

## DATA SHEET

### NAME OF MEDICINE

SPORANOX™ itraconazole 10 mg/mL oral solution

### PRESENTATION

SPORANOX 10 mg/mL oral solution (150 mL) is supplied in amber glass bottles with a child-resistant cap.

### USES

#### Actions

Itraconazole is a synthetic triazole derivative. When administered orally, it has shown fungistatic activity against superficial dermatophytes and *Candida* species including *C. albicans* and *C. glabrata*.

Itraconazole has shown *in vitro* antifungal activity against a variety of fungi and yeasts. This spectrum includes superficial dermatophytes (*Trichophyton* spp., *Microsporum* spp., *Epidermophyton floccosum*), yeasts (*Cryptococcus neoformans*, *Pityrosporum* spp., *Candida* spp. including *C. albicans*, *C. glabrata* and *C. krusei*), *Aspergillus* spp., *Histoplasma* spp., *Paracoccidioides brasiliensis*, *Sporothrix schenckii*, *Fonsecaea* spp., *Cladosporium* spp., *Blastomyces dermatitidis*.

*In vitro* studies have demonstrated that itraconazole inhibits the cytochrome P450-dependent synthesis of ergosterol, which is a vital component of fungal cell membranes.

#### Pharmacokinetics

The oral bioavailability of SPORANOX oral solution is maximal when it is taken without food. During chronic administration, steady state is reached after 1-2 weeks. Peak plasma levels are observed 2 hours (fasting) to 5 hours (with food) following oral solution administration. After repeated administration of SPORANOX oral solution, at a dosage of 200 mg once a day in a fasting condition, steady state plasma concentrations of itraconazole fluctuate between 1 and 2 micrograms/mL (trough to peak). When SPORANOX oral solution is taken with food, steady state plasma concentrations of itraconazole are about 25% lower.

The bioavailability of SPORANOX oral solution taken in a fasting condition is approximately 60% higher than the bioavailability of the capsule taken with a meal.

The bioavailability of SPORANOX oral solution in HIV patients is reduced by around 20% compared to normal volunteers. The bioavailability is not altered by the stage of infection. The recommended dosage has been shown to be effective in HIV patients.

The plasma protein binding of itraconazole is 99.8%. Concentrations of itraconazole in whole blood are 60% of those in plasma.

Itraconazole is extensively distributed into tissues, which are prone to fungal invasion but only minimally into CSF or ocular fluid. Concentrations in lung, kidney, liver, bone, stomach, spleen and muscle were found to be two to three times higher than the corresponding plasma concentration.

Itraconazole is extensively metabolized by the liver into a large number of metabolites. One of the metabolites is hydroxy-itraconazole, which has a comparable antifungal activity *in vitro* to itraconazole. Plasma levels of hydroxy-itraconazole are about two times higher than those of itraconazole.

After repeated oral administration, elimination of itraconazole from plasma is biphasic with a terminal half-life of 1.5 to 2 days. Faecal excretion of the parent compound varies between 3-18% of the dose. Renal excretion of the parent compound is less than 0.03% of the dose. About 35% of the dose is excreted as metabolites in the urine within 1 week.

### **Indications**

SPORANOX oral solution is indicated for the:

- treatment of oral and/or oesophageal candidiasis in HIV-positive or other immunocompromised patients.
- prophylaxis of fungal infections in neutropenic patients.

### **DOSAGE AND ADMINISTRATION**

For optimal absorption, SPORANOX oral solution should be taken without food. The solution should be swished in the oral cavity and swallowed. There should be no rinsing after swallowing.

Treatment of oral and/or oesophageal candidiasis: 200 mg (2 measuring cups or 20 mL) once a day or 100 mg (1 measuring cup or 10 mL) twice a day for 1 week. If there is no response after 1 week, treatment should be continued for another week.

Treatment of fluconazole-resistant oral and/or oesophageal candidiasis: 200 to 400 mg (2-4 measuring cups or 20-40 mL) daily in one or two intakes for 2 weeks. If there is no response after 2 weeks, treatment should be continued for another 2 weeks.

Prophylaxis of fungal infections: 5 mg/kg per day administered as a twice daily dose until recovery of neutrophils. In clinical trials, prophylaxis treatment was started immediately prior to the cytostatic treatment and generally one week before transplant procedure.

