of voriconazole and everolimus	with body weight less than 50 kg, who received 4 mg/kg intravenously every 12 hours, the mean trough concentration of voriconazole was 0.9 mcg/mL (range 0.3 to 1.6 mcg/mL) [see Clinical Studies (14.5)].
* Results based on <i>in vivo</i> c voriconazole to healthy subi	LIKELY TO BE INCREASED	I IS NOT RECOMMENDED.	Patients with Hepatic Impairment After a single oral dose (200 mg) of voriconazole in 8 patients with mild (Child-Pugh Class A) and 4 patients with moderate (Child-Pugh Class B) henatic impairment, the mean systemic experience
** Results based on <i>in vivo</i> c 1 day, then 200 mg every 12 h *** Results based on <i>in vivo</i> c	linical study following repeat oral do iours for at least 2 days voriconazole clinical study following repeat oral do	osing with 400 mg every 12 hours for to healthy subjects osing with 400 mg every 12 hours for	(AUC) was 3.2-fold higher than in age and weight matched controls with normal hepatic function. There was no difference in mean peak plasma concentrations (C _{max}) between the groups. When only the patients with mild (Child-Pugh Class A) hepatic impairment were compared to controls
1 day, then 200 mg every 1 maintenance dose (30-100 m **** Non-Steroidal Anti-Infla	I2 hours for 4 days voriconazole g every 24 hours) mmatory Drug	to subjects receiving a methadone	there was still a 2.3-fold increase in the mean AUC in the group with hepatic impairment compared to controls. In an oral multiple dose study. AUC-, was similar in 6 subjects with moderate hepatic impairment
Non-Nucleoside Rever SE IN SPECIFIC POPULATI Pregnancv	se Transcriptase Inhibitors IONS		(Child-Pugh Class B) given a lower maintenance dose of 100 mg twice daily compared to 6 subjects with normal hepatic function given the standard 200 mg twice daily maintenance dose. The mean peak plasma concentrations (Cmax) were 20% lower in the hepatically impaired group. No
k Summary iconazole can cause fetal ha	arm when administered to a pregn	nant woman. There are no available	pnarmacokinetic data are available for patients with severe hepatic cirrhosis (Child-Pugh Class C) [see Dosage and Administration (2.5)]. Patients with Renal Impairment
iconazole was associated v ates and hydronephrosis/hy anogenesis at and above 1	with fetal malformations in rats droureter were observed in rat pu 0 mg/kg (0.3 times the BMD of	and fetal toxicity in rabbits. Cleft ps exposed to voriconazole during 200 mg every 12 hours based on	In a single oral dose (200 mg) study in 24 subjects with normal renal function and mild to severe renal impairment, systemic exposure (AUC) and peak plasma concentration (C _{max}) of voriconazole were not significantly affected by renal impairment. Therefore, no adjustment is necessarv for oral
ly surface area comparison idence of skeletal variations os when pregnant rabhits v	s). In rabbits, embryomortality, r s, cervical ribs and extrasternal o vere orally dosed at 100 mg/kg	educed fetal weight and increased issification sites were observed in (6 times the RMD based on body	dosing in patients with mild to severe renal impairment. In a multiple dose study of IV voriconazole (6 mg/kg IV loading dose x 2, then 3 mg/kg IV x 5.5 days) in 7 patients with moderate renal dvsfunction (creatinine clearance 30-50 ml/min), the
tace area comparisons) dur weaning experienced increa reased perinatal pup morta	ing organogenesis. Rats exposed ased gestational length and dyst ality at the 10 mg/kg dose <i>[see</i>	to voriconazole from implantation ocia, which were associated with Data]. If this drug is used during	systemic exposure (AUC) and peak plasma concentrations (C_{max}) were not significantly different from those in 6 subjects with normal renal function. However, in patients with moderate renal dysfunction (creatinine clearance 30-50 ml /min)

Γ		6 mg/kg	3 mg/kg	4 mg/kg	400 mg	200 mg	300 mg
		IV (loading	IV every	IV every	Oral (loading	Oral every	Oral ever
		dose)	12 hours	12 hours	dose)	12 hours	12 hours
ſ	N	35	23	40	17	48	16
[AUC ₁₂	13.9 (32)	13.7 (53)	33.9 (54)	9.31 (38)	12.4 (78)	34.0 (53)

Fluconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor): Concurrent administration of oral voriconazole (400 mg every 12 hours for 1 day, then 200 mg every 12 hours for 2.6 days) and oral fluconazole (400 mg on day 1, then 200 mg every 24 hours for 4 days) to 6 healthy male subjects resulted in an increase in C_{max} and AUC_t of voriconazole by an average of 57% (90% CI: 20%, 107%) and 79% (90% CI: 40%, 128%), respectively. In a follow-on clinical study involving 8 healthy male subjects, reduced dosing and/or frequency of voriconazole diffuconazole did not eliminate or diminish this effect [*see Drug Interactions (7)*].

Letermovir (CYP2C9/2C19 inducer)-Coadministration of oral letermovir with oral voriconazole decreased the steady state C_{max} and AUC₀₋₁₂ of voriconazole by an average of 39% and 44%, respectively [see Drug Interactions (7)].

Minor or no significant pharmacokinetic interactions that do not require dosage adjustm **Cimetidine** (non-specific CYP450 inhibitor and increases gastric pH)—Cimetidine (400 mg every 12 hours x 8 days) increased voriconazole steady state G_{max} and AUC_t by an average of 18% (90% CI: 6%, 32%) and 23% (90% CI: 6%, 33%), respectively, following oral doses of 200 mg every 12 hours x 7 days to healthy subjects.

 $\label{eq:resonance} \begin{array}{l} \textbf{Ranitidine} (increases gastric pH) - \text{Ranitidine} (150 \text{ mg every 12 hours}) \text{ had no significant effect on voriconazole } \\ \textbf{V}_{max} \text{ and AUC}_{\tau} \text{ following oral doses of 200 mg every 12 hours x 7 days to healthy subjects.} \end{array}$ Voltable C_{max} and AC_{T} tooking that access of 200 mg every 12 hours Ar tags to hearting subjects. **Macroilde antibiotics**—Coadministration of **erythromycin** (CYP3A4 inhibitor; 1 gram every 12 hours for 7 days) or **azithromycin** (500 mg every 24 hours for 3 days) with voriconazole 200 mg every 12 hours for 14 days had no significant effect on voriconazole steady state C_{max} and AUC_{T} in healthy subjects. The effects of voriconazole on the pharmacokinetics of either erythromycin or azithromycin are not known.

Effects of Voriconazole on Other Drugs

In vitro studies with human hepatic microsomes show that voriconazole inhibits the metabolic activity of the cytochrome P450 enzymes CYP2C19, CYP2C9, and CYP3A4. In these studies, the inhibition potency of voriconazole for CYP3A4 metabolic activity was significantly less than that of two other azoles, ketoconazole and itraconazole. In vitro studies also show that the major metabolite of voriconazole, voriconazole /-oxide, inhibits the metabolic activity of CYP2C9 and CYP3A4 to a greater extent than that of CYP2C19. Therefore, there is potential for voriconazole and its major metabolite to increase the systemic exposure (plasma concentrations) of other drugs metabolized by these CYP450 enzymes.

