43386-038-60
VORICONAZOLE
for Oral Suspension

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.

VORICONAZOLE for Oral Suspension
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	Loading Dose	Maintenance Dose	
	Intravenous infusion	Intravenous infusion	Oral
Invasive Aspergillosis	6 mg/kg every 12 hours for the first 24 hours	4 mg/kg every 12 hours	200 mg every 12 hours
Candidemia in nonneutropenics and other deep tissue *Candida* infections		3-4 mg/kg every 12 hours	200 mg every 12 hours
Scedosporiosis and Fusariosis		4 mg/kg every 12 hours	200 mg every 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)

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

o For pediatric patients 2 to less than 12 years of age and 12 to 14 years of age weighing less than 50 kg see Table below.

Infection	Loading dose	Maintenance Dose	
	Intravenous infusion	Intravenous infusion	Oral
Invasive Aspergillosis	9 mg/kg every 12 hours for the first 24 hours	8 mg/kg every 12 hours after the first 24 hours	9 mg/kg every 12 hours (maximum dose of 350 mg every 12 hours)
Candidemia in nonneutropenics and other deep tissue *Candida* infections			
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)

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 suspension and important administration instructions (2.1, 2.6, 2.7)

DOSAGE 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 reactions (4, 7)
- Coadministration with rifampin, carbamazepine, long-acting barbiturates, efavirenz, ritonavir, rifabutin, ergot alkaloids, and St. John's Wort 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 during voriconazole therapy (5.1)
- *Arrhythmias and QT Prolongation*: Correct potassium, magnesium and calcium prior to use; caution patients with proarrhythmic conditions (5.2)
- *Infusion Related Reactions (including anaphylaxis)*: Stop the infusion (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 periostitis 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 ≥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, peripheral edema, hyperglycemia, tachycardia, dyspnea, hypocalcemia, hypophosphatemia, LFT abnormal, mucosal inflammation, photophobia, abdominal distention, constipation, dizziness, hallucinations, hemoptysis, hypoalbuminemia, hypomagnesemia, renal impairment, upper respiratory tract infection (6)

To 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)
- Voriconazole 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)

USE IN SPECIFIC POPULATIONS

Pediatrics: Safety and effectiveness in patients younger than 2 years has not been established (8.4)

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

Rev. 11/2022

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Invasive Aspergillosis

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)]*.

[illegible]

In patients with moderate or severe renal impairment (creatinine clearance <50 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)]*.

Voriconazole and the intravenous vehicle, SBECD, are dialyzable. A 4-hour hemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment *[see Clinical*

[illegible]

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

	Criteria*	Voriconazole n/N (%)	Fluconazole n /N (%)
T. Bilirubin	>1.5x ULN	8/185 (4.3)	7/186 (3.8)
AST	>3.0x ULN	38/187 (20.3)	15/186 (8.1)
ALT	>3.0x ULN	20/187 (10.7)	12/186 (6.5)
Alkaline Phosphatase	>3.0x ULN	19/187 (10.2)	14/186 (7.5)

*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

Table 6: Protocol 307/602 – Primary Treatment of Invasive Aspergillosis Clinically Significant Laboratory Test Abnormalities

	Criteria*	Voriconazole n/N (%)	Amphotericin B** 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)

*Without regard to baseline value
**Amphotericin B followed by other licensed antifungal therapy
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

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

	Criteria*	Voriconazole n/N (%)	Amphotericin B followed by Fluconazole n/N (%)
T. Bilirubin	>1.5x ULN	50/261 (19.2)	31/115 (27.0)
AST	>3.0x ULN	40/261 (15.3)	16/116 (13.8)
ALT	>3.0x ULN	22/261 (8.4)	15/116 (12.9)
Alkaline Phosphatase	>3.0x ULN	59/261 (22.6)	26/115 (22.6)
Creatinine	>1.3x ULN	39/260 (15.0)	32/118 (27.1)
Potassium	<0.9x LLN	43/258 (16.7)	35/118 (29.7)

[illegible]

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?

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.

Do not take voriconazole if you:

- **are allergic to voriconazole or any of the ingredients in voriconazole.** See the end of this leaflet for a complete list of ingredients in voriconazole.
- **are taking any of the following medicines:**
  - pimozide
  - quinidine
  - sirolimus
  - rifampin
  - carbamazepine
  - long-acting barbiturates like phenobarbital
  - efavirenz
  - ritonavir
  - rifabutin
  - ergotamine, dihydroergotamine (ergot alkaloids)
  - St. John's Wort (herbal supplement)
  - tolvaptan
  - naloxegol
  - lurasidone
  - ivabradine
  - venetoclax

Ask your healthcare provider or pharmacist if you are not sure if you are taking any of the medicines listed above.

Do not start taking a new medicine without talking to your healthcare provider or pharmacist.