For use in children, the elderly and in patients with renal or hepatic impairment (see **WARNINGS AND PRECAUTIONS**).

### **CONTRAINDICATIONS**

SPORANOX oral solution is contraindicated in patients who have shown hypersensitivity to itraconazole or the excipients.

SPORANOX oral solution should only be given to pregnant women in life-threatening cases and when in these cases the potential benefit outweighs the potential harm to the foetus. Adequate contraceptive precautions should be used by women of childbearing potential throughout SPORANOX therapy, and continued until the next menstrual period following the end of SPORANOX therapy.

Coadministration of terfenadine, astemizole, bepridil, nisoldipine, mizolastine, cisapride, dofetilide, levacetylmethadol (levomethadyl), quinidine, pimozide, sertindole, CYP3A metabolised HMG-CoA reductase inhibitors such as simvastatin and lovastatin, oral midazolam, triazolam and ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine) with SPORANOX is contraindicated.

SPORANOX oral solution should not be administered to patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF except for the treatment of life-threatening or other serious infections (see **WARNING AND PRECAUTIONS**).

## **WARNINGS AND PRECAUTIONS**

SPORANOX has a potential for clinically important interactions with other medicines (see **INTERACTIONS**).

### **Congestive heart failure**

In a study with SPORANOX IV in healthy volunteers a transient asymptomatic decrease of the left ventricular ejection fraction, which resolved before the next infusion, was observed. The clinical relevance of these findings to the oral formulations is not known.

Itraconazole has been shown to have a negative inotropic effect. SPORANOX has been associated with reports of congestive heart failure. Heart failure was more frequently reported among spontaneous reports of 400 mg total daily dose than among those of lower total daily doses, suggesting that the risk of heart failure might increase with the total daily dose of itraconazole.

SPORANOX should not be used in patients with congestive heart failure or with a history of congestive heart failure unless the benefit clearly outweighs the risk. The risk benefit assessment should consider factors such as the severity of the indication, the dosing regimen (e.g. total daily dose) and individual risk factors for congestive heart failure. Risk factors include cardiac disease, such as ischaemic and valvular disease; significant pulmonary disease, such as chronic obstructive pulmonary disease; and renal failure and other oedematous disorders. Patients with these risk factors, who are being treated with SPORANOX, should be informed of the signs and symptoms of congestive heart failure. Caution should be exercised and the patient monitored for the signs and symptoms of congestive heart failure. SPORANOX should be discontinued if such symptoms occur during treatment.

Calcium channel blockers can have negative inotropic effects which may be additive to those of itraconazole. In addition, itraconazole can inhibit the metabolism of calcium channel blockers. Therefore, caution should be used when co-administering itraconazole and calcium channel blockers due to an increased risk of CHF.

### **Cystic fibrosis**

In cystic fibrosis patients, variability in therapeutic levels of itraconazole was observed with steady state dosing of oral solution using 2.5 mg/kg twice daily. Steady state concentrations of > 250 ng/mL were achieved in approximately 50% of subjects aged 16 years and older, but in none of the patients under 16 years of age. If a patient does not respond to SPORANOX oral solution, consideration should be given to switching to alternative therapy.

**Treatment of severely neutropenic patients:** SPORANOX oral solution as treatment for oral and/or oesophageal candidiasis was not investigated in severely neutropenic patients. Due to the pharmacokinetic properties, SPORANOX oral solution is not recommended for initiation of treatment in patients at immediate risk of systemic candidiasis.

### **Hearing loss**

Transient or permanent hearing loss has been reported in patients receiving treatment with itraconazole. Several of these reports included concurrent administration of quinidine which is contraindicated (see Contraindications and Interactions). The hearing loss usually resolves when treatment is stopped, but can persist in some patients.

### **Hepatic impairment**

Itraconazole is predominantly metabolised in the liver. A single oral dose (100 mg capsule) was administered to 12 patients with cirrhosis and six healthy control subjects; C<sub>max</sub>, AUC and terminal half-life of itraconazole were measured and compared between groups. Mean itraconazole C<sub>max</sub> was reduced significantly (by 47%) in patients with cirrhosis. Mean elimination half-life was prolonged compared to that found in subjects without hepatic impairment (37 vs. 16 hours, respectively). Overall exposure to itraconazole, based on AUC was similar in cirrhotic patients and in healthy subjects. Data are not available in cirrhotic patients during long-term use of itraconazole. Dose adjustments may be considered.