The systemic exposure of the following drug is significantly increased by coadministration of voriconazole and their use is contraindicated:

Sirolimus (CYP3A4 substrate)-Repeat dose administration of oral voriconazole (400 mg every 12 hours for 1 day, then 200 mg every 12 hours for 8 days) increased the C_{max} and AUC of sirolimus (2 mg single dose) an average of 7-fold (90% Ct 5.7, 7.5) and 11-fold (90% Ct 5.9, 12.6), respectively, in healthy male subjects [see Contraindications (4)].

The subjectively, in relating male subjects (see Contrainfordation (+)). Coadministration of voriconazole with the following agents results in increased exposure to these drugs. Therefore, careful monitoring and/or dosage adjustment of these drugs is needed: Alfentanii (CYP3A4 substrate)–Coadministration of multiple doses of oral voriconazole (400 mg every 12 hours on day 1, 200 mg every 12 hours on day 2) with a single 20 mcg/kg intravenous dose of alfentanii with concomitant naloxone resulted in a 6-fold increase in mean alfentanii AUC_{0-∞} and a 4-fold prolongation of mean alfentanii elimination half-life, compared to when alfentanii was given alone [see Drug Interactions (7)]. Entanul (CYP3A4 substrate) in an ideopendent bublished study, concomitant use of unconcapale

alfentanil was given alone [see Drug Interactions (7)]. Fentanyi (CYP3A4 substrate): In an independent published study, concomitant use of voriconazole (400 mg every 12 hours on Day 1, then 200 mg every 12 hours on Day 2) with a single intravenous dose of fentanyl (5 μ g/kg) resulted in an increase in the mean AUC_{0-∞} of fentanyl by 1.4-fold (range 0.81- to 2.04-fold) (see Drug Interactions (7)]. Dxycodone (CYP3A4 substrate): In an independent published study, coadministration of multiple doses of rail voriconazole (400 mg every 12 hours, on Day 1 followed by five doses of 200 mg every 12 hours on Days 2 to 4) with a single 10 mg oral dose of oxycodone on Day 3 resulted in an increase in the mean C_{max} and AUC_{0-∞} of oxycodone by 1.7-fold (range 1.4-to 2.2-fold) and 3.6-fold (range 2.7- to 5.6-fold), respectively. The mean elimination half-life of oxycodone was also increased by 2.0-fold (range 1.4-to 2.5-fold)(*see Drug Interactions (7)*).

also increased by 2.0-bit (range 1.4- to 2.0-bit) (see Drag interactions (7)). **Cyclosporine** (**CYP3A4 substrate**)–In stable renal transplant recipients receiving chronic cyclosporine therapy, concomitant administration of oral voriconazole (200 mg every 12 hours for 8 days) increased cyclosporine C_{max} and AUC_{r} an average of 1.1 times (90% CI: 0.9, 1.41) and 1.7 times (90% CI: 1.5, 2.0), respectively, as compared to when cyclosporine was administered without voriconazole [see Drug Interactions (7)].

without voriconazole [see Drug Interactions (7)]. Methadone (CYP3A4, CYP2C19, CYP2C9 substrate)—Repeat dose administration of oral voriconazole (400 mg every 12 hours for 1 day, then 200 mg every 12 hours for 4 days) increased the C_{max} and AUC₂ of pharmacologically active Rmethadone by 31% (90% CI: 22%, 40%) and 47% (90% CI: 38%, 57%), respectively, in subjects receiving a methadone maintenance dose (30-100 mg every 24 hours). The C_{max} and AUC of (S)-methadone increased by 65% (90% CI: 53%, 79%) and 103% (90% CI: 85%, 124%), respectively [see Drug Interactions (7)].

Tarchimus (CYP3A4 substrate)–Repeat oral dose administration of voriconazole (400 mg every 12 hours x 1 day, then 200 mg every 12 hours x 6 days) increased tarchimus (0.1 mg/kg single dose) C_{max} and AUC_T in healthy subjects by an average of 2-fold (90% CI: 1.9, 2.5) and 3-fold (90% CI: 2.7, 3.8), respectively [*see Drug Interactions (7)*]. Warlarin (CYP2C9 substrate)–Coadministration of voriconazole (300 mg every 12 hours x 1 day, then 200 mg every 12 hours x 1 day) in the fold of the provided the substrate in the substrate of the provided the provided

mbin time by

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs; CYP2C9 substrates): In two independent published studies, single doses of ibuprofen (400 mg) and diclofenac (50 mg) were coadministered with the last dose of voriconazole (400 mg every 12 hours on Day 1, followed by 200 mg every 12 hours on Day 2). Voriconazole increased the mean C_{max} and AUC of the pharmacologically active isomer, S (+)-ibuprofen by 20% and 100%, respectively. Voriconazole increased the mean C_{max} and AUC of diclofenac by 114% and 78%, respectively [*see Drug Interactions (7)*].

Digoxin (P-glycoprotein mediated transport)-Voriconazole (200 mg every 12 hours x 12 days) had no significant effect on steady state C_{max} and AUC_T of digoxin (0.25 mg once daily for 10 days) in healthy subjects.

 $Mycophenolic acid (UDP-glucuronyl transferase substrate)-Voriconazole (200 mg every 12 hours x 5 days) had no significant effect on the <math display="inline">C_{max}$ and AUC_{τ} of mycophenolic acid and its major metabolite, mycophenolic acid glucuronide after administration of a 1 gram single oral dose of mycophenolate mofetil.

Two-Way Interaction

Two-Way Interactions Concomitant use of the following agents with voriconazole is contraindicated: Rilabutin (potent CYP450 inducer)–Rifabutin (300 mg once daily) decreased the C_{max} and AUC_T of voriconazole at 200 mg twice daily by an average of 67% (90% CI: 58%, 73%) and 79% (90% CI: 71%, 84%), respectively, in healthy subjects. During coadministration with rifabutin (300 mg once daily), the steady state C_{max} and AUC_T of voriconazole following an increased dose of 400 mg twice daily were on average approximately 2 times higher, compared with voriconazole alone at 200 mg twice daily. Coadministration of voriconazole 4400 mg twice daily with rifabutin 300 mg twice daily increased the C_{max} and AUC_T of rifabutin by an average of 3-times (90% CI: 2.2, 4.0) and 4 times (90% CI: 3.5, 5.4), respectively, compared to rifabutin given alone [see Contraindications (4]). tions (4)1

