VORICONAZOLE- voriconazole tablet, film coated
Cardinal Health

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use voriconazole tablets safely and effectively. See full prescribing information for voriconazole tablets.

Voriconazole Tablets
Initial U.S. Approval: 2002

INDICATIONS AND USAGE

Voriconazole tablets are a triazole antifungal drug indicated for use in the treatment of:

- Invasive aspergillosis (1.1)
- Candidemia (nonneutropenics) and disseminated candidiasis in skin, abdomen, kidney, bladder wall and wounds (1.2)
- Esophageal candidiasis (1.3)
- Serious infections caused by *Scedosporium apiospermum* and *Fusarium* spp. including *Fusarium solani*, in patients intolerant of, or refractory to, other therapy (1.4)

DOSAGE AND ADMINISTRATION

Recommended Dosing Regimen (2)

Infection	Loading Dose	Maintenance Dose*†	
	IV	IV	Oral‡
Invasive Aspergillosis§	6 mg/kg q12h for the first 24 hours	4 mg/kg q12h	200 mg q12h
Candidemia in nonneutropenics and other deep tissue *Candida* infections	6 mg/kg q12h for the first 24 hours	3 to 4 mg/kg q12h¶	200 mg q12h
Esophageal Candidiasis	not evaluated	not evaluated	200 mg q12h
Scedosporiosis and Fusariosis	6 mg/kg q12h for the first 24 hours	4 mg/kg q12h	200 mg q12h

* Increase dose when voriconazole is coadministered with phenytoin or efavirenz (7); Decrease dose in patients with hepatic impairment (2.7)

† Oral and intravenous maintenance doses do not produce the same voriconazole exposures. A 200 mg oral dose provides an exposure similar to a 3 mg/kg IV dose; 300 mg oral dose provides an exposure similar to a 4 mg/kg IV dose.

‡ Adult patients who weigh less than 40 kg should receive half of the oral maintenance dose.

§ In a clinical study, the median duration of IV voriconazole therapy was 10 days; the median duration of oral voriconazole therapy was 76 days.

¶ Patients with candidemia received 3 mg/kg q12h; patients with other deep tissue *Candida* infections received 4 mg/kg.

DOSAGE FORMS AND STRENGTHS

- Film-coated tablets: 50 mg, 200 mg voriconazole. (3)

CONTRAINDICATIONS

- Hypersensitivity to voriconazole or its excipients.
- To reduce risk of serious adverse events, do not use voriconazole with terfenadine, astemizole, cisapride, pimozide or quinidine, sirolimus (4, 7)
- To prevent loss of voriconazole efficacy, do not use with rifampin, carbamazepine, long-acting barbiturates, ritonavir, rifabutin, ergot alkaloids and St. John's Wort (4, 7)

WARNINGS AND PRECAUTIONS

- Drug Interactions (5.1): review patient's concomitant medications. Several drugs may significantly alter voriconazole concentrations. Voriconazole may alter PK or PD of several drugs (7)
- Hepatic Toxicity (5.2): serious hepatic reactions have been reported. Evaluate liver function tests at the start of and during the course of voriconazole therapy.
- Visual Disturbances (5.3): monitor visual function if treatment continues beyond 28 days
- Pregnancy Category D (5.4): do not administer to pregnant women
- Galactose Intolerance (5.5): do not administer to patients with galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption
- Arrhythmias and QT Prolongation (5.6): administer with caution to patients with proarrhythmic conditions
- Dermatological Reactions (5.13): exfoliative cutaneous reactions and photosensitivity have been reported
- Skeletal Events (5.14): fluorosis and periostitis have been reported with long-term voriconazole therapy

ADVERSE REACTIONS

Most frequent (all causalities, incidence ≥ 2%): visual disturbances, fever, nausea, rash, vomiting, chills, headache, liver function test abnormal, tachycardia, hallucinations (6)

To report SUSPECTED ADVERSE REACTIONS, contact Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Inhibitors and inducers of CYP3A4, CYP2C9 and CYP2C19 may alter voriconazole concentrations. Adjust the voriconazole dose and monitor for adverse events or lack of efficacy (4, 7)

Voriconazole may increase the concentrations and activity of drugs that are CYP3A4, CYP2C9 and CYP2C19 substrates. Reduce doses of and monitor for lack of efficacy or adverse events associated with drugs that are substrates of these enzymes (4, 7)

USE IN SPECIFIC POPULATIONS

- Pregnant or nursing women: Voriconazole should not be used in pregnant or nursing women (8.1, 8.3)
- Pediatrics: safety/effectiveness in patients < 12 years has not been established (8.4)
- Hepatic impairment: use half the maintenance dose in patients with mild to moderate hepatic impairment (Child-Pugh Class A and B) (2.7)
- Renal impairment: avoid intravenous administration in patients with moderate to severe renal impairment (creatinine clearance < 50 mL/min) (2.8)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 5/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Voriconazole tablets are indicated for use in patients 12 years of age and older in the treatment of the following fungal infections:

1.1 Invasive Aspergillosis

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) and Clinical Pharmacology (12.4)*].

1.2 Candidemia in Nonneutropenic Patients and the Following *Candida* Infections: Disseminated Infections in Skin and Infections in Abdomen, Kidney, Bladder Wall and Wounds

[*See Clinical Studies (14.2) and Clinical Pharmacology (12.4).*]

1.3 Esophageal Candidiasis

[*See Clinical Studies (14.3) and Clinical Pharmacology (12.4).*]

1.4 Serious Fungal Infections Caused by *Scedosporium apiospermum* (Asexual Form of *Pseudallescheria boydii*) and *Fusarium* spp. Including *Fusarium solani*, in Patients Intolerant of, or Refractory to, Other Therapy

[*See Clinical Studies (14.4) and Clinical Pharmacology (12.4).*]

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

2 DOSAGE AND ADMINISTRATION

2.1 Instructions for Use in All Patients

Voriconazole tablets should be taken at least one hour before or after a meal.

2.3 Recommended Dosing in Adults

Invasive aspergillosis and serious fungal infections due to Fusarium spp. and Scedosporium apiospermum

See Table 1. Therapy must be initiated with the specified loading dose regimen of intravenous voriconazole on Day 1 followed by the recommended maintenance dose regimen. Intravenous treatment should be continued for at least 7 days. Once the patient has clinically improved and can tolerate medication given by mouth, the oral tablet form or oral suspension form of voriconazole may be utilized. The recommended oral maintenance dose of 200 mg achieves a voriconazole exposure similar to 3 mg/kg IV; a 300 mg oral dose achieves an exposure similar to 4 mg/kg IV. Switching between the intravenous and oral formulations is appropriate because of the high bioavailability of the oral formulation in adults [*see Clinical Pharmacology (12)*].

Candidemia in nonneutropenic patients and other deep tissue Candida infections

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

Esophageal Candidiasis

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

Table 1. Recommended Dosing Regimen

Infection	**Loading dose**	**Maintenance Dose*†**	
	IV	**IV**	**Oral‡**
Invasive Aspergillosis§	6 mg/kg q12h for the first 24 hours	4 mg/kg q12h	200 mg q12h
Candidemia in non-neutropenic patients and other deep tissue *Candida* infections	6 mg/kg q12h for the first 24 hours	3 to 4 mg/kg q12h¶	200 mg q12h
Esophageal Candidiasis	#	#	200 mg q12h
Scedosporiosis and Fusariosis	6 mg/kg q12h for the first 24 hours	4 mg/kg q12h	200 mg q12h

* Increase dose when voriconazole is coadministered with phenytoin or efavirenz (7); Decrease dose in patients with hepatic impairment (2.7)

† In healthy volunteer studies, the 200 mg oral q12h dose provided an exposure (AUC_τ) similar to a 3 mg/kg IV q12h dose; the 300 mg oral q12h dose provided an exposure (AUC_τ) similar to a 4 mg/kg IV q12h dose [*see Clinical Pharmacology (12)*]

‡ Adult patients who weigh less than 40 kg should receive half of the oral maintenance dose.

§ In a clinical study of invasive aspergillosis, the median duration of IV voriconazole therapy was 10 days (range 2 to 90 days). The median duration of oral voriconazole therapy was 76 days (range 2 to 232 days) [*see Clinical Studies (14.1)*]

¶ In clinical trials, patients with candidemia received 3 mg/kg IV q12h as primary therapy, while patients with other deep tissue *Candida* infections received 4 mg/kg q12h as salvage therapy. Appropriate dose should be based on the severity and nature of the infection.

\# Not evaluated in patients with esophageal candidiasis.

2.4 Dosage Adjustment

If patient response is inadequate, the oral maintenance dose may be increased from 200 mg every 12 hours (similar to 3 mg/kg IV q12h) to 300 mg every 12 hours (similar to 4 mg/kg IV q12h). For adult patients weighing less than 40 kg, the oral maintenance dose may be increased from 100 mg every 12 hours to 150 mg every 12 hours. If patient is unable to tolerate 300 mg orally every 12 hours, reduce the oral maintenance dose by 50 mg steps to a minimum of 200 mg every 12 hours (or to 100 mg every 12 hours for adult patients weighing less than 40 kg).

If patient is unable to tolerate 4 mg/kg IV q12h, reduce the intravenous maintenance dose to 3 mg/kg q12h.

The maintenance dose of voriconazole should be increased when coadministered with phenytoin or efavirenz [*see Drug Interactions (7)*].

The maintenance dose of voriconazole should be reduced in patients with mild to moderate hepatic impairment, Child-Pugh Class A and B [*see Dosage and Administration (2.7)*]. There are no PK data to allow for dosage adjustment recommendations in patients with severe hepatic impairment (Child-Pugh Class C). Duration of therapy should be based on the severity of the patient’s underlying disease, recovery from immunosuppression and clinical response.

2.7 Use in Patients with Hepatic Impairment

In the clinical program, patients were included who had baseline liver function tests (ALT, AST) up to 5 times the upper limit of normal. No dose adjustment is necessary in patients with this degree of abnormal liver function, but continued monitoring of liver function tests for further elevations is recommended [*see Warnings and Precautions (5.9)*].

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

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

2.8 Use in Patients with Renal Impairment

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

In patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min), 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 (5.10)*].

Voriconazole is hemodialyzed 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.

