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

RECENT MAJOR CHANGES

Indications and Usage (1)	1/2019
Dosage and Administration (2)	1/2019
Contraindications (4)	1/2019
Warnings and Precautions (5)	1/2019

INDICATIONS AND USAGE

Voriconazole for injection is an azole antifungal indicated for the treatment of adults and pediatric patients aged 12 to 14 years weighing greater than or equal to 50 kg and those aged 15 years and older regardless of body weight with:
- Invasive aspergillosis (1.1)
- Candidemia in non-neutropenics and other deep tissue *Candida* infections (1.2)
- Esophageal candidiasis (1.3)
- Serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* species including *Fusarium solani*, in patients intolerant of, or refractory to, other therapy (1.4)

DOSAGE AND ADMINISTRATION

- **Dosage in Adults (2.3)**

Infection	Loading dose	Maintenance Dose	
	Intravenous infusion	Intravenous infusion	Oral
Invasive Aspergillosis	6 mg/kg every 12 hours for the first 24 hours	4 mg/kg every 12 hours	200 mg every 12 hours
Candidemia in nonneutropenics and other deep tissue *Candida* infections		3-4 mg/kg every 12 hours	200 mg every 12 hours
Scedosporiosis and Fusariosis		4 mg/kg every 12 hours	200 mg every 12 hours
Esophageal Candidiasis	Not Evaluated	Not Evaluated	200 mg every 12 hours

- o Adult patients weighing less than 40 kg: oral maintenance dose 100 mg or 150 mg every 12 hours
- o *Hepatic Impairment:* Use half the maintenance dose in adult patients with mild to moderate hepatic impairment (Child-Pugh Class A and B) (2.5)
- o *Renal Impairment:* Avoid intravenous administration in adult patients with moderate to severe renal impairment (creatinine clearance <50 mL/min) (2.6)
- **Dosage in Pediatric Patients (2.4)**
- o For pediatric patients aged 12 to 14 years weighing greater than or equal to 50 kg and those aged 15 years and older regardless of body weight use adult dosage. (2.4)
- o Dosage adjustment of Voriconazole for Injection in pediatric patients with renal or hepatic impairment has not been established (2.5, 2.6)
- See full prescribing information for instructions on reconstitution of voriconazole for injection lyophilized powder for intravenous use (2.1, 2.6, 2.7)

DOSAGE FORMS AND STRENGTHS

- *For Injection:* Lyophilized powder containing 200 mg of voriconazole and 3,200 mg of sulfobutyl ether beta-cyclodextrin sodium (SBECD); after reconstitution 10 mg/mL of voriconazole and 160 mg/mL of SBECD (3)

CONTRAINDICATIONS

- Hypersensitivity to voriconazole or its excipients (4)
- Coadministration with 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

- *Hepatic Toxicity:* Serious hepatic reactions reported. Evaluate liver function tests at start of and during voriconazole for injection therapy (5.1)
- *Arrhythmias and QT Prolongation*: Correct potassium, magnesium and calcium prior to use; caution patients with proarrhythmic conditions (5.2)
- *Infusion Related Reactions (including anaphylaxis)*: Stop the infusion (5.3)
- *Visual Disturbances* (including optic neuritis and papilledema): Monitor visual function if treatment continues beyond 28 days (5.4)
- *Serious Exfoliative Cutaneous Reactions*: Discontinue for exfoliative cutaneous reactions (5.5)
- *Photosensitivity*: Avoid sunlight due to risk of photosensitivity (5.6)
- *Embryo-Fetal Toxicity*: Voriconazole can cause fetal harm when administered to a pregnant woman. Inform pregnant patients of the potential hazard to the fetus. Advise females of reproductive potential to use effective contraception during treatment with voriconazole for injection (5.8, 8.1, 8.3)
- *Skeletal Adverse Reactions*: Fluorosis and periostitis with long-term voriconazole therapy. Discontinue if these adverse reactions occur (5.11)
- *Clinically Significant Drug Interactions*: Review patient's concomitant medications (5.12, 7)

ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176 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 or Efavirenz: With co-administration, increase maintenance oral and intravenous dosage of voriconazole for injection (2.3, 2.7, 7)

USE IN SPECIFIC POPULATIONS

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

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

Additional pediatric use information is approved for PF PRISM C.V.'s VFEND (voriconazole). However, due to PF PRISM C.V.'s marketing exclusivity rights, this drug product is not labeled with that information.

Revised: 04/2020

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Invasive Aspergillosis
Voriconazole for injection is indicated in adults and pediatric patients (aged 12 to 14 years weighing greater than or equal to 50 kg and those aged 15 years and older regardless of body weight) for the treatment of invasive aspergillosis (IA). In clinical trials, the majority of isolates recovered were *Aspergillus fumigatus*. There was a small number of cases of culture-proven disease due to species of *Aspergillus* other than *A. fumigatus [see Clinical Studies (14.1, 14.5) and Microbiology (12.4)]*.

1.2 Candidemia in Non-neutropenic Patients and Other Deep Tissue *Candida* Infections
Voriconazole for injection is indicated in adults and pediatric patients (aged 12 to 14 years weighing greater than or equal to 50 kg and those aged 15 years and older regardless of body weight) for the treatment of candidemia in non-neutropenic patients and the following *Candida* infections: disseminated infections in skin and infections in abdomen, kidney, bladder wall, and wounds *[see Clinical Studies (14.2, 14.5) and Microbiology (12.4)]*.

1.3 Esophageal Candidiasis
Voriconazole for injection is indicated in adults and pediatric patients (aged 12 to 14 years weighing greater than or equal to 50 kg and those aged 15 years and older regardless of body weight) for the treatment of esophageal candidiasis (EC) *[see Clinical Studies (14.3, 14.5) and Microbiology (12.4)]*.

1.4 Scedosporiosis and Fusariosis
Voriconazole for injection is indicated for the treatment of serious fungal infections caused by *Scedosporium apiospermum* (asexual form of *Pseudallescheria boydii*) and *Fusarium spp.* including *Fusarium solani*, in adults and pediatric patients (aged 12 to 14 years weighing greater than or equal to 50 kg and those aged 15 years and older regardless of body weight) intolerant of, or refractory to, other therapy *[see Clinical Studies (14.4) and Microbiology (12.4)]*.

1.5 Usage
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.

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2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions for Use in All Patients
Voriconazole for injection I..V. 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 I.V. by intravenous infusion over 1 to 2 hours only. Do not administer as an IV bolus injection.

2.2 Use of voriconazole for injection I.V. With Other Parenteral Drug Products
Blood products and concentrated electrolytes

Voriconazole for injection I.V. 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 (5.9)]*.

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

Total parenteral nutrition (TPN)
Voriconazole for injection I.V. 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 I.V.

2.3 Recommended Dosing Regimen 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 I.V on Day 1 followed by the recommended maintenance dose (RMD) regimen. Intravenous treatment should be continued for at least 7 days. Once the patient has clinically improved and can tolerate medication given by mouth, the oral tablet form or oral suspension form of voriconazole for injection 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.

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

Table 1: Recommended Dosing Regimen (Adults)

Infection	Loading Dose	Maintenance Dose[a,b]	
	Intravenous infusion	Intravenous infusion	Oral[c]
Invasive Aspergillosis[d]	6 mg/kg every 12 hours for the first 24 hours	4 mg/kg every 12 hours	200 mg every 12 hours
Candidemia in nonneutropenic patients and other deep tissue *Candida* infections	6 mg/kg every 12 hours for the first 24 hours	3-4 mg/kg every 12 hours[e]	200 mg every 12 hours
Esophageal Candidiasis	Not Evaluated[f]	Not Evaluated[f]	200 mg every 12 hours
Scedosporiosis and Fusariosis	6 mg/kg every 12 hours for the first 24 hours	4 mg/kg every 12 hours	200 mg every 12 hours

[a] Increase dose when voriconazole for injection is co-administered with phenytoin or efavirenz (7); Decrease dose in patients with hepatic impairment (2.5)
[b] In healthy volunteer studies, the 200 mg oral every 12 hours dose provided an exposure (AUCτ) similar to a 3 mg/kg intravenous infusion every 12 hours dose; the 300 mg oral every 12 hours dose provided an exposure (AUCτ) similar to a 4 mg/kg intravenous infusion every 12 hours dose (12).
[c] Adult patients who weigh less than 40 kg should receive half of the oral maintenance dose.
[d] In a clinical study of IA, the median duration of intravenous voriconazole for injection therapy was 10 days (range 2 to 85 days). The median duration of oral voriconazole therapy was 76 days (range 2 to 232 days) (14.1).
[e] In clinical trials, patients with candidemia received 3 mg/kg intravenous infusion every 12 hours as primary therapy, while patients with other deep tissue *Candida* infections received 4 mg/kg every 12 hours as salvage therapy. Appropriate dose should be based on the severity and nature of the infection.
[f] Not evaluated in patients with EC.

