the oral maintenance dose by 50 mg steps to a minimum of 200 mg every 12 hours (or to 100 mg every 12 hours). If patient response is inadequate, the oral maintenance dose may be increased from 200 mg every 12 hours to 500 mg every 12 hours.

2.1 Instructions for Use in All Patients

- Oral: Swallow voriconazole tablets whole. Do not crush, break, or chew tablets.
- Oral suspension: V voriconazole suspension should be taken at least one hour before or after a meal.

2.2 Storage

Store voriconazole tablets at room temperature (15° to 30°C (59° to 86°F)). Voriconazole suspension should be stored at 2° to 25°C (36° to 77°F).

3. DOSAGE FORMS AND STRENGTHS

Voriconazole is available in the following dosage forms:

- Tablets: 200 mg (contains voriconazole 200 mg)
- Oral suspension: 2 mg/mL (contains voriconazole 2 mg/mL)

4. CONTRAINDICATIONS

Voriconazole is contraindicated in patients with known hypersensitivity to voriconazole or any of its components.

5. WARNINGS AND PRECAUTIONS

5.1 Allergic Reactions

- Discontinue voriconazole if an allergic reaction occurs and initiate appropriate treatment.

5.2 Hypersensitivity Reactions

- Discontinue voriconazole and initiate appropriate treatment if skin reactions occur.

5.3 Serious Adverse Drug Reactions

- Discontinue voriconazole and initiate appropriate treatment for any serious adverse drug reaction.

5.4 Hypertension

- Monitor blood pressure during voriconazole therapy.

5.5 Cataract Formation

- Monitor vision during voriconazole therapy.

5.6 Arrhythmias and QT Prolongation

- Monitor ECG during voriconazole therapy.

6. ADVERSE REACTIONS

6.1 General

- Headache
- Nausea
- Vomiting

6.2 Gastrointestinal

- Diarrhea
- Flatulence

6.3 Dermatological

- Rash
- Pruritus

6.4 Respiratory

- Hypersensitivity reactions
- Asthma

6.5 Cardiac

- Myocarditis
- Pericarditis

6.6 Neurological

- Seizures
- Nystagmus

6.7 Ocular

- Blurred vision
- Cataracts

6.8 Hematological

- Anemia
- Thrombocytopenia

6.9 Renal

- Nephrotoxicity
- Renal failure

6.10 Liver

- Hepatitis
- Liver failure

6.11 Other Adverse Reactions

- Abnormal taste
- Hypersensitivity reactions

7. DRUG INTERACTIONS

CYP3A4, CYP2C9 and CYP2C19 inhibitors and inducers: Adjust voriconazole dosage and monitor for adverse reactions.

Phenytoin or Efavirenz: with co-administration, increase maintenance oral and intravenous dosage of voriconazole.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

- Use during pregnancy only if the benefit to the mother outweighs the risk to the fetus.

8.2 Lactation

- Nursing mothers should not breastfeed.

8.3 Children

- Safety and effectiveness in children have not been established.

8.4 Elderly

- Use with caution in elderly patients.

9. DRUG ABUSE AND DEPENDENCE

No drug dependence or abuse potential has been reported for voriconazole.

10. OVERDOSAGE

Overdosage of voriconazole is not expected to be a problem as it is generally well tolerated.

11. DESCRIPTION

Voriconazole is an azole antifungal drug indicated for use in the treatment of:

- Candidemia in non-neutropenic patients
- Other than C. albicans
- Non-neutropenic patients
- Infections in skin and abdomen, kidney, bladder, and wound
- Esophageal candidiasis

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Voriconazole inhibits fungal cytochrome P450, preventing the synthesis of ergosterol.

12.2 Pharmacodynamics

Voriconazole is highly bound to plasma proteins and is metabolized in the liver.

12.3 Pharmacokinetics

Voriconazole is rapidly absorbed following oral administration.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Voriconazole was not carcinogenic in rats and mice.

13.2 Teratogenic Effects

Voriconazole was not teratogenic in rats and rabbits.

14. CLINICAL STUDIES

14.1 Invasive Aspergillosis

Voriconazole has been studied in clinical trials for the treatment of invasive aspergillosis.

14.2 Esophageal Candidiasis

Voriconazole has been studied in clinical trials for the treatment of esophageal candidiasis.

15. PATIENT COUNSELING INFORMATION

Inform patients about the importance of adhering to the prescribed dosage regimen.

16. HOW SUPPLIED

Voriconazole is available in the following dosage forms:

- Tablets: 200 mg
- Oral suspension: 2 mg/mL

17. FULL PRESCRIBING INFORMATION

For complete prescribing information, including warnings and precautions, see Prescribing Information.
5.13 Dermatological Reactions

- Treatment discontinuation of voriconazole may be required in patients with dermatological reactions. Patients should be referred to a dermatologist if necessary.

5.12 Monitoring Pancreatic Function

- Patients should be monitored for the development of abnormal pancreatic function, which includes changes in stool color, fat intolerance, and weight loss.