3 DOSAGE FORMS AND STRENGTHS

Tablets: Voriconazole 50 mg tablets; white, film-coated, oval, unscored, debossed with **V26** on one side of the tablet and blank on the other side.

Voriconazole 200 mg tablets; white, film-coated, capsule-shaped, unscored, debossed with **M164** on one side of the tablet and blank on the other side.

4 CONTRAINDICATIONS

- Voriconazole tablets are contraindicated in patients with known hypersensitivity to voriconazole or its excipients. There is no information regarding cross-sensitivity between voriconazole and other azole antifungal agents. Caution should be used when prescribing voriconazole to patients with hypersensitivity to other azoles.
- Coadministration of terfenadine, astemizole, cisapride, pimozide or quinidine with voriconazole is contraindicated because increased plasma concentrations of these drugs can lead to QT prolongation and rare occurrences of *torsade de pointes* [*see Drug Interactions (7) and Clinical Pharmacology (12.3)*].
- Coadministration of voriconazole with sirolimus is contraindicated because voriconazole significantly increases sirolimus concentrations [*see Drug Interactions (7) and Clinical Pharmacology (12.3)*].
- Coadministration of voriconazole with rifampin, carbamazepine and long-acting barbiturates is contraindicated because these drugs are likely to decrease plasma voriconazole concentrations significantly [*see Drug Interactions (7) and Clinical Pharmacology (12.3)*].
- Coadministration of voriconazole with high-dose ritonavir (400 mg q12h) is contraindicated because ritonavir (400 mg q12h) significantly decreases plasma voriconazole concentrations. Coadministration of voriconazole and low-dose ritonavir (100 mg q12h) should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole [*see Drug Interactions (7) and Clinical Pharmacology (12.3)*].
- Coadministration of voriconazole with rifabutin is contraindicated since voriconazole significantly increases rifabutin plasma concentrations and rifabutin also significantly decreases voriconazole plasma concentrations [*see Drug Interactions (7) and Clinical Pharmacology (12.3)*].
- Coadministration of voriconazole with ergot alkaloids (ergotamine and dihydroergotamine) is contraindicated because voriconazole may increase the plasma concentration of ergot alkaloids, which may lead to ergotism [*see Drug Interactions (7) and Clinical Pharmacology (12.3)*].
- Coadministration of voriconazole with St. John's Wort is contraindicated because this herbal supplement may decrease voriconazole plasma concentration [*see Drug Interactions (7) and Clinical Pharmacology (12.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Drug Interactions

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

5.2 Hepatic Toxicity

In clinical trials, there have been uncommon cases of serious hepatic reactions during treatment with voriconazole (including clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities). Instances of hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly hematological malignancy). Hepatic reactions, including hepatitis and jaundice, have occurred among patients with no other identifiable risk factors. Liver dysfunction has usually been reversible on discontinuation of therapy [*see Warnings and Precautions (5.9) and Adverse Reactions (6.3)*].

Monitoring of Hepatic Function

Liver function tests should be evaluated at the start of and during the course of voriconazole therapy. Patients who develop abnormal liver function tests during voriconazole therapy should be monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of voriconazole must be considered if clinical signs and symptoms consistent with liver disease develop that may be attributable to voriconazole [*see Warnings and Precautions (5.9), Dosage and Administration (2.4, 2.7) and Adverse Reactions (6.3)*].

5.3 Visual Disturbances

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

5.4 Pregnancy Category D

Voriconazole can cause fetal harm when administered to a pregnant woman.

In animals, voriconazole administration was associated with teratogenicity, embryotoxicity, increased gestational length, dystocia and embryomortality. Please refer to section 8.1 (Pregnancy) for additional details.

If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to the fetus.

5.5 Galactose Intolerance

Voriconazole tablets contain lactose and should not be given to patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

5.6 Arrhythmias and QT Prolongation

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

Voriconazole should be administered with caution to patients with these potentially proarrhythmic conditions.

Rigorous attempts to correct potassium, magnesium and calcium should be made before starting voriconazole [*see Clinical Pharmacology (12.3)*].

5.8 Laboratory Tests

Electrolyte disturbances such as hypokalemia, hypomagnesemia and hypocalcemia should be corrected prior to initiation of voriconazole therapy.

Patient management should include laboratory evaluation of renal (particularly serum creatinine) and hepatic function (particularly liver function tests and bilirubin).

5.9 Patients with Hepatic Impairment

It is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B) receiving voriconazole [*see Clinical Pharmacology (12.3) and Dosage and Administration (2.7)*].

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

5.10 Patients with Renal Impairment

In patients with moderate to severe renal dysfunction (creatinine clearance < 50 mL/min), 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 Clinical Pharmacology (12.3) and Dosage and Administration (2.8)*].

5.11 Monitoring of Renal Function

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

Patients should be monitored for the development of abnormal renal function. This should include laboratory evaluation, particularly serum creatinine.

5.12 Monitoring of Pancreatic Function

Patients with risk factors for acute pancreatitis (e.g., recent chemotherapy, hematopoietic stem cell transplantation [HSCT]) should be monitored for the development of pancreatitis during voriconazole treatment.

5.13 Dermatological Reactions

Serious exfoliative cutaneous reactions, such as Stevens-Johnson Syndrome, have been reported during treatment with voriconazole. If a patient develops an exfoliative cutaneous reaction, voriconazole should be discontinued.

In addition voriconazole has been associated with photosensitivity skin reaction. Patients should avoid intense or prolonged exposure to direct sunlight during voriconazole treatment. In patients with photosensitivity skin reactions squamous cell carcinoma of the skin and melanoma have been reported during long-term therapy. If a patient develops a skin lesion consistent with squamous cell carcinoma or melanoma, voriconazole should be discontinued.

5.14 Skeletal Adverse Events

Fluorosis and periostitis have been reported during long-term voriconazole therapy. If a patient develops skeletal pain and radiologic findings compatible with fluorosis or periostitis, voriconazole should be discontinued [*see Adverse Reactions (6.4)*].

6 ADVERSE REACTIONS

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

6.1 Overview

The most frequently reported adverse events (all causalities) in the therapeutic trials were visual disturbances (18.7%), fever (5.7%), nausea (5.4%), rash (5.3%), vomiting (4.4%), chills (3.7%), headache (3.0%), liver function test increased (2.7%), tachycardia (2.4%), hallucinations (2.4%). The treatment-related adverse events which most often led to discontinuation of voriconazole therapy were elevated liver function tests, rash and visual disturbances [*see Warning and Precautions (5.2, 5.3) and Adverse Reactions (6.2, 6.3)*].

6.2 Clinical Trial Experience in Adults

The data described in Table 2 reflect exposure to voriconazole in 1,655 patients in the therapeutic studies. This represents a heterogeneous population, including immunocompromised patients, e.g., patients with hematological malignancy or HIV and non-neutropenic patients. This subgroup does not include healthy subjects and patients treated in the compassionate use and non-therapeutic studies. This patient population was 62% male, had a mean age of 46 years (range 11 to 90, including 51 patients aged 12 to 18 years) and was 78% white and 10% black. Five hundred sixty one patients had a duration of voriconazole therapy of greater than 12 weeks, with 136 patients receiving voriconazole for over 6 months. Table 2 includes all adverse events which were reported at an incidence of ≥ 2% during voriconazole therapy in the all therapeutic studies population, studies 307/602 and 608 combined or study 305, as well as events of concern which occurred at an incidence of < 2%.

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

Table 2. Treatment Emergent Adverse Events Rate ≥ 2% on Voriconazole or Adverse Events of Concern in All Therapeutic Studies Population, Studies 307/602-608 Combined or Study 305. Possibly Related to Therapy or Causality Unknown*

	All Therapeutic Studies	**Studies 307/602 and 608 (IV/oral therapy)**			**Study 305 (oral therapy)**	
	Voriconazole n = 1,655	Voriconazole n = 468	Ampho B† n = 185	Ampho B→ Fluconazole n = 131	Voriconazole n = 200	Fluconazole n = 191
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Special Senses‡						
Abnormal vision	310 (18.7)	63 (13.5)	1 (0.5)	0	31 (15.5)	8 (4.2)
Photophobia	37 (2.2)	8 (1.7)	0	0	5 (2.5)	2 (1)
Chromatopsia	20 (1.2)	2 (0.4)	0	0	2 (1)	0
Body as a Whole						
Fever	94 (5.7)	8 (1.7)	25 (13.5)	5 (3.8)	0	0
Chills	61 (3.7)	1 (0.2)	36 (19.5)	8 (6.1)	1 (0.5)	0
Headache	49 (3)	9 (1.9)	8 (4.3)	1 (0.8)	0	1 (0.5)
Cardiovascular System						
Tachycardia	39 (2.4)	6 (1.3)	5 (2.7)	0	0	0
Digestive System						
Nausea	89 (5.4)	18 (3.8)	29 (15.7)	2 (1.5)	2 (1)	3 (1.6)
Vomiting	72 (4.4)	15 (3.2)	18 (9.7)	1 (0.8)	2 (1)	1 (0.5)
Liver function tests abnormal	45 (2.7)	15 (3.2)	4 (2.2)	1 (0.8)	6 (3)	2 (1)
Cholestatic jaundice	17 (1)	8 (1.7)	0	1 (0.8)	3 (1.5)	0
Metabolic and Nutritional Systems						
Alkaline phosphatase increased	59 (3.6)	19 (4.1)	4 (2.2)	3 (2.3)	10 (5)	3 (1.6)
Hepatic enzymes increased	30 (1.8)	11 (2.4)	5 (2.7)	1 (0.8)	3 (1.5)	0
SGOT increased	31 (1.9)	9 (1.9)	0	1 (0.8)	8 (4)	2 (1)
SGPT increased	29 (1.8)	9 (1.9)	1 (0.5)	2 (1.5)	6 (3)	2 (1)
Hypokalemia	26 (1.6)	3 (0.6)	36 (19.5)	16 (12.2)	0	0
Bilirubinemia	15 (0.9)	5 (1.1)	3 (1.6)	2 (1.5)	1 (0.5)	0

Creatinine increased	4 (0.2)	0	59 (31.9)	10 (7.6)	1 (0.5)	0
Nervous System						
Hallucinations	39 (2.4)	13 (2.8)	1 (0.5)	0	0	0
Skin and Appendages						
Rash	88 (5.3)	20 (4.3)	7 (3.8)	1 (0.8)	3 (1.5)	1 (0.5)
Urogenital						
Kidney function abnormal	10 (0.6)	6 (1.3)	40 (21.6)	9 (6.9)	1 (0.5)	1 (0.5)
Acute kidney failure	7 (0.4)	2 (0.4)	11 (5.9)	7 (5.3)	0	0

* **Study 307/602: invasive aspergillosis; Study 608: candidemia; Study 305: esophageal candidiasis**

† Amphotericin B followed by other licensed antifungal therapy

‡ See Warnings and Precautions (5.3)

Visual Disturbances

Voriconazole treatment-related visual disturbances are common. In therapeutic trials, approximately 21% of patients experienced abnormal vision, color vision change and/or photophobia. Visual disturbances may be associated with higher plasma concentrations and/or doses.