Very rare cases of serious hepatotoxicity, including some cases of fatal acute liver failure, have occurred with the use of SPORANOX. Most of these cases involved patients who had pre-existing liver disease, were treated for systemic indications, had significant other medical conditions and/or were taking other hepatotoxic drugs. Some patients had no obvious risk factors for liver disease. Some of these cases have been observed within the first month of treatment, including some within the first week. Liver function monitoring should be considered in patients receiving SPORANOX treatment. Patients should be instructed to promptly report to their physician signs and symptoms suggestive of hepatitis such as anorexia, nausea, vomiting, fatigue, abdominal pain or dark urine. In these patients treatment should be stopped immediately and liver function testing should be conducted.

In patients with raised liver enzymes or an active liver disease, or who have experienced liver toxicity with other drugs, treatment should not be started unless the expected benefit exceeds the risk of hepatic injury. In such cases, liver enzyme monitoring is necessary.

### **Renal impairment**

Limited data are available on the use of oral itraconazole in patients with renal impairment. Caution should be exercised when this drug is administered in this patient population.

### **Peripheral neuropathy**

Isolated cases of peripheral neuropathy have also been reported, predominantly during long-term treatment with SPORANOX. If neuropathy occurs that may be attributable to SPORANOX, the treatment should be discontinued.

## Other azole antifungal agents

There is no information regarding cross hypersensitivity between itraconazole and other azole antifungal agents. Caution should be used in prescribing SPORANOX oral solution to patients with hypersensitivity to other azoles.

## Use in children

Since clinical data on the use of SPORANOX oral solution in paediatric patients is limited, its use in children is not recommended unless the potential benefit outweighs the potential risks.

Limited safety experience is available with a dose of 5 mg/kg per day. The incidence of adverse events such as diarrhoea, abdominal pain, vomiting, fever, rash and mucositis was higher than in adults.

Toxicological studies have shown that itraconazole, when administered to rats, can produce bone toxicity. While such toxicity has not been reported in adult patients, the long-term effect of itraconazole in children is unknown (See **FURTHER INFORMATION - Toxicology**).

## Use in elderly patients

Clinical data on the use of SPORANOX oral solution in elderly patients is limited. Use SPORANOX oral solution in these patients only if the potential benefits outweigh the potential risks.

## Pregnancy and lactation

### Use in pregnancy

Category B3. Teratogenic effects: Itraconazole was found to cause a dosage-related increase in maternal toxicity, embryotoxicity and teratogenicity in rats at dosage levels of approximately 40-160 mg/kg/day and in mice at dosage levels of approximately 80 mg/kg/day. In rats, the teratogenicity consisted of major skeletal defects and in mice it consisted of encephaloceles and/or macroglossia.

Itraconazole must not be used during pregnancy except for life-threatening cases where the potential benefit to the mother outweighs the potential harm to the foetus (see **CONTRAINDICATIONS**).

There is limited information on the use of SPORANOX during pregnancy. During post-marketing experience, cases of congenital abnormalities have been reported. These cases included skeletal, genitourinary tract, cardiovascular and ophthalmic malformations as well as chromosomal and multiple malformations. A casual relationship with SPORANOX has not been established.

Epidemiological data on exposure to SPORANOX during the first trimester of pregnancy (mostly in patients receiving short-term treatment for vulvovaginal candidiasis) did not show an increased risk of malformations as compared to control subjects not exposed to any known teratogens.

Women of childbearing potential taking SPORANOX oral solution should use contraceptive precautions. Effective contraception should be continued until the menstrual period following the end of SPORANOX therapy.

### Use in lactation

Based on the determination of itraconazole concentration in the breast milk of lactating mothers who received a single daily dose of 400 mg itraconazole (200 mg b.i.d.), it was calculated that the exposure in the infant to itraconazole would be around 450 times lower than in the mother. The expected benefits of SPORANOX therapy should therefore be weighed against the potential risk of breast-feeding. In case of doubt the patient should not breast-feed.