5.10 Patients With Renal Impairment

- In patients with mild to moderate renal impairment (creatinine clearance > 50 mL/min), the maintenance dose of voriconazole should be reduced.

5.9 Drug Interactions

- Voriconazole is contraindicated in patients with QT interval prolongation or history of cardiac arrhythmias.

5.8 Pregnancy

- Voriconazole is not recommended for use in pregnant women due to the potential for harm to the fetus.

5.7 Nursing Mothers

- Voriconazole is not recommended for use in breastfeeding mothers.

5.6 Pediatric Use

- Voriconazole is not recommended for use in children due to the potential for adverse effects.

5.5 Animal Data

- Voriconazole has been evaluated in animals and has shown no evidence of teratogenicity or embryotoxicity.

5.4 Embryo-Fetal Toxicity

- Voriconazole has been evaluated in animal studies and has shown no evidence of embryotoxicity.

5.3 Breastfeeding

- Voriconazole is not recommended for use in breastfeeding mothers.

5.2 Hepatic Toxicity

- In clinical trials, there have been uncommon cases of serious hepatic reactions during treatment with voriconazole.

5.11 Hypersensitivity Reactions

- Patients should be monitored for the development of hypersensitivity reactions, which may include rash, urticaria, and anaphylaxis.

5.1 Measurement

- Patients should be measured for the development of myelosuppression, which may include decreases in hemoglobin, white blood cell count, and platelets.

5.10 Administration

- Voriconazole should be administered intravenously for the initial dose and then orally for maintenance doses.

5.9 Drug Administration

- Voriconazole should be administered orally for maintenance doses.

4.9 Pharmacodynamic Properties

- Voriconazole has been shown to have antifungal activity against a wide range of fungal organisms.

4.8 Pharmacokinetics

- Voriconazole is metabolized by the liver and excreted in the urine.

4.7 Treatment of Yeast Infections

- Voriconazole is effective in the treatment of yeast infections, including candidiasis and aspergillosis.

4.6 Administration

- Voriconazole should be administered orally for maintenance doses.

4.4 Pharmacokinetics

- Voriconazole is metabolized by the liver and excreted in the urine.

4.3 Treatment of Yeast Infections

- Voriconazole is effective in the treatment of yeast infections, including candidiasis and aspergillosis.

4.2 Treatment of Fungi

- Voriconazole is effective in the treatment of fungi, including Candida species and Aspergillus species.

4.1 Clinical Information

- Voriconazole is effective in the treatment of invasive fungal infections, including candidiasis and aspergillosis.

3.8 Administration

- Voriconazole should be administered orally for maintenance doses.

3.7 Treatment of Yeast Infections

- Voriconazole is effective in the treatment of yeast infections, including candidiasis and aspergillosis.

3.6 Administration

- Voriconazole should be administered orally for maintenance doses.

3.5 Treatment of Fungi

- Voriconazole is effective in the treatment of fungi, including Candida species and Aspergillus species.

3.4 Administration

- Voriconazole should be administered orally for maintenance doses.

3.3 Treatment of Yeast Infections

- Voriconazole is effective in the treatment of yeast infections, including candidiasis and aspergillosis.

3.2 Administration

- Voriconazole should be administered orally for maintenance doses.

3.1 Treatment of Fungi

- Voriconazole is effective in the treatment of fungi, including Candida species and Aspergillus species.

2.8 Dosage and Administration

- Voriconazole should be administered orally for maintenance doses.

2.7 Instructions for Use

- Voriconazole should be administered orally for maintenance doses.

2.6 Oral Suspension

- Voriconazole should be administered orally for maintenance doses.

2.5 Oral Tablet

- Voriconazole should be administered orally for maintenance doses.

2.4 Powder for Oral Suspension

- Voriconazole should be administered orally for maintenance doses.

2.3 Tablet

- Voriconazole should be administered orally for maintenance doses.

2.2 Powder for Oral Suspension

- Voriconazole should be administered orally for maintenance doses.

2.1 Tablet

- Voriconazole should be administered orally for maintenance doses.

2.0 Indications

- Voriconazole is effective in the treatment of invasive fungal infections, including candidiasis and aspergillosis.

1.9 Pharmacokinetics

- Voriconazole is metabolized by the liver and excreted in the urine.

1.8 Treatment of Yeast Infections

- Voriconazole is effective in the treatment of yeast infections, including candidiasis and aspergillosis.

1.7 Administration

- Voriconazole should be administered orally for maintenance doses.

1.6 Treatment of Fungi

- Voriconazole is effective in the treatment of fungi, including Candida species and Aspergillus species.

1.5 Administration

- Voriconazole should be administered orally for maintenance doses.

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- Voriconazole is effective in the treatment of yeast infections, including candidiasis and aspergillosis.

1.3 Administration

- Voriconazole should be administered orally for maintenance doses.

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- Voriconazole is effective in the treatment of fungi, including Candida species and Aspergillus species.

1.1 Administration

- Voriconazole should be administered orally for maintenance doses.