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

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

2.4 Recommended Dosing Regimen in Pediatric Patients
For pediatric patients 12 to 14 years of age with a body weight greater than or equal to 50 kg and those 15 years of age and above regardless of body weight, administer the adult dosing regimen of voriconazole for injection *[see Dosage and Administration (2.3)]*.

Initiate therapy with an intravenous infusion regimen. Consider an oral regimen only after there is a significant clinical improvement.

Method for Adjusting the Dosing Regimen in Pediatric Patients:

Pediatric patients 12 to 14 years of age weighing greater than or equal to 50kg and 15 years of age and older regardless of body weight:

Use the optimal method for titrating dosage recommended for adults *[see Dosage and Administration (2.3)]*.

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2.5 Dosage Modifications in Patients With Hepatic Impairment
Adults
The maintenance dose of voriconazole should be reduced in adult patients with mild to moderate hepatic impairment, Child-Pugh Class A and B. There are no PK data to allow for dosage adjustment recommendations in patients with severe hepatic impairment (Child-Pugh Class C).

Duration of therapy should be based on the severity of the patient's underlying disease, recovery from immunosuppression, and clinical response.

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

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

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

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

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

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

Voriconazole is hemodialyzed with clearance of 121 mL/min. The intravenous vehicle, SBECD, is hemodialyzed with clearance of 55 mL/min. A 4-hour hemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment.

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

2.7 Dosage Adjustment When Co-Administered With Phenytoin or Efavirenz
The maintenance dose of voriconazole should be increased when co-administered with phenytoin or efavirenz. Use the optimal method for titrating dosage *[see Drug Interactions (7) and Dosage and Administration (2.3)]*.

2.8 Preparation and Intravenous Administration of Voriconazole for Injection
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.

Dilution
Voriconazole for injection must be infused over 1 to 3 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 3).
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 Partially Used Vials**.

The final voriconazole for injection solution must be infused over 1 to 3 hours at a maximum rate of 3 mg/kg per hour.

Table 3: 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 mL (1)	12 mL (1)	18 mL (1)
35	10.5 mL (1)	14 mL (1)	21 mL (2)
40	12 mL (1)	16 mL (1)	24 mL (2)
45	13.5 mL (1)	18 mL (1)	27 mL (2)
50	15 mL (1)	20 mL (1)	30 mL (2)
55	16.5 mL (1)	22 mL (2)	33 mL (2)
60	18 mL (1)	24 mL (2)	36 mL (2)
65	19.5 mL (1)	26 mL (2)	39 mL (2)
70	21 mL (2)	28 mL (2)	42 mL (3)
75	22.5 mL (2)	30 mL (2)	45 mL (3)
80	24 mL (2)	32 mL (2)	48 mL (3)
85	25.5 mL (2)	34 mL (2)	51 mL (3)
90	27 mL (2)	36 mL (2)	54 mL (3)
95	28.5 mL (2)	38 mL (2)	57 mL (3)
100	30 mL (2)	40 mL (2)	60 mL (3)

Voriconazole for injection I.V. is a single-dose unpreserved sterile lyophile. 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°C to 8°C (36°F to 46°F). This medicinal product is for single use only and any unused solution should be discarded. Only clear solutions without particles should be used.

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 I.V. with diluents other than those described above is unknown (see Incompatibilities below).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Incompatibilities
Voriconazole for injection I.V. must not be diluted with 4.2% Sodium Bicarbonate Infusion. The mildly alkaline nature of this diluent caused slight degradation of voriconazole for injection 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.

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3 DOSAGE FORMS AND STRENGTHS

Powder for Solution for Injection
Voriconazole for injection I.V. is supplied in a single-dose vial as a sterile lyophilized powder equivalent to 200 mg voriconazole and 3,200 mg sulfobutyl ether beta-cyclodextrin sodium (SBECD).

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 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 for injection 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 24 hours or higher is contraindicated, because efavirenz significantly decreases plasma voriconazole concentrations in healthy subjects at these doses. Voriconazole also significantly increases efavirenz plasma concentrations *[see Drug Interactions (7) and Clinical Pharmacology (12.3)]*.
- Coadministration of voriconazole for injection with high-dose ritonavir (400 mg every 12 hours) is contraindicated because ritonavir (400 mg every 12 hours) significantly decreases plasma voriconazole concentrations. Coadministration of voriconazole and low-dose ritonavir (100 mg every 12 hours) should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole *[see Drug Interactions (7) and Clinical Pharmacology (12.3)]*.
- Coadministration of voriconazole for injection with rifabutin is contraindicated since voriconazole for injection 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 for injection 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 Hepatic Toxicity
In clinical trials, there have been uncommon cases of serious hepatic reactions during treatment with voriconazole for injection (including clinical hepatitis, cholestasis and fulminant hepatic failure, including fatalities). Instances of hepatic reactions were noted to occur primarily in patients with serious underlying medical conditions (predominantly hematological malignancy). Hepatic reactions, including hepatitis and jaundice, have occurred among patients with no other identifiable risk factors. Liver dysfunction has usually been reversible on discontinuation of therapy *[see Adverse Reactions (6.1)]*.

A higher frequency of liver enzyme elevations was observed in the pediatric population *[see Adverse Reactions (6.1)]*.Hepatic function should be monitored in both adult and pediatric patients.

Measure serum transaminase levels and 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 Dosage and Administration (2.5) and Adverse Reactions (6.1)]*.

5.2 Arrhythmias and QT Prolongation
Some azoles, including voriconazole for injection, 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 for injection 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)]*.

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

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

5.5 Serious Exfoliative Cutaneous Reactions
Serious exfoliative cutaneous reactions, such as Stevens-Johnson syndrome, have been reported during treatment with voriconazole for injection. If a patient develops an exfoliative cutaneous reaction, voriconazole for injection should be discontinued.

5.6 Photosensitivity
Voriconazole for injection has been associated with photosensitivity skin reaction. Patients, including pediatric patients, 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 for injection 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. In addition, voriconazole for injection has been associated with photosensitivity related skin reactions such as pseudoporphyria, cheilitis, and cutaneous lupus erythematosus. Patients should avoid strong, direct sunlight during voriconazole for injection therapy.

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.

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

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

5.8 Embryo-Fetal Toxicity
Voriconazole can cause fetal harm when administered to a pregnant woman.

In animals, voriconazole administration was associated with fetal malformations, embryotoxicity, increased gestational length, dystocia and embryomortality *[see Use in Specific Populations (8.1)]*.

If voriconazole for injection is used during pregnancy, or if the patient becomes pregnant while taking voriconazole for injection, inform the patient of the potential hazard to the fetus. Advise females of reproductive potential to use effective contraception during treatment with voriconazole for injection *[see Use in Specific Populations (8.3)]*.

5.9 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).

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

5.11 Skeletal Adverse Reactions
Fluorosis and periostitis have been reported during long-term voriconazole for injection therapy. If a patient develops skeletal pain and radiologic findings compatible with fluorosis or periostitis, voriconazole for injection should be discontinued *[see Adverse Reactions (6.2)]*.

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

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

Hepatic Toxicity *[see Warnings and Precautions (5.1)]*
Arrhythmias and QT Prolongation *[see Warnings and Precautions (5.2)]*
Infusion Related Reactions *[see Warnings and Precautions (5.3)]*
Visual Disturbances *[see Warnings and Precautions (5.4)]*
Serious Exfoliative Cutaneous Reactions *[see Warnings and Precautions (5.5)]*
Photosensitivity *[see Warnings and Precautions (5.6)]*
Renal Toxicity *[see Warnings and Precautions (5.7)]*

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

Clinical Trials Experience in Adults

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

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

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

Table 4:

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

	Therapeutic Studies*	Studies 307/602 and 608 (IV/ oral therapy)			Study 305 (oral therapy)	
	Voriconazole N=1655	Voriconazole N=468	Ampho B** N=185	Ampho B→ Fluconazole N=131	Voriconazole N=200	Fluconazole N=191
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Special Senses* **						
Abnormal vision	310 (18.7)	63 (13.5)	1 (0.5)	0	31 (15.5)	8 (4.2)
Photophobia	37 (2.2)	8 (1.7)	0	0	5 (2.5)	2 (1.0)
Chromatopsia	20 (1.2)	2 (0.4)	0	0	2 (1.0)	0
Body as a Whole						
Fever	94 (5.7)	8 (1.7)	25 (13.5)	5 (3.8)	0	0
Chills	61 (3.7)	1 (0.2)	36 (19.5)	8 (6.1)	1 (0.5)	0
Headache	49 (3.0)	9 (1.9)	8 (4.3)	1 (0.8)	0	1 (0.5)
Cardiovascular System						
Tachycardia	39 (2.4)	6 (1.3)	5 (2.7)	0	0	0
Digestive System						
Nausea	89 (5.4)	18 (3.8)	29 (15.7)	2 (1.5)	2 (1.0)	3 (1.6)
Vomiting	72 (4.4)	15 (3.2)	18 (9.7)	1 (0.8)	2 (1.0)	1 (0.5)
Liver function tests abnormal	45 (2.7)	15 (3.2)	4 (2.2)	1 (0.8)	6 (3.0)	2 (1.0)
Cholestatic jaundice	17 (1.0)	8 (1.7)	0	1 (0.8)	3 (1.5)	0
Metabolic and Nutritional Systems						
Alkaline phosphatase increased	59 (3.6)	19 (4.1)	4 (2.2)	3 (2.3)	10 (5.0)	3 (1.6)
Hepatic enzymes increased	30 (1.8)	11 (2.4)	5 (2.7)	1 (0.8)	3 (1.5)	0
SGOT increased	31 (1.9)	9 (1.9)	0	1 (0.8)	8 (4.0)	2 (1.0)
SGPT increased	29 (1.8)	9 (1.9)	1 (0.5)	2 (1.5)	6 (3.0)	2 (1.0)
Hypokalemia	26 (1.6)	3 (0.6)	36 (19.5)	16 (12.2)	0	0
Bilirubinemia	15 (0.9)	5 (1.1)	3 (1.6)	2 (1.5)	1 (0.5)	0
Creatinine increased	4 (0.2)	0	59 (31.9)	10 (7.6)	1 (0.5)	0
Nervous System						
Hallucinations	39 (2.4)	13 (2.8)	1 (0.5)	0	0	0
Skin and Appendages						
Rash	88 (5.3)	20 (4.3)	7 (3.8)	1 (0.8)	3 (1.5)	1 (0.5)
Urogenital						
Kidney function abnormal	10 (0.6)	6 (1.3)	40 (21.6)	9 (6.9)	1 (0.5)	1 (0.5)
Acute kidney failure	7 (0.4)	2 (0.4)	11 (5.9)	7 (5.3)	0	0

† Study 307/602: IA; Study 608: candidemia; Study 305: EC
* Studies 303, 304, 305, 307, 309, 602, 603, 604, 608
**Amphotericin B followed by other licensed antifungal therapy
***See Warnings and Precautions (5.4)

Visual Disturbances
Voriconazole for injection 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. 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 for injection caused a decrease in the electroretinogram (ERG) waveform amplitude, a decrease in the visual field, and an alteration in color perception. The ERG measures electrical currents in the retina. These effects were noted early in administration of voriconazole for injection and continued through the course of study drug treatment. Fourteen days after the end of dosing, ERG, visual fields and color perception returned to normal *[see Warnings and Precautions (5.4)]*.

Dermatological Reactions
Dermatological reactions were common in patients treated with voriconazole for injection. 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 for injection *[see Warnings and Precautions (5.5)]*.

Voriconazole for injection has also been associated with additional photosensitivity related skin reactions such as pseudoporphyria, cheilitis, and cutaneous lupus erythematosus *[see Warnings and Precautions (5.6)]*.

Less Common Adverse Reactions
The following adverse reactions occurred in <2% of all voriconazole-treated patients in all therapeutic studies (N=1655). This listing includes events where a causal relationship to voriconazole cannot be ruled out or those which may help the physician in managing the risks to the patients. The list does not include events included in Table 4 above and does not include every event reported in the voriconazole clinical program.

Body as a Whole: abdominal pain, abdomen enlarged, allergic reaction, anaphylactoid reaction *[see Warnings and Precautions (5.3)]*, ascites, asthenia, back pain, chest pain, cellulitis, edema, 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 (5.2)]*.

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

Voriconazole for injection 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 (5.1)]*.

Acute renal failure has been observed in severely ill patients undergoing treatment with voriconazole for injection. Patients being treated with voriconazole for injection are likely to be treated concomitantly with nephrotoxic medications and may have concurrent conditions that can result in decreased renal function. It is recommended that patients are monitored for the development of abnormal renal function. This should include laboratory evaluation of serum creatinine.

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

Table 5:

Protocol 305 – Patients with Esophageal Candidiasis

Clinically Significant Laboratory Test Abnormalities

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

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

Table 6:

Protocol 307/602 – Primary Treatment of Invasive Aspergillosis

Clinically Significant Laboratory Test Abnormalities

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

*Without regard to baseline value
**Amphotericin B followed by other licensed antifungal therapy
n = number of patients with a clinically significant abnormality while on study therapy
N = total number of patients with at least one observation of the given lab test while on study therapy
AST = Aspartate aminotransferase; ALT = alanine aminotransferase
ULN = upper limit of normal
LLN = lower limit of normal

Table 7:

Protocol 608 – Treatment of Candidemia

Clinically Significant Laboratory Test Abnormalities

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

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

Clinical Trials Experience in Pediatric Patients
The safety of Voriconazole for injection was investigated in pediatric patients, including 52 pediatric patients less than 18 years of age who were enrolled in the adult therapeutic studies.

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

Additional pediatric use information is approved for PF PRISM C.V.'s VFEND (voriconazole). However, due to PF PRISM C.V.'s marketing exclusivity rights, this drug product is not labeled with that information.

6.2 Postmarketing Experience in Adult and Pediatric Patients
The following adverse reactions have been identified during post-approval use of voriconazole for injection. 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.

Adults
Skeletal: fluorosis and periostitis have been reported during long-term voriconazole therapy *[see Warnings and Precautions (5.11)]*.

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

Pediatric Patients
There have been postmarketing reports of pancreatitis in pediatric patients.

7 DRUG INTERACTIONS

Voriconazole is metabolized by, and inhibits the activity of, cytochrome P450 isoenzymes, CYP2C19, CYP2C9, and CYP3A4. Inhibitors or inducers of these isoenzymes may increase or decrease voriconazole plasma concentrations, respectively, and there is potential for voriconazole to increase the plasma concentrations of substances metabolized by these CYP450 isoenzymes.

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

Table 10:

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 AUCτ after 200 mg every 12 hours)	Recommendations for Voriconazole Dosage Adjustment/Comments
Rifampin* and Rifabutin* (CYP450 Induction)	Significantly Reduced	**Contraindicated**
Efavirenz (400 mg every 24 hours)** (CYP450 Induction) Efavirenz (300 mg every 24 hours)** (CYP450 Induction)	Significantly Reduced Slight Decrease in AUCτ	**Contraindicated** When voriconazole is coadministered with efavirenz, voriconazole oral maintenance dose should be increased to 400 mg every 12 hours and efavirenz should be decreased to 300 mg every 24 hours.
High-dose Ritonavir (400 mg every 12 hours)** (CYP450 Induction) Low-dose Ritonavir (100 mg every 12 hours)** (CYP450 Induction)	Significantly Reduced Reduced	**Contraindicated** Coadministration of voriconazole and low-dose ritonavir (100 mg every 12 hours) should be avoided, unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.
Carbamazepine (CYP450 Induction)	Not Studied *In Vivo* or *In Vitro*, but Likely to Result in Significant Reduction	**Contraindicated**
Long Acting Barbiturates (CYP450 Induction)	Not Studied *In Vivo* or *In Vitro*, but Likely to Result in Significant Reduction	**Contraindicated**
Phenytoin* (CYP450 Induction)	Significantly Reduced	Increase voriconazole maintenance dose from 4 mg/kg to 5 mg/kg IV every 12 hours or from 200 mg to 400 mg orally every 12 hours (100 mg to 200 mg orally every 12 hours in patients weighing less than 40 kg).
St. John's Wort (CYP450 inducer; P-gp inducer)	Significantly Reduced	**Contraindicated**
Oral Contraceptives** containing ethinyl estradiol and norethindrone (CYP2C19 Inhibition)	Increased	Monitoring for adverse events and toxicity related to voriconazole is recommended when coadministered with oral contraceptives.
Fluconazole** (CYP2C9, CYP2C19 and CYP3A4 Inhibition)	Significantly Increased	Avoid concomitant administration of voriconazole and fluconazole. Monitoring for adverse events and toxicity related to voriconazole is started within 24 hours 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.

* Results based on *in vivo* clinical studies generally following repeat oral dosing with 200 mg every 12 hours voriconazole to healthy subjects
** Results based on *in vivo* clinical study following repeat oral dosing with 400 mg every 12 hours for 1 day, then 200 mg every 12 hours for at least 2 days voriconazole to healthy subjects
*** Non-Nucleoside Reverse Transcriptase Inhibitors

Table 11:

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 AUCτ)	Recommendations for Drug Dosage Adjustment/Comments
Sirolimus* (CYP3A4 Inhibition)	Significantly Increased	**Contraindicated**
Rifabutin* (CYP3A4 Inhibition)	Significantly Increased	**Contraindicated**
Efavirenz (400 mg every 24 hours)** (CYP3A4 Inhibition) Efavirenz (300 mg every 24 hours)** (CYP3A4 Inhibition)	Significantly Increased Slight Increase in AUCτ	**Contraindicated** When voriconazole is coadministered with efavirenz, voriconazole oral maintenance dose should be increased to 400 mg every 12 hours and efavirenz should be decreased to 300 mg every 24 hours.
High-dose Ritonavir (400 mg every 12hours)**(CYP3A4 Inhibition) Low-dose Ritonavir (100 mg every 12 hours)**	No Significant Effect of Voriconazole on Ritonavir C_{max} or AUCτ Slight Decrease in Ritonavir C_{max} and AUCτ	**Contraindicated** because of significant reduction of voriconazole C_{max} and AUCτ. Coadministration of voriconazole and low-dose ritonavir (100 mg every 12 hours) should be avoided (due to the reduction in voriconazole C_{max} and AUCτ) unless an assessment of the benefit/risk to the patient justifies the use of voriconazole.
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**

Table 11: Effect of Voriconazole on Pharmacokinetics of Other Drugs *[see Clinical Pharmacology (12.3)]* (Cont'd.)