There have been post-marketing reports of prolonged visual adverse events, including optic neuritis and papilledema [*see Warnings and Precautions (5.3)*].

The mechanism of action of the visual disturbance is unknown, although the site of action is most likely to be within the retina. In a study in healthy subjects investigating the effect of 28-day treatment with voriconazole on retinal function, voriconazole caused a decrease in the electroretinogram (ERG) waveform amplitude, a decrease in the visual field and an alteration in color perception. The ERG measures electrical currents in the retina. The effects were noted early in administration of voriconazole and continued through the course of study drug dosing. Fourteen days after end of dosing, ERG, visual fields and color perception returned to normal [*see Warnings an Precautions (5)*].

Dermatological Reactions

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

Serious cutaneous reactions, including Stevens-Johnson Syndrome, toxic epidermal necrolysis and erythema multiforme have been reported during treatment with voriconazole. If a patient develops an exfoliative cutaneous reaction, voriconazole should be discontinued.

In addition, voriconazole has been associated with photosensitivity skin reactions. Patients should avoid strong, direct sunlight during voriconazole therapy. In patients with photosensitivity skin reactions, squamous cell carcinoma of the skin and melanoma have been reported during long-term therapy. If a patient develops a skin lesion consistent with squamous cell carcinoma or melanoma, voriconazole should be discontinued [*see Warnings and Precautions (5.13)*].

Less Common Adverse Events

The following adverse events occurred in < 2% of all voriconazole-treated patients in all therapeutic studies (n = 1,655). This listing includes events where a causal relationship to voriconazole cannot be ruled out or those which may help the physician in managing the risks to the patients. The list does not include events included in Table 2 above and does not include every event reported in the voriconazole clinical program.

Body as a Whole: abdominal pain, abdomen enlarged, allergic reaction, anaphylactoid reaction [*see Warnings and Precautions (5.6)*], ascites, asthenia, back pain, chest pain, cellulitis, edema, face edema, flank pain, flu syndrome, graft versus host reaction, granuloma, infection, bacterial infection, fungal infection, injection site pain, injection site infection/inflammation, mucous membrane disorder, multi-organ failure, pain, pelvic pain, peritonitis, sepsis, substernal chest pain

Cardiovascular: atrial arrhythmia, atrial fibrillation, AV block complete, bigeminy, bradycardia, bundle branch block, cardiomegaly, cardiomyopathy, cerebral hemorrhage, cerebral ischemia, cerebrovascular accident, congestive heart failure, deep thrombophlebitis, endocarditis, extrasystoles, heart arrest, hypertension, hypotension, myocardial infarction, nodal arrhythmia, palpitation, phlebitis, postural hypotension, pulmonary embolus, QT interval prolonged, supraventricular extrasystoles, supraventricular tachycardia, syncope, thrombophlebitis, vasodilatation, ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia (including torsade de pointes) [*see Warnings and*

Precautions (5.6)].

Digestive: anorexia, cheilitis, cholecystitis, cholelithiasis, constipation, diarrhea, duodenal ulcer perforation, duodenitis, dyspepsia, dysphagia, dry mouth, esophageal ulcer, esophagitis, flatulence, gastroenteritis, gastrointestinal hemorrhage, GGT/LDH elevated, gingivitis, glossitis, gum hemorrhage, gum hyperplasia, hematemesis, hepatic coma, hepatic failure, hepatitis, intestinal perforation, intestinal ulcer, jaundice, enlarged liver, melena, mouth ulceration, pancreatitis, parotid gland enlargement, periodontitis, proctitis, pseudomembranous colitis, rectal disorder, rectal hemorrhage, stomach ulcer, stomatitis, tongue edema

Endocrine: adrenal cortex insufficiency, diabetes insipidus, hyperthyroidism, hypothyroidism

Hemic and Lymphatic: agranulocytosis, anemia (macrocytic, megaloblastic, microcytic, normocytic), aplastic anemia, hemolytic anemia, bleeding time increased, cyanosis, DIC, ecchymosis, eosinophilia, hypervolemia, leukopenia, lymphadenopathy, lymphangitis, marrow depression, pancytopenia, petechia, purpura, enlarged spleen, thrombocytopenia, thrombotic thrombocytopenic purpura

Metabolic and Nutritional: albuminuria, BUN increased, creatine phosphokinase increased, edema, glucose tolerance decreased, hypercalcemia, hypercholesteremia, hyperglycemia, hyperkalemia, hypermagnesemia, hypernatremia, hyperuricemia, hypocalcemia, hypoglycemia, hypomagnesemia, hyponatremia, hypophosphatemia, peripheral edema, uremia

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

Nervous System: abnormal dreams, acute brain syndrome, agitation, akathisia, amnesia, anxiety, ataxia, brain edema, coma, confusion, convulsion, delirium, dementia, depersonalization, depression, diplopia, dizziness, encephalitis, encephalopathy, euphoria, Extrapyramidal Syndrome, grand mal convulsion, Guillain-Barré syndrome, hypertonia, hypesthesia, insomnia, intracranial hypertension, libido decreased, neuralgia, neuropathy, nystagmus, oculogyric

crisis, paresthesia, psychosis, somnolence, suicidal ideation, tremor, vertigo

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

Skin and Appendages: alopecia, angioedema, contact dermatitis, discoid lupus erythematosis, eczema, erythema multiforme, exfoliative dermatitis, fixed drug eruption, furunculosis, herpes simplex, maculopapular rash, melanoma, melanosis, photosensitivity skin reaction, pruritus, pseudoporphyria, psoriasis, skin discoloration, skin disorder, skin dry, Stevens-Johnson syndrome, squamous cell carcinoma, sweating, toxic epidermal necrolysis, urticaria

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

Urogenital: anuria, blighted ovum, creatinine clearance decreased, dysmenorrhea, dysuria, epididymitis, glycosuria, hemorrhagic cystitis, hematuria, hydronephrosis, impotence, kidney pain, kidney tubular necrosis, metrorrhagia, nephritis, nephrosis, oliguria, scrotal edema, urinary incontinence, urinary retention, urinary tract infection, uterine hemorrhage, vaginal hemorrhage

6.3 Clinical Laboratory Values

The overall incidence of clinically significant transaminase abnormalities in all therapeutic studies was 12.4% (206/1,655) of patients treated with voriconazole. Increased incidence of liver function test abnormalities may be associated with higher plasma concentrations and/or doses. The majority of abnormal liver function tests either resolved during treatment without dose adjustment or following dose adjustment, including discontinuation of therapy.

Voriconazole has been infrequently associated with cases of serious hepatic toxicity including cases of jaundice and rare cases of hepatitis and hepatic failure leading to death. Most of these patients had other serious underlying conditions.

Liver function tests should be evaluated at the start of and during the course of voriconazole therapy. Patients who develop abnormal liver function tests during voriconazole therapy should be monitored for the development of more severe hepatic injury. Patient management should include laboratory evaluation of hepatic function (particularly liver function tests and bilirubin). Discontinuation of voriconazole must be considered if clinical signs and symptoms consistent with liver disease develop that may be attributable to voriconazole [*see Warnings and Precautions (5.2)*].

Acute renal failure has been observed in severely ill patients undergoing treatment with voriconazole.

Patients being treated with voriconazole are likely to be treated concomitantly with nephrotoxic medications and have concurrent conditions that may result in decreased renal function. It is recommended that patients are monitored for the development of abnormal renal function. This should include laboratory evaluation, particularly serum creatinine.

Tables 3 to 5 show the number of patients with hypokalemia and clinically significant changes in renal and liver function tests in three randomized, comparative multicenter studies. In study 305, patients with esophageal candidiasis were randomized to either oral voriconazole or oral fluconazole. In study 307/602, patients with definite or probable invasive aspergillosis were randomized to either voriconazole or amphotericin B therapy. In study 608, patients with candidemia were randomized to either voriconazole or the regimen of amphotericin B followed by fluconazole.

Table 3. Protocol 305- Patients with Esophageal Candidiasis Clinically Significant Laboratory Test Abnormalities

	Criteria*	Voriconazole	Fluconazole
		n/N (%)	n /N (%)
T. Bilirubin	> 1.5 x ULN	8/185 (4.3)	7/186 (3.8)
AST	> 3 x ULN	38/187 (20.3)	15/186 (8.1)
ALT	> 3 x ULN	20/187 (10.7)	12/186 (6.5)
Alk phos	> 3 x ULN	19/187 (10.2)	14/186 (7.5)

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
ULN upper limit of normal

* Without regard to baseline value

Table 4. Protocol 307/602- Primary Treatment of Invasive Aspergillosis Clinically Significant Laboratory Test Abnormalities

	Criteria*	Voriconazole	Amphotericin B†
		n/N (%)	n/N (%)
T. Bilirubin	> 1.5 x ULN	35/180 (19.4)	46/173 (26.6)
AST	> 3 x ULN	21/180 (11.7)	18/174 (10.3)
ALT	> 3 x ULN	34/180 (18.9)	40/173 (23.1)
Alk phos	> 3 x ULN	29/181 (16)	38/173 (22)
Creatinine	> 1.3 x ULN	39/182 (21.4)	102/177 (57.6)
Potassium	< 0.9 x LLN	30/181 (16.6)	70/178 (39.3)

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
ULN upper limit of normal
LLN lower limit of normal

* Without regard to baseline value

† Amphotericin B followed by other licensed antifungal therapy

Table 5. Protocol 608- Treatment of Candidemia Clinically Significant Laboratory Test Abnormalities

	Criteria*	Voriconazole	Amphotericin B followed by Fluconazole
		n/N (%)	n/N (%)
T. Bilirubin	> 1.5 x ULN	50/261 (19.2)	31/115 (27)
AST	> 3 x ULN	40/261 (15.3)	16/116 (13.8)
ALT	> 3 x ULN	22/261 (8.4)	15/116 (12.9)
Alk phos	> 3 x ULN	59/261 (22.6)	26/115 (22.6)
Creatinine	> 1.3 x ULN	39/260 (15)	32/118 (27.1)
Potassium	< 0.9 x LLN	43/258 (16.7)	35/118 (29.7)

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
ULN upper limit of normal
LLN lower limit of normal

* Without regard to baseline value

6.4 Post-Marketing Experience

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

Skeletal

Fluorosis and periostitis have been reported during long-term voriconazole therapy [*see Warnings and Precautions (5.14)*].

