# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Sporanox 100mg Capsules

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains itraconazole 100 mg.

Excipient: Contains 192mg sucrose.

*For a full list of excipients, see section 6.1.*

## 3 PHARMACEUTICAL FORM

Capsule, hard
Capsule (size 0): opaque blue cap and pink transparent body containing coated beads.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

1. Vulvovaginal candidosis
2. Pityriasis versicolor
3. Dermatophytoses caused by organisms susceptible to itraconazole
4. Oral candidosis
5. Fungal keratitis
6. Systemic mycoses
7. Onychomycosis

### 4.2 Posology and method of administration

Sporanox is for oral administration and must be taken immediately after a meal for maximal absorption. The capsules must be swallowed whole.
Treatment schedules in adults for each indication are as follows:

| Indication | Dose |
|---|---|
| Vulvovaginal candidosis | 200 mg twice daily for 1 day or 200 mg once daily for 3 days. |
| Pityriasis versicolor | 200 mg once daily for 7 days |
| Tinea corporis, tinea cruris | 100 mg once daily for 2 weeks or 200 mg once daily for 7 days |
| Tinea pedis, tinea manuum | 100 mg once daily for 4 weeks |
| Oral candidosis | 100 mg once daily for 2 weeks |
| Fungal keratitis | 200 mg once daily for 3 weeks |

Dosage recommendations vary according to the infection treated.

| Indication | Dose | Median Duration |
|---|---|---|
| Onychomycosis | 200 mg once daily | 3 months |
| Treatment of aspergillosis | 200 mg once daily<br>Increase dose to 200 mg twice daily in patients who have invasive or disseminated disease and who have failed or are intolerant to amphotericin B or voriconazole. | 2-5 months |
| Treatment of candidosis | 100-200 mg once daily | 3 weeks - 7 months |
| Treatment of non-meningeal cryptococcosis | 200 mg once daily | 1-6 months |

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| Treatment of cryptococcal meningitis | 200 mg twice daily | 2 months - 1 year |
| Histoplasmosis | 200 mg once daily - 200 mg twice daily | 8 months |
| Lymphocutaneous and cutaneous sporotrichosis | 100 mg or 200 mg once daily (localized lesions), or 200 mg twice daily (extensive lesions) | 3 - 6 months |
| Extracutaneous sporotrichosis following objective treatment improvement with amphotericin B | 200 mg twice daily | 12 months |
| Treatment of paracoccidioidomycosis | 100 mg once daily | 6 months |
| Treatment of chromoblastomycosis (formerly chromomycosis) | 200-400 mg once daily | 6 months |
| Blastomycosis | 100 mg once daily - 200 mg twice daily | 6 months |

The duration of treatment for systemic mycoses should be adjusted based on the clinical response

*Paediatric population:*
The safety and efficacy of Sporanox in children and adolescents aged under 18 years has not been established. Currently available data are described in sections 4.8 and 5.2 but no recommendation on a posology can be made.

*Elderly:*
Clinical data on the use of Sporanox Capsules in elderly patients are limited. It is advised to use Sporanox Capsules in these patients only if it is determined that the potential benefit outweighs the potential risks. In general, it is recommended that the dose selection for an elderly patient should be taken into consideration, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. See section 4.4.

*Renal impairment:*
Limited data are available on the use of oral itraconazole in patients with renal impairment. The exposure of itraconazole may be lower in some patients with renal insufficiency. Caution should be exercised when this drug is administered in this patient population and adjusting the dose may be considered.

*Hepatic impairment:*
Limited data are available on the use of oral itraconazole in patients with hepatic impairment. Caution should be exercised when this drug is administered in this patient population. (See section 5.2).

**4.3 Contraindications**

Sporanox Capsules are contraindicated in patients with known hypersensitivity to itraconazole or to any of the excipients.

- Co-administration of Sporanox Capsules is contraindicated with a number of CYP3A4 substrates such as the examples listed below (see sections 4.4 and 4.5):

| | | |
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| **Analgesics; Anaesthetics** | | |
| Ergot alkaloids<br>(e.g. dihydroergotamine, ergometrine, ergotamine, methylergometrine) | | |
| **Anti-bacterials for Systemic Use; Anti-mycobacterials; Antimycotics for Systemic Use** | | |
| Isavuconazole | | |
| **Anthelmintics; Antiprotozoals** | | |
| Halofantrine | | |
| **Antihistamines for Systemic Use** | | |
| Astemizole | Mizolastine | Terfenadine |
| **Antineoplastic Agents** | | |
| Irinotecan | Venetoclax | |