Before you take voriconazole, tell your healthcare provider about all of your medical conditions, including if you:

- have or ever had heart disease, or an abnormal heart rate or rhythm. Your healthcare provider may order a test to check your heart (EKG) before starting voriconazole.
- have low potassium levels, low magnesium levels, and low calcium levels. Your healthcare provider may do blood tests before starting and during treatment with voriconazole
- have liver or kidney problems. Your healthcare provider may do blood tests to make sure you can take voriconazole.
- have trouble digesting dairy products, lactose (milk sugar), or regular table sugar. Voriconazole for oral suspension contains sucrose (table sugar).
- 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 be right for you.
- 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 if you take voriconazole.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.
Voriconazole may affect the way other medicines work, and other medicines may affect how voriconazole works.

Know what medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I take voriconazole?

- **Voriconazole may be prescribed to you as:**
  - Voriconazole for oral suspension
- Take voriconazole for oral suspension exactly as your healthcare provider tells you to.
- Take voriconazole for oral suspension at least 1 hour before or at least 1 hour after meals.
- 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 medicine, flavored liquid, or syrup.
- If you take too much voriconazole, call your healthcare provider or go to the nearest hospital emergency room.

What should I avoid while taking voriconazole?

- You should not drive at night while taking voriconazole. Voriconazole can cause changes in your vision such as blurring or sensitivity to light.
- Do not drive or operate machinery, or do other dangerous activities until you know how voriconazole affects you.
- 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 provider if you get sunburn.

What are possible side effects of voriconazole?

Voriconazole may cause serious side effects including:

- **liver problems.** Symptoms of liver problems may include:
  - itchy skin
  - yellowing of your eyes
  - feeling very tired
  - flu-like symptoms
  - nausea or vomiting
- **vision changes.** Symptoms of vision changes may include:
  - blurred vision
  - changes in the way you see colors
  - sensitivity to light or sun (photosensitivity). voriconazole can cause serious photosensitivity. There is an increased chance of skin toxicity while taking voriconazole. This can happen with or without taking other medicines like methotrexate.

  Photosensitivity reactions may also increase your risk of:
  - faster skin aging from the sun
  - skin cancer

Call your healthcare provider right away if you get a new skin rash or your skin rash gets worse.

- **serious heart problems.** Voriconazole may cause changes in your heart rate or rhythm, including your heart stopping (cardiac arrest).
- **allergic reactions.** Symptoms of an allergic reaction may include:
  - fever
  - sweating
  - feels like your heart is beating fast (tachycardia)
  - chest tightness
  - trouble breathing
  - feel faint
  - nausea
  - itching
  - skin rash
- **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 voriconazole
- **serious skin reactions.** Symptoms of serious skin reactions may include:
  - rash or hives
  - 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 weakness
o nausea and vomiting
o feeling dizzy or lightheaded
o weight loss
o abdominal pain

Symptoms of Cushing's syndrome include:

- o weight gain
- o fatty hump between the shoulders (buffalo hump) and a rounded face (moon face)
- o darkening of the skin on the stomach, thighs, breasts, and arms
- o thinning skin
- 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 or hearing things that are not there)
- abnormal liver function tests
- fever
- chills

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 membranes
- abnormal liver function tests
- low blood pressure
- constipation
- low blood calcium levels
- high blood sugar levels
- low blood magnesium levels
- low blood phosphate levels
- vision changes
- rash
- headache
- fast heart beat (tachycardia)
- Fullness of the stomach area
- vomiting
- 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.

What are the ingredients of voriconazole?

Active ingredient: voriconazole

Inactive ingredients:

Voriconazole oral suspension: colloidal silicon dioxide, titanium dioxide, xanthan gum, sodium citrate dihydrate, sodium benzoate, anhydrous citric acid, natural and artificial orange flavor, and sucrose

This Patient Information has been approved by the U.S. Food and Drug Administration.

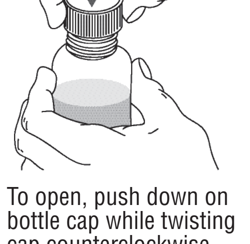
The brands listed are trademarks of their respective owners.

Assembly Instructions

CHECK WITH YOUR PHARMACIST TO ENSURE VORICONAZOLE FOR ORAL SUSPENSION HAS BEEN RECONSTITUTED (i.e. is in liquid form).

SHAKE CLOSED BOTTLE FOR APPROXIMATELY 10 SECONDS BEFORE EACH USE.

1

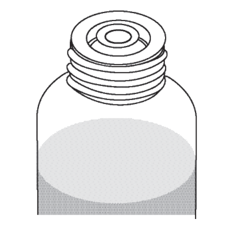


To open, push down on bottle cap while twisting cap counterclockwise. Remove cap from bottle.

2

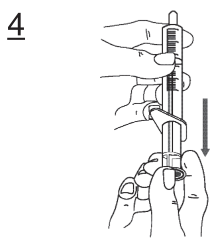
Push bottle adapter ALL THE WAY into bottle top (if pharmacist has not done so). Once bottle adapter is inserted, leave in place.

3



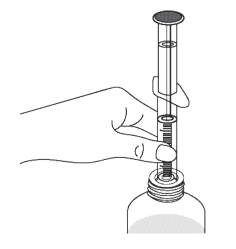
IMPORTANT: Adapter must be fully inserted prior to use.

4



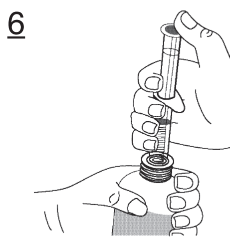
Pull back on oral dispenser plunger to prescribed dose.