1.0 Indications

- Voriconazole is effective in the treatment of invasive fungal infections, including candidiasis and aspergillosis.
6.1 Overview

Table 6 summarizes the all-cause discontinuation rates during primary treatment and treatment following relapse or breakthrough infections in all studies. Almost all discontinuations occurred in patients who had adverse events, with the most common adverse events being hepatic adverse events (2.1% to 3.3% discontinuations) and visual adverse events (0.8% to 1.5% discontinuations). The discontinuation rate for voriconazole in study 306 was higher than in study 307/602, likely because patients in study 306 were heavily pre-treated with amphotericin B and other antifungal treatment.

6.2 Test Abnormalities

Table 7 reports test abnormalities for all voriconazole-treated patients and patients who received concomitant voriconazole. Test abnormalities were largely reversible and were not considered to be of clinical significance. The incidence of abnormalities was slightly higher in study 305 compared with study 307/602.

Table 8 provides a summary of the all-cause discontinuation rates in all studies due to test abnormalities, including laboratory test abnormalities and visual adverse events. The discontinuation rate due to test abnormalities was similar in study 305 compared with study 307/602, and was higher in study 306.

6.3 Clinical Laboratory Values

Table 9 provides a summary of the incidence of selected laboratory test abnormalities in patients treated with voriconazole. The incidence of laboratory test abnormalities was generally low, with the most common abnormalities being increases in bilirubin, AST, ALT, and creatinine. The incidence of abnormal laboratory test results was similar in study 305 compared with study 307/602, and was higher in study 306.

6.4 Visual Adverse Events

Table 10 summarizes the visual adverse events observed in patients treated with voriconazole. The incidence of visual adverse events was low, with the most common events being photophobia, visual field defects, and reduced visual acuity. The incidence of visual adverse events was slightly higher in study 305 compared with study 307/602, and was higher in study 306.

6.5 Skin Reactions

Table 11 provides a summary of the skin reactions observed in patients treated with voriconazole. The incidence of skin reactions was low, with the most common reactions being pruritus, rash, and urticaria. The incidence of skin reactions was similar in study 305 compared with study 307/602, and was higher in study 306.

6.6 Urogenital Adverse Events

Table 12 provides a summary of the urogenital adverse events observed in patients treated with voriconazole. The incidence of urogenital adverse events was low, with the most common events being urinary tract infection and altered micturition. The incidence of urogenital adverse events was similar in study 305 compared with study 307/602, and was higher in study 306.

6.7 Special Senses

Table 13 provides a summary of the special senses adverse events observed in patients treated with voriconazole. The incidence of special senses adverse events was low, with the most common events being diplopia,眩晕, and tinnitus. The incidence of special senses adverse events was similar in study 305 compared with study 307/602, and was higher in study 306.

6.8 Nervous System

Table 14 provides a summary of the nervous system adverse events observed in patients treated with voriconazole. The incidence of nervous system adverse events was low, with the most common events being headache, dizziness, and paresthesia. The incidence of nervous system adverse events was similar in study 305 compared with study 307/602, and was higher in study 306.

6.9 Cardiovascular

Table 15 provides a summary of the cardiovascular adverse events observed in patients treated with voriconazole. The incidence of cardiovascular adverse events was low, with the most common events being tachycardia, hypotension, and hypertension. The incidence of cardiovascular adverse events was similar in study 305 compared with study 307/602, and was higher in study 306.

6.10 Respiratory, Thoracic, and Abdominal

Table 16 provides a summary of the respiratory, thoracic, and abdominal adverse events observed in patients treated with voriconazole. The incidence of respiratory, thoracic, and abdominal adverse events was low, with the most common events being respiratory tract infection, pneumonia, and abdominal pain. The incidence of respiratory, thoracic, and abdominal adverse events was similar in study 305 compared with study 307/602, and was higher in study 306.

6.11 Gastrointestinal

Table 17 provides a summary of the gastrointestinal adverse events observed in patients treated with voriconazole. The incidence of gastrointestinal adverse events was low, with the most common events being diarrhea, abdominal pain, and vomiting. The incidence of gastrointestinal adverse events was similar in study 305 compared with study 307/602, and was higher in study 306.

6.12 Hematologic

Table 18 provides a summary of the hematologic adverse events observed in patients treated with voriconazole. The incidence of hematologic adverse events was low, with the most common events being neutropenia, anemia, and thrombocytopenia. The incidence of hematologic adverse events was similar in study 305 compared with study 307/602, and was higher in study 306.

6.13 Metabolic and Nutritional

Table 19 provides a summary of the metabolic and nutritional adverse events observed in patients treated with voriconazole. The incidence of metabolic and nutritional adverse events was low, with the most common events being hyperglycemia, hypoglycemia, and hyperlipidemia. The incidence of metabolic and nutritional adverse events was similar in study 305 compared with study 307/602, and was higher in study 306.

6.14 Skeletal Adverse Events

Table 20 provides a summary of the skeletal adverse events observed in patients treated with voriconazole. The incidence of skeletal adverse events was low, with the most common events being bone pain, arthralgia, and myalgia. The incidence of skeletal adverse events was similar in study 305 compared with study 307/602, and was higher in study 306.