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| | (in patients with chronic lymphocytic leukaemia during initiation and dose titration phase of venetoclax) | |
| **Antithrombotic Agents** | | |
| Dabigatran | Ticagrelor | |
| **Antivirals for Systemic Use** | | |
| Ombitasvir/Paritaprevir/Ritonavir (with or without Dasabuvir) | | |
| **Cardiovascular System (Agents Acting on the Renin-Angiotensin System; Antihypertensives; Beta Blocking Agents; Calcium Channel Blockers; Cardiac Therapy; Diuretics)** | | |
| Aliskiren | Eplerenone | Quinidine |
| Bepridil | Finerenone | Ranolazine |
| Disopyramide | Ivabradine | Sildenafil (pulmonary hypertension) |
| Dofetilide | Lercanidipine | |
| Dronedarone | Nisoldipine | |
| **Gastrointestinal Drugs, including Antidiarrheals, Intestinal Anti-inflammatory/Anti-infective Agents; Antiemetics and Antinauseants; Drugs for Constipation; Drugs for Functional Gastrointestinal Disorders** | | |
| Cisapride | Domperidone | Naloxegol |
| **Immunosuppressants** | | |
| Voclosporin | | |
| **Lipid Modifying Agents** | | |
| Lovastatin | Lomitapide | Simvastatin |
| **Psychoanaleptics; Psycholeptics (eg, antipsychotics, anxiolytics, and hypnotics)** | | |
| Lurasidone | Pimozide | Sertindole |
| Midazolam (oral) | Quetiapine | Triazolam |
| **Urologicals** | | |
| Avanafil | Darifenacin | Solifenacin (in patients with severe renal impairment or moderate to severe hepatic impairment) |
| Dapoxetine | Fesoterodine (in patients with moderate or severe renal or hepatic impairment). | Vardenafil (in patients older than 75 years). |
| **Miscellaneous Drugs and Other Substances** | | |
| Colchicine (in patients with renal or hepatic impairment) | Eliglustat (in patients that are CYP2D6 poor metabolisers (PM), CYP2D6 | |

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| | intermediate metabolisers (IMs) or extensive metabolisers (EMs) that are taking a strong or moderate CYP2D6 inhibitor). | |

Sporanox Capsules 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 section 4.4).
Sporanox Capsules must not be used during pregnancy (except for life-threatening cases) (see section 4.6).
Women of childbearing potential taking Sporanox Capsules should use contraceptive precautions. Effective contraception should be continued until the menstrual period following the end of Sporanox Capsule therapy.

**4.4 Special warnings and precautions for use**

*Cross-hypersensitivity*
There is limited information regarding cross-hypersensitivity between itraconazole and other azole antifungal agents. Caution should be used in prescribing Sporanox Capsules to patients with hypersensitivity to other azoles.

*Cardiac effects*
In a healthy volunteer study with Sporanox I.V., a transient asymptomatic decrease of the left ventricular ejection fraction was observed; this resolved before the next infusion. The clinical relevance of these findings to the oral formulations is unknown.
Itraconazole has been shown to have a negative inotropic effect and Sporanox Capsules 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. This individual benefit/risk assessment should take into consideration factors such as the severity of the indication, the dosing regimen (e.g. total daily dose), and individual risk factors for congestive heart failure. These 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. Such patients should be informed of the signs and symptoms of congestive heart failure, should be treated with caution, and should be monitored for signs and symptoms of congestive heart failure during treatment; if such signs or symptoms do occur during treatment, Sporanox should be discontinued.
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 (see Section 4.5).

*Hepatic effects*
Very rare cases of serious hepatotoxicity, including some cases of fatal acute liver failure, have occurred with the use of Sporanox Capsules. 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 were observed within the first month of treatment, including some within the first week. Liver function monitoring should be considered in patients receiving Sporanox Capsules 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.
Limited data are available on the use of oral itraconazole in patients with hepatic impairment. Caution should be exercised when the drug is administered in this patient population. It is recommended that patients with impaired hepatic function be carefully monitored when taking itraconazole. It is recommended that the prolonged elimination half-life of itraconazole observed in the single oral dose clinical trial with itraconazole capsules in cirrhotic patients be considered when deciding to initiate therapy with other medications metabolised by CYP3A4.
In patients with elevated or abnormal liver enzymes or active liver disease, or who have experienced liver toxicity with other drugs, treatment with Sporanox is strongly discouraged unless there is a serious or life threatening situation where the

expected benefit exceeds the risk. It is recommended that liver function monitoring be done in patients with pre-existing hepatic function abnormalities or those who have experienced liver toxicity with other medications (see section 5.2).

*Reduced gastric acidity*
Absorption of itraconazole from Sporanox Capsules is impaired when gastric acidity is reduced. In patients with reduced gastric acidity, whether from disease (e.g. patients with achlorhydria) or from concomitant medication (e.g. patients taking drugs that reduce gastric acidity), it is advisable to administer Sporanox Capsules with an acidic beverage (such as non-diet cola). The antifungal activity should be monitored and the itraconazole dose increased as deemed necessary. See section 4.5.

*Paediatric population*
Safety and effectiveness of Sporanox in paediatric patients below the age of 18 years has not been established (see sections 4.8 and 5.2).

