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

VORICONAZOLE for injection, for intravenous use
Initial U.S. Approval: 2002

--------------------------INDICATIONS AND USAGE----------------------------
Voriconazole for injection is an azole antifungal 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)
- Serious infections caused by *Scedosporium apiospermum* and *Fusarium* species including *Fusarium solani*, in patients intolerant of, or refractory to, other therapy (1.3)

----------------------DOSAGE AND ADMINISTRATION---------------------
Recommended Dosage (2.3)

Infection	**Loading dose**	**Maintenance Dose**
	Intravenously	
Invasive Aspergillosis	6 mg/kg every 12h for the first 24 hours	4 mg/kg every 12h
Candidemia in non-neutropenics and other deep tissue *Candida* infections	6 mg/kg every 12h for the first 24 hours	3–4 mg/kg every 12h
Scedosporiosis and Fusariosis	6 mg/kg every 12h for the first 24 hours	4 mg/kg every 12h

- See full prescribing information for instructions on reconstitution of lyophilized powder for intravenous use (2.5)

--------------------DOSAGE FORMS AND STRENGTHS--------------------
For Injection: lyophilized white to off white cake or powder containing 200 mg voriconazole and 3200 mg of hydroxypropyl β-cyclodextrin (HPβCD); after reconstitution 10 mg/mL of voriconazole and 160 mg/mL of HPβCD (3)

----------------------------CONTRAINDICATIONS-----------------------------

- Hypersensitivity to voriconazole or its excipients (4)
- Coadministration with terfenadine, astemizole, cisapride, pimozide or quinidine, sirolimus due to risk of serious adverse reactions (4, 7)
- Coadministration with rifampin, carbamazepine, long-acting barbiturates, efavirenz, ritonavir, rifabutin, ergot alkaloids, and St. John's Wort due to risk of loss of efficacy (4, 7)

----------------------WARNINGS AND PRECAUTIONS-----------------------

- *Clinically Significant Drug Interactions*: Review patient's concomitant medications (5.1, 7)
- *Hepatic Toxicity*: Serious hepatic reactions reported. Evaluate liver function tests at start of and during voriconazole therapy (5.2)
- *Visual Disturbances* (including optic neuritis and papilledema): Monitor visual function if treatment continues beyond 28 days (5.3)
- *Embryo-Fetal Toxicity*: Do not administer to pregnant women unless the benefit to the mother outweighs the risk to the fetus. Inform pregnant patient of hazard (5.4, 8.1)
- *Arrhythmias and QT Prolongation*: Correct potassium, magnesium and calcium prior to use; caution patients with proarrhythmic conditions (5.5)
- *Infusion Related Reactions (including anaphylactic reaction)*: Stop the infusion (5.6)
- *Dermatological Reactions*: Discontinue for exfoliative cutaneous reactions or phototoxicity. Avoid sunlight due to risk of photosensitivity (5.12)
- *Skeletal Events*: Fluorosis and periostitis with long-term voriconazole therapy. Discontinue if these events occur (5.13)

-------------------------------ADVERSE REACTIONS----------------------------
Most common adverse reactions (incidence ≥2%): visual disturbances, fever, nausea, rash, vomiting, chills, headache, liver function test abnormal, tachycardia, hallucinations (6)

To report SUSPECTED ADVERSE REACTIONS, contact X-GEN Pharmaceuticals Inc at 866-390-4411 , or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-------------------------------DRUG INTERACTIONS----------------------------

- CYP3A4, CYP2C9, and CYP2C19 inhibitors and inducers: Adjust Voriconazole for injection dosage and monitor for adverse reactions or lack of efficacy (4, 7)
- Voriconazole for injection may increase the concentrations and activity of drugs that are CYP3A4, CYP2C9 and CYP2C19 substrates. Reduce dosage of these other drugs and monitor for adverse reactions (4, 7)
- Phenytoin: with co-administration, increase maintenance intravenous dosage of Voriconazole for injection (2.3, 7)

-------------------------USE IN SPECIFIC POPULATIONS--------------------

- *Pregnancy*: Voriconazole can cause fetal harm when administered to a pregnant woman. Administer to pregnant women only when the benefit to the mother clearly outweighs the risk to the fetus. Inform pregnant woman of risk (8.1)
- *Pediatrics*: Safety and 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) (2.6)
- *Renal impairment*: Consider using an alternate antifungal therapy in patients with moderate to severe renal dysfunction (creatinine clearance <50 mL/min) (2.7, 5.9)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 3/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Voriconazole for injection is 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 Non-neutropenic Patients and the Following *Candida* Infections: Disseminated Infections in Skin and Infections in Abdomen, Kidney, Bladder Wall, and Wounds

[*see Clinical Studies (14.2) and Clinical Pharmacology (12.4)*]

1.3 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 (14.3) 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 for injection requires reconstitution to 10 mg/mL and subsequent dilution to 5 mg/mL or less prior to administration as an infusion, at a maximum rate of 3 mg/kg per hour over 1 to 2 hours.

Administer diluted Voriconazole for injection by intravenous administration over 1-2 hours. Do not administer as an intravenous bolus injection.

2.2 Use of Voriconazole for injection with Other Parenteral Drug Products

<u>Blood products and concentrated electrolytes</u>

Voriconazole for injection must not be infused concomitantly with any blood product or short-term infusion of concentrated electrolytes, even if the two infusions are running in separate intravenous lines (or cannulas). Electrolyte disturbances such as hypokalemia, hypomagnesemia and hypocalcemia should be corrected prior to initiation of and during Voriconazole for injection therapy [*see Warnings and Precautions (5.7)*].

<u>Intravenous solutions containing (non-concentrated) electrolytes</u>

Voriconazole for injection can be infused at the same time as other intravenous solutions containing (non-concentrated) electrolytes, but must be infused through a separate line.

<u>Total parenteral nutrition (TPN)</u>

Voriconazole for injection can be infused at the same time as total parenteral nutrition, but must be infused in a separate line. If infused through a multiple-lumen catheter, TPN needs to be administered using a different port from the one used for Voriconazole for injection.