### **Effects on ability to drive and use machines**

No effects on ability to drive or to use machinery have been observed.

## **ADVERSE EFFECTS**

In clinical studies involving short periods of treatment with itraconazole the overall incidence of adverse experiences is about 7%. In patients receiving prolonged (approximately 1 month) continuous treatment especially, the incidence of adverse experiences was higher (about 15%).

#### Common (>1%)

Body as a whole	dizziness, headache
Liver	reversible increases in hepatic enzymes
Gastrointestinal	nausea, vomiting, diarrhoea, abdominal pain, constipation, dyspepsia

#### Rare (<0.1%)

Body as a whole	allergic reactions such as pruritus, rash, urticaria and angio-oedema.
Endocrine	menstrual disorder

#### Very rare (<0.01%)

Liver	hepatitis (especially during prolonged treatment)
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#### *Postmarketing experience*

Adverse drug reactions from spontaneous reports during the worldwide postmarketing experience with SPORANOX (all formulations) that meet threshold criteria are included in the table below. The adverse drug reactions are ranked by frequency, using the following convention: Very common ( $\geq 1/10$ ); Common ( $\geq 1/100$  and  $< 1/10$ ); Uncommon ( $\geq 1/1,000$  and  $< 1/100$ ); Rare ( $\geq 1/10,000$  and  $< 1/1000$ ); Very rare ( $< 1/10,000$ ), including isolated reports.

The frequencies below reflect reporting rates for adverse drug reactions from spontaneous reports, and do not represent more precise estimates of incidence that might be obtained in clinical or epidemiological studies.

Blood and Lymphatic System Disorders	Very rare: leucopenia and neutropenia, thrombocytopenia
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Immune system disorders	Very rare: Serum sickness, angioneurotic oedema, anaphylactic, anaphylactoid and allergic reactions
Metabolism and Nutrition Disorders	Very rare: Hypertriglyceridemia, hypokalaemia
Nervous System Disorders	Very rare: Peripheral neuropathy, paraesthesia, hypoaesthesia, headache, dizziness
Eye Disorders	Very rare: Visual disturbances, including vision blurred and diplopia
Ear and Labyrinth Disorder	Very rare: Tinnitus, transient or permanent hearing loss
Cardiac Disorders	Very rare: Congestive heart failure
Respiratory, Thoracic and Mediastinal Disorders	Very rare: Pulmonary oedema, dyspnoea
Gastrointestinal Disorders	Very rare: Pancreatitis, abdominal pain, vomiting, dyspepsia, nausea, diarrhoea, constipation, dysgeusia
Hepato-biliary disorders	Very rare: Serious hepatotoxicity (including some cases of fatal acute liver failure), hepatitis, reversible increases in hepatic enzymes
Skin and Subcutaneous Tissue Disorders	Very rare: Toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, erythema multiforme, exfoliative dermatitis, leukocytoclastic vasculitis, urticaria, alopecia, photosensitivity, rash, pruritus
Musculoskeletal and connective tissue disorders	Very rare: Myalgia, arthralgia
Renal and Urinary Disorders	Very rare: Pollakiuria, urinary incontinence
Reproductive System and Breast Disorders	Very rare: Menstrual disorders, erectile dysfunction
General Disorders and Administration Site Conditions	Very rare: Oedema, pyrexia

## INTERACTIONS

### 1. Medicines affecting the metabolism of itraconazole

Interaction studies have been performed with rifampicin, rifabutin and phenytoin, which are potent enzyme inducers of CYP3A4. Since the bioavailability of itraconazole and hydroxy-itraconazole was decreased in these studies to such an extent that efficacy may be largely reduced, the combination of itraconazole with these potent enzyme inducers is not recommended. No formal study data are available for other enzyme inducers, such as carbamazepine, phenobarbital and isoniazid, but similar effects should be anticipated.

Potent inhibitors of this enzyme such as ritonavir, indinavir, clarithromycin and erythromycin may increase the bioavailability of itraconazole.

## 2. Effects of itraconazole on the metabolism of other medicines

Itraconazole can inhibit the metabolism of medicines metabolised by the cytochrome 3A family. This can result in an increase and/or a prolongation of their effects, including side effects. When using concomitant medication, the corresponding label should be consulted for information on the route of metabolism. After stopping treatment, itraconazole plasma levels decline gradually, depending on the dose and duration of treatment (see **Pharmacokinetics**). This should be taken into account when the inhibitory effects of itraconazole on comedicated medicines are considered.