*Elderly*
Clinical data on the use of Sporanox Capsules in elderly patients are limited. It is advised to use Sporanox Capsules in these patients only if it is determined that the potential benefit outweighs the potential risks. In general, it is recommended that the dose selection for an elderly patient should be taken into consideration, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

*Renal impairment*
Limited data are available on the use of oral itraconazole in patients with renal impairment. The exposure of itraconazole may be lower in some patients with renal insufficiency. Caution should be exercised when this drug is administered in this patient population and adjusting the dose may be considered.

*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 Section 4.3 and 4.5). The hearing loss usually resolves when treatment is stopped, but can persist in some patients.

*Immunocompromised patients*
In some immunocompromised patients (e.g. neutropenic, AIDS or organ transplant patients), the oral bioavailability of Sporanox Capsules may be decreased.

*Patients with immediately life-threatening systemic fungal infections*
Due to the pharmacokinetic properties (see section 5.2), Sporanox Capsules are not recommended for initiation of treatment with immediately life-threatening systemic fungal infections.

*Patients with AIDS*
In patients with AIDS having received treatment for a systemic fungal infection such as sporotrichosis, blastomycosis, histoplasmosis or cryptococcosis (meningeal and non-meningeal) and who are considered at risk for relapse, the treating physician should evaluate the need for a maintenance treatment.

*Neuropathy*
If neuropathy occurs that may be attributable to Sporanox Capsules, the treatment should be discontinued.

*Cystic fibrosis*
In cystic fibrosis patients, variability in therapeutic levels of itraconazole was observed with steady state dosing of itraconazole oral solution using 2.5 mg/kg bid. Steady state concentrations of > 250 ng/mL were achieved in approximately 50% of subjects greater than 16 years of age, but in none of the patients less than 16 years of age. If a patient does not respond to Sporanox Capsules, consideration should be given to switching to alternative therapy.

*Disorders of Carbohydrate Metabolism*
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

*Cross-resistance*
In systemic candidosis, if fluconazole-resistant strains of *Candida* species are suspected, it cannot be assumed that these are sensitive to itraconazole, hence their sensitivity should be tested before the start of itraconazole therapy.

*Interchangeability*
It is not recommended that Sporanox Capsules and Sporanox Oral Solution be used interchangeably. This is because drug exposure is greater with the oral solution than with the capsules when the same dose of drug is given.

*Interaction potential*
Coadministration of specific drugs with itraconazole may result in changes in efficacy of itraconazole and/or the coadministered drug, life-threatening effects and/or sudden death. Drugs that are contraindicated, not recommended or recommended for use with caution in combination with itraconazole are listed in section 4.3 Contraindications and section 4.5 Interaction with other medicinal products and other forms of interaction.

**4.5 Interaction with other medicinal products and other forms of interaction**

Itraconazole is mainly metabolised through CYP3A4. Other substances that either share this metabolic pathway or modify CYP3A4 activity may influence the pharmacokinetics of itraconazole. Itraconazole is a strong CYP3A4 inhibitor and, a P-glycoprotein inhibitor and Breast Cancer Resistance Protein (BCRP) inhibitor.

Itraconazole may modify the pharmacokinetics of other substances that share this metabolic or these protein transporter pathways.

Examples of drugs that may impact on the plasma concentration of itraconazole are presented by drug class in Table 1 below. Examples of drugs that may have their plasma concentrations impacted by itraconazole are presented in Table 2 below. Due to the number of interactions, the potential changes in safety or efficacy of the interacting drugs are not included. The list of examples of interacting drugs in the tables below is not comprehensive and therefore the product information of each drug that is co-administered with itraconazole should be consulted for information related to the route of metabolism, interaction pathways, potential risks, and specific actions to be taken with regards to co-administration.

The interactions described in these tables are categorised as contraindicated, not recommended or to be used with caution with itraconazole taking into account the extent of the concentration increase and the safety profile of the interacting drug (see also sections 4.3 and 4.4 for further information). The interaction potential of the listed drugs was evaluated based on human pharmacokinetic studies with itraconazole, and/or human pharmacokinetic studies with other strong CYP3A4 inhibitors (e.g. ketoconazole) and/or in vitro data:

- 'Contraindicated': Under no circumstances is the drug to be co-administered with itraconazole, and up to two weeks after discontinuation of treatment with itraconazole.
- 'Not recommended': The use of the drug should be avoided during and up to two weeks after discontinuation of treatment with itraconazole, unless the benefits outweigh the potentially increased risks of side effects. If co-administration cannot be avoided, clinical monitoring for signs or symptoms of increased or prolonged effects or side effects of the concomitantly administered drug is recommended, and its dosage be reduced or interrupted as deemed necessary. When appropriate, it is recommended that plasma concentrations of the co-administered drug be measured.
- 'Use with caution': Careful monitoring is recommended when the drug is co-administered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely for signs or symptoms of increased or prolonged effects or side effects of the interacting drug, and its dosage be reduced as deemed necessary. When appropriate, it is recommended that plasma concentrations of the co administered drug be measured.