Significant drug interactions that may require dosage adjustment, frequent monitoring of drug levels and/or frequent monitoring of drug-related adverse reactions/toxicity:

levels and/or frequent monitoring of drug-related adverse reactions/toxicity: Efavirenz, a non-nucleoside reverse transcriptase inhibitor (CYP450 inducer; CYP3A4 inhibitor and substrate)-Standard doses of voriconazole and efavirenz (400 mg every 24 hours or higher) must not be coadministered [see Drug Interactions (7]). Steady state efavirenz (400 mg P0 every 24 hours) decreased the steady state (max and AUC- of voriconazole (400 mg P0 every 12 hours for 1 day, then 200 mg P0 every 12 hours for 8 days) by an average of 61% and 77%, respectively, in healthy male subjects. Voriconazole at steady state (400 mg P0 every 12 hours for 1 day, then 200 mg every 12 hours for 8 days) by an average of 38% and 44%, respectively, in healthy subjects. The pharmacokinetics of adjusted doses of voriconazole and efavirenz were studied in healthy male subjects following administration of voriconazole (400 mg P0 every 12 hours on Days 2 to 7) with efavirenz (300 mg P0 every 24 hours on Days 1-7), relative to steady state administration of

ouccess by openes			
	Succes		
Overall success	76/144 (53)	42/133 (32)	
Mycologically confirmed ^e	37/84 (44)	16/67 (24)	
A			
Aspergillus spp.			
A. fumigatus	28/63 (44)	12/47 (26)	
A. flavus	3/6	4/9	
A. terreus	2/3	0/3	
A. niger	1/4	0/9	
A. nidulans	1/1	0/0	

^a Assessed by independent Data Review Committee (DRC)
 ^b Proportion of subjects alive
 ^c Amphotericin B followed by other licensed antifungal therapy
 ^d Difference and corresponding 95% confidence interval are stratified by protocol
 ^e Not all mycologically confirmed specimens were speciated
 ^f Some patients had more than one species isolated at baseline

Study 304 – Primary and Salvage Therapy of Aspergillosis In this non-comparative study, an overall success rate of 52% (26/50) was seen in patients treated with voriconazole for primary therapy. Success was seen in 17/29 (59%) with Aspergillus fumigatus infections and 3/6 (50%) patients with infections due to non-fumigatus species [A. flavus (1/1); A. nidulans (0/2); A. niger (2/2); A. terreus (0/1)]. Success in patients who received voriconazole as salvage therapy is presented in Table 14.

Study 309/604 – Treatment of Patients with Invasive Aspergillosis who were Refractory to, or Intolerant of, other Antifungal Therapy

Additional data regarding response rates in patients who were refractory to, or intolerant of, other antifungal agents are also provided in Table 16. In this non-comparative study, overall mycological eradication for culture- documented infections due to *fumigatus* and non-*fumigatus* species of Aspergillus was 36/82 (44%) and 12/30 (40%), respectively, in voriconazole treated patients. Patients had various underlying diseases and species other than *A. fumigatus* contributed to mixed infections in some case. ections in some cases.

For patients who were infected with a single pathogen and were refractory to, or intolerant of other antifungal agents, the satisfactory response rates for voriconazole in studies 304 and 309/604 are presented in Table 14.

Table 14: Combined Response Data in Salvage Patients with Single *Aspergillus* Species (Studies 304 and 309/604)

Success = /M

	Success II/N
A. fumigatus	43/97 (44%)
A. flavus	5/12
A. nidulans	1/3
A. niger	4/5
A. terreus	3/8
A. versicolor	0/1

teen patients had more than one species of Aspergillus isolated. Success was seen in 4/17 (24%) of these patients.

14.2 Candidemia in Non-neutropenic Patients and Other Deep Tissue Candida Infection

14.2 Candidemia in Non-neutropenic Patients and Other Deep Tissue Candida Infections Voriconazole was compared to the regimen of amphotericin B followed by fluconazole in Study 608, an open-label, comparative study in nonneutropenic patients with candidemia associated with clinical signs of infection. Patients were randomized in 2:1 ratio to receive either voriconazole (n=283) or the regimen of amphotericin B followed by fluconazole (n=139). Patients were treated with randomized study drug for a median of 15 days. Most of the candidemia in patients evaluated for efficacy was caused by *C. albicans* (46%), followed by *C. tropicalis* (19%), *C. parapsilosis* (17%), *C. glabrata* (15%), and *C. krusei* (1%).
An independent Data Review Committee (DRC), blinded to study treatment, reviewed the clinical and mycological data from this study, and generated one assessment of response for each patient. A successful response required all of the following: resolution or improvement in all clinical signs and symptoms of infection, blood cultures negative for *Candida*, infected deep tissue sites negative for *Candida* or resolution of all local signs of infection, and no systemic antifungal therapy other than study drug. The primary analysis, which counted DRC-assessed successes at the fixed time point (12 weeks after End of Therapy [EOT]), demonstrated that voriconazole was comparable to the regime of amphotericin B followed by fluconazole (response rates of 41% and 41%, respectively) in the treatment focandidemia. Patients who did not have a 12-week assessment for any reason were considered a treatment failure.

The overall clinical and mycological success rates by *Candida* species in Study 150-608 are presented in Table 15.

Table 15: Overall Success Rates Sustained From EOT to The Fixed 12-Week Follow-Up Time Point By

Baseline Pathogen	Clinical and Mycological Success (%)		
	Voriconazole	Amphotericin B> Fluconazole	
C. albicans	46/107 (43%)	30/63 (48%)	
C. tropicalis	17/53 (32%)	1/16 (6%)	
C. parapsilosis	24/45 (53%)	10/19 (53%)	
C. glabrata	12/36 (33%)	7/21 (33%)	
C. krusei	1/4	0/1	

^a A few patients had more than one pathogen at baseline. ^b Patients who did not have a 12-week assessment for any reason were considered a treatment failure. In a secondary analysis, which counted DRC-assessed successes at any time point (EOT, or 2, 6, or 12 weeks after EOT), the response rates were 65% for voriconazole and 71% for the regimen of amphotericin B followed by fluconazole.

of amphotencin B followed by fluconazole. In Studies 608 and 309/604 (non-comparative study in patients with invasive fungal infections who were refractory to, or intolerant of, other antifungal agents), voriconazole was evaluated in 35 patients with deep tissue *Candida* infections. A favorable response was seen in 4 of 7 patients with intra-abdominal infections, 5 of 6 patients with kidney and bladder wall infections, 3 of 3 patients with deep tissue abscess or wound infection, 1 of 2 patients with pneuronia/pleural space infections, 2 of 4 patients with suppurative phlebitis, 1 of 3 patients with negatosplenic infection, 1 of 5 patients with other supplications of 1 with liver infection, and 0 of 1 with cervical lymph node infection.