7 DRUG INTERACTIONS

Table 6. Effect of Other Drugs on Voriconazole Pharmacokinetics [see Clinical Pharmacology (12.3)]

Drug/Drug Class (Mechanism of Interaction by the Drug)	Voriconazole Plasma Exposure (C_{max} and AUC_{τ} after 200 mg q12h)	Recommendations for Voriconazole Dosage Adjustment/Comments
Rifampin* and Rifabutin* (CYP450 Induction)	Significantly Reduced	**Contraindicated**
Efavirenz† (CYP450 Induction)	Significantly Reduced	When voriconazole is coadministered with efavirenz, voriconazole maintenance dose should be increased to 400 mg q12h and efavirenz should be decreased to 300 mg q24h
High dose Ritonavir (400 mg q12h)† (CYP450 Induction) Low dose Ritonavir (100 mg q12h)† (CYP450 Induction)	Significantly Reduced Reduced	**Contraindicated** Coadministration of voriconazole and low dose ritonavir (100 mg q12h) should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole
Carbamazepine (CYP450 Induction)	Not Studied *In Vivo* or *In Vitro*, but Likely to Result in Significant Reduction	**Contraindicated**
Long-acting Barbiturates (CYP450 Induction)	Not Studied *In Vivo* or *In Vitro*, but Likely to Result in Significant Reduction	**Contraindicated**
Phenytoin* (CYP450 Induction)	Significantly Reduced	Increase voriconazole maintenance dose from 4 mg/kg to 5 mg/kg IV q12h or from 200 mg to 400 mg orally q12h (100 mg to 200 mg orally q12h in patients weighing less than 40 kg)
St. John's Wort (CYP450 inducer; P-gp inducer)	Significantly Reduced	**Contraindicated**
Oral Contraceptives† containing ethinyl estradiol and norethindrone (CYP2C19 Inhibition)	Increased	Monitoring for adverse events and toxicity related to voriconazole is recommended when coadministered with oral contraceptives
Fluconazole† (CYP2C9, CYP2C19 and CYP3A4 Inhibition)	Significantly Increased	Avoid concomitant administration of voriconazole and fluconazole. Monitoring for adverse events and toxicity related to voriconazole is started within 24 h after the last dose of fluconazole.
Other HIV Protease Inhibitors (CYP3A4 Inhibition)	*In Vivo* Studies Showed No Significant Effects of Indinavir on Voriconazole Exposure *In Vitro* Studies Demonstrated Potential for Inhibition of Voriconazole Metabolism (Increased Plasma Exposure)	No dosage adjustment in the voriconazole dosage needed when coadministered with indinavir Frequent monitoring for adverse events and toxicity related to voriconazole when coadministered with other HIV protease inhibitors
Other NNRTIs‡ (CYP3A4 Inhibition or CYP450 Induction)	*In Vitro* Studies Demonstrated Potential for Inhibition of Voriconazole Metabolism by Delavirdine and Other NNRTIs (Increased Plasma Exposure) A Voriconazole-Efavirenz Drug Interaction Study Demonstrated the	Frequent monitoring for adverse events and toxicity related to voriconazole Careful assessment of voriconazole effectiveness

	Potential for the Metabolism of Voriconazole to be Induced by Efavirenz and Other NNRTIs (Decreased Plasma Exposure)	

* Results based on *in vivo* clinical studies generally following repeat oral dosing with 200 mg q12h voriconazole to healthy subjects

† Results based on *in vivo* clinical study following repeat oral dosing with 400 mg q12h for 1 day, then 200 mg q12h for at least 2 days voriconazole to healthy subjects

‡ Non-Nucleoside Reverse Transcriptase Inhibitors

Table 7. Effect of Voriconazole on Pharmacokinetics of Other Drugs [see Clinical Pharmacology (12.3)]

Drug/Drug Class (Mechanism of Interaction by Voriconazole)	Drug Plasma Exposure (C_{max} and AUC_{τ})	Recommendations for Drug Dosage Adjustment/Comments
Sirolimus* (CYP3A4 Inhibition)	Significantly Increased	**Contraindicated**
Rifabutin* (CYP3A4 Inhibition)	Significantly Increased	**Contraindicated**
Efavirenz† (CYP3A4 Inhibition)	Significantly Increased	When voriconazole is coadministered with efavirenz, voriconazole oral maintenance dose should be increased to 400 mg q12h and efavirenz should be decreased to 300 mg q24h
High dose Ritonavir (400 mg q12h)† (CYP3A4 Inhibition) Low dose Ritonavir (100mg q12h)†	No Significant Effect of Voriconazole on Ritonavir C_{max} or AUC_{τ} Slight Decrease in Ritonavir C_{max} and AUC_{τ}	**Contraindicated** because of significant reduction of voriconazole C_{max} and AUC_{τ} Coadministration of voriconazole and low dose ritonavir (100 mg q12h) should be avoided (due to the reduction in voriconazole C_{max} and AUC_{τ}) unless an assessment of the benefit/risk to the patient justifies the use of voriconazole
Terfenadine, Astemizole, Cisapride, Pimozide, Quinidine (CYP3A4 Inhibition)	Not Studied *In Vivo* or *In Vitro*, but Drug Plasma Exposure Likely to be Increased	**Contraindicated** because of potential for QT prolongation and rare occurrence of *Torsades de pointes*
Ergot Alkaloids (CYP450 Inhibition)	Not Studied *In Vivo* or *In Vitro*, but Drug Plasma Exposure Likely to be Increased	**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 events 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 events may be necessary [*see Drug Interactions (7)*].

Alfentanil (CYP3A4 Inhibition)	Significantly Increased	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 events may be necessary [*see Drug Interactions (7)*].
Oxycodone (CYP3A4 Inhibition)	Significantly Increased	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 events may be necessary [*see Drug Interactions (7)*].
NSAIDs[§] including: ibuprofen and diclofenac (CYP2C9 Inhibition)	Increased	Frequent monitoring for adverse events and toxicity related to NSAIDs. Dose reduction of NSAIDs may be needed [*see Drug Interactions (7)*].
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 events related to oral contraceptives is recommended during coadministration.
Warfarin[*] (CYP2C9 Inhibition)	Prothrombin Time Significantly Increased	Monitor PT or other suitable anti-coagulation tests. Adjustment of warfarin dosage may be needed.
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 events 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 events and toxicity related to NNRTI
Benzodiazepines (CYP3A4 Inhibition)	*In Vitro* Studies Demonstrated Potential for Voriconazole to Inhibit Metabolism (Increased Plasma Exposure)	Frequent monitoring for adverse events and toxicity (i.e., prolonged sedation) related to benzodiazepines metabolized by CYP3A4 (e.g., midazolam, triazolam, alprazolam). Adjustment of

		benzodiazepine dosage may be needed.
HMG-CoA Reductase Inhibitors (Statins) (CYP3A4 Inhibition)	*In Vitro* Studies Demonstrated Potential for Voriconazole to Inhibit Metabolism (Increased Plasma Exposure)	Frequent monitoring for adverse events 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 events 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 events and toxicity (i.e., neurotoxicity) related to vinca alkaloids. Adjustment of vinca alkaloid dosage may be needed.

* 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 q12h for 1 day, then 200 mg q12h for at least 2 days voriconazole to healthy subjects

‡ Results based on *in vivo* clinical study following repeat oral dosing with 400 mg q12h for 1 day, then 200 mg q12h for 4 days voriconazole to subjects receiving a methadone maintenance dose (30 mg to 100 mg QD)

§ Non-Steroidal Anti-Inflammatory Drug

¶ Non-Nucleoside Reverse Transcriptase Inhibitors

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

Voriconazole can cause fetal harm when administered to a pregnant woman and should not be taken in pregnancy except in patients where the benefit to the mother clearly outweighs the potential risk to the fetus. There are no adequate and well controlled studies in pregnant women.

If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patients should be informed of the potential hazard to the fetus [*see Warnings and Precautions (5.4)*].

Animal Data

Voriconazole was teratogenic in rats (cleft palates, hydronephrosis/hydroureter) from 10 mg/kg (0.3 times the recommended maintenance dose (RMD) on a mg/m^2 basis) and embryotoxic in rabbits at 100 mg/kg (6 times the RMD). Other effects in rats included 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. Plasma estradiol in pregnant rats was reduced at all dose levels. Voriconazole treatment in rats produced increased gestational length and dystocia, which were associated with increased perinatal pup mortality at the 10 mg/kg dose. The effects seen in rabbits were an increased embryomortality, reduced fetal weight and increased incidences of skeletal variations, cervical ribs and extrasternebral ossification sites.

8.3 Nursing Mothers

It is not known whether voriconazole is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from voriconazole, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

A total of 22 patients aged 12 to 18 years with invasive aspergillosis were included in the therapeutic studies. Twelve out of 22 (55%) patients had successful response after treatment with a maintenance dose of voriconazole 4 mg/kg q12h.

Sparse plasma sampling for pharmacokinetics in adolescents was conducted in the therapeutic studies [*see Clinical Pharmacology (12.3)*].

There have been post-marketing reports of pancreatitis in pediatric patients.

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 ten 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)*].

8.6 Women of Childbearing Potential

Women of childbearing potential should use effective contraception during treatment. 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 events associated with oral contraceptives and voriconazole is recommended [*see Drug Interactions (7) and 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 5 times the recommended intravenous dose of voriconazole. A single adverse event of photophobia of 10 minutes duration was reported.