Cyclosporine* (CYP3A4 Inhibition)	AUCτ 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 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 Exposure)	Frequent monitoring for adverse events and toxicity related to NNRTI.
Benzodiazepines (CYP3A4 Inhibition)	*In Vitro* Studies Demonstrated Potential for Voriconazole to Inhibit Metabolism (Increased Plasma Exposure)	Frequent monitoring for adverse events and toxicity (i.e., prolonged sedation) related to benzodiazepines metabolized by CYP3A4 (e.g., midazolam, triazolam, alprazolam). Adjustment of benzodiazepine dosage may be needed.
HMG-CoA Reductase Inhibitors (Statins) (CYP3A4 Inhibition)	*In Vitro* Studies Demonstrated Potential for Voriconazole to Inhibit Metabolism (Increased Plasma Exposure)	Frequent monitoring for adverse events and toxicity related to statins. Increased statin concentrations in plasma have been associated with rhabdomyolysis. Adjustment of the statin dosage may be needed.
Dihydropyridine Calcium Channel Blockers (CYP3A4 Inhibition)	*In Vitro* Studies Demonstrated Potential for Voriconazole to Inhibit Metabolism (Increased Plasma Exposure)	Frequent monitoring for adverse events and toxicity related to calcium channel blockers. Adjustment of calcium channel blocker dosage may be needed.
Sulfonylurea Oral Hypoglycemics (CYP2C9 Inhibition)	Not Studied *In Vivo* or *In Vitro*, but Drug Plasma Exposure Likely to be Increased	Frequent monitoring of blood glucose and for signs and symptoms of hypoglycemia. Adjustment of oral hypoglycemic drug dosage may be needed.
Vinca Alkaloids (CYP3A4 Inhibition)	Not Studied *In Vivo* or *In Vitro*, but Drug Plasma Exposure Likely to be Increased	Frequent monitoring for adverse events and toxicity (i.e., neurotoxicity) related to vinca alkaloids. Reserve azole antifungals, including voriconazole, for patients receiving a vinca alkaloid who have no alternative antifungal treatment options.
Everolimus (CYP3A4 Inhibition)	Not Studied *In Vivo* or *In Vitro*, but Drug Plasma Exposure Likely to be Increased	Concomitant administration of voriconazole and everolimus is not recommended.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
Voriconazole can cause fetal harm when administered to a pregnant woman. There are no available data on the use of voriconazole in pregnant women. In animal reproduction studies, oral voriconazole was associated with fetal malformations in rats and fetal toxicity in rabbits. Cleft palates and hydronephrosis/hydroureter were observed in rat pups exposed to voriconazole during organogenesis at and above 10 mg/kg (0.3 times the RMD of 200 mg every 12 hours based on body surface area comparisons). In rabbits, embryomortality, reduced fetal weight and increased incidence of skeletal variations, cervical ribs and extrasternal ossification sites were observed in pups when pregnant rabbits were orally dosed at 100 mg/kg (6 times the RMD based on body surface area comparisons) during organogenesis. Rats exposed to voriconazole from implantation to weaning experienced increased gestational length and dystocia, which were associated with increased perinatal pup mortality at the 10 mg/kg dose *[see Data]*. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, inform the patient of the potential hazard to the fetus *[see Warnings and Precautions (5.8)]*.

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

Data

Animal Data
Voriconazole was administered orally to pregnant rats during organogenesis (gestation days 6-17) at 10, 30, and 60 mg/kg/day. Voriconazole was associated with increased incidences in hydroureter and hydronephrosis at 10 mg/kg/day or greater, approximately 0.3 times the recommended human dose (RMD) based on mg/m², and cleft palate at 60 mg/kg, approximately 2 times the RMD based on mg/m². Reduced ossification of sacral and caudal vertebrae, skull, pubic, and hyoid bone, supernumerary ribs, anomalies of the sternbrae, and dilatation of the ureter/renal pelvis were also observed at doses of 10 mg/kg or greater. There was no evidence of maternal toxicity at any dose.

Voriconazole was administered orally to pregnant rabbits during the period of organogenesis (gestation days 7-19) at 10, 40, and 100 mg/kg/day. Voriconazole was associated with increased post-implantation loss and decreased fetal body weight, in association with maternal toxicity (decreased body weight gain and food consumption) at 100 mg/kg/day (6 times the RMD based on mg/m²). Fetal skeletal variations (increases in the incidence of cervical rib and extra sternebral ossification sites) were observed at 100 mg/kg/day.

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

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

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

8.4 Pediatric Use
The safety and effectiveness of Voriconazole for injection have been established in pediatric patients aged 12 to 14 years weighing greater than or equal to 50 kg and those aged 15 years and older regardless of body weight based on evidence from adequate and well-controlled studies in adult and pediatric patients and additional pediatric pharmacokinetic and safety data. A total of 51 pediatric patients aged 12 to less than 18[N=51] from eight adult therapeutic trials provided safety information for Voriconazole for injection use in the pediatric population *[see Adverse Reactions (6.1),Clinical Pharmacology(12.3), and Clinical Studies (14)]*. Safety and effectiveness in pediatric patients below the age of 2 years has not been established. Therefore, Voriconazole for injection is not recommended for pediatric patients less than 2 years of age.

A higher frequency of liver enzyme elevations was observed in the pediatric patients *[see Dosage and Administration (2.5),Warnings and Precautions (5.1), and Adverse Reactions (6.1)]*.

The frequency of phototoxicity reactions is higher in the pediatric population. Squamous cell carcinoma has been reported in patients who experience photosensitivity reactions. Stringent measures for photo protection are warranted. Sun avoidance and dermatologic follow-up are recommended in pediatric patients experiencing photo aging injuries, such as lentigines or ephelides, even after treatment discontinuation *[see Warnings and Precautions (5.6)]*.

Voriconazole for injection has not been studied in pediatric patients with hepatic or renal impairment *[see Dosage and Administration (2.5, 2.6)]*. Hepatic function and serum creatinine levels should be closely monitored in pediatric patients *[see Dosage and Administration (2.6) and Warnings and Precautions (5.1,5.9)]*.

Additional pediatric use information is approved for PF PRISM C.V.'s VFEND (voriconazole). However, due to PF PRISM C.V.'s marketing exclusivity rights, this drug product is not labeled with that information.

8.5 Geriatric Use
In multiple dose therapeutic trials of voriconazole, 9.2% of patients were ≥65 years of age and 1.8% of patients were ≥75 years of age. In a study in healthy subjects, the systemic exposure (AUC) and peak plasma concentrations (C_{max}) were increased in elderly males compared to young males. Pharmacokinetic data obtained from 552 patients from 10 voriconazole therapeutic trials showed that voriconazole plasma concentrations in the elderly patients were approximately 80% to 90% higher than those in younger patients after either IV or oral administration. However, the overall safety profile of the elderly patients was similar to that of the young so no dosage adjustment is recommended *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

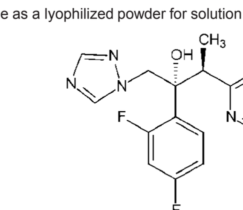
In clinical trials, there were three cases of accidental overdose. All occurred in pediatric patients who received up to five times the recommended intravenous dose of voriconazole. A single adverse event of photophobia of 10 minutes duration was reported.

There is no known antidote to voriconazole.

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

11 DESCRIPTION

Voriconazole, an azole antifungal agent is available as a lyophilized 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 to light-colored powder.

Voriconazole for injection I.V. is a white lyophilized powder containing nominally 200 mg voriconazole and 3200 mg sulfobutyl ether beta-cyclodextrin sodium in a 30 mL Type I clear glass vial.

Voriconazole for injection I.V. is intended for administration by intravenous infusion. It is a single-dose, unpreserved product. 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 sulfobutyl ether beta-cyclodextrin sodium. 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 antifungal drug *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Exposure-Response Relationship For Efficacy and Safety

In 10 clinical trials (N=1121), the median values for the average and maximum voriconazole plasma concentrations in individual patients across these studies was 2.51 μg/mL (inter-quartile range 1.21 to 4.44 μg/mL) and 3.79 μg/mL (inter-quartile range 2.06 to 6.31 μg/mL), respectively. A pharmacokinetic-pharmacodynamic analysis of patient data from 6 of these 10 clinical trials (N=280) could not detect a positive association between mean, maximum or minimum plasma voriconazole concentration and efficacy.