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 for injection 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 intravenously; a 300 mg oral dose achieves an exposure similar to 4 mg/kg intravenously. 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 non-neutropenic patients and other deep tissue Candida infections

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

Table 1: Recommended Dosing Regimen

Infection	Loading dose	Maintenance Dose*
	Intravenously	**Intravenously**
Invasive Aspergillosis§	6 mg/kg every 12h for the first 24 hours	4 mg/kg every 12h
Candidemia in nonneutropenic patients and other deep tissue *Candida* infections	6 mg/kg every 12h for the first 24 hours	3–4 mg/kg every 12h¶
Scedosporiosis and Fusariosis	6 mg/kg every 12h for the first 24 hours	4 mg/kg every 12h

* Increase dose when Voriconazole for injection is co-administered with phenytoin(7); Decrease dose in patients with hepatic impairment (2.6)

§ In a clinical study of invasive aspergillosis, the median duration of intravenous Voriconazole for injection therapy was 10 days (range 2–85 days) [*see Clinical Studies (14.1)*].

¶ In clinical trials, patients with candidemia received 3 mg/kg intravenously every 12h as primary therapy, while patients with other deep tissue *Candida* infections received 4 mg/kg every 12h as salvage therapy. Appropriate dose should be based on the severity and nature of the infection.

2.4 Dosage Adjustment

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

The maintenance dose of voriconazole should be increased when co-administered with phenytoin [*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 (2.6)*]. 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.

2.5 Preparation and Intravenous Administration

Reconstitution

The powder is reconstituted with 19 mL of Water for Injection to obtain an extractable volume of 20 mL of clear concentrate containing 10 mg/mL of voriconazole. It is recommended that a standard 20 mL (non-automated) syringe be used to ensure that the exact amount (19.0 mL) of Water for Injection is dispensed. Discard the vial if a vacuum does not pull the diluent into the vial. Shake the vial until all the powder is dissolved.

Voriconazole for injection is an unpreserved sterile lyophile in a single dose vial. Therefore, from a microbiological point of view, once reconstituted, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2° to 8°C (36° to 46°F).

Dilution

Voriconazole for injection must be infused over 1–2 hours, at a concentration of 5 mg/mL or less. Therefore, the required volume of the 10 mg/mL Voriconazole for injection concentrate should be further diluted as follows (appropriate diluents listed below):

1. Calculate the volume of 10 mg/mL Voriconazole for injection concentrate required based on the patient's weight (see Table 2).
2. In order to allow the required volume of Voriconazole for injection concentrate to be added, withdraw and discard at least an equal volume of diluent from the infusion bag or bottle to be used. The volume of diluent remaining in the bag or bottle should be such that when the 10 mg/mL Voriconazole for injection concentrate is added, the final concentration is not less than 0.5 mg/mL nor greater than 5 mg/mL.
3. Using a suitable size syringe and aseptic technique, withdraw the required volume of Voriconazole for injection concentrate from the appropriate number of vials and add to the infusion bag or bottle. **Discard Unused Portion**.

The final Voriconazole for injection solution must be infused over 1–2 hours at a maximum rate of 3 mg/kg per hour. **Infusion should commence immediately after dilution of the concentrate.**

Table 2: Required Volumes of 10 mg/mL Voriconazole for injection Concentrate

Body Weight (kg)	**Volume of Voriconazole for injection Concentrate (10 mg/mL) required for:**		
	3 mg/kg dose (number of vials)	**4 mg/kg dose (number of vials)**	**6 mg/kg dose (number of vials)**
30	9.0 mL (1)	12 mL (1)	18 mL (1)
35	10.5 mL (1)	14 mL (1)	21 mL (2)
40	12.0 mL (1)	16 mL (1)	24 mL (2)
45	13.5 mL (1)	18 mL (1)	27 mL (2)
50	15.0 mL (1)	20 mL (1)	30 mL (2)
55	16.5 mL (1)	22 mL (2)	33 mL (2)
60	18.0 mL (1)	24 mL (2)	36 mL (2)
65	19.5 mL (1)	26 mL (2)	39 mL (2)
70	21.0 mL (2)	28 mL (2)	42 mL (3)

Body Weight (kg)	Volume of Voriconazole for injection Concentrate (10 mg/mL) required for:		
	3 mg/kg dose (number of vials)	**4 mg/kg dose (number of vials)**	**6 mg/kg dose (number of vials)**
75	22.5 mL (2)	30 mL (2)	45 mL (3)
80	24.0 mL (2)	32 mL (2)	48 mL (3)
85	25.5 mL (2)	34 mL (2)	51 mL (3)
90	27.0 mL (2)	36 mL (2)	54 mL (3)
95	28.5 mL (2)	38 mL (2)	57 mL (3)
100	30.0 mL (2)	40 mL (2)	60 mL (3)

The reconstituted solution can be diluted with:

0.9% Sodium Chloride USP
Lactated Ringers USP
5% Dextrose and Lactated Ringers USP
5% Dextrose and 0.45% Sodium Chloride USP
5% Dextrose USP
5% Dextrose and 20 mEq Potassium Chloride USP
0.45% Sodium Chloride USP
5% Dextrose and 0.9% Sodium Chloride USP

The compatibility of Voriconazole for injection with diluents other than those described above is unknown.

Incompatibilities

Voriconazole for injection must not be diluted with 4.2% Sodium Bicarbonate Infusion. The mildly alkaline nature of this diluent caused slight degradation of voriconazole after 24 hours storage at room temperature. Although refrigerated storage is recommended following reconstitution, use of this diluent is not recommended as a precautionary measure. Compatibility with other concentrations is unknown.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Only clear solutions without particles should be used.

Once the reconstituted product is further diluted for infusion, it should be used immediately. This medicinal product is for single use only and any unused solution should be discarded.

2.6 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 (5.8)*].

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 has 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 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 impairment if the benefit outweighs the potential risk. Patients with hepatic insufficiency must be carefully monitored for drug toxicity.

2.7 Use in Patients with Renal Impairment

In patients with moderate to severe renal dysfunction (creatinine clearance <50 mL/min), accumulation of the intravenous vehicle of Voriconazole for injection, hydroxypropyl β-cyclodextrin (HPβCD), occurs. There is insufficient information to recommend dosage adjustments to Voriconazole for injection in patients with renal impairment. Therefore, an alternate antifungal therapy should be considered in patients with renal impairment [see *Warnings and Precautions (5.9)*]. In patients on hemodialysis, a 4-hour hemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment [see *Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

Powder for Solution for Injection

Voriconazole for injection is supplied in a single dose vial as a sterile lyophilized white to off white cake or powder equivalent to 200 mg voriconazole and 3200 mg hydroxypropyl β-cyclodextrin (HPβCD).