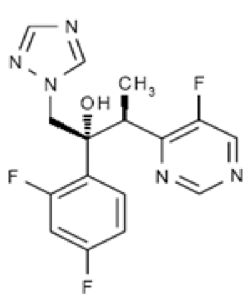
There is no known antidote to voriconazole.

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.

The minimum lethal oral dose in mice and rats was 300 mg/kg (equivalent to 4 and 7 times the recommended maintenance dose (RMD), based on body surface area). At this dose, clinical signs observed in both mice and rats included salivation, mydriasis, titubation (loss of balance while moving), depressed behavior, prostration, partially closed eyes and dyspnea. Other signs in mice were convulsions, corneal opacification and swollen abdomen.

11 DESCRIPTION

Voriconazole, a triazole antifungal agent, is available as film-coated tablets for oral administration. The structural formula is:



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

Voriconazole drug substance is a white to off-white powder.

Voriconazole tablets contain 50 mg or 200 mg of voriconazole. The inactive ingredients include croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, povidone, pregelatinized starch, titanium dioxide and triacetin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

General Pharmacokinetic Characteristics

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 in healthy subjects from 200 mg q12h to 300 mg q12h leads to a 2.5-fold increase in exposure (AUC_{τ}), while increasing the intravenous dose from 3 mg/kg q12h to 4 mg/kg q12h produces a 2.3-fold increase in exposure (Table 8).

Table 8. Population Pharmacokinetic Parameters of Voriconazole in Subjects

	200 mg Oral q12h	300 mg Oral q12h	3 mg/kg IV q12h	4 mg/kg IV q12h
AUCτ * (mcg•h/mL) (CV%)	19.86 (94%)	50.32 (74%)	21.81 (100%)	50.4 (83%)

* Mean AUC_{τ} are predicted values from population pharmacokinetic analysis of data from 236 subjects

During oral administration of 200 mg or 300 mg twice daily for 14 days in patients at risk of aspergillosis (mainly patients with malignant neoplasms of lymphatic or hematopoietic tissue), the observed pharmacokinetic characteristics were similar to those observed in healthy subjects (Table 9).

Table 9. Pharmacokinetic Parameters of Voriconazole in Patients at Risk for Aspergillosis

	200 mg Oral q12h (n = 9)	300 mg Oral q12h (n = 9)
AUCτ * (mcg•h/mL) (CV%)	20.31 (69%)	36.51 (45%)
Cmax * (mcg/mL) (CV%)	3 (51%)	4.66 (35%)

* Geometric mean values on Day 14 of multiple dosing in two cohorts of patients

Sparse plasma sampling for pharmacokinetics was conducted in the therapeutic studies in patients aged 12 to 18 years. In 11 adolescent patients who received a mean voriconazole maintenance dose of 4 mg/kg IV, the median of the calculated mean plasma concentrations was 1.60 mcg/mL (inter-quartile range 0.28 to 2.73 mcg/mL). In 17 adolescent patients for whom mean plasma concentrations were calculated following a mean oral maintenance dose of 200 mg q12h, the median of the calculated mean plasma concentrations was 1.16 mcg/mL (inter-quartile range 0.85 to 2.14 mcg/mL).

When the recommended intravenous or oral loading dose regimens are administered to healthy subjects, peak plasma concentrations close to steady-state are achieved within the first 24 hours of dosing. Without the loading dose, accumulation occurs during twice-daily multiple dosing with steady-state peak plasma voriconazole concentrations being achieved by Day 6 in the majority of subjects (Table 10).

Table 10. Pharmacokinetic Parameters of Voriconazole from Loading Dose and Maintenance Dose Regimens (Individual Studies in Subjects)

	400 mg Oral q12h on Day 1, 200 mg Oral q12h on Days 2 to 10 (n = 17)		6 mg/kg IV* q12h on Day 1, 3 mg/kg IV q12h on Days 2 to 10 (n = 9)	
	Day 1, 1st dose	Day 10	Day 1, 1st dose	Day 10
AUCτ † (mcg•h/mL) (CV%)	9.31 (38%)	11.13 (103%)	13.22 (22%)	13.25 (58%)
C_{max} (mcg/mL) (CV%)	2.30 (19%)	2.08 (62%)	4.70 (22%)	3.06 (31%)

* IV infusion over 60 minutes

† AUC_τ values are calculated over dosing interval of 12 hours Pharmacokinetic parameters for loading and maintenance doses summarized for same cohort of subjects

Steady-state trough plasma concentrations with voriconazole are achieved after approximately 5 days of oral or intravenous dosing without a loading dose regimen. However, when an intravenous loading dose regimen is used, steady-state trough plasma concentrations are achieved within one day.

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 q12h loading dose followed by a 200 mg q12h maintenance dose.

Maximum plasma concentrations (C_{max}) are achieved 1 to 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 to 15 mcg/mL). Varying degrees of hepatic and renal insufficiency do not affect the protein binding of voriconazole.

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. For example, 15% to 20% of Asian populations may be expected to be poor metabolizers. For Caucasians and Blacks, the prevalence of poor metabolizers is 3% to 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.

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 nonlinear pharmacokinetics, the terminal half-life of voriconazole is dose dependent and therefore not useful in predicting the accumulation or elimination of voriconazole.

Pharmacokinetic-Pharmacodynamic Relationships

Clinical Efficacy and Safety

In ten clinical trials, the median values for the average and maximum voriconazole plasma concentrations in individual patients across these studies (n = 1,121) was 2.51 mcg/mL (inter-quartile range 1.21 to 4.44 mcg/mL) and 3.79 mcg/mL (inter-quartile range 2.06 to 6.31 mcg/mL), respectively. A pharmacokinetic-pharmacodynamic analysis of patient data from six of these ten 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 ten clinical trials identified positive associations between plasma voriconazole concentrations and rate of both liver function test abnormalities and visual disturbances [*see Adverse Reactions (6)*].

Electrocardiogram

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 mg, 1200 mg 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)*].

Pharmacokinetics in Special Populations

Gender

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 to 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

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 to 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 to 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 ten 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

A population pharmacokinetic analysis was conducted on pooled data from 35 immunocompromised pediatric patients aged 2 to < 12 years old who were included in two pharmacokinetic studies of intravenous voriconazole (single dose and multiple dose). Twenty-four of these patients received multiple intravenous maintenance doses of 3 mg/kg and 4 mg/kg. A comparison of the pediatric and adult population pharmacokinetic data revealed that the predicted average steady-state plasma concentrations were similar at the maintenance dose of 4 mg/kg every 12 hours in children and 3 mg/kg every 12 hours in adults (medians of 1.19 mcg/mL and 1.16 mcg/mL in children and adults, respectively) [*see Use in Specific Populations (8.4)*].

Hepatic Impairment

After a single oral dose (200 mg) of voriconazole in eight patients with mild (Child-Pugh Class A) and four patients with moderate (Child-Pugh Class B) hepatic insufficiency, 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 insufficiency were compared to controls, there was still a 2.3-fold increase in the mean AUC in the group with hepatic insufficiency compared to controls.

In an oral multiple-dose study, AUC_{τ} was similar in six subjects with moderate hepatic impairment (Child-Pugh Class B) given a lower maintenance dose of 100 mg twice daily compared to six 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.

It is recommended that the standard loading dose regimens be used but that the maintenance dose be halved in patients with mild to moderate hepatic cirrhosis (Child-Pugh Class A and B) receiving voriconazole. No pharmacokinetic data are available for patients with severe hepatic cirrhosis (Child-Pugh Class C) [*see Dosage and Administration (2.7)*].

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 seven patients with moderate renal dysfunction (creatinine clearance 30 to 50 mL/min), the systemic exposure (AUC) and peak plasma concentrations (C_{max}) were not significantly different from those in six subjects with normal renal function.

However, in patients with moderate renal dysfunction (creatinine clearance 30 to 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.

Intravenous voriconazole should be avoided in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min), unless an assessment of the benefit/risk to the patient justifies the use of intravenous voriconazole [*see Dosage and Administration (2.8)*].

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.

Drug Interactions

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 or is expected to be 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 q12h x 7 days) by an average of 93% and 96%, respectively, in healthy subjects. Doubling the dose of voriconazole to 400 mg q12h does not restore adequate exposure to voriconazole during coadministration with rifampin. **Coadministration of voriconazole and rifampin is contraindicated** [*see Contraindications (4) and Warnings and Precautions (5.1)*].

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 q12h for 9 days) decreased the steady-state C_{max} and AUC_{τ} of oral voriconazole (400 mg q12h for 1 day, then 200 mg q12h for 8 days) by an average of 66% and 82%, respectively, in healthy subjects. Low-dose ritonavir (100 mg q12h for 9 days) decreased the steady-state C_{max} and AUC_{τ} of oral voriconazole (400 mg q12h for 1 day, then 200 mg q12h 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. **Coadministration of voriconazole and high-dose ritonavir (400 mg q12h) is contraindicated. Coadministration of voriconazole and low-dose ritonavir (100 mg q12h) should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole** [*see Contraindications (4) and Warnings and Precautions (5.1)*].

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 3 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 $AUC_{0-\infty}$. Because long-term use of St. John's Wort could lead to reduced voriconazole exposure, c**oncomitant use of voriconazole with St. John's Wort is contraindicated** [*see Contraindications (4)*].

Carbamazepine and long-acting barbiturates (potent CYP450 inducers)

Although not studied *in vitro* or *in vivo*, carbamazepine and long-acting barbiturates (e.g., phenobarbital, mephobarbital) are likely to significantly decrease plasma voriconazole concentrations. **Coadministration of voriconazole with carbamazepine or long-acting barbiturates is contraindicated** [*see Contraindications (4) and Warnings and Precautions (5.1)*].

Significant drug interactions that may require voriconazole dosage adjustment, or frequent monitoring of voriconazole-related adverse events/toxicity:

Fluconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor)

Concurrent administration of oral voriconazole (400 mg q12h for 1 day, then 200 mg q12h for 2.5 days) and oral fluconazole (400 mg on Day 1, then 200 mg q24h for 4 days) to six 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 eight healthy male subjects, reduced dosing and/or frequency of voriconazole and fluconazole did not eliminate or diminish this effect. Concomitant administration of voriconazole and fluconazole at any dose is not recommended. Close monitoring for adverse events related to voriconazole is recommended if voriconazole is used sequentially after fluconazole, especially within 24 hours of the last dose of fluconazole [*see Warnings and Precautions (5.1)*].