6.15 Local CNS Effects

Table 21 provides a summary of the local CNS effects observed in patients treated with voriconazole. The incidence of local CNS effects was low, with the most common events being dizziness, somnolence, and headache. The incidence of local CNS effects was similar in study 305 compared with study 307/602, and was higher in study 306.

6.16 Injury, Poisoning, and Procedural Complications

Table 22 provides a summary of the injury, poisoning, and procedural complications observed in patients treated with voriconazole. The incidence of injury, poisoning, and procedural complications was low, with the most common events being accidental falls, drug-induced injury, and burns. The incidence of injury, poisoning, and procedural complications was similar in study 305 compared with study 307/602, and was higher in study 306.

6.17 Infections and Infestations

Table 23 provides a summary of the infections and infestations observed in patients treated with voriconazole. The incidence of infections and infestations was low, with the most common events being infection of the respiratory tract, urinary tract, and skin. The incidence of infections and infestations was similar in study 305 compared with study 307/602, and was higher in study 306.

6.18 Neoplasms

Table 24 provides a summary of the neoplasms observed in patients treated with voriconazole. The incidence of neoplasms was low, with the most common events being benign neoplasms and malignant neoplasms. The incidence of neoplasms was similar in study 305 compared with study 307/602, and was higher in study 306.

6.19 Sexual and Reproductive System

Table 25 provides a summary of the sexual and reproductive system adverse events observed in patients treated with voriconazole. The incidence of sexual and reproductive system adverse events was low, with the most common events being decreased libido, impotence, and amenorrhea. The incidence of sexual and reproductive system adverse events was similar in study 305 compared with study 307/602, and was higher in study 306.

6.20 General Physical health

Table 26 provides a summary of the general physical health adverse events observed in patients treated with voriconazole. The incidence of general physical health adverse events was low, with the most common events being arthralgia, myalgia, and bone pain. The incidence of general physical health adverse events was similar in study 305 compared with study 307/602, and was higher in study 306.

6.21 Clinical Laboratory Values

Table 36 summarizes the clinical laboratory values observed in patients treated with voriconazole. The laboratory test abnormalities were largely reversible and were not considered to be of clinical significance. The incidence of abnormalities was similar in study 305 compared with study 307/602, and was higher in study 306.

6.3 Clinical Laboratory Values

Table 37 provides a summary of the incidence of selected laboratory test abnormalities in patients treated with voriconazole. The incidence of laboratory test abnormalities was generally low, with the most common abnormalities being increases in bilirubin, AST, ALT, and creatinine. The incidence of abnormal laboratory test results was similar in study 305 compared with study 307/602, and was higher in study 306.
### 3.4. Postmarketing Experience

In clinical studies, voriconazole has been associated with the following adverse events:

- **Cardiovascular**: Torsades de pointes (arrhythmia) in patients with prolonged QT interval.
- **Gastrointestinal**: Stomatitis, nausea, vomiting, diarrhea, and abdominal pain.
- **Renal**: Hematuria, proteinuria, and azotemia.
- **Skin**: Rash, pruritus, and photosensitivity.
- **Hematologic**: Neutropenia, thrombocytopenia, and anemia.
- **Respiratory**: Bronchitis and pulmonary edema.

### 6.4. Postmarketing Experience

In postmarketing experience, voriconazole has been associated with the following adverse events:

- **Cardiovascular**: Torsades de pointes (arrhythmia) in patients with prolonged QT interval.
- **Dermatologic**: Rash, pruritus, and photosensitivity.
- **Hematologic**: Neutropenia, thrombocytopenia, and anemia.
- **Gastrointestinal**: Diarrhea, nausea, and vomiting.

### 10.2. Reports of Body As a Filter

In overdose situations, hemodialysis may assist in the removal of voriconazole.

### Table 4. Treatment of Cardiovascular Toxicity

<table>
<thead>
<tr>
<th>Drug Interactions</th>
<th>Therapy</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
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</tr>
<tr>
<td><strong>Metabolism</strong></td>
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</tr>
<tr>
<td><strong>Respiratory</strong></td>
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<td>None</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
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</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
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### Table 5. Recommendations for Treatment of Voriconazole Overdose

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<tr>
<th>Drug Interactions</th>
<th>Therapy</th>
<th>Recommendations</th>
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</tr>
<tr>
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</tr>
<tr>
<td><strong>Renal</strong></td>
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</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
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</table>

### Table 6. Omeprazole Drug Interaction Study

<table>
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<th>Recommendations</th>
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<tr>
<td><strong>Metabolism</strong></td>
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<td>None</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
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</tr>
<tr>
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<tr>
<td><strong>Gastrointestinal</strong></td>
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### Table 7. Sirolimus Drug Interaction Study

<table>
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<th>Drug Interactions</th>
<th>Therapy</th>
<th>Recommendations</th>
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<tr>
<td><strong>Metabolism</strong></td>
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<tr>
<td><strong>Respiratory</strong></td>
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<tr>
<td><strong>Renal</strong></td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

**Note**: The data in this section is based on clinical studies following repeat oral dosing with 400 mg q12h for 1 day, then 200 mg q12h for 4 days voriconazole to subjects receiving a methadone maintenance dose (30-100 mg q24h).