14.3 Esophageal Candidiasis (EC)

14.3 Esophageal Candidiasis (EC) The efficacy of oral voriconazole 200 mg twice daily compared to oral fluconazole 200 mg once daily in the primary treatment of EC was demonstrated in Study 150-305, a double-blind, double-dummy study in immunocompromised patients with endoscopically-proven EC. Patients were treated for a median of 15 days (range 1 to 49 days). Outcome was assessed by repeat endoscopy at end of treatment (EOT). A successful response was defined as a normal endoscopy at EOT or at least a 1 grade improvement over baseline endoscopic score. For patients in the Intent-to-Treat (IT) population with only a baseline endoscopy. a successful response was defined as symptomatic cure or improvement at EOT compared to baseline. Voriconazole and fluconazole (200 mg once daily) showed comparable efficacy rates against EC, as presented in Table 16. Table 16:

Table 16: Success Rates in Patients Treated for Esophageal Candidiasis Population Voriconazole Fluconazole Difference % (95% Cl)^a PPb 113/115 (98.2%) 134/141 (95.0%) 3.2 (-1.1, 7.5) ITT^c 175/200 (87.5%) 171/191 (89.5%) -2.0 (-8.3, 4.3)

a Confidence Interval for the difference (Voriconazole – Fluconazole) in success rates.
 b PP (Per Protocol) patients had confirmation of *Candida* esophagitis by endoscopy, received at least 12 days of treatment, and had a repeat endoscopy at EOT (end of treatment).
 c ITT (Intert to Treat) patients without endoscopy or colincial assessment at EOT were treated as failures.
 Microbiologic success rates by *Candida* species are presented in Table 17.

days) with warfarin (30 mg single dose) significantly increased maximum prothromb approximately 2 times that of placebo in healthy subjects [see Drug Interactions (7)].

No significant pharmacokinetic interactions were observed when voriconazole was caadministered with the following agents. Therefore, no dosage adjustment for these agents is recommended:

Prednisolone (CYP3A4 substrate)-Voriconazole (200 mg every 12 hours x 30 days) increased C_{max} and AUC of prednisolone (60 mg single dose) by an average of 11% and 34%, respectively, in healthy subjects *[see Warnings and Precautions (5.8)]*.

What are the ingredients of voriconazole?	Inhibition)**	In Vivo S
Active ingredient: voriconazole	corticosteroids (CYP3A4 Inhibition)	Signif
Inactive ingredients:		Not Studie
Voriconazole oral suspension: colloidal silicon diox titanium dioxide, xanthan gum, sodium citrate dihyd sodium benzoate. anhydrous citric acid. natural	xide, rate, and (CYP2C9 Inhibition)	for Othe but Drug to I
artificial orange flavor, and sucrose	Other Oral Coumarin	Not Studie
This Patient Information has been approved by the Food and Drug Administration.	U.S. (CYP2C9/3A4 Inhibition)	Anticoa Plasma to I
The brands listed are trademarks of their respectively owners.	Ctive Ivacatfor (CYP3A4 Inhibition)	Not Studie but Drug Likely to I may Inc
Assembly Instructions	Eszopiclone (CYP3A4 Inhibition)	Not Studie but Drug
CHECK WITH YOUR PHARMACIST TO ENSURE VORICONAZOLE FOR ORAL SUSPENSION HAS BEEN RECONSTITUTED (i.e. is in liquid form).	Omeprazole* (CYP2C19/3A4 Inhibition)	may Increas of Signific
Bottle Cap —		
Bottle Bottle adapter Oral Dispenser	The other HIV Protease	In Vivo
	Inhibitors (CYP3A4	No Sign Indin
SHAKE CLOSED BOTTLE FOR APPROXIMATELY 10 SECO Before Each USE.	INDS	<i>In Vitro</i> St Potential Inhibit Me Plas
	Other NNRTIS***** (CYP3A4 Inhibition)	A Vorico Drug I Demonstra Vorico Metabolis
	Tretinoin (CYP3A4 Inhibition)	Altho Voricon Tretinoin (Incre
	Midazolam (CYP3A4 Inhibition)	Signifi
To open push down on Push bottle adapter ALL	Other benzodiazepines including triazolam and	In Vitro Str Potential
bottle cap while twisting THE WAY into bottle top	(if (CYP3A4 Inhibition)	Inhib (Increased
Remove cap from bottle. so). Once bottle adapter inserted, leave in place.	INMG-CoA Reductase IS Inhibitors (Statins) (CYP3A4 Inhibition)	In Vitro Str Potential Inhibit Me Plas
$\underline{3}$ $\underline{\bigcirc}$ $\underline{4}$ $\underline{}$	Dihydropyridine Calcium Channel Blockers	In Vitro Sto Potential
	(CYP3A4 Inhibition)	Inhibit Me Plas
	Sulfonylurea Oral Hypoglycemics (CYP2C9 Inhibition)	Not Studie but Drug Likely
IMPORTANT: Adapter must Pull back on oral dispen- be fully inserted prior to use. Plunger to prescribed do	Ser Vinca Alkaloids (CYP3A4 Inhibition) OSE.	Not Studie but Drug Likely
<u>5 T 6</u>		
	Everolimus (CYP3A4 Inhibition)	Not Studie but Drug
	* Results based on <i>in vivo</i>	Likely
	 voriconazole to healthy su ** Results based on <i>in vivo</i> 1 day, then 200 mg every 12 	bjects clinical study for hours for at lea
	*** Results based on <i>in viv</i> 1 day, then 200 mg every maintenance dose (30-100)	clinical study f 12 hours for ma every 24 ho
Insert and dispanser into Holding the bottle with	**** Non-Steroidal Anti-Inf ***** Non-Nucleoside Rev	lammatory Dru erse Transcripta
bottle top. one hand, push down on oral dispenser plunger to push air into bottle.	8 USE IN SPECIFIC POPULA 8.1 Pregnancy Network Summary Voriconazole can cause fetal data on the upon of vorigon	harm when adr
7 8 1	voriconazole was associated	I with fetal many
	organogenesis at and above body surface area compariso incidence of skeletal variation	no mg/kg (0.3 ns). In rabbits ns, cervical rit
	pups when pregnant rabbits surface area comparisons) du to weaning experienced incr	were orally d uring organoge eased gestation
	increased perinatal pup mor pregnancy, or if the patient	tality at the 1 becomes preg
	The background risk of ma unknown. In the U.S. general miscarriage in clinically reco	jor birth defect population, th gnized pregnation
Turn hottle unside down Remove oral dispenser	Data Animal Data	ad overline in

from bottle. Dispense

medicine into mouth by

slowly pushing on oral

Remember to leave the bottle

adapter in the bottle and put

the cap back on the bottle.