5



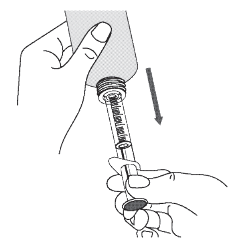
Insert oral dispenser into bottle top.

6



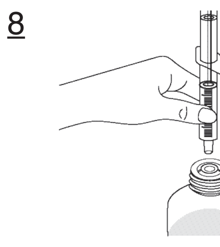
Holding the bottle with one hand, push down on oral dispenser plunger to push air into bottle.

7



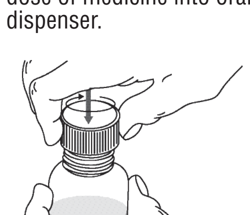
Turn bottle upside down and pull back oral dispenser plunger. Draw prescribed dose of medicine into oral dispenser.

8



Remove oral dispenser from bottle. Dispense medicine into mouth by slowly pushing on oral dispenser plunger.

9



Remember to leave the bottle adapter in the bottle and put the cap back on the bottle. Store at room temperature.

Rinse the oral dispenser with water after each dose.

Manufactured by:
Novel Laboratories, Inc.
Somerset, NJ 08873

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

SAP Code: 271950
Rev. 11/2022

Drug/Drug Class (Mechanism of Interaction by Voriconazole)	Drug Plasma Exposure (C_{max} and AUC_τ)	Recommendations for Drug Dosage Adjustment/Comments
		For patients with acute myeloid leukemia (AML), dose reduction and safety monitoring are recommended across all dosing phases when coadministering voriconazole with venetoclax. Refer to the venetoclax prescribing information for dosing instructions.
Lemborexant (CYP3A4 Inhibition)	Not Studied *In Vivo* or *In Vitro*, but Drug Plasma Exposure Likely to be Increased	Avoid concomitant use of Voriconazole with lemborexant.
Glasdegib (CYP3A4 Inhibition)	Not Studied *In Vivo* or *In Vitro*, but Drug Plasma Exposure Likely to be Increased	Consider alternative therapies. If concomitant use cannot be avoided, monitor patients for increased risk of adverse reactions including QTc interval prolongation.
Tyrosine kinase inhibitors (including but not limited to axitinib, bosutinib, cabozantinib, ceritinib, cobimetinib, dabrafenib, dasatinib, nilotinib, sunitinib, ibrutinib, ribociclib) (CYP3A4 Inhibition)	Not Studied *In Vivo* or *In Vitro*, but Drug Plasma Exposure Likely to be Increased	Avoid concomitant use of Voriconazole. If concomitant use cannot be avoided, dose reduction of the tyrosine kinase inhibitor is recommended. Refer to the prescribing information for the relevant product.
Lurasidone (CYP3A4 Inhibition)	Not Studied *In Vivo* or *In Vitro*, but Voriconazole is Likely to Significantly Increase the Plasma Concentrations of Lurasidone	**Contraindicated**
Cyclosporine* (CYP3A4 Inhibition)	AUC_τ Significantly Increased; No Significant Effect on C_{max}	When initiating therapy with voriconazole in patients already receiving cyclosporine, reduce the cyclosporine dose to one-half of the starting dose and follow with frequent monitoring of cyclosporine blood levels. Increased cyclosporine levels have been associated with nephrotoxicity. When voriconazole is discontinued, cyclosporine concentrations must be frequently monitored and the dose increased as necessary.
Methadone*** (CYP3A4 Inhibition)	Increased	Increased plasma concentrations of methadone have been associated with toxicity including QT prolongation. Frequent monitoring for adverse reactions and toxicity related to methadone is recommended during coadministration. Dose reduction of methadone may be needed.
Fentanyl (CYP3A4 Inhibition)	Increased	Reduction in the dose of fentanyl and other long-acting opiates metabolized by CYP3A4 should be considered when coadministered with voriconazole. Extended and frequent monitoring for opiate-associated adverse reactions may be necessary.
Alfentanil (CYP3A4 Inhibition)	Significantly Increased	An increase in the incidence of delayed and persistent alfentanil-associated nausea and vomiting were observed when coadministered with voriconazole. Reduction in the dose of alfentanil and other opiates metabolized by CYP3A4 (e.g., sufentanil) should be considered when coadministered with voriconazole. A longer period for monitoring respiratory and other opiate-associated adverse reactions may be necessary.
Oxycodone (CYP3A4 Inhibition)	Significantly Increased	Increased visual effects (heterophoria and miosis) of oxycodone were observed when coadministered with voriconazole. Reduction in the dose of oxycodone and other long-acting opiates metabolized by CYP3A4 should be considered when coadministered with voriconazole. Extended and frequent monitoring for opiate-associated adverse reactions may be necessary.
NSAIDs**** including. ibuprofen and diclofenac (CYP2C9 Inhibition)	Increased	Frequent monitoring for adverse reactions and toxicity related to NSAIDs. Dose reduction of NSAIDs may be needed.
Tacrolimus* (CYP3A4 Inhibition)	Significantly Increased	When initiating therapy with voriconazole in patients already receiving tacrolimus, reduce the tacrolimus dose to one-third of the starting dose and follow with frequent monitoring of tacrolimus blood levels. Increased tacrolimus levels have been associated with nephrotoxicity. When voriconazole is discontinued, tacrolimus concentrations must be frequently monitored and the dose increased as necessary.
Phenytoin* (CYP2C9 Inhibition)	Significantly Increased	Frequent monitoring of phenytoin plasma concentrations and frequent monitoring of adverse effects related to phenytoin.