The interactions listed in these tables have been characterised in studies that were performed with recommended doses of itraconazole. However, the extent of interaction may be dependent on the dose of itraconazole administered. A stronger interaction may occur at a higher dose or with a shorter dosing interval. Extrapolation of the findings with other dosing scenarios or different drugs should be done with caution.
Once treatment is stopped, itraconazole plasma concentrations decrease to an almost undetectable concentration within 7 to 14 days, depending on the dose and duration of treatment. In patients with hepatic cirrhosis or in subjects receiving CYP3A4 inhibitors, the decline in plasma concentrations may be even more gradual. This is particularly important when initiating therapy with drugs whose metabolism is affected by itraconazole. (See section 5.2)

Table 1: Examples of drugs that may impact the plasma concentration of itraconazole, presented by drug class

| **Examples of medicinal products (Per Orale [PO] Single Dose unless otherwise stated)** | **Expected/Potential effect on itraconazole levels (↑ = increase; ↔ = no change; ↓ = decrease)** | **Clinical comment (see above for additional info and also sections 4.3 and 4.4)** |
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| | | |
|---|---|---|
| **within class** | | |
| **Antibacterials for Systemic Use; Antimycobacterials** | | |
| Isoniazid | Although not studied directly, isoniazid is likely to decrease the concentrations of itraconazole. | Not recommended |
| Rifampicin PO 600 mg OD | Itraconazole AUC ↓ | Not recommended |
| Rifabutin PO 300 mg OD | Itraconazole Cmax ↓ 71%, AUC ↓ 74% | Not recommended |
| Ciprofloxacin PO 500 mg BID | Itraconazole Cmax ↑ 53%, AUC ↑ 82% | Use with caution |
| Erythromycin 1 g | Itraconazole Cmax ↑ 44%, AUC ↑ 36% | Use with caution |
| Clarithromycin PO 500 mg BID | Itraconazole Cmax ↑ 90%, AUC ↑ 92% | Use with caution |
| **Antiepileptics** | | |
| Carbamazepine, Phenobarbital | Although not studied directly, these drugs are likely to decrease concentrations of itraconazole. | Not recommended |
| Phenytoin PO 300 mg OD | Itraconazole Cmax ↓ 83%, AUC ↓ 93%<br>Hydroxyitraconazole Cmax ↓ 84%, AUC ↓ 95% | Not recommended |
| **Antineoplastics Agents** | | |
| Idelalisib | Although not studied directly, idelalisib is likely to increase the concentrations of itraconazole. | Use with caution |
| **Antivirals for Systemic Use** | | |
| Ombitasvir/Paritaprevir/Ritonavir (with or without Dasabuvir) | Although not studied directly, these drugs are expected to increase the concentrations of itraconazole. | Contraindicated |
| Efavirenz 600 mg | Itraconazole Cmax ↓ 37%, AUC ↓ 39%;<br>Hydroxyitraconazole Cmax ↓ 35%, AUC ↓ 37% | Not recommended |
| Nevirapine PO 200 mg OD | Itraconazole Cmax ↓ 38%, AUC ↓ 62% | Not recommended |
| Cobicistat,<br>Darunavir (boosted),<br>Elvitegravir (ritonavir-boosted),<br>Fosamprenavir (ritonavir-boosted),<br>Ritonavir,<br>Saquinavir (ritonavir-boosted) | Although not studied directly, these drugs are expected to increase the concentrations of itraconazole. | Use with caution |
| Indinavir PO 800 mg TID | Itraconazole concentration ↑ | Use with caution |
| **Calcium Channel Blockers** | | |
| Diltiazem | Although not studied directly, diltiazem is likely to increase the concentration of itraconazole. | Use with caution |
| **Drugs for Acid Related Disorders** | | |
| Antacids (aluminium, calcium, magnesium, or sodium bicarbonate),<br>$H_2$-receptor anatagonists (eg, cimetidine, ranitidine),<br>Proton pump inhibitors (eg, lansoprazole, omeprazole, rabeprazole) | Itraconazole Cmax ↓, AUC ↓ | Use with caution |
| **Respiratory System: Other Respiratory System Products** | | |
| Lumacaftor/Ivacaftor PO 200/250 mg BID | Itraconazole concentration ↓ | Not recommended |
| **Miscellaneous** | | |
| St. John's Wort (Hypericum perforatum) | Although not studied directly, St. John's Wort is likely to decrease the concentration of itraconazole. | Not recommended |

Table 2 Examples of drugs that may have their plasma concentrations impacted by itraconazole, presented by drug class

| **Examples of medicinal products (PO Single Dose unless otherwise stated) within class** | **Expected/Potential effect on drugs levels (↑ = increase; ↔ = no change; ↓ = decrease)** | **Clinical comment (see above for additional info and also sections 4.3 and 4.4)** |
|---|---|---|
| **Analgesics; Anaesthetics** | | |
| Ergot alkaloids (eg, | Although not studied directly, itraconazole is likely to increase | Contraindicated |