4 CONTRAINDICATIONS

- Voriconazole for injection is contraindicated in patients with known hypersensitivity to voriconazole or its excipients. There is no information regarding cross-sensitivity between voriconazole and other azole antifungal agents. Caution should be used when prescribing voriconazole to patients with hypersensitivity to other azoles.
- Coadministration of terfenadine, astemizole, cisapride, pimozide or quinidine with Voriconazole for injection 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 for injection with sirolimus is contraindicated because voriconazole significantly increases sirolimus concentrations [*see Drug Interactions (7) and Clinical Pharmacology (12.3)*].
- Coadministration of Voriconazole for injection 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 standard doses of voriconazole with efavirenz doses of 400 mg every 24h or higher is contraindicated, because efavirenz significantly decreases plasma voriconazole concentrations in healthy subjects at these doses. Voriconazole also significantly increases efavirenz plasma concentrations [*see Drug Interactions (7) and Clinical Pharmacology (12.3)*].
- Coadministration of Voriconazole for injection with high-dose ritonavir (400 mg every 12h) is contraindicated because ritonavir (400 mg every 12h) significantly decreases plasma voriconazole concentrations [*see Drug Interactions (7) and Clinical Pharmacology (12.3)*].
- Coadministration of Voriconazole for injection 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 for injection 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 for injection 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 (5.8) and Adverse Reactions (6.1)*].

Measure serum transaminase levels and bilirubin at the initiation of Voriconazole for injection therapy and monitor at least weekly for the first month of treatment. Monitoring frequency can be reduced to monthly during continued use if no clinically significant changes are noted. If liver function tests become markedly elevated compared to baseline, Voriconazole for injection should be discontinued unless the medical judgment of the benefit-risk of the treatment for the patient justifies continued use [*see Warnings and Precautions (5.8), Dosage and Administration (2.4,* 2.6*), and Adverse Reactions (6.1)*].

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 (6.1)*].

5.4 Embryo-Fetal Toxicity

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, under *Use in Specific Populations* 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 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 potentially proarrhythmic conditions, such as:

- Congenital or acquired QT-prolongation
- Cardiomyopathy, in particular when heart failure is present
- Sinus bradycardia
- Existing symptomatic arrhythmias
- Concomitant medicinal product that is known to prolong QT interval [*see Contraindications (4), Drug Interactions (7), and Clinical Pharmacology (12.3)*]

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

5.6 Infusion Related Reactions

During infusion of the intravenous formulation of voriconazole in healthy subjects, anaphylactic reactions, including flushing, fever, sweating, tachycardia, chest tightness, dyspnea, faintness, nausea, pruritus and rash, have occurred uncommonly. Symptoms appeared immediately upon initiating the infusion. Consideration should be given to stopping the infusion should these reactions occur.

5.7 Monitoring: Laboratory Tests

Electrolyte disturbances such as hypokalemia, hypomagnesemia and hypocalcemia should be corrected prior to initiation of and during Voriconazole for injection therapy.

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

5.8 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 for injection [*see Clinical Pharmacology (12.3) and Dosage and Administration (2.6)*].

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.

5.9 Risk in Patients with Renal Impairment

Hydroxypropyl-β-cyclodextrin (HPβCD), the intravenous vehicle of Voriconazole for injection, is eliminated through glomerular filtration. Therefore, in patients with moderate to severe renal dysfunction (creatinine clearance <50 mL/min), accumulation of HPβCD occurs. Serum creatinine (S_{cr}) levels should be closely monitored in patients with renal impairment. If increases in S_{cr} occur, consideration should be given to changing to alternate antifungal therapy with similar coverage, unless an assessment of the benefit/risk to the patient justifies the continued use of intravenous voriconazole [*see Dosage and Administration (2.7) and Clinical Pharmacology (12.3)*].

5.10 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.

5.11 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 for injection treatment.

5.12 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 for injection should be discontinued.

Voriconazole has been associated with photosensitivity skin reaction. Patients, including children, should avoid exposure to direct sunlight during Voriconazole for injection treatment and should use measures such as protective clothing and sunscreen with high sun protection factor (SPF). If phototoxic reactions occur, the patient should be referred to a dermatologist and Voriconazole for injection discontinuation should be considered. If Voriconazole for injection is continued despite the occurrence of phototoxicity-related lesions, dermatologic evaluation should be performed on a systematic and regular basis to allow early detection and management of premalignant lesions. Squamous cell carcinoma of the skin and melanoma have been reported during long-term voriconazole therapy in patients with photosensitivity skin reactions. If a patient develops a skin lesion consistent with premalignant skin lesions, squamous cell carcinoma or melanoma, Voriconazole for injection should be discontinued.

The frequency of phototoxicity reactions is higher in the pediatric population. Because squamous cell carcinoma has been reported in patients who experience photosensitivity reactions, stringent measures for photoprotection are warranted in children. In children experiencing photoaging injuries such as lentigines or ephelides, sun avoidance and dermatologic follow-up are recommended even after treatment discontinuation.

5.13 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 (6.2)*].

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 Clinical Trials Experience

The most frequently reported adverse reactions (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 reactions 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), Clinical Trial Experience in Adult and Pediatric Patients and Clinical Laboratory Values*].

<u>Clinical Trial Experience in Adult and Pediatric Patients</u>

The data described in Table 3 reflect exposure to voriconazole in 1655 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 11–90, including 51 patients aged 12–18 years), and was 78% White and 10% Black. Five hundred sixty one patients had a duration of voriconazole therapy of greater than 12 weeks, with 136 patients receiving voriconazole for over six months. Table 3 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, 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 reactions was

21.4% (42/196 patients). In study 608, 403 patients with candidemia were treated to compare voriconazole (272 patients) to the regimen of amphotericin B followed by fluconazole (131 patients). The rate of discontinuation from voriconazole study medication due to adverse reactions was 19.5% out of 272 patients. Laboratory test abnormalities for these studies are discussed under Clinical Laboratory Values below.