Oral Contraceptives containing ethinyl estradiol and norethindrone (CYP3A4 Inhibition)**	Increased	Monitoring for adverse reactions related to oral contraceptives is recommended during coadministration.
Prednisolone and other corticosteroids (CYP3A4 Inhibition)	*In Vivo* Studies Showed No Significant Effects of voriconazole on Prednisolone Exposure Not Studied *In Vivo* or *In Vitro*, for Other Corticosteroids, but Drug Exposure Likely to be Increased	No dosage adjustment for for prednisolone when coadministered with voriconazole *[see Clinical Pharmacology (12.3)]*. Monitor for potential adrenal dysfunction when voriconazole is administered with other corticosteroids *[See Warnings and Precautions (5.8)]*.
Warfarin* (CYP2C9 Inhibition) Other Oral Coumarin Anticoagulants (CYP2C9/3A4 Inhibition)	Prothrombin Time Significantly Increased Not Studied *In Vivo* or *In Vitro* for other Oral Coumarin Anticoagulants, but Drug Plasma Exposure Likely to be Increased	If patients receiving coumarin preparations are treated simultaneously with voriconazole, the prothrombin time or other suitable anticoagulation tests should be monitored at close intervals and the dosage of anticoagulants adjusted accordingly.
Ivacaftor (CYP3A4 Inhibition)	Not Studied *In Vivo* or *In Vitro*, but Drug Plasma Exposure Likely to be Increased which may Increase the Risk of Adverse Reactions	Dose reduction of ivacaftor is recommended. Refer to the prescribing information for ivacaftor
Eszopiclone (CYP3A4 Inhibition)	Not Studied *In Vivo* or *In Vitro*, but Drug Plasma Exposure Likely to be Increased which may Increase the Sedative Effect of Eszopiclone	Dose reduction of eszopiclone is recommended. Refer to the prescribing information for eszopiclone.
Omeprazole* (CYP2C19/3A4 Inhibition)	Significantly Increased	When initiating therapy with voriconazole in patients already receiving omeprazole doses of 40 mg or greater, reduce the omeprazole dose by one-half. The metabolism of other proton pump inhibitors that are CYP2C19 substrates may also be inhibited by voriconazole and may result in increased plasma concentrations of other proton pump inhibitors.
Other HIV Protease Inhibitors (CYP3A4 Inhibition)	*In Vivo* Studies Showed No Significant Effects on Indinavir Exposure *In Vitro* Studies Demonstrated Potential for Voriconazole to Inhibit Metabolism (Increased Plasma Exposure)	No dosage adjustment for indinavir when coadministered with voriconazole Frequent monitoring for adverse reactions and toxicity related to other HIV protease inhibitors.
Other NNRTIs***** (CYP3A4 Inhibition)	A Voriconazole-Efavirenz Drug Interaction Study Demonstrated the Potential for Voriconazole to Inhibit Metabolism of Other NNRTIs (Increased Plasma Exposure)	Frequent monitoring for adverse reactions and toxicity related to NNRTI
Tretinoin (CYP3A4 Inhibition)	Although Not Studied, Voriconazole may Increase Tretinoin Concentrations and Increase the Risk of Adverse Reactions	Frequent monitoring for signs and symptoms of pseudotumor cerebri or hypercalcemia.
Midazolam (CYP3A4 Inhibition) Other benzodiazepines including triazolam and alprazolam (CYP3A4 Inhibition)	Significantly Increased *In Vitro* Studies Demonstrated Potential for Voriconazole to Inhibit Metabolism (Increased Plasma Exposure)	Increased plasma exposures may increase the risk of adverse reactions and toxicities related to benzodiazepines. Refer to drug-specific labeling for details.
HMG-CoA Reductase Inhibitors (Statins) (CYP3A4 Inhibition)	*In Vitro* Studies Demonstrated Potential for Voriconazole to Inhibit Metabolism (Increased Plasma Exposure)	Frequent monitoring for adverse reactions and toxicity related to statins. Increased statin concentrations in plasma have been associated with rhabdomyolysis. Adjustment of the statin dosage may be needed.
Dihydropyridine Calcium Channel Blockers (CYP3A4 Inhibition)	*In Vitro* Studies Demonstrated Potential for Voriconazole to Inhibit Metabolism (Increased Plasma Exposure)	Frequent monitoring for adverse reactions and toxicity related to calcium channel blockers. Adjustment of calcium channel blocker dosage may be needed.
Sulfonylurea Oral Hypoglycemics (CYP2C9 Inhibition)	Not Studied *In Vivo* or *In Vitro*, but Drug Plasma Exposure Likely to be Increased	Frequent monitoring of blood glucose and for signs and symptoms of hypoglycemia. Adjustment of oral hypoglycemic drug dosage may be needed.
Vinca Alkaloids (CYP3A4 Inhibition)	Not Studied *In Vivo* or *In Vitro*, but Drug Plasma Exposure Likely to be Increased	Frequent monitoring for adverse reactions and toxicity (i.e., neurotoxicity) related to vinca alkaloids. Reserve azole antifungals, including voriconazole, for patients receiving a vinca alkaloid who have no alternative antifungal treatment options.
Everolimus (CYP3A4 Inhibition)	Not Studied *In Vivo* or *In Vitro*, but Drug Plasma Exposure Likely to be Increased	Concomitant administration of voriconazole and everolimus is not recommended.