Store at room temperature

dispenser plunger.

beak plasma concentration (C_{max}) of voriconazole nt. Therefore, no adjustment is necessary for oral ng/kg IV loading dose x 2, then 3 mg/kg IV x 5.5 nction (creatinine clearance 30-50 mL/min), the entrations (C_{max}) were not significantly different unction (creatinine clearance 30-50 mL/min) accumulation of the intravenous vehicle, SBECD, occurs. The mean systemic exposure (AUC) and peak plasma concentrations (C_{max}) of SBECD were increased 4-fold and almost 50%, respectively in the moderately impaired group compared to the normal control group. A pharmacokinetic study in subjects with renal failure undergoing hemodialysis showed that voriconazole is dialyzed with clearance of 121 mL/min. The intravenous vehicle, SBECD, is hemodialyzed with clearance of 55 mL/min. A 4-hour hemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment [see Dosage and Administration (2.6)]. Patients at Risk of Aspergillosis The observed voriconazole pharmacokinetics in patients at risk of aspergillosis (mainly patients with malignant neoplasms of lymphatic or hematopoietic tissue) were similar to healthy subjects. Drug Interaction Studies

Effects of Other Drugs on Voriconazole Voriconazole is metabolized by the human hepatic cytochrome P450 enzymes CYP2C19, CYP2C9, and CYP3A4. Results of *in vitro* metabolism studies indicate that the affinity of voriconazole is highest for CYP2C19, followed by CYP2C9, and is appreciably lower for CYP3A4. Inhibitors or inducers of these three enzymes may increase or decrease voriconazole systemic exposure (plasma concentratione), concertively entrations), respectively

concentrations), respectively. The systemic exposure to voriconazole is significantly reduced by the concomitant administration of the following agents and their use is contraindicated:

Rifampin (potent CYP450 inducer)–Rifampin (600 mg once daily) decreased the steady state G_{max} and AUC_T of voriconazole (200 mg every 12 hours x 7 days) by an average of 93% and 96%, respectively, in healthy subjects. Doubling the dose of voriconazole to 400 mg every 12 hours does not restore adequate exposure to voriconazole during coadministration with rifampin [see Contraindications (4)].

efavirenz (sub mg PU every 24 nours on Jays 1-7), relative to steady state administration of voriconazole (400 mg for 1 day, then 200 mg PO every 12 hours for 2 days) or efavirenz (600 mg every 24 hours for 9 days). Coadministration of voriconazole 400 mg every 12 hours with efavirenz 300 mg every 24 hours (adcreased voriconazole 400 LC_T by 7% (90% Cl: -2%), 13%) and increased C_{max} by 23% (90% Cl: -1%, 53%); efavirenz AUC_T was increased by 17% (90% Cl: -6%, 29%) and C_{max} was equivalent [see Dosage and Administration (2.7), Contraindications (4), and Drug Interactions (7)].

Interactions (7)]. Phenytoin (CYP2O9 substrate and potent CYP450 inducer)—Repeat dose administration of phenytoin (300 mg once daily) decreased the steady state C_{max} and AUC_r of orally administered voriconazole (200 mg every 12 hours x 14 days) by an average of 50% and 70%, respectively, in healthy subjects. Administration of a higher voriconazole dose (400 mg every 12 hours x 7 days) with phenytoin (300 mg once daily) resulted in comparable steady state voriconazole C_{max} and AUC_r estimates as compared to when voriconazole was given at 200 mg every 12 hours without phenytoin [see Dosage and Administration (2.7) and Drug Interactions (7)].

Repeat dose administration of voriconazole (400 mg every 12 hours x 10 days) increased the steady state C_{max} and AUC_{τ} of phenytoin (300 mg once daily) by an average of 70% and 80%, respectively, in healthy subjects. The increase in phenytoin C_{max} and AUC when coadministered with voriconazole may be expected to be as high as 2 times the C_{max} and AUC estimates when phenytoin is given without voriconazole [see Drug Interactions (7)].

pnenytoin is given without voriconazole [see Drug Interactions (7)]. **Omeprazole (CYP2C19 inhibitor: CYP2C19 and CYP3A4 substrate)**-Coadministration of omeprazole (12 hours x 9 days) with oral voriconazole (400 mg every 12 hours x 1 day, then 200 mg every 12 hours x 9 days) increased the steady state (max and AUC_r of voriconazole by an average of 15% (90% CI: 5%, 25%) and 40% (90% CI: 29%, 55%), respectively, in healthy subjects. No dosage adjustment of voriconazole is recommended. Coadministration of voriconazole (400 mg every 12 hours x 1 day, then 200 mg x 6 days) with omeprazole (40 mg once daily x 7 days) to healthy subjects significantly increased the steady state (max and AUC_r of omeprazole an average of 2 times (90% CI: 3.3, 4.4), respectively, as compared to when omeprazole is given without voriconazole [see Drug Interactions (7)]. Dral Contraceptives (CYP3A4 substrate: CYP2C19 inhibition Conduction in the substrate in t

Oral Contraceptives (CYP3A4 substrate; CYP2C19 inhibitor)-Coadmin brain contraceptives (c) roles subscription of oral and contraceptive (c) the subscription of the contraceptive (c) the subscriptive (c) the subscription of the contraceptive (c) the subscription o

No significant pharmacokinetic interaction was seen and no dosage adjustment of these drugs

Indinavir (CYP3A4 inhibitor and substrate)–Repeat dose administration of indinavir (800 mg TID for 10 days) had no significant effect on voriconazole C_{max} and AUC following repeat dose administration (200 mg every 12 hours for 17 days) in healthy subjects. Repeat dose administration of voriconazole (200 mg every 12 hours for 7 days) did not have a significant effect on steady state C_{max} and AUC_T of indinavir following repeat dose administration (800 mg TID for 7 days) in healthy subjects.

12.4 Microbiology en genders. The steady state trough voriconazole 1% and 91% higher than in males receiving the Mechanism of Action

Voriconazole is an azole antifungal drug. The primary mode of action of voriconazole is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell wall and may be responsible for the antifungal transformation. activity of voriconazole.

<u>Resistance</u>

Residuate A potential for development of resistance to voriconazole is well known. The mechanisms of resistance may include mutations in the gene ERG11 (encodes for the target enzyme, lanosterol $14-\alpha$ -demethylase), upregulation of genes encoding the ATP-binding cassette efflux transporters i.e., Candida drug resistance (CDR) pumps and reduced access of the drug to the target, or some combination of those mechanisms. The frequency of drug resistance development for the various transformation bit bit drug is included to the pott power. fungi for which this drug is indicated is not known.

Fungal isolates exhibiting reduced susceptibility to fluconazole or itraconazole may also show reduced susceptibility to voriconazole, suggesting cross-resistance can occur among these azoles. The relevance of cross-resistance and clinical outcome has not been fully characterized. Clinical cases where azole cross-resistance is demonstrated may require alternative antifungal therapy. Antimicrobial Activity

Voriconazole has been shown to be active against most isolates of the following microorganisms, **both** *in vitro* and in clinical infections.

both <i>in vitro</i> and in clinical infections.	
Aspergillus fumigatus	Candida krusei
Aspergillus flavus	Candida parapsilosi
A share wailloon minen	On a dida tura di anti-

Aspergillus niger *Candida tropicalis Fusarium* spp. including *Fusarium solani* Aspergillus terreus Candida albicans Scedosporium apiospermum

Candida glabrata (In clinical studies, the voriconazole MIC90 was 4 µg/mL)*

* In clinical studies, voriconazole MIC_{Q0} for *C. glabrata* baseline isolates was 4 µg/mL; 13/50 (26%) *C. glabrata* baseline isolates were resistant (MIC \ge 4 µg/mL) to voriconazole. However, based on 1054 isolates tested in surveillance studies the MIC₉₀ was 1 µg/mL.