Table 3: Adverse Reactions Rate ≥ 2% on Voriconazole or Adverse Reactions of Concern in All Therapeutic Studies Population, Studies 307/602-608 Combined, Possibly Related to Therapy or Causality Unknown*

	All Therapeutic Studies	Studies 307/602 and 608		
	Voriconazole N=1655 N (%)	Voriconazole N=468 N (%)	Ampho B† N=185 N (%)	Ampho B→ Fluconazole N=131 N (%)
Special Senses‡				
Abnormal vision	310 (18.7)	63 (13.5)	1 (0.5)	0
Photophobia	37 (2.2)	8 (1.7)	0	0
Chromatopsia	20 (1.2)	2 (0.4)	0	0
Body as a Whole				
Fever	94 (5.7)	8 (1.7)	25 (13.5)	5 (3.8)
Chills	61 (3.7)	1 (0.2)	36 (19.5)	8 (6.1)
Headache	49 (3.0)	9 (1.9)	8 (4.3)	1 (0.8)
Cardiovascular System				
Tachycardia	39 (2.4)	6 (1.3)	5 (2.7)	0
Digestive System				
Nausea	89 (5.4)	18 (3.8)	29 (15.7)	2 (1.5)
Vomiting	72 (4.4)	15 (3.2)	18 (9.7)	1 (0.8)
Liver function tests abnormal	45 (2.7)	15 (3.2)	4 (2.2)	1 (0.8)
Cholestatic jaundice	17 (1.0)	8 (1.7)	0	1 (0.8)
Metabolic and Nutritional Systems				
Alkaline phosphatase increased	59 (3.6)	19 (4.1)	4 (2.2)	3 (2.3)
Hepatic enzymes increased	30 (1.8)	11 (2.4)	5 (2.7)	1 (0.8)
SGOT increased	31 (1.9)	9 (1.9)	0	1 (0.8)
SGPT increased	29 (1.8)	9 (1.9)	1 (0.5)	2 (1.5)
Hypokalemia	26 (1.6)	3 (0.6)	36 (19.5)	16 (12.2)
Bilirubinemia	15 (0.9)	5 (1.1)	3 (1.6)	2 (1.5)
Creatinine increased	4 (0.2)	0	59 (31.9)	10 (7.6)
Nervous System				
Hallucinations	39 (2.4)	13 (2.8)	1 (0.5)	0
Skin and Appendages				
Rash	88 (5.3)	20 (4.3)	7 (3.8)	1 (0.8)
Urogenital				
Kidney function abnormal	10 (0.6)	6 (1.3)	40 (21.6)	9 (6.9)
Acute kidney failure	7 (0.4)	2 (0.4)	11 (5.9)	7 (5.3)

* Study 307/602: invasive aspergillosis; Study 608: candidemia
† 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 and Precautions (5.6)*].

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 for injection should be discontinued.

In addition, voriconazole has been associated with photosensitivity skin reactions. Patients should avoid strong, direct sunlight during Voriconazole for injection 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 for injection should be discontinued [*see Warnings and Precautions (5.12)*].

Less Common Adverse Reactions

The following adverse reactions occurred in <2% of all voriconazole-treated patients in all therapeutic studies (N=1655). This listing includes events where a causal relationship to voriconazole cannot be ruled out or those which may help the physician in managing the risks to the patients. The list does not include events included in Table 5 above and does not include every event reported in the voriconazole clinical program.

Body as a Whole: abdominal pain, abdomen enlarged, allergic reaction, anaphylactic reaction [*see Warnings and Precautions (5.5)*], 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 (5.5)*].

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.

Clinical Laboratory Values

The overall incidence of clinically significant transaminase abnormalities in all therapeutic studies was 12.4% (206/1655) 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 for injection therapy. Patients who develop abnormal liver function tests during Voriconazole for injection 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 for injection must be considered if clinical signs and symptoms consistent with liver disease develop that may be attributable to Voriconazole for injection [*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 4 and 5 show the number of patients with hypokalemia and clinically significant changes in renal and liver function tests in two randomized, comparative multicenter studies. 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 4: Study 307/602 – Primary Treatment of Invasive Aspergillosis Clinically Significant Laboratory Test Abnormalities

	Criteria*	Voriconazole n/N (%)	Amphotericin B† n/N (%)
T. Bilirubin	>1.5× ULN	35/180 (19.4)	46/173 (26.6)
AST	>3.0× ULN	21/180 (11.7)	18/174 (10.3)
ALT	>3.0× ULN	34/180 (18.9)	40/173 (23.1)
Alk phos	>3.0× ULN	29/181 (16.0)	38/173 (22.0)
Creatinine	>1.3× ULN	39/182 (21.4)	102/177 (57.6)
Potassium	<0.9× 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: Study 608 – Treatment of Candidemia Clinically Significant Laboratory Test Abnormalities

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

	Criteria*	Voriconazole n/N (%)	Amphotericin B followed by Fluconazole n/N (%)

therapy
ULN = upper limit of normal
LLN = lower limit of normal
* Without regard to baseline value

6.2 Postmarketing 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 (5.13)*].

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 every 12h)	Recommendations for Voriconazole Dosage Adjustment/Comments
Rifampin and Rifabutin (CYP450 Induction)	Significantly Reduced	**Contraindicated**
Efavirenz (400 mg every 24h) (CYP450 Induction)	Significantly Reduced	**Contraindicated**
High-dose Ritonavir (400 mg every 12h) (CYP450 Induction) Low-dose Ritonavir (100 mg every 12h) (CYP450 Induction)	Significantly Reduced Reduced	**Contraindicated** Coadministration of voriconazole and low-dose ritonavir (100 mg every 12h) 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	Significantly Reduced	Increase voriconazole maintenance dose from 4

Drug/Drug Class (Mechanism of Interaction by the Drug)	Voriconazole Plasma Exposure (C_{max} and AUC_{τ} after 200 mg every 12h)	Recommendations for Voriconazole Dosage Adjustment/Comments
(CYP450 Induction)		mg/kg to 5 mg/kg intravenously every12h
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 Potential for the Metabolism of Voriconazole to be Induced by Efavirenz and Other NNRTIs (Decreased Plasma Exposure)	Frequent monitoring for adverse events and toxicity related to voriconazole Careful assessment of voriconazole effectiveness

‡ 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**

Drug/Drug Class (Mechanism of Interaction by Voriconazole)	Drug Plasma Exposure (C_{max} and AUC_{τ})	Recommendations for Drug Dosage Adjustment/Comments
Efavirenz (400 mg every 24h) (CYP3A4 Inhibition)	Significantly Increased	**Contraindicated**
High-dose Ritonavir (400 mg every 12h) (CYP3A4 Inhibition) Low-dose Ritonavir (100 mg every 12h)	No Significant Effect of Voriconazole on Ritonavir C_{max} or AUC_{τ} Slight Decrease in Ritonavir C_{max} and $AUC\tau$	**Contraindicated** because of significant reduction of voriconazole C_{max} and AUC_{τ} Coadministration of voriconazole and low-dose ritonavir (100 mg every 12h) 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 *torsade 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 for injection 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 for injection 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 for injection. 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 for injection. 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

Drug/Drug Class (Mechanism of Interaction by Voriconazole)	**Drug Plasma Exposure (C_{max} and AUC_{τ})**	**Recommendations for Drug Dosage Adjustment/Comments**
		coadministered with Voriconazole for injection. 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 for injection 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 for injection 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 for injection 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 for injection 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	Frequent monitoring for adverse events and toxicity related to NNRTI

Drug/Drug Class (Mechanism of Interaction by Voriconazole)	Drug Plasma Exposure (C_{max} and AUC_{τ})	Recommendations for Drug Dosage Adjustment/Comments
	Exposure)	
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.
Everolimus (CYP3A4 Inhibition)	Not Studied *In Vivo* or *In Vitro*, but Drug Plasma Exposure Likely to be Increased	Concomitant administration of voriconazole and everolimus is not recommended.