* Results based on *in vivo* clinical studies generally following repeat oral dosing with 200 mg BID voriconazole to healthy subjects
** Results based on *in vivo* clinical study following repeat oral dosing with 400 mg every 12 hours for 1 day, then 200 mg every 12 hours for at least 2 days voriconazole to healthy subjects
*** Results based on *in vivo* clinical study following repeat oral dosing with 400 mg every 12 hours for 1 day, then 200 mg every 12 hours for 4 days voriconazole to subjects receiving a methadone maintenance dose (30-100 mg every 24 hours)
**** Non-Steroidal Anti-Inflammatory Drug
***** Non-Nucleoside Reverse Transcriptase Inhibitors

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Voriconazole can cause fetal harm when administered to a pregnant woman. There are no available data on the use of voriconazole in pregnant women. In animal reproduction studies, oral voriconazole was associated with fetal malformations in rats and fetal toxicity in rabbits. Cleft palates and hydronephrosis/hydroureter were observed in rat pups exposed to voriconazole during organogenesis at and above 10 mg/kg (0.3 times the RMD of 200 mg every 12 hours based on body surface area comparisons). In rabbits, embryomortality, reduced fetal weight and increased incidence of skeletal variations, cervical ribs and extrasternal ossification sites were observed in pups when pregnant rabbits were orally dosed at 100 mg/kg (6 times the RMD based on body surface area comparisons) during organogenesis. Rats exposed to voriconazole from implantation to weaning experienced increased gestational length and dystocia, which were associated with increased perinatal pup mortality at the 10 mg/kg dose *[see Data]*. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, inform the patient of the potential hazard to the fetus *[see Warnings and Precautions (5.9)]*.

The background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20% respectively.

Data

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. Reduced ossification of sacral and caudal vertebrae, skull, pubic, and hyoid bone, supernumerary 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 organogenesis (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 (6 times the RMD based on body surface area comparisons). Fetal skeletal variations (increases in the incidence of cervical rib and extra sternebral ossification sites) were observed at 100 mg/kg/day. In a peri- and postnatal 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.

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 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 voriconazole use in the pediatric population *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

Safety and effectiveness in pediatric patients below the age of 2 years has not been established. 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 *[see Dosage and Administration (2.5), Warnings and Precautions (5.1), and Adverse Reactions (6.1)]*.

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 recommended in pediatric patients experiencing photoaging injuries, such as lentigines or ephelides, even after treatment discontinuation *[see Warnings and Precautions (5.6)]*.

Voriconazole has not been studied in pediatric patients with hepatic or renal impairment *[see 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)]*.

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 (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 therapeutic trials showed that voriconazole plasma concentrations in the elderly patients were approximately 80% 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 Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

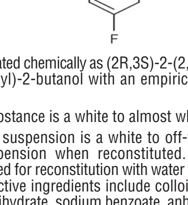
In clinical trials, there were three cases of accidental overdose. All occurred in pediatric patients who received up to five times the recommended intravenous dose of voriconazole. A single adverse reaction of photophobia of 10 minutes duration was reported.

There is no known antidote to voriconazole.

Voriconazole is hemodialyzed with clearance of 121 mL/min. The intravenous vehicle, SBECD, is hemodialyzed with clearance of 55 mL/min. In an overdose, hemodialysis may assist in the removal of voriconazole and SBECD from the body.

11 DESCRIPTION

Voriconazole, an azole antifungal agent is available as a lyophilized powder for oral suspension. The structural formula is:



Voriconazole is designated chemically as (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4- pyrimidinyl)-1-(1H-1,2,4 triazol-1-yl)-2-butanol with an empirical formula of $C_{16}H_{14}F_3N_5O$ and a molecular weight of 349.3.

Voriconazole drug substance is a white to almost white powder.

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 mg/mL 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Voriconazole is an antifungal drug *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Exposure-Response Relationship For Efficacy and Safety

In 10 clinical trials (N=1121), the median values for the average and maximum voriconazole 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 pharmacokinetic-pharmacodynamic analysis of patient data from 6 of these 10 clinical trials (N=280) could not detect a positive association between mean, maximum or minimum plasma voriconazole concentration and efficacy. However, pharmacokinetic/pharmacodynamic analyses of the data from all 10 clinical trials identified positive associations between plasma voriconazole concentrations and rate of both liver function test abnormalities and visual disturbances *[see Adverse Reactions (6)]*.