**Recommendations**: When initiating therapy with Voriconazole in patients already receiving omeprazole doses of 40 mg or greater, reduce the omeprazole dose by one-third of the starting dose and follow with frequent monitoring of tacrolimus blood levels. Increased tacrolimus levels have been associated with toxicity including QT prolongation. Frequent monitoring of tacrolimus plasma concentrations and reduction of the dose of tacrolimus when indicated may be necessary to avoid toxicity. When switching from another antifungal to voriconazole, reduce the dose of the previous antifungal to one-third and follow with frequent monitoring of tacrolimus blood levels. Increased tacrolimus levels have been associated with toxicity including QT prolongation. Frequent monitoring of tacrolimus plasma concentrations and reduction of the dose of tacrolimus when indicated may be necessary to avoid toxicity. Voriconazole is contraindicated in patients with severe hepatic impairment (Child Pugh score > 10) and severe renal impairment (creatinine clearance < 30 mL/min).

**Monitoring**: When switching from another antifungal to voriconazole, perform frequent monitoring of tacrolimus plasma concentrations. When initiating therapy with Voriconazole in patients already receiving omeprazole doses of 40 mg or greater, perform frequent monitoring of tacrolimus plasma concentrations.

**Dosing**: When initiating therapy with Voriconazole in patients already receiving omeprazole doses of 40 mg or greater, reduce the omeprazole dose by one-third of the starting dose and follow with frequent monitoring of tacrolimus blood levels. Increased tacrolimus levels have been associated with toxicity including QT prolongation. Frequent monitoring of tacrolimus plasma concentrations and reduction of the dose of tacrolimus when indicated may be necessary to avoid toxicity. When switching from another antifungal to voriconazole, reduce the dose of the previous antifungal to one-third and follow with frequent monitoring of tacrolimus blood levels. Increased tacrolimus levels have been associated with toxicity including QT prolongation. Frequent monitoring of tacrolimus plasma concentrations and reduction of the dose of tacrolimus when indicated may be necessary to avoid toxicity. Voriconazole is contraindicated in patients with severe hepatic impairment (Child Pugh score > 10) and severe renal impairment (creatinine clearance < 30 mL/min).

**Monitoring of Drug Interactions**: With voriconazole, the potential for drug interactions is increased due to its metabolism through the cytochrome P450 3A4 (CYP3A4) isozyme. Voriconazole is a potent inhibitor of CYP3A4 and other cytochrome P450 enzymes, which can result in increased plasma concentrations of coadministered drugs and potential for drug interactions. It is important to monitor for any changes in the plasma concentrations of drugs administered concurrently with voriconazole.

**Recommendations for Drug Interactions**: When initiating therapy with voriconazole, perform frequent monitoring of tacrolimus plasma concentrations. When switching from another antifungal to voriconazole, perform frequent monitoring of tacrolimus plasma concentrations. Voriconazole is contraindicated in patients with severe hepatic impairment (Child Pugh score > 10) and severe renal impairment (creatinine clearance < 30 mL/min). Voriconazole is generally well tolerated, but it is important to monitor for any changes in the plasma concentrations of drugs administered concurrently with voriconazole.
Voriconazole is an antifungal agent belonging to the subclass of triazoles used in the treatment of invasive aspergillosis, pulmonary candidiasis, and some other fungal infections that are not responsive to other antifungal agents. It is a prodrug in which the active metabolites are formed in vivo from voriconazole via oxidation of the hydantoin group to the corresponding imidazole (N-hydroxy-voriconazole) and the diketo metabolite (N-hydroxy-voriconazole diketo). The dihydrodiol metabolite is not antimicrobial.

**Chemical Properties**
- *Formula*: C31H35F2N5O2
- *Molecular Weight*: 572.67
- *Dihydrate*: C31H35F2N5O5·2H2O
- *Active ingredients*: Voriconazole dihydrate, sodium benzoate, anhydrous citric acid, natural and artificial orange flavor, and sucrose.
- *Inactive ingredients*: Colloidal silicon dioxide, titanium dioxide, xanthan gum, sodium citrate dihydrate, and sodium benzoate.

**Pharmacokinetics**
- **Absorption**: Voriconazole is absorbed from the gastrointestinal tract with peak plasma concentrations occurring approximately 1-2 hours after oral administration. The oral bioavailability is approximately 80%.
- **Distribution**: The volume of distribution at steady state is approximately 20 liters/kg. Voriconazole is distributed into the cerebrospinal fluid.
- **Metabolism**: Voriconazole is metabolized by the human hepatic cytochrome P450 enzymes CYP2C19, CYP2C9, and CYP3A4. Inhibitors or inducers of these enzymes can affect the pharmacokinetics of voriconazole.
- **Excretion**: Voriconazole is excreted mainly unchanged in the urine (approximately 83% of the dose) and as metabolites (approximately 17% of the dose). The renal clearance of voriconazole is approximately 1200 mL/min, similar to creatinine clearance.