The following data are available, but their clinical significance is unknown. At least 90 percent of the following fungi exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for voriconazole against isolates of similar genus or organism group. However, the effectiveness of voriconazole in treating clinical infections due to these fungi has not been established in adequate and well-controlled clinical trials:

Candida lusitaniae Candida guillie

Susceptibility Testing For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: 12.5 Pharmacogenomics

12.5 Praimacogenomics CYP2C19, significantly involved in the metabolism of voriconazole, exhibits genetic polymorphism. Approximately 15-20% of Asian populations may be expected to be poor metabolizers. For Caucasians and Blacks, the prevalence of poor metabolizers is 3-5%. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolizers have, on average, 4-fold higher voriconazole exposure (AUC_x) than their homozygous extensive metabolizer counterparts. Subjects who are heterozygous extensive metabolizers have, on average, 2-fold higher voriconazole exposure than their homozygous extensive metabolizer counterparts [see *Clinical Pharmacology* (12.3)].

13 NONCLINICAL TOXICOLOGY

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
11.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
11.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
11.1 Vor-year carcinogenicity studies were conducted in rats and mice. Rats were given oral doses of 6, 18 or 50 mg/kg voriconazole, or 0.2, 0.6, or 1.6 times the RMD on a body surface area basis. Hepatocellular actionmas were detected in females at 50 mg/kg undo and hepatocellular carcinomas were detected in males and females and hepatocellular carcinomas were detected in males and females and hepatocellular carcinomas were detected in males at 1.4 times the RMD on a body surface area basis. In mice, hepatocellular adenomas were detected classed classingenic activity (mostly chromosome breaks) in human lymphocyte cultures *in vitro*. Voriconazole was not genotoxic in the Ames assay, CHO HGPRT assay, the mouse micronucleus assay or the *in vivo* DNA repair test (Unscheduled DNA Synthesis assay).

Voriconazole administration induced no impairment of male or female fertility in rats dosed at

ts with normal renal function and mild to severe 50 mg/kg, or 1.6 times the RMD.

14 CLINICAL STUDIES /oriconazole, administered orally or parenterally, has been evaluated as primary or salvage therapy in 520 patients aged 12 years and older with infections caused by *Aspergillus* spp., *Fusarium* spp. and *Scedosporium* spp.

14.1 Invasive Aspergillosis (IA)

Voriconazole was studied in patients for primary therapy of IA (randomized, controlled study 307/602), for primary and salvage therapy of aspergillosis (non-comparative study 304) and for treatment of patients with IA who were refractory to, or intolerant of, other antifungal therapy (non-comparative study 309/604).

Study 307/602 - Primary Therapy of Invasive Aspergillosis

Study 30//602 – Primary inerapy of invasive Asperginiosis The efficacy of voriconazole compared to amphotericin B in the primary treatment of acute IA was demonstrated in 277 patients treated for 12 weeks in a randomized, controlled study (Study 307/602). The majority of study patients had underlying hematologic malignancies, including bone marrow transplantation. The study also included patients with solid organ transplantation, solid tumors, and AIDS. The patients were mainly treated for definite or probable IA of the lungs. Other aspergillosis infections included disseminated disease, CNS infections and sinus infections. Diagnosis of definite or probable IA was made according to criteria modified from those established by the National Institute of Allergy and Infectious Diseases Mycoses Study Group/European Organisation for Research and Treatment of Cancer (NIAID MSG/EORTC).

Organisation for Research and Treatment of Cancer (NIAID MSG/EORTC). Voriconazole was administered intravenously with a loading dose of 6 mg/kg every 12 hours for the first 24 hours followed by a maintenance dose of 4 mg/kg every 12 hours for a minimum of 7 days. Therapy could then be switched to the oral formulation at a dose of 200 mg every 12 hours. Median duration of IV voriconazole therapy was 10 days (range 2-85 days). After IV voriconazole therapy, the median duration of PO voriconazole therapy was 10 days (range 2-85 days). After IV voriconazole therapy, the median duration of PO voriconazole therapy was 10 days (range 2-82 days). Patients in the comparator group received conventional amphotericin B as a slow infusion at daily dose of 1.0-1.5 mg/kg/day. Median duration of IV amphotericin therapy was 12 days (range 1-85 days). Treatment was then continued with OLAT, including itraconazole and lipid amphotericin B formulations. Although initial therapy with conventional amphotericin of B was to be continued for at least two weeks, actual duration of therapy was at the discrition of the investigator. Patients who discontinued initial randomized therapy due to toxicity or lack of efficacy were eligible to continue in the study with OLAT reatment. A satisfactory olobal response at 12 weeks (complete or partial resolution of all attributable

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Table 17: Clinical and Mycological Outcome by Baseline Pathogen in Patients with Esophageal Candidiasis (Study-150-305) Voriconazole Favorable endoscopic N Pathogena Mycological Favorable endoscopic eradicationb response^b Success/Total eradicationb responseb Success/Total Eradication/Total Fradication/Tota
 Interface
 <thInterface</th>
 Interface
 <thInterface</th>
 Interface
 (%) 91/115 (79%) 1/4 (25%)

a Some patients had more than one species isolated at baselin Patients with endoscopic and/or mycological assessment at end of therapy

14.4 Other Serious Fungal Pathogens

In pooled analyses of patients, voriconazole was shown to be effective against the following

additional fungal pathogens: Scedosporium range patilogens. Scedosporium apiospermum - Successful response to voriconazole therapy was seen in 15 of 24 patients (63%). Three of these patients relapsed within 4 weeks, including 1 patient with pulmonary, skin and eye infections, 1 patient with cerebral disease, and 1 patient with skin infection. Ten patients had evidence of cerebral disease and 6 of these had a successful outcome (1 relapse). In addition, a successful response was seen in 1 of 3 patients with mixed organism infections.

Infections. Fusarium spp. - Nine of 21 (43%) patients were successfully treated with voriconazole. Of these 9 patients, 3 had eye infections, 1 had an eye and blood infection, 1 had a skin infection, 1 had a blood infection alone, 2 had sinus infections, and 1 had disseminated infection (pulmonary, skin, hepatosplenic). Three of these patients (1 with disseminated disease, 1 with an eye infection and 1 with a blood infection) had *Fusarium solani* and were complete successes. Two of these patients relapsed, 1 with a sinus infection and profound neutropenia and 1 post surgical patient with blood and eye infections.