Cardiac Electrophysiology

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 ketoconazole. Serial ECGs 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 <10 msec. Females exhibited a greater increase in QTc than males, although all mean changes were <10 msec. Age was not found to affect the magnitude of increase in QTc. No subject in any group had an increase in QTc of ≥60 msec from baseline. No subject experienced an interval exceeding the potentially clinically relevant threshold of 500 msec. However, the QT effect of voriconazole combined with drugs known to prolong the QT interval is unknown *[see Contraindications (4) and Drug Interactions (7)]*.

12.3 Pharmacokinetics

The pharmacokinetics of voriconazole have been characterized in healthy subjects, special populations and patients.

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 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_τ); 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 (Table 12).

Table 12:
Geometric Mean (%CV) Plasma Voriconazole Pharmacokinetic Parameters in Adults Receiving Different Dosing Regimens

	6 mg/kg IV (loading dose)	3 mg/kg IV every 12 hours	4 mg/kg IV every 12 hours	400 mg Oral (loading dose)	200 mg Oral every 12 hours	300 mg Oral every 12 hours
N	35	23	40	17	48	16
AUC_{12} (µg•h/mL)	13.9 (32)	13.7 (53)	33.9 (54)	9.31 (38)	12.4 (78)	34.0 (53)
C_{max} (µg/mL)	3.13 (20)	3.03 (25)	4.77 (36)	2.30 (19)	2.31 (48)	4.74 (35)
C_{min} (µg/mL)	-	0.46 (97)	1.73 (74)	-	0.46 (120)	1.63 (79)

Note: Parameters were estimated based on non-compartmental analysis from 5 pharmacokinetic studies. AUC_{12} = area under the curve over 12 hour dosing interval, C_{max} = maximum plasma concentration, C_{min} = 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., 6 mg/kg IV every 12 hours on day 1 followed by 3 mg/kg IV 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.

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 healthy subjects (N=207), the oral bioavailability of voriconazole is estimated to be 96% (CV 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 maintenance dose.

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_τ are reduced by 34% and 24%, respectively when administered as a tablet and by 58% and 37% respectively when administered as the oral suspension *[see Dosage and Administration (2)]*.

In healthy subjects, the absorption of voriconazole is not affected by coadministration of oral ranitidine, cimetidine, or omeprazole, drugs that are known to increase gastric pH.

Distribution

The volume of distribution at steady state for voriconazole is estimated to be 4.6 L/kg, suggesting extensive distribution into tissues. Plasma protein binding is estimated to be 58% 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 µg/mL). Varying degrees of hepatic and renal impairment do not affect the protein binding of voriconazole.

Elimination

Metabolism

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. 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 metabolites in plasma. Since this metabolite has minimal antifungal activity, it does not contribute to the overall efficacy of voriconazole.

Excretion

Voriconazole is eliminated via hepatic metabolism with less than 2% of the dose excreted unchanged in the urine. 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 urine. The majority (>94%) of the total radioactivity is excreted in the first 96 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 predicting the accumulation or elimination of voriconazole.

Specific Populations

Male and Female Patients

In a multiple oral dose study, the mean C_{max} and AUC_τ 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 C_{max} and AUC_τ were observed between healthy elderly males and healthy elderly females (>65 years). In a similar study, after dosing with the oral 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_{min}) seen in females were 100% and 91% higher than in males receiving the 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 were similar. Therefore, no dosage adjustment based on gender is necessary.

Geriatric Patients

In an oral multiple dose study the mean C_{max} and AUC_τ in healthy elderly males (≥65 years) were 61% and 86% higher, respectively, than in young males (18-45 years). No significant differences in the mean C_{max} and AUC_τ were observed between healthy elderly females (≥65 years) and healthy young females (18-45 years).

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 the median voriconazole plasma concentrations in the elderly patients (>65 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 similar and, therefore, no dosage adjustment is necessary for the elderly *[see Use in Special Populations (8.5)]*.

Pediatric Patients

The recommended doses in pediatric patients were based on a population pharmacokinetic 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.

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 a 6 mg/kg intravenous loading dose. The predicted total exposures in pediatric patients aged 2 to less than 12 years following intravenous maintenance doses of 4 and 8 mg/kg twice daily were comparable to those in adults following 3 and 4 mg/kg IV twice daily, respectively. The predicted total exposure in pediatric patients aged 2 to less than 12 years following an oral maintenance 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.

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 exposure was observed in some pediatric patients aged 12 to less than 17 years with low body 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 years with IA or invasive candidiasis including candidemia, and EC in two prospective, 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 dose on the first day of treatment, followed by 8 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 years and aged 12 to 14 years, 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)]*.

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) hepatic impairment, the mean systemic exposure (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, 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_τ was similar in 6 subjects with moderate hepatic impairment (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 (C_{max}) were 20% lower in the hepatically impaired group. No pharmacokinetic data are available for patients with severe hepatic cirrhosis (Child-Pugh Class C) *[see Dosage and Administration (2.5)]*.

Patients with Renal Impairment

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 necessary for oral 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 dysfunction (creatinine clearance 30-50 mL/min), the 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), 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 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 C_{max} and AUC_τ 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)]*.