§ Non-Steroidal Anti-Inflammatory Drug
¶ Non-Nucleoside Reverse Transcriptase Inhibitors

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Voriconazole can cause fetal harm when administered to a pregnant woman 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 a patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to the fetus [*see Warnings and Precautions (5.4)*].
In animals, voriconazole administration was associated with teratogenicity, embryotoxicity, increased gestational length, dystocia and embryomortality at 0.3 times the recommended maintenance dose (RMD) in rats and 6 times the RMD in rabbits *[See Data]*.The background risk of major birth defects and miscarriage for the indicated

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

Data

Animal Data

Oral voriconazole was teratogenic in rats and embryotoxic in rabbits. Cleft palates and hydronephrosis/hydroureter were observed in rat pups exposed to voriconazole during organogenesis at and above 10 mg/kg (0.3 times the recommended maintenance dose (RMD) of 200 mg every 12 hours based on body surface area comparisons).

Embryotoxicity was observed in rabbits orally dosed at 100 mg/kg (6 times the RMD based on body surface area comparisons). Other effects in rats dosed by the oral route, 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. Rats exposed to voriconazole from implantation to weaning experienced increased gestational length and dystocia, which were associated with increased perinatal pup mortality at the 10 mg/kg dose. Rabbit pups showed increased embryomortality, reduced fetal weight and increased incidence of skeletal variations, cervical ribs and extrasternal ossification sites.

8.2 Lactation

Risk Summary

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

8.3 Females and Males of Reproductive Potential

Contraception

Females of reproductive 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)*].

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 every 12h.

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 10 voriconazole therapeutic trials showed that voriconazole plasma concentrations in the elderly patients were approximately 80% to 90% higher than those in younger patients after either intravenously or oral administration. However, the overall safety profile of the elderly patients was similar to that of the young so no dosage adjustment is recommended [*see Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

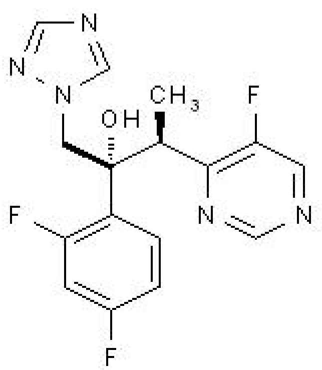
In clinical trials, there were three cases of accidental overdose. All occurred in pediatric patients who received up to five times the recommended intravenous dose of voriconazole. A single adverse event of photophobia of 10 minutes duration was reported.

There is no known antidote to voriconazole.

Voriconazole is hemodialyzed with clearance of 121 mL/min. The intravenous vehicle, HPβCD, is hemodialyzed with clearance of 37.5±24 mL/min. In an overdose, hemodialysis may assist in the removal of voriconazole and HPβCD from the body.

11 DESCRIPTION

Voriconazole for injection, an azole antifungal is available as a sterile lyophilized cake or powder for solution for intravenous infusion. 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 an empirical formula of $C_{16}H_{14}F_3N_5O$ and a molecular weight of 349.3.

Voriconazole drug substance is a white or almost white powder.

Voriconazole for injection, is a white to off white lyophilized cake or powder containing nominally 200 mg voriconazole and 3200 mg hydroxypropyl β-cyclodextrin (HPβCD) in a 30 mL Type I clear glass vial.

Voriconazole for injection is intended for administration by intravenous infusion. It is an unpreserved product in a single dose vial. Vials containing 200 mg lyophilized voriconazole are intended for reconstitution with Water for Injection to produce a solution containing 10 mg/mL Voriconazole for injection and 160 mg/mL of hydroxypropyl β-cyclodextrin (HPβCD). The resultant solution is further diluted prior to administration as an intravenous infusion [*see Dosage and Administration (2)*].

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

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

In patients at risk of aspergillosis (mainly patients with malignant neoplasms of lymphatic or hematopoietic tissue), the observed voriconazole pharmacokinetics were similar to those observed in healthy subjects.

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 intravenous dose from 3 mg/kg every 12h to 4 mg/kg every 12h produces an approximately 2.5-fold increase in exposure (Table 8).

Table 8: Geometric Mean (%CV) Plasma Voriconazole Pharmacokinetic Parameters in Adults Receiving Different Dosing Regimens

	6 mg/kg intravenously (loading dose)	3 mg/kg intravenously every 12h	4 mg/kg intravenously every 12h
N	35	23	40
AUC_{12} (µg·h/mL)	13.9 (32)	13.7 (53)	33.9 (54)
C_{max} (µg/mL)	3.13 (20)	3.03 (25)	4.77 (36)
C_{min} (µg/mL)	--	0.46 (97)	1.73 (74)

Note: Parameters were estimated based on non-compartmental analysis from 5 pharmacokinetic studies. AUC_{12} = area under the curve over 12 hour dosing interval, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration. CV = coefficient of variation.

Sparse plasma sampling for pharmacokinetics was conducted in the therapeutic studies in patients aged 12–18 years. In 11 adolescent patients who received a mean voriconazole maintenance dose of 4 mg/kg intravenously, the median of the calculated mean plasma concentrations was 1.60 µg/mL (inter-quartile range 0.28 to 2.73 µg/mL). When the recommended intravenous loading dose regimen is administered to healthy subjects, plasma concentrations close to steady state are achieved within the first 24 hours of dosing (e.g., 6 mg/kg intravenously every 12h on day 1 followed by 3 mg/kg intravenously every 12h). Without the loading dose, accumulation occurs during twice-daily multiple dosing with steady-state plasma voriconazole concentrations being achieved by day 6 in the majority of subjects.

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 (approximate range: 0.9–15 µg/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, 15–20% of Asian populations may be expected to be poor metabolizers. For Caucasians and Blacks, the prevalence of poor metabolizers is 3–5%. Studies conducted in Caucasian and Japanese healthy subjects have shown that poor metabolizers have, on average, 4-fold higher voriconazole exposure (AUC_τ) than their homozygous extensive metabolizer counterparts. Subjects who are heterozygous extensive metabolizers have, on average, 2-fold higher voriconazole exposure than their homozygous extensive metabolizer counterparts.