14.5 Pediatric Studies

C. krusei

A total of 22 patients aged 12 to 18 years with IA were included in the adult therapeutic studies. Twelve out of 22 (55%) patients had successful response after treatment with a maintenance dose of uncincented a merical to merical to the successful response after treatment with a maintenance dose refunction of the successful response after treatment with a maintenance dose refunction of the successful response after treatment with a maintenance dose refunction of the successful response after treatment with a maintenance dose refunction of the successful response after treatment with a maintenance dose refunction of the successful response after treatment with a maintenance dose refunction of the successful response after treatment with a maintenance dose refunction of the successful response after treatment with a maintenance dose refunction of the successful response after treatment with a maintenance dose refunction of the successful response after treatment with a maintenance dose refunction of the successful response after treatment with a maintenance dose refunction of the successful response after treatment with a maintenance dose refunction of the successful response after treatment with a maintenance dose refunction of the successful response after treatment with a maintenance response after the successful response after treatment with a maintenance response after the successful response after treatment with a maintenance response after the successful response after treatment with a maintenance response after the successful response after treatment with a maintenance response after the successful response after treatment with a maintenance response after tresponse after response response after response after resp of voriconazole 4 mg/kg every 12 hours.

Fifty-three pediatric patients aged 2 to less than 18 years old were treated with voriconazole in two prospective, open-label, non-comparative, multicenter clinical studies.

two prospective, open-label, non-comparative, multicenter clinical studies. One study was designed to enroll pediatric patients with IA or infections with rare molds (such as *Scedosportium or Fusarium*). Patients aged 2 to less than 12 years and 12 to 14 years with body weight less than 50 kg received an intravenous voriconazole loading dose of 9 mg/kg every 12 hours for the first 24-hours followed by an 8 mg/kg intravenous maintenance dose every 12 hours. After completing 7 days of intravenous therapy patients had an option to switch to oral voriconazole. The oral maintenance dose was 9 mg/kg every 12 hours (maximum dose of 350 mg). All other pediatric patients aged 12 to less than 18 years received the adult voriconazole dosage regimen. Patients received voriconazole for at least 6 weeks and up to a maximum of 12 weeks.

The study enrolled 31 patients with possible, proven, or probable IA. Fourteen of 31 patients, 5 of whom were 2 to less than 12 years old and 9 of whom were 12 to less than 18 years old, had proven or probable IA and were included in the modified intent-to-treat (MITT) efficacy analyses. No patients with rare mold were enrolled. A successful global response was defined as resolution or improvement in clinical signs and symptoms and at least 50% resolution of radiological lesions attributed to IA. The overall rate of successful global response at 6 weeks in the MITT population is presented in Table 18 below.

Table 18: Global Response^a in Patients with Invasive Aspergillosis, Modified Intent-to-Treat

(MILL) [®] Population			
	Global Response at Week 6		
Parameter	Ages 2-<12 years	Ages 12-<18 years	Overall
	N=5	N=9	N=14
mber of successes, n (%)	2 (40%)	7 (78%)	9 (64%)

^a Global response rate was defined as the number of subjects with a successful response (complete or partial) as a percentage of all subjects (including subjects with an indeterminate or missing response) at 6 weeks in the MITT population.
^b The Modified Intent-to-Treat (MITT) population was defined as all subjects who received at least 1 dose

of study drug and who were diagnosed with proven or probable IA as defined by the modified EORTC/MSG

The second study enrolled 22 patients with invasive candidiasis including candidemia (ICC) and The second study enrolled 22 patients with invasive canolicitas's including candidering in (LC) and EC requiring either primary or salvage therapy. Patients with ICC aged 2 to less than 12 years and 12 to 14 years with body weight less than 50 kg received an intravenous voriconazole loading dose of 9 mg/kg every 12 hours for the first 24 hours followed by an 8 mg/kg intravenous maintenance dose every 12-hours. After completing 5 days of intravenous therapy patients had an option to switch to oral voriconazole. The oral maintenance dose was 9 mg/kg every 12 hours (maximum dose of 350 mg). All other pediatric patients aged 12 to less than 18 years received the adult uncensered learner agringer Vorigonzele unce administered for at least 14 days effort the adult voriconazole dosage regimen. Voriconazole was administered for at least 14 days after the last positive culture. A maximum of 42 days of treatment was permitted.

Patients with primary or salvage EC aged 2 to less than 12 years and 12 to 14 years with body weight less than 50 kg received an intravenous voriconazole dose of 4 mg/kg every 12 hours followed by an oral voriconazole dose of 9 mg/kg every 12 hours (maximum dose of 350 mg) when criteria for oral switch were met. All other pediatric patients aged 12 to less than 18 years received the adult voriconazole dosage regimen. Voriconazole was administered for at least 7 days after the resolution of clinical signs and symptoms. A maximum of 42 days of treatment was parcented.

For EC, study treatment was initiated without a loading dose of intravenous voriconazole. Seventeen of these patients had confirmed *Candida* infection and were included in the MITT efficacy analyses. Of the 17 patients included in the MITT analyses, 9 were 2 to less than 12 years old (7 with ICC and 2 with EC) and 8 were 12 to less than 18 years old (all with EC). For ICC and EC, a successful global response was defined as clinical cure or improvement with microbiological eradication or presumed eradication. The overall rate of successful global response at EOT in the MITT population presented in Table 19 below

Table 19: Global Response^a at the End of Treatment in the Treatment of Invasive Candidiasis with Candidemia and Esophageal Candidiasis Modified Intent-to-Treat (MITT) Population^b

Global Response at End of Treatment ICC^C N=7
 Falameter
 EL
 NLC²

 Etc
 N=7
 N=7

 Ages 2-<12</th>
 Ages 12-<18</th>
 Overall
 Overall

 N=2
 N=8
 N=10
 N=7

 Number of successes, n (%)
 2 (100%)
 5 (63%)
 7 (70%)
 6 (86%)

^a Global response was determined based on the investigator's assessment of clinical and microbiological response in the Modified Intent-to-Treat (MITT) analysis population at end of treatment. Subjects with the subject is a subject with the subject is a subject of the subject is a subject in the subject in the subject is a subject in the subject is a subject in the subject is a subject in the subject in the subject is a subject in the subject in the subject is a subject in the subject in the subject in the subject is a subject in the subj

nissing data or whose response was deemed indeterminate were considered failures. The MITT population was defined as all subjects who received at least 1 dose of study drug and who had microbiologically confirmed invasive candidiasis with candidemia (ICC) and EC, or subjects with EC who had at least confirmation of oropharyngeal candidiasis without confirmation on esophagoscopy. • All subjects with ICC were aged 2 to less than 12.

16 HOW SUPPLIED/STORAGE AND HANDLING 16.1 How Supplied

Powder for Oral Suspension

Voriconazole for oral suspension is supplied in 100 mL high density polyethylene (HDPE) bottles. Each bottle contains 49 grams of powder for oral suspension. Following reconstitution, the volume of the suspension is 75 mL, providing a usable volume of 70 mL (40 mg voriconazole/mL). A 5 mL oral dispenser and a press-in bottle adaptor are also provided.