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_τ of oral voriconazole (400 mg every 12 hours for 1 day, then 200 mg every 12 hours for 8 days) by 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_τ 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_τ of high-dose ritonavir in healthy subjects, steady state C_{max} and AUC_τ 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 Wort **(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 LI 160 extract three times daily for 15 days) followed by a single 400 mg oral dose of voriconazole, a 59% decrease in mean voriconazole $AUC_{0-\infty}$ was observed. In contrast, coadministration of single oral doses of St. John's Wort and voriconazole had no appreciable effect on voriconazole $AUC_{0-\infty}$. 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:

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 2.5 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_τ 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 and fluconazole 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 AUC_{0-12} 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 adjustment:

Cimetidine **(non-specific CYP450 inhibitor and increases gastric pH)**–Cimetidine (400 mg every 12 hours x 8 days) increased voriconazole steady state C_{max} and AUC_τ by an average of 18% (90% CI: 6%, 32%) and 23% (90% CI: 13%, 33%), respectively, following oral doses of 200 mg every 12 hours x 7 days to healthy subjects.

Ranitidine **(increases gastric pH)**–Ranitidine (150 mg every 12 hours) had no significant effect on voriconazole C_{max} and AUC_τ following oral doses of 200 mg every 12 hours x 7 days to healthy subjects.

Macrolide 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_τ 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 N-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% CI: 5.7, 7.5) and 11-fold (90% CI: 9.9, 12.6), respectively, in healthy male subjects *[see Contraindications (4)]*.

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:

Alfentanil **(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 alfentanil with concomitant naloxone resulted in a 6-fold increase in mean alfentanil $AUC_{0-\infty}$ and a 4-fold prolongation of mean alfentanil elimination half-life, compared to when alfentanil was given alone *[see Drug Interactions (7)]*.

Fentanyl **(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 µg/kg) resulted in an increase in the mean $AUC_{0-\infty}$ of fentanyl by 1.4-fold (range 0.81- to 2.04-fold) *[see Drug Interactions (7)]*.

Oxycodone **(CYP3A4 substrate):** In an independent published study, coadministration of multiple doses of oral 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 $AUC_{0-\infty}$ 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)]*.

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_τ 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)]*.

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 AUC_τ 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)]*.

Tacrolimus **(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 tacrolimus (0.1 mg/kg single dose) C_{max} and AUC_τ 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)]*.

Warfarin **(CYP2C9 substrate)**–Coadministration of voriconazole (300 mg every 12 hours x 12 days) with warfarin (30 mg single dose) significantly increased maximum prothrombin time by approximately 2 times that of placebo in healthy subjects *[see Drug Interactions (7)]*.

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)]*.

No significant pharmacokinetic interactions were observed when voriconazole was coadministered 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)]*.

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_τ 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 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 Interactions

Concomitant use of the following agents with voriconazole is contraindicated:

Rifabutin **(potent CYP450 inducer)**–Rifabutin (300 mg once daily) decreased the C_{max} and AUC_τ 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_τ 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 at 400 mg twice daily with rifabutin 300 mg twice daily increased the C_{max} and AUC_τ 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)]*.

Significant drug interactions that may require dosage adjustment, frequent monitoring of drug 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 PO every 24 hours) decreased the steady state C_{max} and AUC_τ of voriconazole (400 mg PO every 12 hours for 1 day, then 200 mg PO every 12 hours for 8 days) by an average of 61% and 77%, respectively, in healthy male subjects. Voriconazole at steady state (400 mg PO every 12 hours for 1 day, then 200 mg every 12 hours for 8 days) increased the steady state C_{max} and AUC_τ of efavirenz (400 mg PO every 24 hours for 9 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 PO every 12 hours on Days 2 to 7) with efavirenz (300 mg PO every 24 hours on Days 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, decreased voriconazole AUC_τ by 7% (90% CI: -23%, 13%) and increased C_{max} by 23% (90% CI: -1%, 53%); efavirenz AUC_τ was increased by 17% (90% CI: 6%, 29%) and C_{max} was equivalent *[see Dosage and Administration (2.7), Contraindications (4), and Drug Interactions (7)]*.

Phenytoin **(CYP2C9 substrate and potent CYP450 inducer)**–Repeat dose administration of phenytoin (300 mg once daily) decreased the steady state C_{max} and AUC_τ 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_τ 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)]*.

Omeprazole **(CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate)**–Coadministration of omeprazole (40 mg once daily x 10 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 C_{max} and AUC_τ 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 C_{max} and AUC_τ of omeprazole an average of 2 times (90% CI: 1.8, 2.6) and 4 times (90% CI: 3.3, 4.4), respectively, as compared to when omeprazole is given without voriconazole *[see Drug Interactions (7)]*.