**Pharmacodynamics**
Voriconazole exerts its antifungal activity by inhibiting fungal mitochondrial electron transport and has been shown to alter the morphology of yeast cells. In vitro studies have demonstrated that voriconazole has a broad spectrum of activity against a wide range of fungal species, including Candida, Aspergillus, and Fusarium.

**Interactions**
- **Drug Interactions**: Voriconazole is a potent CYP3A4 inhibitor and can affect the pharmacokinetics of other drugs that are CYP3A4 substrates.

**Contraindications**
- Voriconazole is contraindicated in patients with a history of voriconazole or related antifungal allergy.

**Dosage and Administration**
- The dosage of voriconazole is individualized based on the severity of the fungal infection and the patient's underlying health status.
- For oral administration, the usual maintenance dose is 4 mg/kg every 12 hours, adjusted based on the patient's creatinine clearance (minimum dose is 2 mg/kg every 24 hours).
- For intravenous administration, the usual loading dose is 6 mg/kg followed by 4 mg/kg every 12 hours.

**Adverse Reactions**
- The most common adverse reactions associated with voriconazole include nausea, vomiting, and alopecia.

**References**
- FDA prescribing information for voriconazole.
- Clinical trial data from voriconazole studies.

**Further Information**
- For comprehensive information, refer to the official prescribing information and recent clinical trials.

**Disclaimer**
- The information provided is for educational purposes only and should not be used as a substitute for professional medical advice.
to 400 mg q12h and the efavirenz dose is decreased to 300 mg q24h. When treatment with Voriconazole voriconazole 400 mg q12h with efavirenz 300 mg q24h, decreased voriconazole AUC for 9 days) by an average of 38% and 44%, respectively, in healthy subjects.

**Two-Way Interactions**

Mycophenolic acid glucuronide after administration of a 1 g single oral dose of mycophenolate mofetil. During coadministration with rifabutin (300 mg once daily), the Cmax and AUC of mycophenolic acid decreased by 14% and 17%, respectively. In another study, the Cmax and AUC of mycophenolic acid decreased by 24% and 21%, respectively, when coadministered with efavirenz at a dose of 600 mg once daily.

No significant pharmacokinetic interactions were observed when voriconazole was coadministered with cyclosporine. Patients receiving voriconazole concomitantly with other NSAIDs (e.g., celecoxib, ibuprofen, and diclofenac) were exposed to higher plasma concentrations of ibuprofen and diclofenac. A reduction in ibuprofen and diclofenac dosage may be needed during concomitant administration with voriconazole. In a study, single doses of ibuprofen (400 mg) and diclofenac (50 mg) were coadministered with the last dose of voriconazole. The plasma concentration of ibuprofen was increased by 67% and that of diclofenac was increased by 82%. There was no significant change in the plasma concentration of voriconazole.

Increased plasma concentrations of benzodiazepines that are metabolized by CYP3A4 (e.g., diazepam, midazolam, and alprazolam) were observed during coadministration with voriconazole. Frequent monitoring for adverse events and toxicity related to benzodiazepines is recommended. Increased plasma concentrations of statins (e.g., atorvastatin and simvastatin) were observed during coadministration with voriconazole. Frequent monitoring for adverse events and toxicity related to statins is recommended. Increased plasma concentrations of ergot alkaloids (ergotamine and dihydroergotamine) and lead to ergotism. Frequent monitoring for adverse events and toxicity related to ergot alkaloids is recommended.

Concomitant use of voriconazole with certain clozapine concomitantly and 10-fold increase in clozapine plasma concentrations was observed. When concomitantly administered with clozapine, the Cmax and AUC of clozapine were increased by 10-fold and 30-fold, respectively. In addition, the Cmax and AUC of clozapine were increased by 5-fold and 10-fold, respectively, when coadministered with efavirenz at a dose of 600 mg once daily.

Concomitant use of voriconazole with certain sirolimus concomitantly and increased steady state serum concentrations of sirolimus by 3-fold. When concomitantly administered with voriconazole, the Cmax and AUC of sirolimus were increased by 3-fold and 6-fold, respectively. In addition, the Cmax and AUC of sirolimus were increased by 2-fold and 4-fold, respectively, when coadministered with efavirenz at a dose of 600 mg once daily.

Concomitant use of voriconazole with certain fentanyl concomitantly and increased steady state serum concentrations of fentanyl by 2.5-fold. When concomitantly administered with voriconazole, the Cmax and AUC of fentanyl were increased by 2.5-fold and 5-fold, respectively. In addition, the Cmax and AUC of fentanyl were increased by 1.5-fold and 3-fold, respectively, when coadministered with efavirenz at a dose of 600 mg once daily.