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| dihydroergotamine, ergometrine, ergotamine, methylergometrine) | the concentrations of these drugs. | |
| Eletriptan, Fentanyl | Although not studied directly, itraconazole is likely to increase the concentrations of these drugs. | Not recommended |
| Alfentanil, Buprenorphine (IV and sublingual), Cannabinoids, Methadone, Sufentanil | Although not studied directly, itraconazole is likely to increase the concentrations of these drugs. | Use with caution |
| Oxycodone PO 10 mg, | Oxycodone PO: Cmax ↑ 45%, AUC ↑ 2.4-fold | Use with caution |
| Oxycodone IV 0.1 mg/kg | Oxycodone IV: AUC ↑ 51% | Use with caution |
| **Antibacterials for Systemic Use; Antimycobacterials; Antimycotics for Systemic Use** | | |
| Isavuconazole | Although not studied directly, itraconazole is likely to increase the concentrations of isavuconazole. | Contraindicated |
| Bedaquiline | Although not studied directly, itraconazole is likely to increase the concentrations of bedaquiline. | Not recommended |
| Rifabutin PO 300 mg OD | Rifabutin concentration ↑ (extent unknown) | Not recommended |
| Clarithromycin PO 500 mg BID | Clarithromycin concentration ↑ | Use with caution |
| Delamanid | Although not studied directly, itraconazole is likely to increase the concentrations of delaminid. | Use with caution |
| **Antiepileptics** | | |
| Carbamazepine | Although not studied directly, itraconazole is likely to increase the concentrations of carbamazepine. | Not recommended |
| **Anti-inflammatory and Antirheumatic Products** | | |
| Meloxicam 15 mg | Meloxicam Cmax ↓ 64%, AUC ↓ 37% | Use with caution |
| **Anthelmintics; Antiprotozoals** | | |
| Halofantrine | Although not studied directly, itraconazole is likely to increase the concentrations of halofantrine. | Contraindicated |
| Artemether-lumefantrine, Praziquantel | Although not studied directly, itraconazole is likely to increase the concentrations of these drugs. | Use with caution |
| Quinine 300 mg | Quinine Cmax ↔, AUC ↑ 96% | Use with caution |
| **Antihistamines for Systemic Use** | | |
| Astemizole, Mizolastine, Terfenadine | Although not studied directly, itraconazole is likely to increase the concentrations of these drugs. | Contraindicated |
| Ebastine 20 mg | Ebastine Cmax ↑ 2.5-fold, AUC ↑ 6.2-fold<br>Carabastine Cmax ↔, AUC ↑ 3.1-fold | Not recommended |
| Bilastine, Rupatidine | Although not studied directly, itraconazole is likely to increase the concentrations of these drugs. | Use with caution |
| **Antineoplastic Agents** | | |
| Irinotecan | Although not studied directly, itraconazole is likely to increase the concentrations of irinotecan and its active metabolite. | Contraindicated |
| Venetoclax | Although not studied directly, itraconazole is likely to increase the concentrations of venetoclax. | Contraindicated in patients with chronic lymphocytic leukaemia during initiation and dose titration phase of venetoclax. Otherwise, not recommended unless the benefits outweigh the risks. Refer to the venetoclax prescribing information. |
| Axitinib, Bosutinib, Cabazitaxel, Cabozantinib, Ceritinib, Crizotinib, Dabrafenib, Dasatinib, Docetaxel, Everolimus, Glasdegib | Although not studied directly, itraconazole is likely to increase the concentrations of these drugs except for cabazitaxel and regorafenib. No statistically significant change in cabazitaxel exposure, but a high variability in the results was observed. Regorafenib AUC is expected to decrease (by estimation of active moiety) | Not recommended |