Minor or no significant pharmacokinetic interactions that do not require dosage adjustment:

Cimetidine (non-specific CYP450 inhibitor and increases gastric pH)

Cimetidine (400 mg q12h 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 q12h x 7 days to healthy subjects.

Ranitidine (increases gastric pH)

Ranitidine (150 mg q12h) had no significant effect on voriconazole C_{max} and AUC_{τ} following oral doses of 200 mg q12h x 7 days to healthy subjects.

Macrolide antibiotics

Coadministration of **erythromycin** (CYP3A4 inhibitor; 1 g q12h for 7 days) or **azithromycin** (500 mg qd for 3 days) with voriconazole 200 mg q12h 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 drugs is significantly increased or is expected to be significantly increased by coadministration of voriconazole and their use is contraindicated:

Sirolimus (CYP3A4 substrate)

Repeat dose administration of oral voriconazole (400 mg q12h for 1 day, then 200 mg q12h 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. **Coadministration of voriconazole and sirolimus is contraindicated** [*see Contraindications (4) and Warnings and Precautions (5.1)*].

Terfenadine, astemizole, cisapride, pimozide and quinidine (CYP3A4 substrates)

Although not studied *in vitro* or *in vivo*, concomitant administration of voriconazole with terfenadine, astemizole, cisapride, pimozide or quinidine may result in inhibition of the metabolism of these drugs. Increased plasma concentrations of these drugs can lead to QT prolongation and rare occurrences of torsade de pointes. **Coadministration of voriconazole and terfenadine, astemizole, cisapride, pimozide and quinidine is contraindicated** [*see Contraindications (4) and Warnings and Precautions (5.1)*].

Ergot alkaloids

Although not studied *in vitro* or *in vivo*, voriconazole may increase the plasma concentration of ergot alkaloids (ergotamine and dihydroergotamine) and lead to ergotism. **Coadministration of voriconazole with ergot alkaloids is contraindicated** [*see Contraindications (4) and Warnings and Precautions (5.1)*].

Coadministration of voriconazole with the following agents results in increased exposure or is expected to result 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 q12h on Day 1, 200 mg q12h 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. An increase in the incidence of delayed and persistent alfentanil-associated nausea and vomiting during coadministration of voriconazole and alfentanil was also observed. Reduction in the dose of alfentanil or other opiates that are also metabolized by CYP3A4 (e.g., sufentanil) and extended close monitoring of patients for respiratory and other opiate-associated adverse events, may be necessary when any of these opiates is coadministered with voriconazole [*see Warnings and Precautions (5.1)*].

Fentanyl (CYP3A4 substrate)

In an independent published study, concomitant use of voriconazole (400 mg q12h on Day 1, then 200 mg q12h on Day 2) with a single intravenous dose of fentanyl (5 mcg/kg) resulted in an increase in the mean $AUC_{0-\infty}$ of fentanyl by 1.4-fold (range 0.81- to 2.04-fold). When voriconazole is coadministered with fentanyl IV, oral or transdermal dosage forms, extended and frequent monitoring of patients for respiratory depression and other fentanyl-associated adverse events is recommended and fentanyl dosage should be reduced if warranted [*see Warnings and Precautions (5.1)*].

Oxycodone (CYP3A4 substrate)

In an independent published study, coadministration of multiple doses of oral voriconazole (400 mg q12h, on Day 1 followed by five doses of 200 mg q12h 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-fold (range 1.4- to 2.5-fold). Voriconazole also increased the visual effects (heterophoria and miosis) of oxycodone. A reduction in oxycodone dosage may be needed during voriconazole treatment to avoid opioid related adverse effects. Extended and frequent monitoring for adverse effects associated with oxycodone and other long-acting opiates metabolized by CYP3A4 is recommended [*see Warnings and Precautions (5.1)*].

Cyclosporine (CYP3A4 substrate)

In stable renal transplant recipients receiving chronic cyclosporine therapy, concomitant administration of oral voriconazole (200 mg q12h 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), respectively, as compared to when cyclosporine was administered without voriconazole. When initiating therapy with voriconazole in patients already receiving cyclosporine, it is recommended that the cyclosporine dose be reduced to one-half of the original dose and followed with frequent monitoring of the cyclosporine blood levels. Increased cyclosporine levels have been associated with nephrotoxicity. When voriconazole is discontinued, cyclosporine levels should be frequently monitored and the dose increased as necessary [*see Warnings and Precautions (5.1)*].

Methadone (CYP3A4, CYP2C19, CYP2C9 substrate)

Repeat dose administration of oral voriconazole (400mg q12h for 1 day, then 200mg q12h for 4 days) increased the C_{max} and AUC_{τ} of pharmacologically active R-methadone by 31% (90% CI: 22%, 40%) and 47% (90% CI: 38%, 57%), respectively, in subjects receiving a methadone maintenance dose (30 mg to 100 mg QD). The C_{max} and AUC of (S)-methadone increased by 65% (90% CI: 53%, 79%) and 103% (90% CI: 85%, 124%), respectively. Increased plasma concentrations of methadone have been associated with toxicity including QT prolongation. Frequent monitoring for adverse events and toxicity related to methadone is recommended during coadministration. Dose reduction of methadone may be needed [*see Warnings and Precautions (5.1)*].

Tacrolimus (CYP3A4 substrate)

Repeat oral dose administration of voriconazole (400 mg q12h x 1 day, then 200 mg q12h 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. When initiating therapy with voriconazole in patients already receiving tacrolimus, it is recommended that the tacrolimus dose be reduced to one-third of the original dose and followed with frequent monitoring of the tacrolimus blood levels. Increased tacrolimus levels have been associated with nephrotoxicity. When voriconazole is discontinued, tacrolimus levels should be carefully monitored and the dose increased as necessary [*see Warnings and Precautions (5.1)*].

Warfarin (CYP2C9 substrate)

Coadministration of voriconazole (300 mg q12h x 12 days) with warfarin (30 mg single dose) significantly increased maximum prothrombin time by approximately 2 times that of placebo in healthy subjects. Close monitoring of prothrombin time or other suitable anticoagulation tests is recommended if warfarin and voriconazole are coadministered and the warfarin dose adjusted accordingly [*see Warnings and Precautions (5.1)*].

Oral Coumarin Anticoagulants (CYP2C9, CYP3A4 substrates)

Although not studied *in vitro* or *in vivo*, voriconazole may increase the plasma concentrations of coumarin anticoagulants and therefore may cause an increase in prothrombin time. If patients receiving coumarin preparations are treated simultaneously with voriconazole, the prothrombin time or other suitable anti-coagulation tests should be monitored at close intervals and the dosage of anticoagulants adjusted accordingly [*see Warnings and Precautions (5.1)*].

Statins (CYP3A4 substrates)

Although not studied clinically, voriconazole has been shown to inhibit lovastatin metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase the plasma concentrations of statins that are metabolized by CYP3A4. It is recommended that dose adjustment of the statin be considered during coadministration. Increased statin concentrations in plasma have been associated with rhabdomyolysis [*see Warnings and Precautions (5.1)*].

Benzodiazepines (CYP3A4 substrates)

Although not studied clinically, voriconazole has been shown to inhibit midazolam metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase the plasma concentrations of benzodiazepines that are metabolized by CYP3A4 (e.g., midazolam, triazolam, and alprazolam) and lead to a prolonged sedative effect. It is recommended that dose adjustment of the benzodiazepine be considered during coadministration [*see Warnings and Precautions (5.1)*].

Calcium Channel Blockers (CYP3A4 substrates)

Although not studied clinically, voriconazole has been shown to inhibit felodipine metabolism *in vitro* (human liver microsomes). Therefore, voriconazole may increase the plasma concentrations of calcium channel blockers that are metabolized by CYP3A4. Frequent monitoring for adverse events and toxicity related to calcium channel blockers is recommended during coadministration. Dose adjustment of the calcium channel blocker may be needed [*see Warnings and Precautions (5.1)*].

Sulfonylureas (CYP2C9 substrates)

Although not studied *in vitro* or *in vivo*, voriconazole may increase plasma concentrations of sulfonylureas (e.g., tolbutamide, glipizide and glyburide) and therefore cause hypoglycemia. Frequent monitoring of blood glucose and appropriate adjustment (i.e., reduction) of the sulfonylurea dosage is recommended during coadministration [*see Warnings and Precautions (5.1)*].

Vinca Alkaloids (CYP3A4 substrates)

Although not studied *in vitro* or *in vivo*, voriconazole may increase the plasma concentrations of the vinca alkaloids (e.g., vincristine and vinblastine) and lead to neurotoxicity. Therefore, it is recommended that dose adjustment of the vinca alkaloid be considered [*see Warnings and Precautions (5.1)*].

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 q12h on Day 1, followed by 200 mg q12h 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.

A reduction in ibuprofen and diclofenac dosage may be needed during concomitant administration with voriconazole. Patients receiving voriconazole concomitantly with other NSAIDs (e.g., celecoxib, naproxen, lornoxicam, meloxicam) that are also metabolized by CYP2C9 should be carefully monitored for NSAID-related adverse events and toxicity and dosage reduction should be made if warranted [*see Warnings and Precautions (5.1)*].

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 q12h 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.

Digoxin (P-glycoprotein mediated transport)

Voriconazole (200 mg q12h 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 q12h 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 g 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) and 4 times (90% CI: 3.5, 5.4), respectively, compared to rifabutin given alone. **Coadministration of voriconazole and rifabutin is**

contraindicated [*see Contraindications (4)*].

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

Efavirenz, a Non-Nucleoside Reverse Transcriptase Inhibitor (CYP450 inducer; CYP3A4 inhibitor and substrate)

Standard doses of voriconazole and standard doses of efavirenz must not be coadministered [*see Drug Interactions (7)*]. Steady-state efavirenz (400 mg PO q24h) decreased the steady-state C_{max} and AUC_{τ} of voriconazole (400 mg PO q12h for 1 day, then 200 mg PO q12h for 8 days) by an average of 61% and 77%, respectively, in healthy male subjects. Voriconazole at steady-state (400 mg PO q12h for 1 day, then 200 mg q12h for 8 days) increased the steady-state C_{max} and AUC_{τ} of efavirenz (400 mg PO q24h 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 q12h on Days 2 to 7) with efavirenz (300 mg PO q24h on Days 1 to 7), relative to steady-state administration of voriconazole (400 mg for 1 day, then 200 mg PO q12h for 2 days) or efavirenz (600 mg q24h for 9 days). Coadministration of voriconazole 400 mg q12h with efavirenz 300 mg q24h, 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.