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 intravenous voriconazole, preceded by multiple intravenous 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 intravenous dosing.

As a result of non-linear pharmacokinetics, the terminal half-life of voriconazole is dose dependent and therefore not useful in predicting the accumulation or elimination of voriconazole.

Pharmacokinetic-Pharmacodynamic Relationships

Clinical Efficacy and Safety-In 10 clinical trials, the median values for the average and maximum voriconazole plasma concentrations in individual patients across these studies (N=1121) was 2.51 µg/mL (inter-quartile range 1.21 to 4.44 µg/mL) and 3.79 µg/mL (inter-quartile range 2.06 to 6.31 µg/mL), respectively. A pharmacokinetic-pharmacodynamic analysis of patient data from 6 of these 10 clinical trials (N=280) could not detect a positive association between mean, maximum or minimum plasma voriconazole concentration and efficacy. However, pharmacokinetic/pharmacodynamic analyses of the data from all 10 clinical trials identified positive associations between plasma voriconazole concentrations and rate of both liver function test abnormalities and visual disturbances *[see Adverse Reactions (6)]*.

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, 1200 and 1600 mg of voriconazole and after ketoconazole 800 mg were all <10 msec. Females exhibited a greater increase in QTc than males, although all mean changes were <10 msec. Age was not found to affect the magnitude of increase in QTc. No subject in any group had an increase in QTc of ≥60 msec from baseline. No subject experienced an interval exceeding the potentially clinically relevant threshold of 500 msec. However, the QT effect of voriconazole combined with drugs known to prolong the QT interval is unknown [*see Contraindications (4) and Drug Interactions (7)*].

Specific 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 (18–45 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 Cmax 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 (18–45 years). No significant differences in the mean C_{max} and AUC_τ were observed between healthy elderly females (≥ 65 years) and healthy young females (18–45 years).

In the clinical program, no dosage adjustment was made on the basis of age. An analysis of pharmacokinetic data obtained from 552 patients from 10 voriconazole clinical trials showed that the median voriconazole plasma concentrations in the elderly patients (>65 years) were approximately 80% to 90% higher than those in the younger patients (≤65 years) after either intravenous 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 Specific 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 µg/mL and 1.16 µg/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 8 patients with mild (Child-Pugh Class A) and 4 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 6 subjects with moderate hepatic impairment (Child-Pugh Class B) given a lower maintenance dose of 100 mg twice daily compared to 6 subjects with normal hepatic function given the standard 200 mg twice daily maintenance dose. The mean peak plasma concentrations (C_{max}) were 20% lower in the hepatically impaired group.

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 (2.6)*].

Renal Impairment-In a multiple dose study of intravenous voriconazole (6 mg/kg intravenous loading dose × 2, then 3 mg/kg intravenous × 5.5 days) in 7 patients with moderate renal dysfunction (creatinine clearance 30–50 mL/min), the systemic exposure (AUC) and peak plasma concentrations (C_{max}) were not significantly different from those in 6 subjects with normal renal function.

In patients with normal renal function, the pharmacokinetic profile of hydroxypropylbetacyclodextrin (HPβCD), an ingredient of Voriconazole for injection, has a short half-life of 1 to 2 hours, and demonstrates no accumulation following successive daily doses. In healthy subjects and in patients with mild to severe renal insufficiency, the majority (>85 %) of an 8 g dose of HPβCD is eliminated in the urine. In a study investigating another antifungal drug, itraconazole, following a single intravenous 200 mg dose, clearance of hydroxypropyl-ß-cyclodextrin was reduced in subjects with renal impairment, resulting in higher exposure to hydroxypropyl-ß-cyclodextrin. In subjects with mild, moderate, and severe renal impairment, half-life values were increased over normal values by approximately two-, four-, and six-fold, respectively. In these patients, successive infusions may result in accumulation of HPβCD until steady state is reached. HPβCD is removed by hemodialysis.

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 (2.7)*].

A pharmacokinetic study in subjects with renal failure undergoing hemodialysis showed that voriconazole is dialyzed with clearance of 121 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 every 12h × 7 days) by an average of 93% and 96%, respectively, in healthy subjects. Doubling the dose of voriconazole to 400 mg every 12h 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 every 12h for 9 days) decreased the steady state C_{max} and AUC_{τ} of oral voriconazole (400 mg every 12h for 1 day, then 200 mg every 12h for 8 days) by an average of 66% and 82%, respectively, in healthy subjects. Low-dose ritonavir (100 mg every 12h for 9 days) decreased the steady state C_{max} and AUC_{τ} of oral voriconazole (400 mg every 12h for 1 day, then 200 mg every 12h 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 Cmax and AUCτ 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 every 12h) is contraindicated. Coadministration of voriconazole and low-dose ritonavir (100 mg every 12h) 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 three times daily for 15 days) followed by a single 400 mg oral dose of voriconazole, a 59% decrease in mean voriconazole AUC_0–∞ was observed. In contrast, coadministration of single oral doses of St. John's Wort and voriconazole had no appreciable effect on voriconazole AUC_0–∞. Because long-term use of St. John's Wort could lead to reduced voriconazole exposure, **concomitant 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 every 12h for 1 day, then 200 mg every 12h for 2.5 days) and oral fluconazole (400 mg on day 1, then 200 mg every 24h for 4 days) to 6 healthy male subjects resulted in an increase in C_{max} and AUC_{τ} of voriconazole by an average of 57% (90% CI: 20%, 107%) and 79% (90% CI: 40%, 128%), respectively. In a follow-on clinical study involving 8 healthy male subjects, reduced dosing and/or frequency of voriconazole and fluconazole did not eliminate or diminish this effect. 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 every 12h × 8 days) increased voriconazole steady state C_{max} and AUC_{τ} by an average of 18% (90% CI: 6%, 32%) and 23% (90% CI: 13%, 33%), respectively, following oral doses of 200 mg every 12h × 7 days to healthy subjects.

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

Macrolide antibiotics–Coadministration of **erythromycin** (CYP3A4 inhibitor; 1g every 12h for 7 days) or **azithromycin** (500 mg every 24h for 3 days) with voriconazole 200 mg every 12h 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 every 12h for 1 day, then 200 mg every 12h 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)*].