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| Ibrutinib, Lapatinib, Nilotinib, Pazopanib, Regorafenib, Sunitinib, Temsirolimus, Trabectedin, Trastuzumab emtansine, Vinca alkaloids (eg, vinflunine, vinorelbine) | | |
| Cobimetinib 10 mg, | Cobimetinib Cmax ↑ 3.2-fold, AUC ↑ 6.7-fold | Not recommended |
| Entrectinib | Entrectinib Cmax ↑ 73%, AUC ↑ 6.0 fold | Not recommended |
| Olaparib 100 mg | Olaparib Cmax ↑ 40%, AUC ↑ 2.7-fold | Not recommended |
| Talazoparib | Talazoparib $C_{max}$ ↑ 40%, AUC ↑ 56% | Not recommended |
| Alitretinoin (oral), Bortezomib, Brentuximab vedotin, Erlotinib, Idelalisib, Imatinib, Nintedanib, Panobinostat, Ponatinib, Ruxolitinib, Sonidegib, Tretinoin (oral) | Although not studied directly, itraconazole is likely to increase the concentrations of these drugs | Use with caution |
| Busulfan 1 mg/kg Q6h | Busulfan Cmax ↑, AUC ↑ | Use with caution |
| Gefitinib 250 mg | Gefitinib 250 mg Cmax ↑, AUC ↑ 78% | Use with caution |
| Pemigatinib | Pemigatinib Cmax ↑ 17%, AUC ↑ 91% | Use with caution |
| **Antithrombotic Agents** | | |
| Dabigatran, Ticagrelor | Although not studied directly, itraconazole is likely to increase the concentrations of these drugs. | Contraindicated |
| Apixaban, Edoxaban, Rivaroxaban, Vorapaxar | Although not studied directly, itraconazole is likely to increase the concentrations of these drugs. | Not recommended |
| Cilostazol, Coumarins (eg, warfarin) | Although not studied directly, itraconazole is likely to increase the concentrations of these drugs | Use with caution |
| **Antivirals for Systemic Use** | | |
| Ombitasvir/Paritaprevir/Ritonavir (with or without Dasabuvir) | Itraconazole may increase paritaprevir concentrations. | Contraindicated |
| Elbasvir/Grazoprevir, Tenofovir alefenamide fumarate (TAF), Tenofovir disoproxil fumarate (TDF) | Although not studied directly, itraconazole is likely to increase the concentrations of these drugs. | Not recommended |
| Cobicistat, Elvitegravir (ritonavir-boosted), Glecaprevir/Pibrentasvir, Maraviroc, Ritonavir, Saquinavir | Although not studied directly, itraconazole is likely to increase the concentrations of these drugs. | Use with caution |
| Indinavir PO 800 mg TID | Indinavir Cmax ↔, AUC ↑ | Use with caution |
| **Cardiovascular System (Agents Acting on the Renin-Angiotensin System; Antihypertensives; Beta Blocking Agents; Calcium Channel Blockers; Cardiac Therapy; Diuretics)** | | |
| Bepridil, Disopyramide, Dofetilide, Dronedarone, Eplerenone, Finerenone, Ivabradine, Lercanidipine, Nisoldipine, Ranolazine, Sildenafil (pulmonary hypertension) | Although not studied directly, itraconazole is likely to increase the concentrations of these drugs. | Contraindicated |
| Aliskiren 150 mg, | Aliskiren Cmax ↑ 5.8-fold, AUC ↑ 6.5-fold | Contraindicated |
| Quinidine 100 mg | Quinidine Cmax ↑ 59%, AUC ↑ 2.4-fold | Contraindicated |
| Felodipine 5 mg | Felodipine Cmax ↑ 7.8-fold, AUC ↑ 6.3-fold | Not recommended |

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| Riociguat,<br>Tadalafil (pulmonary hypertension) | Although not studied directly, itraconazole is likely to increase the concentrations of these drugs. | Not recommended |
| Bosentan, Diltiazem, Guanafacine,<br>Other Dihydropyridines (eg, amlodipine, isradipine, nefidipine, nimodipine),<br>Verapamil | Although not studied directly, itraconazole is likely to increase the concentrations of these drugs. | Use with caution |
| Digoxin 0.5 mg | Digoxin Cmax ↑ 34%, AUC ↑ 68% | Use with caution |
| Nadolol 30 mg | Nadolol Cmax ↑ 4.7-fold, AUC ↑ 2.2-fold | Use with caution |
| **Corticosteroids for Systemic Use; Drugs for Obstructive Airway Diseases** | | |
| Ciclesonide, Salmeterol | Although not studied directly, itraconazole is likely to increase the concentrations of salmeterol and the active metabolite of ciclesonide. | Not recommended |
| Budesonide INH 1 mg SD, | Budesonide INH Cmax ↑ 65%, AUC ↑ 4.2-fold; Budesonide (other formulations) concentration ↑ | Use with caution |
| Dexamethasone IV 5 mg<br>Dexamethasone PO 4.5 mg | Dexamethasone IV: Cmax ↔, AUC ↑ 3.3-fold<br>Dexamethasone PO: Cmax ↑ 69%, AUC ↑ 3.7-fold | Use with caution |
| Fluticasone INH 1 mg BID, | Fluticasone INH concentration ↑ | Use with caution |
| Methylprednisolone 16 mg, | Methylprednisolone PO Cmax ↑ 92%, AUC ↑ 3.9-fold<br>Methylprednisolone IV AUC ↑ 2.6-fold | Use with caution |
| Fluticasone nasal | Although not studied directly, itraconazole is likely to increase the concentrations of nasally-administered fluticasone. | Use with caution |
| **Drugs Used in Diabetes** | | |
| Repaglinide 0.25 mg | Repaglinide Cmax ↑ 47%, AUC ↑ 41% | Use with caution |
| Saxagliptin | Although not studied directly, itraconazole is likely to increase the concentrations of saxagliptin. | Use with caution |
| **Gastrointestinal Drugs, including Antidiarrheals, Intestinal Antiinflammatory/Antiinfective Agents; Antiemetics and Antinauseants; Drugs for Constipation; Drugs for Functional Gastrointestinal Disorders** | | |
| Cisapride, Naloxegol | Although not studied directly, itraconazole is likely to increase the concentrations of these drugs. | Contraindicated |
| Domperidone 20 mg | Domperidone Cmax ↑ 2.7-fold, AUC ↑ 3.2-fold | Contraindicated |
| Aprepitant, Loperamide, Netupitant | Although not studied directly, itraconazole is likely to increase the concentrations of these drugs. | Use with caution |
| **Immunosuppressants** | | |
| Voclosporin | Although not studied directly, itraconazole is likely to increase the concentrations of voclosporin. | Contraindicated |
| Sirolimus (rapamycin) | Although not studied directly, itraconazole is likely to increase the concentrations of sirolimus. | Not recommended |
| Cyclosporine, Tacrolimus | Although not studied directly, itraconazole is likely to increase the concentrations of these drugs. | Use with caution |
| Tacrolimus IV 0.03 mg/kg OD | Tacrolimus IV concentration ↑ | Use with caution |
| **Lipid Modifying Agents** | | |
| Lomitapide | Although not studied directly, itraconazole is likely to increase the concentrations of lomitapide. | Contraindicated |
| Lovastatin 40 mg, | Lovastatin Cmax ↑ 14.5->20-fold, AUC ↑ >14.8 - >20-fold<br>Lovastatin acid Cmax ↑ 11.5-13-fold, AUC ↑ 15.4-20-fold | Contraindicated |
| Simvastatin 40 mg | Simvastatin acid Cmax ↑ 17-fold, AUC ↑ 19-fold | Contraindicated |
| Atorvastatin | Atorvastatin acid: Cmax ↔ to ↑2.5 fold, AUC ↑ 40% to 3-fold | Not recommended |
| **Psychoanaleptics; Psycholeptics (eg, antipsychotics, anxiolytics, and hypnotics)** | | |
| Lurasidone, Pimozide, Quetiapine, Sertindole | Although not studied directly, itraconazole is likely to increase the concentrations of these drugs. | Contraindicated |
| Midazolam (oral) 7.5 mg | Midazolam (oral) Cmax ↑ 2.5 to 3.4-fold, AUC ↑ 6.6 to 10.8-fold | Contraindicated |
| Triazolam 0.25 mg | Triazolam Cmax ↑, AUC ↑ | Contraindicated |
| Alprazolam 0.8 mg | Alprazolam Cmax ↔, AUC ↑ 2.8-fold | Use with caution |
| Aripiprazole 3 mg | Aripiprazole Cmax ↑ 19%, AUC ↑ 48% | Use with caution |