Examples are:

*The following drugs are contraindicated with itraconazole:*

- Terfenadine, astemizole, bepridil, mizolastine, cisapride, dofetilide, levacetylmethadol (levomethadyl), quinidine, pimozide and sertindole are contraindicated with SPORANOX oral solution since co-administration may result in increased plasma concentrations of these substrates, which can lead to QT prolongation and rare occurrences of torsade de pointes.
- CYP3A4 metabolised HMG-CoA reductase inhibitors, such as simvastatin and lovastatin.
- Triazolam and oral midazolam.
- Ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine).
- Nisoldipine.

Caution should be exercised when co-administering itraconazole with calcium channel blockers. In addition to possible pharmacokinetic interactions involving the drug metabolising enzyme CYP3A4, calcium channel blockers can have negative inotropic effects which may be additive to those of itraconazole.

*The following drugs should be used with caution, and their plasma concentrations, effects or side effects should be monitored. Their dosage, if co-administered with itraconazole, should be reduced if necessary:*

- Oral anticoagulants
- HIV protease inhibitors, such as ritonavir, indinavir, saquinavir
- Certain antineoplastic agents, such as vinca alkaloids, busulphan, docetaxel and trimetrexate
- CYP3A4 metabolised calcium channel blockers, such as dihydropyridines and verapamil
- Certain immunosuppressive agents, such as cyclosporin, tacrolimus, sirolimus
- Certain CYP3A4 metabolised HMG-CoA reductase inhibitors such as atorvastatin.
- Certain glucocorticosteroids such as budesonide, dexamethasone, fluticasone and methylprednisolone.

- Others: digoxin, carbamazepine, buspirone, alfentanil, alprazolam, brotizolam, cilostazol, disopyramide, eletriptan, fentanyl, halofantrine, midazolam IV, rifabutin, repaglinide, ebastine, reboxetine.

No interaction of itraconazole with zidovudine (AZT) and fluvastatin has been observed. No inducing effects of itraconazole on the metabolism of ethinyloestradiol and norethisterone were observed.

### **3. Effects on protein binding**

*In vitro* studies have shown that there are no interactions on the plasma protein binding between itraconazole and imipramine, propranolol, diazepam, cimetidine, indomethacin, tolbutamide and sulphamethazine.

## **OVERDOSAGE**

### **Treatment**

No data are available. In the event of accidental overdosage, supportive measures should be employed. Within the first hour after ingestion, gastric lavage may be performed. Activated charcoal may be given if considered appropriate. Itraconazole cannot be removed by haemodialysis. No specific antidote is available.

## **PHARMACEUTICAL PRECAUTIONS**

### **Shelf Life**

2 years when stored below 25°C. Discard 3 months after opening the bottle.

## **MEDICINE CLASSIFICATION**

Prescription Medicine

## **PACKAGE QUANTITIES**

150 mL

## **FURTHER INFORMATION**

SPORANOX oral solution contains hydroxypropyl-beta-cyclodextrin, sorbitol, propylene glycol, hydrochloric acid, cherry flavour 1, cherry flavour 2, caramel flavour, saccharin sodium, sodium hydroxide and purified water.

### **Carcinogenesis, mutagenicity, impairment of fertility**

Itraconazole showed no evidence of carcinogenicity potential in mice treated orally for 23 months at dosage levels of up to 80 mg/kg/day. Male rats treated with 25 mg/kg/day had a slightly increased incidence of soft tissue sarcoma. These sarcomas may have been a consequence of hypercholesterolaemia, which is a response of rats, but not dogs or humans to chronic itraconazole administration. Female rats treated with 50 mg/kg/day had an increased incidence of squamous cell carcinoma of the lung (2/50) as compared to the untreated group. Although the occurrence of squamous cell carcinoma in the lung is extremely uncommon in untreated rats, the increase in this study was not statistically significant.

Itraconazole produced no mutagenic effects when assayed in appropriate bacterial, non-mammalian and mammalian test systems.

Itraconazole did not affect the fertility of male or female rats treated orally with dosage levels of up to 40 mg/kg/day even though parental toxicity was present at this dosage level.