Oral Contraceptives **(CYP3A4 substrate; CYP2C19 inhibitor)**–Coadministration of oral voriconazole (400 mg every 12 hours for 1 day, then 200 mg every 12 hours for 3 days) and oral contraceptive (Ortho-Novum1/35® consisting of 35 mcg ethinyl estradiol and 1 mg norethindrone, every 24 hours) to healthy female subjects at steady state increased the C_{max} and AUC_τ of ethinyl estradiol by an average of 36% (90% CI: 28%, 45%) and 61% (90% CI: 50%, 72%), respectively, and that of norethindrone by 15% (90% CI: 3%, 28%) and 53% (90% CI: 44%, 63%), respectively in healthy subjects. Voriconazole C_{max} and AUC_τ increased by an average of 14% (90% CI: 3%, 27%) and 46% (90% CI: 32%, 61%), respectively *[see Drug Interactions (7)]*.

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

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_τ of indinavir following repeat dose administration (800 mg TID for 7 days) in healthy subjects.

12.4 Microbiology

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 activity of voriconazole.

Resistance

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-α-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 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.**

Aspergillus fumigatus — *Candida krusei*
Aspergillus flavus — *Candida parapsilosis*
Aspergillus niger — *Candida tropicalis*
Aspergillus terreus — *Fusarium* spp. including *Fusarium solani*
Candida albicans — *Scedosporium apiospermum*
Candida glabrata (In clinical studies, the voriconazole MIC_{90} was 4 µg/mL)*

* In clinical studies, voriconazole MIC_{90} for *C. glabrata* baseline isolates was 4 µg/mL; 13/50 (26%) *C. glabrata* baseline isolates were resistant (MIC ≥4 µg/mL) to voriconazole. However, based on 1054 isolates tested in surveillance studies the MIC_{90} 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 guilliermondii

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: https://www.fda.gov/STIC.

12.5 Pharmacogenomics

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_τ) 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

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-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 adenomas were detected in females at 50 mg/kg and hepatocellular carcinomas were found in males at 6 and 50 mg/kg. Mice were given oral doses of 10, 30 or 100 mg/kg voriconazole, or 0.1, 0.4, or 1.4 times the RMD on a body surface area basis. In mice, hepatocellular adenomas were detected in males and females and hepatocellular carcinomas were detected in males at 1.4 times the RMD of voriconazole.

Voriconazole demonstrated clastogenic 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 50 mg/kg, or 1.6 times the RMD.

14 CLINICAL STUDIES

Voriconazole, 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

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).

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 76 days (range 2-232 days).

Patients in the comparator group received conventional amphotericin B as a slow infusion at a 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 B was to be continued for at least two weeks, actual duration of therapy was at the discretion 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 treatment.

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).

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

	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%
Success by Species			
	Success n/N (%)		
Overall success	76/144 (53)	42/133 (32)	
Mycologically confirmed[e]	37/84 (44)	16/67 (24)	
Aspergillus spp.[f]			
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 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 n/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

Nineteen 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* 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 regimen of amphotericin B followed by fluconazole (response rates of 41% and 41%, respectively) in the treatment of candidemia. 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[a,b]

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.

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 pneumonia/pleural space infections, 2 of 4 patients with skin lesions, 1 of 1 patients with mixed intra-abdominal and pulmonary infection, 1 of 2 patients with suppurative phlebitis, 1 of 3 patients with hepatosplenic infection, 1 of 5 patients with osteomyelitis, 0 of 1 with liver infection, and 0 of 1 with cervical lymph node infection.

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 (ITT) 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:
Success Rates in Patients Treated for Esophageal Candidiasis

Population	Voriconazole	Fluconazole	Difference % (95% CI)[a]
PP[b]	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 (Intent to Treat) patients without endoscopy or clinical assessment at EOT were treated as failures.

Microbiologic success rates by *Candida* species are presented in Table 17.

Table 17:
Clinical and Mycological Outcome by Baseline Pathogen in Patients with Esophageal Candidiasis (Study-150-305)

Pathogen[a]	Voriconazole		Fluconazole	
	Favorable endoscopic response[b]	Mycological eradication[b]	Favorable endoscopic response[b]	Mycological eradication[b]
	Success/Total (%)	Eradication/Total (%)	Success/Total (%)	Eradication/Total (%)
C. albicans	134/140 (96%)	90/107 (84%)	147/156 (94%)	91/115 (79%)
C. glabrata	8/8 (100%)	4/7 (57%)	4/4 (100%)	1/4 (25%)
C. krusei	1/1	1/1	2/2 (100%)	0/0

[a] Some patients had more than one species isolated at baseline.
[b] 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 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.

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

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 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.

One study was designed to enroll pediatric patients with IA or infections with rare molds (such as *Scedosporium* 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 (MITT)[b] Population

Parameter	Global Response at Week 6		
	Ages 2-<12 years N=5	Ages 12-<18 years N=9	Overall N=14
Number 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 criteria.

The second study enrolled 22 patients with invasive candidiasis including candidemia (ICC) 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 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 permitted.

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 than18 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 is 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]

Parameter	Global Response at End of Treatment			
	EC N=10			ICC[c] N=7
	Ages 2-<12 N=2	Ages 12-<18 N=8	Overall N=10	Overall 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 missing data or whose response was deemed indeterminate were considered failures.
[b] 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.
[c] 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.

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16.2 Storage

Voriconazole powder for oral suspension should be stored at 2°C to 8°C (36°F to 46°F) (in a refrigerator) 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 days after reconstitution.

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.

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