(NDC 43386-038-60) 16.2 Storage

Voriconazole powder for oral suspension should be stored at 2°C to 8°C (36°F to 46°F) (in a efrigerator) before reconstitution. The shelf-life of the powder for oral suspension is 24 months The reconstituted suspension should be stored at 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Do not refrigerate or freeze. Keep the container tightly closed. The shelf-life of the reconstituted suspension is 14 days. Any remaining suspension should be discarded 14 does of the responsibilities and the store of the store

lays after reconstitutio 17 PATIENT COUNSELING INFORMATION

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

Visual Disturbances Patients should be instructed that visual disturbances such as blurring and sensitivity to light may occur with the use of voriconazole

Photosensitivity · Advise patients of the risk of photosensitivity (with or without concomitant methotrexate)

accelerated photoaging, and skin cancer. Advise patients that voriconazole can cause serious photosensitivity and to immediately contact their healthcare provider for new or worsening skin rash.

· Advise patients to avoid exposure to direct sun light and to use measures such as protective clothing and sunscreen with high sun protection factor (SPF).

Embryo-Fetal Toxicity

Advise female patients of the potential risks to a fetus.
 Advise females of reproductive potential to use effective contraception during treatment with voriconazole.

Manufactured for: Lupin Pharmaceuticals, Inc. Baltimore, MD 21202

the stand miscarriage for the indicated populations is e estimated background risk of major birth defects and ncies is 2-4% and 15-20% respectively.

Animal Data Voriconazole was administered orally to pregnant rats during organogenesis (gestation days 6-17) at 10, 30, and 60 mg/kg/day. Voriconazole was associated with increased incidences of the malformations hydroureter and hydronephrosis at 10 mg/kg/day or greater, approximately 0.3 times the recommended human dose (RMD) based on body surface area comparisons, and cleft palate at 60 mg/kg, approximately 2 times the RMD based on body surface area comparisons, and cleft ribs, anomalies of the sternebrae, and dilatation of the ureter/renal pelvis were also observed at doses of 10 mg/kg or greater. There was no evidence of maternal toxicity at any dose. Voriconazole was administered orally to pregnant rabbits during the period of oragnogenesis (gestation days 7-19) at 10, 40, and 100 mg/kg/day. Voriconazole was associated with increased post-implantation loss and decreased fetal body weight, in association with maternal toxicity (decreased body weight gain and food consumption) at 100 mg/kg/day. It mes the RMD based on body surface area comparisons). Fetal skeletal variations (increases in the incidence of cervical rib and extra sternebra) assilication sites) were observed at 100 mg/kg/day. In a peri- and postnatal rokicity study in rats, voriconazole was administered orally to female rats from dopstand rokidy undy in rats, voriconazole was administered orally to female rats from appendix

toxicity study in rats, voriconazole was administered orally to female rats from implantation through the end of lactation at 1, 3, and 10 mg/kg/day. Voriconazole prolonged the duration of gestation and labor and produced dystocia with related increases in maternal mortality and decreases in perinatal survival of F1 pups at 10 mg/kg/day, approximately 0.3 times the RMD.

and Precautions (5.9)].



and pull back oral dispenser

plunger. Draw prescribed

dose of medicine into oral

dispenser.

Æ

9

Rinse the oral dispenser with water after each dose.

Manufactured by: Manufactured for: Novel Laboratories, Inc. Lupin Pharmaceuticals, Inc. Somerset, NJ 08873 Baltimore, MD 21202

SAP Code: 271950 Rev. 11/2022

8.2 Lactation Risk Summary

No data are available regarding the presence of voriconazole in human milk, the effects of voriconazole on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for voriconazole and any potential adverse effects on the breastfed child from voriconazole or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Advise females of reproductive potential to use effective contraception during treatment with voriconazole. The coadministration of voriconazole with the oral contraceptive, Ortho-Novum[®] (35 mcg ethinyl estradiol and 1 mg norethindrone), results in an interaction between these two drugs, but is unlikely to reduce the contraceptive effect. Monitoring for adverse reactions associated with oral contraceptives and voriconazole is recommended [see Drug Interactions (7) and Clinical Pharmacology (12.3)].

8.4 Pediatric Use

The safety and effectiveness of voriconazole have been established in pediatric patients 2 years of age and older based on evidence from adequate and well-controlled studies in adult and pediatric patients and additional pediatric pharmacokinetic and safety data. A total of 105 pediatric patients Contraindications (4)]. **Ritonavir** (potent CYP450 inducer; CYP3A4 inhibitor and substrate)-The effect of the coadministration of voriconazole and ritonavir (400 mg and 100 mg) was investigated in two separate studies. High-dose ritonavir (400 mg every 12 hours for 9 days) decreased the steady state C_{max} and AUC_x of oral voriconazole (400 mg every 12 hours for 9 days) decreased the steady state C_{max} and AUC_x of an average of 66% and 82%, respectively, in healthy subjects. Low-dose ritonavir (100 mg every 12 hours for 9 days) decreased the steady state C_{max} and AUC_y of oral voriconazole (400 mg every 12 hours for 1 day, then 200 mg every 12 hours for 8 days) by an average of 24% and 39%, respectively, in healthy subjects. Although repeat oral administration of voriconazole did not have a significant effect on steady state C_{max} and AUC_y of high-dose ritonavir in healthy subjects, steady state C_{max} and AUC_y of low-dose ritonavir decreased slightly by 24% and 14% respectively, when administered concomitantly with oral voriconazole in healthy subjects [see Contraindications (4)].

St. John's Worl (CYP450 inducer; P-gp inducer)—In an independent published study in healthy volunteers who were given multiple oral doses of St. John's Wort (300 mg Ll 160 extract three times daily for 15 days) followed by a single 400 mg oral dose of voriconazole, a 59% decrease in mean voriconazole AUC₀— ∞ was observed. In contrast, coadministration of single oral doses of St. John's Wort and voriconazole had no appreciable effect on voriconazole AUC₀— ∞ . Long-term use of St. John's Wort could lead to reduced voriconazole exposure [see Contraindications (4]]. Significant drug interactions that may require voriconazole dosage adjustment, or frequent monitoring of voriconazole-related adverse reactions/toxicity: A satisfactory global response at 12 weeks (complete or partial resolution of all attributable symptoms, signs, radiographic/bronchoscopic abnormalities present at baseline) was seen in 53% of voriconazole treated patients compared to 32% of amphotericin B treated patients (Table 15). A benefit of voriconazole compared to amphotericin B on patient survival at Day 84 was seen with a 71% survival rate on voriconazole compared to 58% on amphotericin B (Table 13). Rev. 11/2022

Table 13 also summarizes the response (success) based on mycological confirmation and species.

Table 13: Overall Efficacy and Success by Species in the Primary Treatment of Acute Invasive Aspergillosis Study 307/602

hopolginoolo olaaj ool/ool			
	Voriconazole	Ampho B ^c	Stratified Difference (95% CI) ^d
	n/N (%)	n/N (%)	
Efficacy as Primary Therapy			
Satisfactory Global Response ^a	76/144 (53)	42/133 (32)	21.8% (10.5%, 33.0%) p<0.0001
Survival at Day 84 ^b	102/144 (71)	77/133 (58)	13.1%

11/17/2022 03:54 PM / NP Item# NOVE-NP_750293 / page 2 of 2