However, pharmacokinetic/pharmacodynamic analyses of the data from all 10 clinical trials identified positive associations between plasma voriconazole concentrations and rate of both liver function test abnormalities and visual disturbances *[see Adverse Reactions (6)]*.

Cardiac Electrophysiology

A placebo-controlled, randomized, crossover study to evaluate the effect on the QT interval of healthy male and female subjects was conducted with three single oral doses of voriconazole and ketoconazole. Serial ECGs and plasma samples were obtained at specified intervals over a 24-hour post dose observation period. The placebo-adjusted mean maximum increases in QTc from baseline after 800, 1200, and 1600 mg of voriconazole and after ketoconazole 800 mg were all <10 msec. Females exhibited a greater increase in QTc than males, although all mean changes were <10 msec. Age was not found to affect the magnitude of increase in QTc. No subject in any group had an increase in QTc of ≥60 msec from baseline. No subject experienced an interval exceeding the potentially clinically relevant threshold of 500 msec. However, the QT effect of voriconazole combined with drugs known to prolong the QT interval is unknown *[see Contraindications (4) and Drug Interactions (7)]*.

12.3 Pharmacokinetics

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

The pharmacokinetics of voriconazole are non-linear due to saturation of its metabolism. The interindividual variability of voriconazole pharmacokinetics is high. Greater than proportional increase in exposure is observed with increasing dose. It is estimated that, on average, increasing the oral dose from 200 mg every 12 hours to 300 mg every 12 hours leads to an approximately 2.5-fold increase in exposure (AUC_τ); similarly, increasing the intravenous dose from 3 mg/kg every 12 hours to 4 mg/kg every 12 hours produces an approximately 2.5-fold increase in exposure (Table 12).

Table 12:

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

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

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

When the recommended intravenous loading dose regimen is administered to healthy subjects, plasma concentrations close to steady state are achieved within the first 24 hours of dosing (e.g., 6 mg/kg IV every 12 hours on day 1 followed by 3 mg/kg IV every 12 hours). Without the loading dose, accumulation occurs during twice daily multiple dosing with steady state plasma voriconazole concentrations being achieved by day 6 in the majority of subjects.

Absorption

The pharmacokinetic properties of voriconazole are similar following administration by the intravenous and oral routes. Based on a population pharmacokinetic analysis of pooled data in healthy subjects (N=207), the oral bioavailability of voriconazole is estimated to be 96% (CV 13%). Bioequivalence was established between the 200 mg tablet and the 40 mg/mL oral suspension when administered as a 400 mg every 12 hours loading dose followed by a 200 mg every 12 hours maintenance dose.

Maximum plasma concentrations (C_{max}) are achieved 1-2 hours after dosing. When multiple doses of voriconazole are administered with high-fat meals, the mean C_{max} and AUC_τ are reduced by 34% and 24%, respectively when administered as a tablet and by 58% and 37% respectively when administered as the oral suspension *[see Dosage and Administration (2)]*.

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

Distribution

The volume of distribution at steady state for voriconazole is estimated to be 4.6 L/kg, suggesting extensive distribution into tissues. Plasma protein binding is estimated to be 58% and was shown to be independent of plasma concentrations achieved following single and multiple oral doses of 200 mg or 300 mg (approximate range: 0.9-15 μg/mL). Varying degrees of hepatic and renal impairment do not affect the protein binding of voriconazole.

Elimination

Metabolism

In vitro studies showed that voriconazole is metabolized by the human hepatic cytochrome P450 enzymes, CYP2C19, CYP2C9 and CYP3A4 *[see Drug Interactions (7)]*.

In vivo studies indicated that CYP2C19 is significantly involved in the metabolism of voriconazole. This enzyme exhibits genetic polymorphism *[see Clinical Pharmacology (12.5)]*.

The major metabolite of voriconazole is the N-oxide, which accounts for 72% of the circulating radiolabelled metabolites in plasma. Since this metabolite has minimal antifungal activity, it does not contribute to the overall efficacy of voriconazole.

Excretion

Voriconazole is eliminated via hepatic metabolism with less than 2% of the dose excreted unchanged in the urine. After administration of a single radiolabelled dose of either oral or IV voriconazole, preceded by multiple oral or IV dosing, approximately 80% to 83% of the radioactivity is recovered in the urine. The majority (>94%) of the total radioactivity is excreted in the first 96 hours after both oral and intravenous dosing.

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

Specific Populations

Male and Female Patients

In a multiple oral dose study, the mean C_{max} and AUC_τ for healthy young females were 83% and 113% higher, respectively, than in healthy young males (18-45 years), after tablet dosing. In the same study, no significant differences in the mean C_{max} and AUC_τ were observed between healthy elderly males and healthy elderly females (>65 years). In a similar study, after dosing with the oral suspension, the mean AUC for healthy young females was 45% higher than in healthy young males whereas the mean C_{max} was comparable between genders. The steady state trough voriconazole concentrations (C_{min}) seen in females were 100% and 91% higher than in males receiving the tablet and the oral suspension, respectively.

In the clinical program, no dosage adjustment was made on the basis of gender. The safety profile and plasma concentrations observed in male and female subjects were similar. Therefore, no dosage adjustment based on gender is necessary.

Geriatric Patients

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

In the clinical program, no dosage adjustment was made on the basis of age. An analysis of pharmacokinetic data obtained from 552 patients from 10 voriconazole clinical trials showed that the median voriconazole plasma concentrations in the elderly patients (>65 years) were approximately 80% to 90% higher than those in the younger patients (≤65 years) after either IV or oral administration. However, the safety profile of voriconazole in young and elderly subjects was similar and, therefore, no dosage adjustment is necessary for the elderly *[see Use in Special Populations (8.5)]*.

Pediatric Patients

Voriconazole exposures in the majority of pediatric patients aged 12 to less than 17 years were comparable to those in adults receiving the same dosing regimens. However, lower voriconazole exposure was observed in some pediatric patients aged 12 to less than 17 years with low body weight compared to adults *[see Dosage and Administration (2.4)]*.

Additional pediatric use information is approved for PF PRISM C.V.'s VFEND (voriconazole). However, due to PF PRISM C.V.'s marketing exclusivity rights, this drug product is not labeled with that information.

Patients with Hepatic Impairment

After a single oral dose (200 mg) of voriconazole in 8 patients with mild (Child-Pugh Class A) and 4 patients with moderate (Child- Pugh Class B) hepatic impairment, the mean systemic exposure (AUC) was 3.2-fold higher than in age and weight matched controls with normal hepatic function. There was no difference in mean peak plasma concentrations (C_{max}) between the groups. When only the patients with mild (Child-Pugh Class A) hepatic impairment were compared to controls, there was still a 2.3-fold increase in the mean AUC in the group with hepatic impairment compared to controls.

In an oral multiple dose study, AUC_τ was similar in 6 subjects with moderate hepatic impairment (Child-Pugh Class B) given a lower maintenance dose of 100 mg twice daily compared to 6 subjects with normal hepatic function given the standard 200 mg twice daily maintenance dose. The mean peak plasma concentrations (C_{max}) were 20% lower in the hepatically impaired group. No pharmacokinetic data are available for patients with severe hepatic cirrhosis (Child-Pugh Class C) *[see Dosage and Administration (2.5)]*.

Patients with Renal Impairment

In a single oral dose (200 mg) study in 24 subjects with normal renal function and mild to severe renal impairment, systemic exposure (AUC) and peak plasma concentration (C_{max}) of voriconazole were not significantly affected by renal impairment. Therefore, no adjustment is necessary for oral dosing in patients with mild to severe renal impairment.

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

However, in patients with moderate renal dysfunction (creatinine clearance 30-50 mL/min), accumulation of the intravenous vehicle, SBECD, occurs. The mean systemic exposure (AUC) and peak plasma concentrations (C_{max}) of SBECD were increased 4-fold and almost 50%, respectively, in the moderately impaired group compared to the normal control group.

A pharmacokinetic study in subjects with renal failure undergoing hemodialysis showed that voriconazole is dialyzed with clearance of 121 mL/min. The intravenous vehicle, SBECD, is hemodialyzed with clearance of 55 mL/min. A 4-hour hemodialysis session does not remove a sufficient amount of voriconazole to warrant dose adjustment *[see Dosage and Administration (2.6)]*.

Patients at Risk of Aspergillosis

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

Drug Interaction Studies

Effects of Other Drugs on Voriconazole

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

The systemic exposure to voriconazole is significantly reduced 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 12 hours x 7 days) by an average of 93% and 96%, respectively, in healthy subjects. Doubling the dose of voriconazole to 400 mg every 12 hours does not restore adequate exposure to voriconazole during coadministration with rifampin. **Coadministration of voriconazole and rifampin is contraindicated** *[see Contraindications (4) and Warnings and Precautions (5.12)]*.