Concomitant use of voriconazole with certain cyclosporine concomitantly and increased steady state serum concentrations of cyclosporine by 2-fold. When concomitantly administered with voriconazole, the Cmax and AUC of cyclosporine were increased by 2-fold and 4-fold, respectively. In addition, the Cmax and AUC of cyclosporine were increased by 1.5-fold and 3-fold, respectively, when coadministered with efavirenz at a dose of 600 mg once daily.
Voriconazole was administered intravenously with a loading dose of 6 mg/kg every 12 hours for the Study Group/European Organisation for Research and Treatment of Cancer (NIAID MSG/EORTC). Infections were treated in body sites where the drugs are physiologically concentrated or when a high dosage of drug is needed. Diagnosis of definite or probable invasive aspergillosis was made according to criteria established by the Pan-American Aspergillosis Study Group (Study 307/602). The majority of study patients had underlying hematologic malignancies, including malignancies of the hematopoietic and lymphatic systems. Some patients had solid tumors, such as small-cell lung cancer, including patients who presented with metastatic disease. No patients with prior infection due to Aspergillus were included. Other aspergillosis infections included disseminated disease, CNS infections and sinus infections. Voriconazole administration induced no impairment of male or female fertility in rats dosed at 50 mg/kg, but carcinogenicity studies showed a significant increase in the incidence of mammary gland tumors in rats treated with 500 mg/kg of voriconazole. Voriconazole demonstrated clastogenic activity (mostly chromosome breaks) in human lymphocyte cultures. Two-year carcinogenicity studies were conducted in rats and mice. Rats were given oral doses of 6, 18 or 50 mg/kg of voriconazole twice daily. Mice were given oral doses of 10, 30 or 100 mg/kg of voriconazole twice daily. No evidence of a dose-related effect on survival was observed in any species at any dose. Two-year carcinogenicity studies were conducted in rats and mice. Rats were given oral doses of 6, 18 or 50 mg/kg of voriconazole twice daily. Mice were given oral doses of 10, 30 or 100 mg/kg of voriconazole twice daily. No evidence of a dose-related effect on survival was observed in any species at any dose. Two-year carcinogenicity studies were conducted in rats and mice. Rats were given oral doses of 6, 18 or 50 mg/kg of voriconazole twice daily. Mice were given oral doses of 10, 30 or 100 mg/kg of voriconazole twice daily. No evidence of a dose-related effect on survival was observed in any species at any dose. Two-year carcinogenicity studies were conducted in rats and mice. Rats were given oral doses of 6, 18 or 50 mg/kg of voriconazole twice daily. Mice were given oral doses of 10, 30 or 100 mg/kg of voriconazole twice daily. No evidence of a dose-related effect on survival was observed in any species at any dose.
It is not known if voriconazole is safe and effective in children younger than 12 years old.

What is voriconazole?

Voriconazole is a synthetic compound from the class of medicines called antifungal agents, which are used to treat fungal infections. It works by preventing the fungus from producing a substance necessary for growth and reproduction.

How should voriconazole be used?

Voriconazole is used parenterally for the prevention and treatment of life-threatening fungal infections such as invasive aspergillosis and deep tissue candida infections.

The reconstituted suspension should be stored at 15°-30°C (59°-86°F). [See USP Controlled Room Temperature].

Each bottle contains 49 g of powder for oral suspension. Following reconstitution, the volume of the reconstituted suspension is 120 mL.

Drug Interactions

Drugs that alter the protein binding of voriconazole may affect the antifungal activity of voriconazole.

Contraindications

Voriconazole is contraindicated in patients with a known hypersensitivity to voriconazole or other agents in the triazole class.

Warnings

Superinfections: Voriconazole may cause superinfections, such as candidiasis or aspergillosis. New superinfections may also occur due to the infection being cleared from an infected site. Close monitoring and prompt treatment should be undertaken in patients who develop superinfections.

Lung Toxicity: Lung toxicity may occur in patients treated with voriconazole. Although rare, mortality associated with this side effect has been reported.

Hepatic Impairment: Voriconazole undergoes hepatic metabolism by CYP3A4, and may elevate serum levels of certain drugs that are also metabolized by CYP3A4.

Adverse Reactions

The most common adverse reactions to voriconazole are headache, nausea, vomiting, and abdominal pain.

Preclinical studies have shown that voriconazole is excreted in human milk. It is unknown if voriconazole is capable of causing adverse reactions in nursing infants. Women should choose whether to use voriconazole or breastfeed. It is unknown if voriconazole passes into breast milk.

Precautions

Voriconazole is a potent antifungal agent. It is not known if voriconazole is capable of causing adverse reactions in nursing infants. Women should choose whether to use voriconazole or breastfeed. It is unknown if voriconazole passes into breast milk.

Patient counseling information

Patients should be counseled to report any signs of toxicity to their healthcare provider.

Manufactured by:

Otsuka Laboratories, Inc.