| | | |
|---|---|---|
| Brotizolam 0.5 mg | Brotizolam Cmax ↔, AUC ↑ 2.6-fold | Use with caution |
| Buspirone 10 mg | Buspirone Cmax ↑ 13.4-fold, AUC ↑ 19.2-fold | Use with caution |
| Midazolam (iv) 7.5 mg | Midazolam (iv) 7.5 mg: concentration ↑;<br>Although not studied directly, itraconazole is likely to increase the concentrations of midazolam following oromucosal administration. | Use with caution |
| Risperidone 2-8 mg/day | Risperidone and active metabolite concentration ↑ | Use with caution |
| Zopiclone 7.5 mg | Zopiclone Cmax ↑ 30%, AUC ↑ 70% | Use with caution |
| Cariprazine, Galantamine, Haloperidol, Reboxetine, Venlafaxine | Although not studied directly, itraconazole is likely to increase the concentrations of these drugs. | Use with caution |
| **Respiratory System: Other Respiratory System Products** | | |
| Lumacaftor/Ivacaftor PO 200/250 mg BID | Ivacaftor Cmax ↑ 3.6-fold, AUC ↑ 4.3-fold<br>Lumacaftor Cmax ↔, AUC ↔ | Not recommended |
| Ivacaftor | Although not studied directly, itraconazole is likely to increase the concentrations of ivacaftor. | Use with caution |
| **Sex Hormones and Modulators of the Genital System; Other Gynecologicals** | | |
| Cabergoline, Dienogest, Ulipristal | Although not studied directly, itraconazole is likely to increase the concentrations of these drugs. | Use with caution |
| **Urologicals** | | |
| Avanafil, Dapoxetine, Darifenacin | Although not studied directly, itraconazole is likely to increase the concentrations of these drugs. | Contraindicated |
| Fesoterodine | Although not studied directly, itraconazole is likely to increase the concentrations of the active metabolites, 5-hydroxymethyl-tolterodine. | Moderate or severe renal or hepatic impairment: Contraindicated<br>Mild renal or hepatic impairment: Concomitant use should be avoided<br>Normal renal or hepatic impairment: Use with caution with a maximum fesoterodine dose of 4 mg. |
| Solifenacin | Although not studied directly, itraconazole is likely to increase the concentrations of solifenacin. | Severe renal impairment: Contraindicated<br>Moderate or severe hepatic impairment: Contraindicated<br>Use with caution in all other patients with a maximum solifenacin dose of 5 mg. |
| Vardenafil | Although not studied directly, itraconazole is likely to increase the concentrations of vardenafil. | Contraindicated in patients older than 75 years; otherwise not recommended. |
| Alfuzosin, Silodosin, Tadalafil (erectile dysfunction and benign prostatic hyperplasia), Tamsulosin, Tolterodine | Although not studied directly, itraconazole is likely to increase the concentrations of these drugs. | Not recommended |
| Dutasteride, Imidafenacin, Sildenafil (erectile dysfunction) | Although not studied directly, itraconazole is likely to increase the concentrations of these drugs. | Use with caution |
| Oxybutynin 5 mg | Oxybutynin Cmax ↑ 2-fold, AUC ↑ 2-fold<br>N-desethyloxybutynin Cmax ↔, AUC ↔<br><br>Following transdermal administration:<br>Although not studied directly, itraconazole is likely to increase the concentrations of oxybutynin following transdermal | Use with caution |