***Everolimus* (CYP3A4 substrate, P-gp substrate)**–Although not studied *in vitro* or *in vivo*, voriconazole may increase plasma concentrations of everolimus, which could potentially lead to exacerbation of everolimus toxicity. Currently there are insufficient data to allow dosing recommendations in this situation. Therefore, co-administration of voriconazole with everolimus is not recommended [*see Drug Interactions (7)*].

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 every 12h on day 1, 200 mg every 12h 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 co-administration 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 every 12h on Day 1, then 200 mg every 12h on Day 2) with a single intravenous dose of fentanyl (5 µg/kg) resulted in an increase in the mean $AUC_{0-\infty}$ of fentanyl by 1.4-fold (range 0.81- to 2.04-fold). When voriconazole is co-administered with fentanyl intravenous, 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 every 12h, on Day 1 followed by five doses of 200 mg every 12h on Days 2 to 4) with a single 10 mg oral dose of oxycodone on Day 3 resulted in an increase in the mean C_{max} and $AUC_{0}–\infty$ of oxycodone by 1.7-fold (range 1.4- to 2.2-fold) and 3.6-fold (range 2.7- to 5.6-fold), respectively. The mean elimination half-life of oxycodone was also increased by 2.0-fold (range 1.4- to 2.5-fold). 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 every 12h for 8 days) increased cyclosporine C_{max} and AUC_{τ} an average of 1.1 times (90% CI: 0.9, 1.41) and 1.7 times (90% CI: 1.5, 2.0), respectively, as compared to when cyclosporine was administered without voriconazole. 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. <u>When voriconazole is discontinued, cyclosporine levels should be frequently monitored and the dose increased as necessary</u> [*see Warnings and Precautions (5.1)*].

Methadone **(CYP3A4, CYP2C19, CYP2C9 substrate)**–Repeat dose administration of oral voriconazole (400 mg every 12h for 1 day, then 200 mg every 12h for 4 days) increased the C_{max} and AUC_{τ} of pharmacologically active Rmethadone by 31% (90% CI: 22%, 40%) and 47% (90% CI: 38%, 57%), respectively, in subjects receiving a methadone maintenance dose (30–100 mg every 24h). 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 every 12h × 1 day, then 200 mg every 12h × 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. <u>When voriconazole is discontinued, tacrolimus levels should be carefully monitored and the dose increased as necessary</u> [*see Warnings and Precautions (5.1)*].

Warfarin **(CYP2C9 substrate)**–Coadministration of voriconazole (300 mg every 12h × 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 every 12h on Day 1, followed by 200 mg every 12h 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 every 12h × 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 every 12h × 12 days) had no significant effect on steady state C_{max} and AUC_τ of digoxin (0.25 mg once daily for 10 days) in healthy subjects.

Mycophenolic acid **(UDP-glucuronyl transferase substrate)**–Voriconazole (200 mg every 12h × 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, 4.0) 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 efavirenz (400 mg every 24h or higher) must not be coadministered [*see Drug Interactions (7)*]. Steady state efavirenz (400 mg PO every 24h) decreased the steady state Cmax and

AUCτ of voriconazole (400 mg PO every 12h for 1 day, then 200 mg PO every 12h for 8 days) by an average of 61% and 77%, respectively, in healthy male subjects. Voriconazole at steady state (400 mg PO every 12h for 1 day, then 200 mg every 12h for 8 days) increased the steady state C_{max} and AUC_{τ} of efavirenz (400 mg PO every 24h for 9 days) by an average of 38% and 44%, respectively, in healthy subjects.

Coadministration of standard doses of voriconazole and efavirenz (400 mg every 24h or higher) is contraindicated. [*see Contraindications (4) and Drug Interactions (7)*].

***Phenytoin* (CYP2C9 substrate and potent CYP450 inducer)–**Repeat dose administration of phenytoin (300 mg once daily) decreased the steady state C_{max} and AUC_{τ} of orally administered voriconazole (200 mg every 12h × 14 days) by an average of 50% and 70%, respectively, in healthy subjects.

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 [*see Dosage and Administration (2.4) and Drug Interactions (7)*].

Repeat dose administration of voriconazole (400 mg every 12h × 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 × 10 days) with oral voriconazole (400 mg every 12h × 1 day, then 200 mg every 12h × 9 days) increased the steady state C_{max} and AUC_{τ} of voriconazole by an average of 15% (90% CI: 5%, 25%) and 40% (90% CI: 29%, 55%), respectively, in healthy subjects. No dosage adjustment of voriconazole is recommended.

Coadministration of voriconazole (400 mg every 12h × 1 day, then 200 mg × 6 days) with omeprazole (40 mg once daily × 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 every 12h for 1 day, then 200 mg every 12h for 3 days) and oral contraceptive (Ortho-Novum1/35® consisting of 35 mcg ethinyl estradiol and 1 mg norethindrone, every 24h) 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 Cmax 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 every 12h for 17 days) in healthy subjects.

Repeat dose administration of voriconazole (200 mg every 12h 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 (5.8)*]. 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 co-administered with efavirenz [*see Drug Interactions (7) and Warnings and Precautions (5.1)*].

12.4 Microbiology

Mechanism of Action

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

Resistance

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.

Antimicrobial Activity

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 µg/mL)[1]
Candida krusei
Candida parapsilosis
Candida tropicalis
Fusarium spp. including *Fusarium solani*
Scedosporium apiospermum

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

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

Candida lusitaniae
Candida guilliermondii

[1]In clinical studies, voriconazole MIC90 for *C. glabrata* baseline isolates was 4 µg/mL; 13/50 (26%) *C. glabrata* baseline isolates were resistant (MIC ≥4 µg/mL) to voriconazole. However, based on 1054 isolates tested in surveillance studies the MIC90 was 1 µg/mL (see Table 12).

Susceptibility Testing Methods[1,2]

***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.[1,2]

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.[1] 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 9.

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.[2] This procedure uses paper disks impregnated with 1 µg of voriconazole to test the susceptibility of yeasts to voriconazole at 24 hours. Disk diffusion interpretive criteria are also provided in Table 9.

Table 9: Susceptibility Interpretive Criteria for Voriconazole against *Candida* species[1,2]

	Broth Microdilution at 48 hours (MIC in µg/mL)			**Disk Diffusion at 24 hours (Zone diameters in mm)**		
	Susceptible (S)	**Intermediate (I)**	**Resistant (R)**	**Susceptible (S)**	**Intermediate (I)**	**Resistant (R)**
Voriconazole	≤1.0	2.0	≥4.0	≥17	14–16	≤13

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

A report of *Susceptible* (*S*) indicates that the antimicrobial drug is likely to inhibit growth of the microorganism if the antimicrobial drug reaches the concentration usually achievable at the site of infection. A report of *Intermediate* (*I*) indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of the drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistant* (*R*) indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentrations usually achievable at the infection site; other therapy should be selected.