Address:

17 PATIENT COUNSELING INFORMATION

Somerset, NJ 08873

1/2010

FUSARIUM INFECTIONS (NDC 40032-038-60)

Table 16. Efficacy and Safety of Voriconazole Compared to Fluconazole in Patients with Non-neutropenic Candidemia

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Voriconazole</th>
<th>Fluconazole</th>
<th>Difference (Voriconazole – Fluconazole)</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida albicans</td>
<td>90/107 (84%)</td>
<td>134/140 (96%)</td>
<td>-2.0 (-8.3, 4.3)</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Candida tropicalis</td>
<td>3/8 (38%)</td>
<td>28/63 (44%)</td>
<td>7.5 (1.1, 13.9)</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>64/76 (84%)</td>
<td>76/144 (53%)</td>
<td>3.2 (-1.1, 7.5)</td>
<td>0.15</td>
<td></td>
</tr>
</tbody>
</table>

Table 17. Efficacy and Safety of Voriconazole Compared to Lipid Amphotericin B Followed by Fluconazole in Patients with Non-neutropenic Candidemia

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Voriconazole</th>
<th>Lipid Amphotericin B followed by Fluconazole</th>
<th>Difference (Voriconazole – Lipid Amphotericin B followed by Fluconazole)</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
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<td>0.15</td>
<td></td>
</tr>
</tbody>
</table>
Voriconazole Oral Suspension:

Active ingredient: voriconazole

What are the ingredients of voriconazole?

Voriconazole for oral suspension contains:
- Voriconazole (active ingredient)
- Citrate dihydrate, sodium benzoate, anhydrous citric acid, natural and artificial orange flavor, and water.

Voriconazole may cause serious side effects including:
- Kidney failure. Voriconazole can make your kidney function worse, even if you have never had kidney problems before. Voriconazole can cause your kidney function to get worse while you are taking it.
- Vision changes. Voriconazole may affect your vision. Your healthcare provider will check your vision.
- Serious skin reactions. Voriconazole can cause serious skin reactions that can lead to death. Your healthcare provider will check your skin for any changes.
- Allergic reactions. Voriconazole can cause allergic reactions. Your healthcare provider will check your skin if you have an allergic reaction to voriconazole.

How should I store voriconazole?

- Store voriconazole for oral suspension at room temperature.
- Do not freeze or refrigerate.
- Voriconazole for oral suspension should be thrown away after 14 days.

How should I take voriconazole?

- Take voriconazole for oral suspension at least 1 hour before or at least 1 hour after meals.
- Know what medicines you take. Keep a list of them to show your healthcare provider or pharmacist.
- Voriconazole may affect the way other medicines work, and other medicines may affect how voriconazole works.

What should I avoid while taking voriconazole?

- Do not start taking a new medicine without talking to your healthcare provider or pharmacist.
- Do not drink alcohol while taking voriconazole.
- Voriconazole can make you sensitive to the sun and the light from some electronic devices.
- Voriconazole can change how some medicines work. This can cause serious side effects. Voriconazole can also make you sensitive to light.

What should I tell my healthcare provider before taking voriconazole?

- Tell your healthcare provider about all medicines you take.
- Tell your healthcare provider if you have or ever had heart disease or an abnormal heart rate.
- Tell your healthcare provider if you have liver or kidney problems.
- Tell your healthcare provider if you have or ever had diabetes.
- Tell your healthcare provider if you have trouble digesting dairy products or regular table sugar.
- Tell your healthcare provider if you are allergic to voriconazole or any of the ingredients in voriconazole.
- Tell your healthcare provider if you use St. John's Wort (herbal supplement).
- Tell your healthcare provider if you take ergotamine, dihydroergotamine (ergot alkaloids).
- Tell your healthcare provider if you take rifabutin (Mycobutin®) or ritonavir (Norvir®) or efavirenz (Sustiva®) or carbamazepine (Tegretol®) or quinidine (like Quinaglute®).
- Do not take voriconazole if you:
  - Are allergic to voriconazole or any of the ingredients in voriconazole
  - Are a breastfeeding woman or plan to breast-feed. It is not known if voriconazole passes into breast milk. Your healthcare provider will decide if you can keep taking voriconazole.
  - Are pregnant. Voriconazole can harm your unborn baby. Talk to your healthcare provider if you are pregnant or plan to become pregnant.

What should I tell my healthcare provider if I am pregnant, nursing, or planning pregnancy?

- Women who are or plan to become pregnant should not take voriconazole. It is not known if voriconazole passes into breast milk. If you are breastfeeding, your healthcare provider will decide if you can keep taking voriconazole.

How do I get medical advice about side effects?

- Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
- Talk to your healthcare provider or pharmacist if you have questions about the best way to feed your baby if you take voriconazole.

What should I tell my healthcare provider before taking voriconazole?

- Your healthcare provider will give you information that explains how to use voriconazole properly.
- Voriconazole should be used only by people who need to take it. Voriconazole should be prescribed by a healthcare provider who knows the symptoms of your disease and how voriconazole works.
- Voriconazole is a prescription medicine.
- Voriconazole should not be used by children.
- Voriconazole should not be used by people who are allergic to voriconazole.
- Voriconazole should not be used by people who have or ever had heart problems.
- Voriconazole should not be used by people who have vision changes.
- Voriconazole should not be used by people who have allergic reactions.
Insert oral dispenser into bottle top.

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

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

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

9. Remember to leave the bottle adapter in the bottle and put the cap back on the bottle. Store at room temperature. Rinse the oral dispenser with water after each dose.