Ritonavir **(potent CYP450 inducer; CYP3A4 inhibitor and substrate)**–The effect of the coadministration of voriconazole and ritonavir (400 mg and 100 mg) was investigated in two separate studies. High-dose ritonavir (400 mg every 12 hours for 9 days) decreased the steady state C_{max} and AUC_τ of oral voriconazole (400 mg every 12 hours for 1 day, then 200 mg every 12 hours for 8 days) by an average of 66% and 82%, respectively, in healthy subjects. Low-dose ritonavir (100 mg every 12 hours for 9 days) decreased the steady state C_{max} and AUC_τ of oral voriconazole (400 mg every 12 hours for 1 day, then 200 mg every 12 hours for 8 days) by an average of 24% and 39%, respectively, in healthy subjects. Although repeat oral administration of voriconazole did not have a significant effect on steady state C_{max} and AUC_τ of high-dose ritonavir in healthy subjects, steady state C_{max} and AUC_τ of low- dose ritonavir decreased slightly by 24% and 14% respectively, when administered concomitantly with oral voriconazole in healthy subjects. **Coadministration of voriconazole and high-dose ritonavir (400 mg every 12 hours) is contraindicated. Coadministration of voriconazole and low-dose ritonavir (100 mg every 12 hours) 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 (5.12)]*.

St. John's Wort **(CYP450 inducer; P-gp inducer)**–In an independent published study in healthy volunteers who were given multiple oral doses of St. John's Wort (300 mg LI 160 extract three times daily for 15 days) followed by a single 400 mg oral dose of voriconazole, a 59% decrease in mean voriconazole $AUC_{0-\infty}$ was observed. In contrast, coadministration of single oral doses of St. John's Wort and voriconazole had no appreciable effect on voriconazole $AUC_{0-\infty}$. 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 (5.12)]*.

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 12 hours for 1 day, then 200 mg every 12 hours for 2.5 days) and oral fluconazole (400 mg on day 1, then 200 mg every 24 hours for 4 days) to 6 healthy male subjects resulted in an increase in C_{max} and AUC_τ of voriconazole by an average of 57% (90% CI: 20%, 107%) and 79% (90% CI: 40%, 128%), respectively. In a follow-on clinical study involving 8 healthy male subjects, reduced dosing and/or frequency of voriconazole and fluconazole did not eliminate or diminish this effect. 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 (5.12)]*.

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

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

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

Macrolide antibiotics–Coadministration of **erythromycin** (CYP3A4 inhibitor; 1g every 12 hours for 7 days) or **azithromycin** (500 mg every 24 hours for 3 days) with voriconazole 200 mg every 12 hours for 14 days had no significant effect on voriconazole steady state C_{max} and AUC_τ in healthy subjects. The effects of voriconazole on the pharmacokinetics of either erythromycin or azithromycin are not known.

Effects of Voriconazole on Other Drugs

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

The systemic exposure of the following 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 12 hours for 1 day, then 200 mg every 12 hours for 8 days) increased the C_{max} and AUC of sirolimus (2 mg single dose) an average of 7-fold (90% CI: 5.7, 7.5) and 11- fold (90% CI: 9.9, 12.6), respectively, in healthy male subjects. **Coadministration of voriconazole and sirolimus is contraindicated** *[see Contraindications (4) and Warnings and Precautions (5.12)]*.

Cisapride, pimozide and quinidine **(CYP3A4 substrates)**–Although not studied *in vitro* or *in vivo*, concomitant administration of voriconazole with 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, cisapride, pimozide and quinidine is contraindicated** *[see Contraindications (4) and Warnings and Precautions (5.12)]*.

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 (5.12)]*.

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 12 hours on day 1, 200 mg every 12 hours on day 2) with a single 20 mcg/kg intravenous dose of alfentanil with concomitant naloxone resulted in a 6-fold increase in mean alfentanil $AUC_{0-\infty}$ and a 4-fold prolongation of mean alfentanil elimination half-life, compared to when alfentanil was given alone. 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 (5.12)]*.

Fentanyl **(CYP3A4 substrate)**: In an independent published study, concomitant use of voriconazole (400 mg every 12 hours on Day 1, then 200 mg every 12 hours on Day 2) with a single intravenous dose of fentanyl (5 μg/kg) resulted in an increase in the mean $AUC_{0-\infty}$ of fentanyl by 1.4-fold (range 0.81- to 2.04-fold). When voriconazole is co-administered with fentanyl IV, oral or transdermal dosage forms, extended and frequent monitoring of patients for respiratory depression and other fentanyl-associated adverse events is recommended, and fentanyl dosage should be reduced if warranted *[see Warnings and Precautions (5.12)]*.

Oxycodone **(CYP3A4 substrate)**: In an independent published study, coadministration of multiple doses of oral voriconazole (400 mg every 12 hours, on Day 1 followed by five doses of 200 mg every 12 hours on Days 2 to 4) with a single 10 mg oral dose of oxycodone on Day 3 resulted in an increase in the mean C_{max} and $AUC_{0-\infty}$ of oxycodone by 1.7-fold (range 1.4- to 2.2-fold) and 3.6- fold (range 2.7- to 5.6-fold), respectively. The mean elimination half-life of oxycodone was also increased by 2.0-fold (range 1.4- to 2.5-fold). 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 (5.12)]*.

Cyclosporine **(CYP3A4 substrate)**–In stable renal transplant recipients receiving chronic cyclosporine therapy, concomitant administration of oral voriconazole (200 mg every 12 hours for 8 days) increased cyclosporine C_{max} and AUC_τ an average of 1.1 times (90% CI: 0.9, 1.41) and 1.7 times (90% CI: 1.5, 2.0), respectively, as compared to when cyclosporine was administered without voriconazole. When initiating therapy with voriconazole in patients already receiving cyclosporine, it is recommended that the cyclosporine dose be reduced to one-half of the original dose and followed with frequent monitoring of the cyclosporine blood levels. Increased cyclosporine levels have been associated with nephrotoxicity. When voriconazole is discontinued, cyclosporine levels should be frequently monitored and the dose increased as necessary *[see Warnings and Precautions (5.12)]*.

Methadone **(CYP3A4, CYP2C19, CYP2C9 substrate)**–Repeat dose administration of oral voriconazole (400 mg every 12 hours for 1 day, then 200 mg every 12 hours for 4 days) increased the C_{max} and AUC_τ of pharmacologically active Rmethadone by 31% (90% CI: 22%, 40%) and 47% (90% CI: 38%, 57%), respectively, in subjects receiving a methadone maintenance dose (30-100 mg every 24 hours). The C_{max} and AUC of (S)-methadone increased by 65% (90% CI: 53%, 79%) and 103% (90% CI: 85%, 124%), respectively. 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 (5.12)]*.

Tacrolimus **(CYP3A4 substrate)**–Repeat oral dose administration of voriconazole (400 mg every 12 hours x 1 day, then 200 mg every 12 hours x 6 days) increased tacrolimus (0.1 mg/kg single dose) C_{max} and AUC_τ in healthy subjects by an average of 2-fold (90% CI: 1.9, 2.5) and 3-fold (90% CI: 2.7, 3.8), respectively. When initiating therapy with voriconazole in patients already receiving tacrolimus, it is recommended that the tacrolimus dose be reduced to one-third of the original dose and followed with frequent monitoring of the tacrolimus blood levels. Increased tacrolimus levels have been associated with nephrotoxicity. When voriconazole is discontinued, tacrolimus levels should be carefully monitored and the dose increased as necessary *[see Warnings and Precautions (5.12)]*.

Warfarin **(CYP2C9 substrate)**–Coadministration of voriconazole (300 mg every 12 hours x 12 days) with warfarin (30 mg single dose) significantly increased maximum prothrombin time by approximately 2 times that of placebo in healthy subjects. 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 (5.12)]*.

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 anticoagulation tests should be monitored at close intervals and the dosage of anticoagulants adjusted accordingly *[see Warnings and Precautions (5.12)]*.

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 (5.12)]*.

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 (5.12)]*.

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 (5.12)]*.

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 (5.12)]*.

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, reserve azole antifungals, including voriconazole, for patients receiving a vinca alkaloid, including vincristine, who have no alternative antifungal treatment options *[see Warnings and Precautions (5.12)]*.

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

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 (5.12)]*.

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

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

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

Mycophenolic acid **(UDP-glucuronyl transferase substrate)**–Voriconazole (200 mg every 12 hours x 5 days) had no significant effect on the C_{max} and AUC_τ of mycophenolic acid and its major metabolite, mycophenolic acid glucuronide after administration of a 1 gram single oral dose of mycophenolate mofetil.

Two-Way Interactions

Concomitant use of the following agents with voriconazole is contraindicated:

Rifabutin **(potent CYP450 inducer)**–Rifabutin (300 mg once daily) decreased the C_{max} and AUC_τ of voriconazole at 200 mg twice daily by an average of 67% (90% CI: 58%, 73%) and 79% (90% CI: 71%, 84%), respectively, in healthy subjects. During coadministration with rifabutin (300 mg once daily), the steady state C_{max} and AUC_τ of voriconazole following an increased dose of 400 mg twice daily were on average approximately 2 times higher, compared with voriconazole alone at 200 mg twice daily.