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 µg disks should provide the following range of values noted in Table 10.

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 10: Acceptable Quality Control Ranges for Voriconazole to be used in Validation of Susceptibility Test Results

QC Strain	Broth Microdilution (MIC in µg/mL) at 48-hour	Disk Diffusion (Zone diameter in mm) at 24-hour
Candida parapsilosis ATCC 22019	0.03–0.25	28–37
Candida krusei ATCC 6258	0.12–1.0	16–25
Candida albicans ATCC 90028	*	31–42

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.

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

Voriconazole demonstrated clastogenic activity (mostly chromosome breaks) in human lymphocyte cultures *in vitro*. Voriconazole was not genotoxic in the Ames assay, CHO assay, the mouse micronucleus assay or the DNA repair test (Unscheduled DNA Synthesis assay).

Voriconazole administration induced no impairment of male or female fertility in rats dosed at 50 mg/kg, or 1.6 times the RMD (recommended maintenance dose).

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 seven days. Therapy could then be switched to the oral formulation at a dose of 200 mg every 12h. Median duration of intravenous voriconazole therapy was 10 days (range 2–85 days). After intravenous voriconazole therapy, the median duration of PO voriconazole therapy was 76 days (range 2–232 days).

Patients in the comparator group received conventional amphotericin B as a slow infusion at a daily dose of 1.0–1.5 mg/kg/day. Median duration of intravenous amphotericin therapy was 12 days (range 1–85 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 two weeks, actual duration of therapy was at the discretion of the investigator. Patients who discontinued initial randomized therapy due to toxicity or lack of efficacy were eligible to continue in the study with OLAT treatment.

A satisfactory global response at 12 weeks (complete or partial resolution of all attributable symptoms, signs, radiographic/bronchoscopic abnormalities present at baseline) was seen in 53% of voriconazole treated patients compared to 32% of amphotericin B treated patients (Table 12). 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 11).

Table 11 also summarizes the response (success) based on mycological confirmation and species.

Table 11: Overall Efficacy and Success by Species in the Primary Treatment of Acute Invasive Aspergillosis Study 307/602

	Voriconazole n/N (%)	**Ampho B * n/N (%)**	**Stratified Difference (95% CI) †**
Efficacy as Primary Therapy			
Satisfactory Global Response ‡	76/144 (53)	42/133 (32)	21.8% (10.5%, 33.0%) 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	

	Voriconazole n/N (%)	Ampho B * n/N (%)	Stratified Difference (95% CI) †
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 12.

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

Additional data regarding response rates in patients who were refractory to, or intolerant of, other antifungal agents are also provided in Table 13. 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 12.

Table 12: Combined Response Data in Salvage Patients with Single *Aspergillus* Species (Studies 304 and 309/604)

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

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

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

Voriconazole was compared to the regimen of amphotericin B followed by fluconazole in Study 608, an open label, comparative study in nonneutropenic patients with candidemia associated with clinical signs of infection. Patients were randomized in 2:1 ratio to receive either voriconazole (n=283) or the regimen of amphotericin B followed by fluconazole (n=139). Patients were treated with randomized study drug for a median of 15 days. Most of the candidemia in patients evaluated for efficacy was caused by *C. albicans* (46%), followed by *C. tropicalis* (19%), *C. parapsilosis* (17%), *C. glabrata* (15%), and *C. krusei* (1%).

An independent Data Review Committee (DRC), blinded to study treatment, reviewed the clinical and mycological data from this study, and generated one assessment of response for each patient. A successful response required all of the following: resolution or improvement in all clinical signs and symptoms of infection, blood cultures negative for *Candida,* infected deep tissue sites negative for *Candida* or resolution of all local signs of infection, and no systemic antifungal therapy other than study drug. The primary analysis, which counted DRC-assessed successes at the fixed time point (12 weeks after End of Therapy [EOT]), demonstrated that voriconazole was comparable to the regimen of amphotericin B followed by fluconazole (response rates of 41% and 41%, respectively) in the treatment of candidemia. Patients who did not have a 12-week assessment for any reason were considered a treatment failure.

The overall clinical and mycological success rates by *Candida* species in Study 150-608 are presented in Table 13.

Table 13: 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	¼	0/1

* 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 Other Serious Fungal Pathogens

In pooled analyses of patients, voriconazole was shown to be effective against the following additional fungal pathogens:

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

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

15 REFERENCES

1. Clinical Laboratory Standards Institute (CLSI). Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts. Approved Standard M27-A3. Clinical Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898, USA, 2008.
2. Clinical Laboratory Standards Institute (CLSI). Method for Antifungal Disk Diffusion Susceptibility Testing of Yeasts. Approved Guideline M44-A2. Clinical Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898, USA, 2009.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Voriconazole for Injection is supplied in a single dose vial as an unpreserved, sterile white to off white lyophilized cake or powder equivalent to 200 mg voriconazole and 3200 mg hydroxypropyl β-cyclodextrin (HPβCD).

Individually packaged vials of Voriconazole for Injection, 200 mg, NDC 39822-1077-1.

16.2 Storage and Handling

Storage

Powder for Injection: Voriconazole for Injection unreconstituted vials should be stored at 20° – 25°C (68° – 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

Reconstituted Drug Solution: From a microbiological point of view, following reconstitution of the lyophile with Water for Injection, the reconstituted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2° to 8°C (36° to 46°F). Chemical and physical in-use stability has been demonstrated for 24 hours at 2° to 8°C (36° to 46°F). Discard Unused Portion. [*see Dosage and Administration (2.5)*].

Further Diluted Drug Solution for Infusion: Once the reconstituted product is further diluted for infusion, it should be used immediately. Discard Unused Portion. [*see Dosage and Administration (2.5)*].
This medicinal product is for single use only and any unused solution should be discarded. Only clear solutions without particles should be used [*see Dosage and Administration (2.5)*].

Handling

Not made with natural rubber latex.

17 PATIENT COUNSELING INFORMATION

- Patients should be instructed that visual disturbances such as blurring and sensitivity to light may occur with the use of voriconazole.
- Advise patients to avoid direct sunlight due to risk of phototoxicity.
- Inform the patient of the potential hazard to the fetus, if the drug is used during pregnancy [*see Warnings and Precautions (5)*].

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