Voriconazole may be coadministered with efavirenz if the voriconazole maintenance dose is increased to 400 mg q12h and the efavirenz dose is decreased to 300 mg q24h. When treatment with voriconazole is stopped, the initial dosage of efavirenz should be restored [*see Dosage and Administration (2.4) 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 q12h x 14 days) by an average of 50% and 70%, respectively, in healthy subjects. Administration of a higher voriconazole dose (400 mg q12h 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 q12h without phenytoin.

Phenytoin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased from 4 mg/kg to 5 mg/kg intravenously every 12 hours or from 200 mg to 400 mg orally, every 12 hours (100 mg to 200 mg orally, every 12 hours in patients less than 40 kg) [*see Dosage and Administration (2.4) and Drug Interactions (7)*].

Repeat dose administration of voriconazole (400 mg q12h 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. Therefore, frequent monitoring of plasma phenytoin concentrations and phenytoin-related adverse effects is recommended when phenytoin is coadministered with voriconazole [*see Warnings and Precautions (5.1)*].

Omeprazole (CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate)

Coadministration of omeprazole (40 mg once daily x 10 days) with oral voriconazole (400 mg q12h x 1 day, then 200 mg q12h 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 q12h 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. When initiating voriconazole in patients already receiving omeprazole doses of 40 mg or greater, it is recommended that the omeprazole dose be reduced by one-half [*see Warnings and Precautions (5.1)*].

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 these drugs.

Oral Contraceptives (CYP3A4 substrate; CYP2C19 inhibitor)

Coadministration of oral voriconazole (400 mg q12h for 1 day, then 200 mg q12h for 3 days) and oral contraceptive (Ortho-Novum1/35® consisting of 35 mcg ethinyl estradiol and 1 mg norethindrone, q24h) 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. Monitoring for adverse events related to oral contraceptives, in addition to those for voriconazole, is recommended during coadministration [*see Warnings and Precautions (5.1)*].

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 q12h for 17 days) in healthy subjects.

Repeat dose administration of voriconazole (200 mg q12h 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.

Other Two-Way Interactions Expected to be Significant Based on In Vitro and In Vivo Findings:

Other HIV Protease Inhibitors (CYP3A4 substrates and inhibitors)

In vitro studies (human liver microsomes) suggest that voriconazole may inhibit the metabolism of HIV protease inhibitors (e.g., saquinavir, amprenavir and nelfinavir). *In vitro* studies (human liver microsomes) also show that the metabolism of voriconazole may be inhibited by HIV protease inhibitors (e.g., saquinavir and amprenavir). Patients should be frequently monitored for drug toxicity during the coadministration of voriconazole and HIV protease inhibitors [*see Warnings and Precautions (5.1)*].

Other Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (CYP3A4 substrates, inhibitors or CYP450 inducers)

In vitro studies (human liver microsomes) show that the metabolism of voriconazole may be inhibited by a NNRTI (e.g., delavirdine). The findings of a clinical voriconazole-efavirenz drug interaction study in healthy male subjects suggest that the metabolism of voriconazole may be induced by a NNRTI. This *in vivo* study also showed that voriconazole may inhibit the metabolism of a NNRTI [*see Drug Interactions (7) and Warnings and Precautions (5.9)*]. Patients should be frequently monitored for drug toxicity during the coadministration of voriconazole and other NNRTIs (e.g., nevirapine and delavirdine) [*see Warnings and Precautions (5.1)*]. Dose adjustments are required when voriconazole is coadministered with efavirenz [*see Drug Interactions (7) and Warnings and Precautions (5.1)*].

12.4 Microbiology

Mechanism of Action

Voriconazole is a triazole antifungal agent. 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.

Activity *In Vitro* and *In Vivo*

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

Aspergillus fumigatus
Aspergillus flavus
Aspergillus niger
Aspergillus terreus
Candida albicans
Candida glabrata (In clinical studies, the voriconazole MIC90 was 4 mcg/mL)*
Candida krusei
Candida parapsilosis
Candida tropicalis
Fusarium spp. including *Fusarium solani*
Scedosporium apiospermum

*In clinical studies, voriconazole MIC90 for *C. glabrata* baseline isolates was 4 mcg/mL; 13/50 (26%) *C. glabrata* baseline isolates were resistant (MIC ≥ 4 mcg/mL) to voriconazole. However, based on

1,054 isolates tested in surveillance studies the MIC90 was 1 mcg/mL [*see Table 11*].

The following data are available, **but their clinical significance is unknown.**

Voriconazole exhibits *in vitro* minimal inhibitory concentrations (MICs) of 1 mcg/mL or less against most (≥ 90%) isolates of the following microorganisms; however, the safety and effectiveness of voriconazole in treating clinical infections due to these *Candida* species have not been established in adequate and well-controlled clinical trials:

Candida lusitaniae
Candida guilliermondii

Susceptibility Testing Methods[2,3]

Aspergillus Species and Other Filamentous Fungi

No interpretive criteria have been established for *Aspergillus* species and other filamentous fungi.

Candida species

The interpretive standards for voriconazole against *Candida* species are applicable only to tests performed using Clinical Laboratory and Standards Institute (CLSI) microbroth dilution reference method M27 for MIC read at 48 hours or disk diffusion reference method M44 for zone diameter read at 24 hours.[2,3]

Broth Microdilution Techniques

Quantitative methods are used to determine antifungal minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of *Candida* spp. to antifungal agents. MICs should be determined using a standardized procedure at 48 hours.[2] Standardized procedures are based on a microdilution method (broth) with standardized inoculum concentrations and standardized concentrations of voriconazole powder. The MIC values should be interpreted according to the criteria provided in Table 11.

Diffusion Techniques

Qualitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of *Candida* spp. to an antifungal agent. One such standardized procedure requires the use of standardized inoculum concentrations.[3] This procedure uses paper disks impregnated with 1 mcg of voriconazole to test the susceptibility of yeasts to voriconazole at 24 hours. Disk diffusion interpretive criteria are also provided in Table 11.

Table 11. Susceptibility Interpretive Criteria for Voriconazole[2,3]

	Broth Microdilution at 48 hours (MIC in mcg/mL)			Disk Diffusion at 24 hours (Zone diameters in mm)		
	Susceptible (S)	Intermediate (I)	Resistant (R)	Susceptible (S)	Intermediate (I)	Resistant (R)
Voriconazole	≤ 1	2	≥ 4	≥ 17	14 to 16	≤ 13

NOTE: Shown are the breakpoints (mcg/mL) for voriconazole against *Candida* species.

The susceptible category implies that isolates are inhibited by the usually achievable concentrations of antifungal agent tested when the recommended dosage is used for the site of infection. The intermediate category implies that an infection due to the isolate may be appropriately treated in body sites where the drugs are physiologically concentrated or when a high dosage of drug is used. The resistant category implies that isolates are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and clinical efficacy of the agent against the isolate has not been reliably shown in treatment studies.

Quality Control

Standardized susceptibility test procedures require the use of quality control organisms to ensure the accuracy of the technical aspects of the test procedures. Standard voriconazole powder and 1 mcg disks should provide the following range of values noted in Table 12.

NOTE: Quality control microorganisms are specific strains of organisms with intrinsic biological properties relating to resistance mechanisms and their genetic expression within fungi; the specific strains used for microbiological control are not clinically significant.

Table 12. Acceptable Quality Control Ranges for Voriconazole to be used in Validation of

Susceptibility Test Results

QC Strain	Broth Microdilution (MIC in mcg/mL) at 48 hour	Disk Diffusion (Zone diameter in mm) at 24 hour
Candida parapsilosis ATCC 22019	0.03 to 0.25	28 to 37
Candida krusei ATCC 6258	0.12 to 1	16 to 25
Candida albicans ATCC 90028	*	31 to 42
ATCC is a registered trademark of the American Type Culture Collection		

* Quality control ranges have not been established for this strain/antifungal agent combination due to their extensive interlaboratory variation during initial quality control studies.

Activity In Animal Models

Voriconazole was active in normal and/or immunocompromised guinea pigs with systemic and/or pulmonary infections due to *A. fumigatus* (including an isolate with reduced susceptibility to itraconazole) or *Candida* species *[C. albicans* (including an isolate with reduced susceptibility to fluconazole), *C. krusei and C. glabrata]* in which the endpoints were prolonged survival of infected animals and/or reduction of mycological burden from target organs. In one experiment, voriconazole exhibited activity against *Scedosporium apiospermum* infections in immune competent guinea pigs.

Drug Resistance

Voriconazole drug-resistance development has not been adequately studied *in vitro* against *Candida, Aspergillus, Scedosporium* and *Fusarium* species. 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.

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 recommended maintenance dose (RMD) on a mg/m^2 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 mg/m^2 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 assay, the mouse micronucleus assay or the DNA repair test (Unscheduled DNA Synthesis assay).

Voriconazole produced a reduction in the pregnancy rates of rats dosed at 50 mg/kg, or 1.6 times the RMD. This was statistically significant only in the preliminary study and not in a larger fertility study.

13.2 Teratogenic Effects

Pregnancy Category D

[*See Warnings and Precautions (5.4) and Use is Specific Populations (8.1).*]

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

Voriconazole was studied in patients for primary therapy of invasive aspergillosis (randomized, controlled study 307/602), for primary and salvage therapy of aspergillosis (non-comparative study 304) and for treatment of patients with invasive aspergillosis 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 invasive aspergillosis 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 invasive aspergillosis of the lungs. Other aspergillosis infections included disseminated disease, CNS infections and sinus infections. Diagnosis of definite or probable invasive aspergillosis 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 q12h. Median duration of IV voriconazole therapy was 10 days (range 2 to 90 days). After IV voriconazole therapy, the median duration of PO voriconazole therapy was 76 days (range 2 to 232 days).