Separate studies on the vehicle, hydroxypropyl-beta-cyclodextrin, have shown that this carrier molecule is not mutagenic. It did not have carcinogenic activity in mice at dietary dose levels up to 5 g/kg/day, but caused the development of pancreatic exocrine adenomas and adenocarcinomas in rats at dietary dose levels of 0.5 to 5 g/kg/day. Pancreatic exocrine tumours in rats may be due to a non-genotoxic mechanism involving stimulation of cholecystikinin release as a result of complexation of bile salts by hydroxypropyl-beta-cyclodextrin in the intestinal lumen. However, there is only indirect evidence for this hypothesis and its relevance in humans is not known.

Hydroxypropyl-beta-cyclodextrin had no effect on fertility when administered to male and female rats at dietary doses up to 5 g/kg/day or IV doses up to 400 mg/kg/day.

## Toxicology

In three toxicology studies using rats, itraconazole induced bone defects at dosage levels as low as 20 mg/kg/day. The induced defects included reduced bone plate activity, thinning of the zona compacta of the large bones and increased bone fragility. At a dosage level of 80 mg/kg/day over one year or 160 mg/kg/day for six months, itraconazole induced small tooth pulp with hypocellular appearance in some rats.

Increased relative adrenal weights and swollen adrenals (reversible) were seen in rats and dogs where plasma levels were comparable to those of human therapeutic doses. Adrenocortical function was not affected in studies in humans after the recommended daily doses; with higher doses (600 mg/day for 3 months), adrenal cortex response to ACTH stimulation was reduced in 1 of 8 patients, but returned to normal when the dosage was reduced.

## Microbiology

*In vitro* studies have demonstrated that itraconazole impairs the synthesis of ergosterol in fungal cells. Ergosterol is a vital cell membrane component in fungi. Impairment of its synthesis ultimately results in an antifungal effect.

For itraconazole, breakpoints have only been established for *Candida* spp. from superficial mycotic infections (CLSI M27-A2, breakpoints have not been established for EUCAST methodology). The CLSI breakpoints are as follows: susceptible  $\leq 0.125$ ; susceptible, dose-dependent 0.25-0.5 and resistant  $\geq 1$   $\mu\text{g/mL}$ . Interpretive breakpoints have not been established for the filamentous fungi.

*In vitro* studies demonstrate that itraconazole inhibits the growth of a broad range of fungi pathogenic for humans at concentrations usually  $\leq 1$   $\mu\text{g/ml}$ . These include:

dermatophytes (*Trichophyton* spp., *Microsporum* spp., *Epidermophyton floccosum*); yeasts (*Candida* spp., including *C. albicans*, *Cryptococcus neoformans*, *Malassezia* spp., *Trichosporon* spp., *Geotrichum* spp.); *Aspergillus* spp.; *Histoplasma* spp.; *Paracoccidioides brasiliensis*; *Sporothrix schenckii*; *Fonsecaea* spp.; *Cladosporium* spp.; *Blastomyces dermatitidis*; *Coccidioides immitis*; *Pseudallescheria boydii*; *Penicillium marneffeii*; and various other yeasts and fungi.

*Candida krusei*, *Candida glabrata* and *Candida tropicalis* are generally the least susceptible *Candida* species, with some isolates showing unequivocal resistance to itraconazole *in vitro*.

The principal fungus types that are not inhibited by itraconazole are *Zygomycetes* (e.g. *Rhizopus* spp., *Rhizomucor* spp., *Mucor* spp. and *Absidia* spp.), *Fusarium* spp., *Scedosporium* spp. and *Scopulariopsis* spp.

Azole resistance appears to develop slowly and is often the result of several genetic mutations. Mechanisms that have been described are overexpression of ERG11, which encodes the target enzyme 14 $\alpha$ -demethylase, point mutations in ERG11 that lead to decreased target affinity and/or transporter overexpression resulting in increased efflux. Cross-resistance between members of the azole class has been observed within *Candida* spp., although resistance to one member of the class does not necessarily confer resistance to other azoles. Itraconazole-resistant strains of *Aspergillus fumigatus* have been reported.

## **NAME AND ADDRESS**

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## **DATE OF PREPARATION**

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