Coadministration of voriconazole at 400 mg twice daily with rifabutin 300 mg twice daily increased the C_{max} and AUC_τ of rifabutin by an average of 3-times (90% CI: 2.2, 4.0) and 4 times (90% CI: 3.5, 5.4), respectively, compared to rifabutin given alone. **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 24 hours or higher) must not be coadministered *[see Drug Interactions (7)]*. Steady state efavirenz (400 mg PO every 24 hours) decreased the steady state C_{max} and AUC_τ of voriconazole (400 mg PO every 12 hours for 1 day, then 200 mg PO every 12 hours for 8 days) by an average of 61% and 77%, respectively, in healthy male subjects. Voriconazole at steady state (400 mg PO every 12 hours for 1 day, then 200 mg every 12 hours for 8 days) increased the steady state C_{max} and AUC_τ of efavirenz (400 mg PO every 24 hours for 9 days) by an average of 38% and 44%, respectively, in healthy subjects.

The pharmacokinetics of adjusted doses of voriconazole and efavirenz were studied in healthy male subjects following administration of voriconazole (400 mg PO every 12 hours on Days 2 to 7) with efavirenz (300 mg PO every 24 hours on Days 1-7), relative to steady state administration of voriconazole (400 mg for 1 day, then 200 mg PO every 12 hours for 2 days) or efavirenz (600 mg every 24 hours for 9 days). Coadministration of voriconazole 400 mg every 12 hours with efavirenz 300 mg every 24 hours, decreased voriconazole AUC_τ by 7% (90% CI: -23%, 13%) and increased C_{max} by 23% (90% CI: -1%, 53%); efavirenz AUC_τ was increased by 17% (90% CI: 6%, 29%) and C_{max} was equivalent.

Coadministration of standard doses of voriconazole and efavirenz (400 mg every 24 hours or higher) is contraindicated. Voriconazole may be coadministered with efavirenz if the voriconazole maintenance dose is increased to 400 mg every 12 hours and the efavirenz dose is decreased to 300 mg every 24 hours. When treatment with voriconazole is stopped, the initial dosage of efavirenz should be restored *[see Dosage and Administration (2.7), Contraindications (4), and Drug Interactions (7)]*.

Phenytoin **(CYP2C9 substrate and potent CYP450 inducer)**–Repeat dose administration of phenytoin (300 mg once daily) decreased the steady state C_{max} and AUC_τ of orally administered voriconazole (200 mg every 12 hours x 14 days) by an average of 50% and 70%, respectively, in healthy subjects. Administration of a higher voriconazole dose (400 mg every 12 hours x 7 days) with phenytoin (300 mg once daily) resulted in comparable steady state voriconazole C_{max} and AUC_τ estimates as compared to when voriconazole was given at 200 mg every 12 hours without phenytoin.

Phenytoin may be coadministered with voriconazole if the maintenance dose of voriconazole is increased from 4 mg/kg to 5 mg/kg intravenously every 12 hours or from 200 mg to 400 mg orally, every 12 hours (100 mg to 200 mg orally, every 12 hours in patients less than 40 kg) *[see Dosage and Administration (2.7) and Drug Interactions (7)]*.

Repeat dose administration of voriconazole (400 mg every 12 hours x 10 days) increased the steady state C_{max} and AUC_τ of phenytoin (300 mg once daily) by an average of 70% and 80%, respectively, in healthy subjects. The increase in phenytoin C_{max} and AUC when coadministered with voriconazole may be expected to be as high as 2 times the C_{max} and AUC estimates when phenytoin is given without voriconazole. Therefore, frequent monitoring of plasma phenytoin concentrations and phenytoin-related adverse effects is recommended when phenytoin is coadministered with voriconazole *[see Warnings and Precautions (5.12)]*.

Omeprazole **(CYP2C19 inhibitor; CYP2C19 and CYP3A4 substrate)**–Coadministration of omeprazole (40 mg once daily x 10 days) with oral voriconazole (400 mg every 12 hours x 1 day, then 200 mg every 12 hours x 9 days) increased the steady state C_{max} and AUC_τ of voriconazole by an average of 15% (90% CI: 5%, 25%) and 40% (90% CI: 29%, 55%), respectively, in healthy subjects. No dosage adjustment of voriconazole is recommended.

Coadministration of voriconazole (400 mg every 12 hours x 1 day, then 200 mg x 6 days) with omeprazole (40 mg once daily x 7 days) to healthy subjects significantly increased the steady state C_{max} and AUC_τ of omeprazole an average of 2 times (90% CI: 1.8, 2.6) and 4 times (90% CI: 3.3, 4.4), respectively, as compared to when omeprazole is given without voriconazole. 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 (5.12)]*.

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 12 hours for 1 day, then 200 mg every 12 hours for 3 days) and oral contraceptive (Ortho-Novum1/35® consisting of 35 mcg ethinyl estradiol and 1 mg norethindrone, every 24 hours) to healthy female subjects at steady state increased the C_{max} and AUC_τ of ethinyl estradiol by an average of 36% (90% CI: 28%, 45%) and 61% (90% CI: 50%, 72%), respectively, and that of norethindrone by 15% (90% CI: 3%, 28%) and 53% (90% CI: 44%, 63%), respectively in healthy subjects. Voriconazole C_{max} and AUC_τ increased by an average of 14% (90% CI: 3%, 27%) and 46% (90% CI: 32%, 61%), respectively. Monitoring for adverse events related to oral contraceptives, in addition to those for voriconazole, is recommended during coadministration *[see Warnings and Precautions (5.12)]*.

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

Indinavir **(CYP3A4 inhibitor and substrate)**–Repeat dose administration of indinavir (800 mg TID for 10 days) had no significant effect on voriconazole C_{max} and AUC following repeat dose administration (200 mg every 12 hours for 17 days) in healthy subjects.

Repeat dose administration of voriconazole (200 mg every 12 hours for 7 days) did not have a significant effect on steady state C_{max} and AUC_τ of indinavir following repeat dose administration (800 mg TID for 7 days) in healthy subjects.

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 (5.12)]*.

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 (5.1)]*. 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 (5.12)]*. Dose adjustments are required when voriconazole is co-administered with efavirenz *[see Drug Interactions (7) and Warnings and Precautions (5.12)]*.

12.4 Microbiology

Mechanism of Action

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

Resistance

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

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

Antimicrobial Activity

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

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

* In clinical studies, voriconazole MIC_{90} for *C. glabrata* baseline isolates was 4 μg/mL; 13/50 (26%) *C. glabrata* baseline isolates were resistant (MIC ≥4 μg/mL) to voriconazole. However, based on 1054 isolates tested in surveillance studies the MIC_{90} was 1 μg/mL.

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

Candida lusitaniae
Candida guilliermondii

Susceptibility Testing

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

12.5 Pharmacogenomics

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies were conducted in rats and mice. Rats were given oral doses of 6, 18 or 50 mg/kg voriconazole, or 0.2, 0.6, or 1.6 times the RMD on a mg/m² basis. Hepatocellular adenomas were detected in females at 50 mg/kg and hepatocellular carcinomas were found in males at 6 and 50 mg/kg. Mice were given oral doses of 10, 30 or 100 mg/kg voriconazole, or 0.1, 0.4, or 1.4 times the RMD on a mg/m² basis. In mice, hepatocellular adenomas were detected in males and females and hepatocellular carcinomas were detected in males at 1.4 times the RMD of voriconazole.

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

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

14 CLINICAL STUDIES

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

14.1 Invasive Aspergillosis (IA)

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

Study 307/602 – Primary Therapy of Invasive Aspergillosis

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

Voriconazole was administered intravenously with a loading dose of 6 mg/kg every 12 hours for the first 24 hours followed by a maintenance dose of 4 mg/kg every 12 hours for a minimum of 7 days. Therapy could then be switched to the oral formulation at a dose of 200 mg every 12 hours. Median duration of IV voriconazole therapy was 10 days (range 2-85 days). After IV voriconazole therapy, the median duration of PO voriconazole therapy was 76 days (range 2-232 days).

Patients in the comparator group received conventional amphotericin B as a slow infusion at a daily dose of 1.0-1.5 mg/kg/day. Median duration of IV amphotericin therapy was 12 days (range 1-85 days). Treatment was then continued with OLAT, including itraconazole and lipid amphotericin B formulations. Although initial therapy with conventional amphotericin B was to be continued for at least two weeks, actual duration of therapy was at the discretion of the investigator. Patients who discontinued initial randomized therapy due to toxicity or lack of efficacy were eligible to continue in the study with OLAT treatment.

A satisfactory global response at 12 weeks (complete or partial resolution of all attributable symptoms, signs, radiographic/bronchoscopic abnormalities present at baseline) was seen in 53% of voriconazole treated patients compared to 32% of amphotericin B treated patients (Table 15). A benefit of voriconazole compared to amphotericin B on patient survival at Day 84 was seen with a 71% survival rate on voriconazole compared to 58% on amphotericin B (Table 13).