Patients in the comparator group received conventional amphotericin B as a slow infusion at a daily dose of 1 to 1.5 mg/kg/day. Median duration of IV amphotericin therapy was 12 days (range 1 to 85 days). Treatment was then continued with other licensed antifungal therapy (OLAT), including itraconazole and lipid amphotericin B formulations. Although initial therapy with conventional amphotericin B was to be continued for at least 2 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 13). 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**[*]	Stratified Difference (95% CI)[†]
	n/N (%)	n/N (%)	
Efficacy as Primary Therapy			
Satisfactory Global Response[‡]	76/144 (53)	42/133 (32)	21.8% (10.5%, 33%) $p < 0.0001$
Survival at Day 84[§]	102/144 (71)	77/133 (58)	13.1% (2.1%, 24.2%)
Success by Species			
	Success n/N (%)		
Overall success	76/144 (53)	42/133 (32)	
Mycologically confirmed[¶]	37/84 (44)	16/67 (24)	
Aspergillus spp.[#]			
A. fumigatus	28/63 (44)	12/47 (26)	
A. flavus	3/6	4/9	
A. terreus	2/3	0/3	
A. niger	1/4	0/9	
A. nidulans	1/1	0/0	

* Amphotericin B followed by other licensed antifungal therapy

† Difference and corresponding 95% confidence interval are stratified by protocol

‡ Assessed by independent Data Review Committee (DRC)

§ Proportion of subjects alive

¶ Not all mycologically confirmed specimens were speciated

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 Antifugal Therapy

Additional data regarding response rates in patients who were refractory to, or intolerant of, other antifungal agents are also provided in Table 14. 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 Nonneutropenic 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*†

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 (25)	0/1 (0)

* A few patients had more than one pathogen at baseline.

† 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 intraabdominal 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

The efficacy of oral voriconazole 200 mg twice daily compared to oral fluconazole 200 mg once daily in the primary treatment of esophageal candidiasis was demonstrated in Study 150-305, a double-blind, double-dummy study in immunocompromised patients with endoscopically-proven esophageal candidiasis. 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 esophageal candidiasis, as presented in Table 16.

Table 16. Success Rates in Patients Treated for Esophageal Candidiasis

Population	Voriconazole (%)	Fluconazole (%)	Difference % (95% CI)*
PP†	113/115 (98.2)	134/141 (95)	3.2 (-1.1, 7.5)
ITT‡	175/200 (87.5)	171/191 (89.5)	-2 (-8.3, 4.3)

* Confidence Interval for the difference (Voriconazole – Fluconazole) in success rates.

† 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).

‡ 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*	Voriconazole		Fluconazole	
	Favorable endoscopic response†	Mycological eradication†	Favorable endoscopic response†	Mycological eradication†
	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 (100)	1/1 (100)	2/2 (100)	0/0

* Some patients had more than one species isolated at baseline

† 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 one patient with pulmonary, skin and eye infections, one patient with cerebral disease and one patient with skin infection. Ten patients had evidence of cerebral disease and six of these had a successful outcome (one 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 nine patients, three had eye infections, one had an eye and blood infection, one had a skin infection, one had a blood infection alone, two had sinus infections and one had disseminated infection (pulmonary, skin, hepatosplenic). Three of these patients (one with disseminated disease, one with an eye infection and one with a blood infection) had *Fusarium solani* and were complete successes. Two of these patients relapsed, one with a sinus infection and profound neutropenia and one post surgical patient with blood and eye infections.

15 REFERENCES

1. Clinical Laboratory Standards Institute. Reference method for broth dilution antifungal susceptibility testing of conidium-forming filamentous fungi. Approved Standard M38-P. Clinical Laboratory Standards Institute, Villanova, Pa.
2. Clinical Laboratory Standards Institute. Reference method for broth dilution antifungal susceptibility testing of yeasts. Approved Standard M27-A. Clinical Laboratory Standards Institute, Villanova, Pa.
3. Clinical Laboratory Standards Institute. Method for antifungal disk diffusion susceptibility testing of yeasts. Approved guideline M44-A. Clinical Laboratory Standards Institute, Villanova, Pa.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Voriconazole Tablets are available containing 50 mg or 200 mg of voriconazole.

The 50 mg tablets are white, film-coated, oval, unscored tablets, debossed with **V26** on one side of the tablet and blank on the other side. They are available as follows:

NDC 51079-164-03 - Unit dose blister packages of 30 (3 cards of 10 tablets each).

The 200 mg tablets are white, film-coated, capsule-shaped, unscored tablets, debossed with **M164** on one side of the tablet and blank on the other side. They are available as follows:

NDC 51079-165-03 - Unit dose blister packages of 30 (3 cards of 10 tablets each).

16.2 Storage

Voriconazole tablets should be stored at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

17 PATIENT COUNSELING INFORMATION

VORICONAZOLE TABLETS
(vor" i kon' a zole)

50 mg and 200 mg

Read the Patient Information that comes with voriconazole tablets 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 are voriconazole tablets?

Voriconazole tablets are 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 tablets are safe and effective in children younger than 12 years old.

Who should not take voriconazole tablets?

Do not take voriconazole tablets if you:

- **are allergic to voriconazole or any of the ingredients in voriconazole tablets**. See the end of this leaflet for a complete list of ingredients in voriconazole tablets.
- **are taking any of the following medicines:**
  - cisapride (Propulsid®)
  - pimozide (Orap®)
  - quinidine (like Quinaglute®)
  - sirolimus (Rapamune®)
  - rifampin (Rifadin®)
  - carbamazepine (Tegretol®)
  - long-acting barbiturates like phenobarbital (Luminal®)
  - ritonavir (Norvir®)
  - rifabutin (Mycobutin®)
  - ergotamine, dihydroergotamine (ergot alkaloids)
  - St. John's Wort (herbal supplement)

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.

What should I tell my healthcare provider before taking voriconazole tablets?

Before you take voriconazole tablets, tell your healthcare provider if you:

- have or ever had an abnormal heart rate or rhythm. Your healthcare provider may order a test to check your heart (EKG) before starting voriconazole tablets.
- have liver or kidney problems. Your healthcare provider may do blood tests to make sure you can take voriconazole tablets.
- have trouble digesting dairy products, lactose (milk sugar). Voriconazole tablets contain lactose.
- are pregnant or plan to become pregnant. Voriconazole tablets 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 tablets.

are breast-feeding or plan to breast-feed. 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 tablets.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins and herbal supplements.

Voriconazole tablets 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 tablets?

- **Voriconazole may be prescribed to you as:**
  - Voriconazole tablets

- Take voriconazole tablets exactly as your healthcare provider tells you to.
- Take voriconazole tablets at least one hour before or at least one hour after meals.
- 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 tablets?

- You should not drive at night while taking voriconazole tablets. Voriconazole tablets 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 tablets affect you.
- Avoid direct sunlight. Voriconazole tablets 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 tablets?

Voriconazole tablets 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 (photophobia)
- **serious heart problems.** Voriconazole tablets 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 tablets 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 tablets. Your healthcare provider will decide if you can keep taking voriconazole tablets.
- **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

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 tablets include:

- vision changes
- rash
- vomiting
- nausea
- headache
- fast heart beat (tachycardia)
- hallucinations (seeing or hearing things that are not there)
- abnormal liver function tests

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 tablets. For more information, ask your healthcare provider or pharmacist.

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 tablets?

- Store voriconazole tablets at room temperature, 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.] Do not refrigerate or freeze.
- Keep voriconazole tablets in a tightly closed container.
- Safely throw away medicine that is out of date or no longer needed.
- **Keep voriconazole tablets, as well as all other medicines, out of the reach of children.**

General information about the safe and effective use of voriconazole tablets

Medicines are sometimes prescribed for purposs other than those listed in a Patient Information leaflet. Do not use voriconazole tablets for a condition for which it was not prescribed. Do not give voriconazole tablets to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information Leaflet summarizes the most important information about voriconazole tablets. If you would like more information, talk to your healthcare provider. You can ask your healthcare provider or pharmacist for information about voriconazole tablets that is written for health professionals.

For more information, call Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX).

What are the ingredients of voriconazole tablets?

Active ingredient: voriconazole

Inactive ingredients: croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, povidone, pregelatinized starch, titanium dioxide and triacetin.

Manufactured in India by:
Mylan Laboratories Limited
Hyderabad—500 034, India
Code No.: MH/DRUGS/25/NKD/89

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Distributed by:
UDL Laboratories, Inc.
Rockford, IL 61103

S-11000 R2
5/12

Principal Display Panel

Voriconazole Tablets

200 mg

10 Tablets

NDC 55154-5385-0

M86

VORICONAZOLE TABLETS
200 mg

10 TABLETS

Each film-coated tablet contains:
Voriconazole 200 mg

Usual Dosage: See product insert for prescribing information, precautions and warnings.

STORAGE: Store at 20 to 25 C (68 to 77 F). [See USP Controlled Room Temperature.]

RX ONLY

WARNING: This package is intended for institutional use only. Keep this and all drugs out of the reach of children. This unit dose package is not child resistant.

Code No.: MH/DRUGS/25/NKD/89

Manufactured for:
Mylan Pharmaceuticals Inc.
Morgantown, WV 26505 U.S.A.

Made in India

Packaged and Distributed by:
UDL LABORATORIES, INC.
ROCKFORD, IL 61103
www.udllabs.com

Repackaged by Cardinal Health
Zanesville, OH 43701
L47264511012

LOT #: XXXX

EXP. DATE: 12/34

VORICONAZOLE
voriconazole tablet, film coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:55154-5385(NDC:51079-165)
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
VORICONAZOLE (VORICONAZOLE)	VORICONAZOLE	200 mg

Inactive Ingredients	
Ingredient Name	**Strength**
CROSCARMELLOSE SODIUM	
HYPROMELLOSES	
LACTOSE MONOHYDRATE	
MAGNESIUM STEARATE	
POVIDONES	
STARCH, CORN	
TITANIUM DIOXIDE	
TRIACETIN	

Product Characteristics			
Color	WHITE	**Score**	no score
Shape	OVAL (capsule-shaped)	**Size**	16mm
Flavor		**Imprint Code**	M164
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:55154-5385-0	10 in 1 BAG		
1		1 in 1 BLISTER PACK		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA090547	09/21/2012	

Labeler - Cardinal Health (188557102)

Establishment

Name	Address	ID/FEI	Business Operations
Cardinal Health		188557102	REPACK(55154-5385)