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

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

	Voriconazole n/N (%)	Ampho B[c] n/N (%)	Stratified Difference (95% CI)[d]
Efficacy as Primary Therapy			
Satisfactory Global Response[a]	76/144 (53)	42/133 (32)	21.8% (10.5%, 33.0%) p<0.0001
Survival at Day 84[b]	102/144 (71)	77/133 (58)	13.1% (2.1%, 24.2%)
Success by Species			
	Success n/N (%)		
Overall success	76/144 (53)	42/133 (32)	
Mycologically confirmed[e]	37/84 (44)	16/67 (24)	
Aspergillus spp.[f]			
A. fumigatus	28/63 (44)	12/47 (26)	
A. flavus	3/6	4/9	
A. terreus	2/3	0/3	
A. niger	1/4	0/9	
A. nidulans	1/1	0/0	

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

Study 304 – Primary and Salvage Therapy of Aspergillosis

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

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

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

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

Table 14:

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

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

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

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

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

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

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

Table 15:

Overall Success Rates Sustained From EOT To The Fixed 12-Week Follow-Up Time Point By Baseline Pathogen[a,b]

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

[a] A few patients had more than one pathogen at baseline.
[b] Patients who did not have a 12-week assessment for any reason were considered a treatment failure.

In a secondary analysis, which counted DRC-assessed successes at any time point (EOT, or 2, 6, or 12 weeks after EOT), the response rates were 65% for voriconazole and 71% for the regimen of amphotericin B followed by fluconazole.

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

14.3 Esophageal Candidiasis (EC)

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

Table 16:

Success Rates in Patients Treated for Esophageal Candidiasis

Population	Voriconazole	Fluconazole	Difference % (95% CI)[a]
PP[b]	113/115 (98.2%)	134/141 (95.0%)	3.2 (-1.1, 7.5)
ITT[c]	175/200 (87.5%)	171/191 (89.5%)	-2.0 (-8.3, 4.3)

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

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

Table 17:

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

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

[a] Some patients had more than one species isolated at baseline.
[b] Patients with endoscopic and/or mycological assessment at end of therapy.

14.4 Other Serious Fungal Pathogens

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

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

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

14.5 Pediatric Studies

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

Additional pediatric use information is approved for PF PRISM C.V.'s VFEND (voriconazole). However, due to PF PRISM C.V.'s marketing exclusivity rights, this drug product is not labeled with that information.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Powder for Solution for Injection

Voriconazole for injection I.V. is supplied in a single-dose vial as a sterile lyophilized powder equivalent to 200 mg voriconazole and 3,200 mg sulfobutyl ether beta-cyclodextrin sodium (SBECD). It does not contain preservatives and is not made with natural rubber latex.

Product Code	Unit of Sale	Strength
219030	65219-190-30 Individually Packaged	200 mg per vial

16.2 Storage

Voriconazole for injection I.V. unreconstituted vials should be stored at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Voriconazole for injection is a single dose unpreserved sterile lyophile. 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°C to 8°C (36°F to 46°F). Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C (36°F to 46°F). 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 (2.1)]*.

17 PATIENT COUNSELING INFORMATION

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

Embryo-Fetal Toxicity

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

Manufactured for:
FRESENIUS KABI
Lake Zurich, IL 60047
www.fresenius-kabi.com/us

451665

Made in India

PATIENT INFORMATION
Voriconazole for injection, for intravenous use

Read the Patient Information that comes with voriconazole for injection before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your condition or treatment.

What is voriconazole for injection?
Voriconazole for injection is a prescription medicine used to treat certain serious fungal infections in your blood and body. These infections are called "aspergillosis," "esophageal candidiasis," "*Scedosporium*," "*Fusarium*," and "candidemia".
It is not known if voriconazole for injection is safe and effective in children younger than 2 years old.

Do not take voriconazole for injection if you:
- **are allergic to voriconazole or any of the ingredients in voriconazole for injection**. See the end of this leaflet for a complete list of ingredients in voriconazole for injection.
- **are taking any of the following medicines:**
  - cisapride
  - pimozide
  - quinidine
  - sirolimus
  - rifampin
  - carbamazepine
  - long-acting barbiturates like phenobarbital
  - efavirenz
  - ritonavir
  - rifabutin
  - ergotamine, dihydroergotamine (ergot alkaloids)
  - St. John's Wort (herbal supplement)

Ask your healthcare provider or pharmacist if you are not sure if you are taking any of the medicines listed above. Do not start taking a new medicine without talking to your healthcare provider or pharmacist.

Before you take voriconazole for injection, tell your healthcare provider about all of your medical conditions, including if you:
- have or ever had heart disease, or an abnormal heart rate or rhythm. Your healthcare provider may order a test to check your heart (EKG) before starting voriconazole for injection.
- have liver or kidney problems. Your healthcare provider may do blood tests to make sure you can take voriconazole for injection.
- are pregnant or plan to become pregnant. Voriconazole for injection can harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant. Women who can become pregnant should use effective birth control while taking voriconazole for injection. Talk to your healthcare provider about birth control methods that may be right for you.
- are breast-feeding or plan to breast-feed. It is not known if voriconazole for injection passes into breast milk. Talk to your healthcare provider about the best way to feed your baby if you take voriconazole for injection.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements.
Voriconazole for injection may affect the way other medicines work, and other medicines may affect how voriconazole for injection works.
Know what medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I take voriconazole for injection?
- **voriconazole may be prescribed to you as**:
  - voriconazole for injection I.V. (intravenous infusion)
- Voriconazole for injection I.V. will be given to you by a healthcare provider over 1 to 2 hours.
- If you take too much voriconazole for injection, call your healthcare provider or go to the nearest hospital emergency room.

What should I avoid while taking voriconazole for injection?
- You should not drive at night while taking voriconazole for injection. Voriconazole for injection can cause changes in your vision such as blurring or sensitivity to light.
- Do not drive or operate machinery, or do other dangerous activities until you know how voriconazole for injection affects you.
- Avoid direct sunlight. Voriconazole for injection can make your skin sensitive to the sun and the light from sunlamps and tanning beds. You could get a severe sunburn. Use sunscreen and wear a hat and clothes that cover your skin if you have to be in sunlight. Talk to your healthcare provider if you get sunburn.

What are possible side effects of voriconazole for injection?
Voriconazole for injection may cause serious side effects including:
- **liver problems.** Symptoms of liver problems may include:
  - itchy skin
  - yellowing of your eyes
  - feeling very tired
  - flu-like symptoms
  - nausea or vomiting
- **vision changes.** Symptoms of vision changes may include:
  - blurred vision
  - changes in the way you see colors
  - sensitivity to light (photophobia)
- **serious heart problems.** Voriconazole for injection may cause changes in your heart rate or rhythm, including your heart stopping (cardiac arrest).
- **allergic reactions.** Symptoms of an allergic reaction may include:
  - fever
  - sweating
  - feels like your heart is beating fast (tachycardia)
  - chest tightness
  - trouble breathing
  - feel faint
  - nausea
  - itching
  - skin rash
- **kidney problems**. Voriconazole for injection may cause new or worse problems with kidney function, including kidney failure. Your healthcare provider should check your kidney function while you are taking voriconazole for injection. Your healthcare provider will decide if you can keep taking voriconazole for injection.
- **serious skin reactions**. Symptoms of serious skin reactions may include:
  - rash or hives
  - mouth sores
  - blistering or peeling of your skin
  - trouble swallowing or breathing

Call your healthcare provider or go to the nearest hospital emergency room right away if you have any of the symptoms listed above.

The most common side effects of voriconazole for injection include:
- vision changes
- rash
- vomiting
- nausea
- headache
- fast heart beat (tachycardia)
- hallucinations (seeing or hearing things that are not there)
- abnormal liver function tests
- fever
- chills

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of voriconazole for injection.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store voriconazole for injection?
- Store voriconazole for injection at room temperature, 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Do not refrigerate or freeze.
- Safely throw away medicine that is out of date or no longer needed.
- Keep voriconazole for injection, as well as all other medicines, out of the reach of children.

General information about the safe and effective use of voriconazole for injection
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use voriconazole for injection for a condition for which it was not prescribed. Do not give voriconazole for injection to other people, even if they have the same symptoms that you have. It may harm them.
You can ask your healthcare provider or pharmacist for information about voriconazole for injection that is written for health professionals.

What are the ingredients of voriconazole for injection?

Active ingredient: voriconazole

Inactive ingredients in voriconazole for injection IV: sulfobutyl ether beta-cyclodextrin sodium

For more information, contact Fresenius Kabi USA, LLC at 1-800-551-7176.

Additional pediatric use information is approved for PF PRISM C.V.'s VFEND (voriconazole). However, due to PF PRISM C.V.'s marketing exclusivity rights, this drug product is not labeled with that information.

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