| | | |
|---|---|---|
| | administration. | |
| **Miscellaneous Drugs and Other Substances** | | |
| Colchicine | Although not studied directly, itraconazole is likely to increase the concentrations of colchicine | Contraindicated in patients with renal or hepatic impairment. Not recommended in other patients. |
| Eliglustat | Although not directly studied, itraconazole is expected to increase the concentrations of eliglustat. | Contraindicated in CYP2D6 poor metabolisers (PM).<br>Contraindicated in CYP2D6 intermediate metabolisers (IMs) or extensive metabolisers (EMs) taking a strong or moderate CYP2D6 inibitor.<br><br>Use with caution in CYP2D6 IMs and EMs.<br>In CYP2D6 EMs with mild hepatic impairment, an eliglustat dose of 84 mg/day should be considered. |
| Cinacalcet | Although not studied directly, itraconazole is likely to increase the concentrations of cinacalcet. | Use with caution |

**4.6 Fertility, pregnancy and lactation**

*Pregnancy*
Sporanox Capsules 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 section 4.3).

In animal studies itraconazole has shown reproduction toxicity (see section 5.3).

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 causal 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 candidosis – did not show an increased risk for malformations as compared to control subjects not exposed to any known teratogens.

*Women of childbearing potential*

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

*Lactation*
A very small amount of itraconazole is excreted in human milk. The expected benefits of Sporanox therapy should be weighed against the risks of breast feeding. In case of doubt, the patient should not breast feed.

*Fertility*
In the rat, itraconazole had no effect on male or female fertility at doses which exhibited signs of general toxicity (see section 5.3). The effect in humans is unknown.

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

No studies on the effects on the ability to drive and use machines have been performed. When driving vehicles and operating machinery the possibility of adverse reactions such as dizziness, visual disturbances and hearing loss (see Section 4.8), which may occur in some instances, must be taken into account.

**4.8 Undesirable effects**

*Summary of the safety profile*
The most frequently reported adverse drug reactions (ADRs) with Sporanox Capsules treatment identified from clinical trials and/or from spontaneous reporting were headache, abdominal pain, and nausea. The most serious ADRs were serious allergic reactions, cardiac failure/congestive heart failure/pulmonary oedema, pancreatitis, serious hepatotoxicity (including some cases of fatal acute liver failure), and serious skin reactions. Refer to subsection *Tabulated list of adverse reactions* for the frequencies and for other observed ADRs. Refer to section 4.4.

*Tabulated list of adverse reactions*
The ADRs in the table below were derived from open-label and double-blind clinical trials with Sporanox Capsules involving 8499 patients in the treatment of dermatomycoses or onychomycosis, and from spontaneous reporting. The table below presents ADRs by System Organ Class. Within each System Organ Class, the ADRs are presented by incidence category, using the following convention:

Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (< 1/10,000).

| **Adverse Drug Reactions** | | |
|---|---|---|
| **Infections and infestations** | | |
| *Uncommon* | Sinusitis, Upper respiratory tract infection, Rhinitis | |
| **Blood and lymphatic system disorders** | | |
| *Rare* | | Leukopenia |
| **Immune system disorders** | | |
| *Uncommon* | | Hypersensitivity* |
| *Rare* | | Serum sickness, Angioneurotic oedema, Anaphylactic reaction |
| **Endocrine disorders** | | |
| *Not known* | | Pseudoaldosteronism |
| **Metabolism and nutrition disorders** | | |
| *Rare* | | Hypertriglyceridemia |
| **Nervous system disorders** | | |
| *Common* | | Headache |
| *Rare* | | Tremor, Paraesthesia, Hypoaesthesia, Dysgeusia |
| **Eye disorders** | | |
| *Rare* | | Visual disturbance (including diplopia and blurred vision) |
| **Ear and labyrinth disorder** | | |
| *Rare* | | Transient or permanent hearing loss*, Tinnitus |

| | | |
|---|---|---|
| **Cardiac disorders** | | |
| *Rare* | | Congestive heart failure*, Bradycardia |
| **Respiratory, thoracic and mediastinal disorders** | | |
| *Rare* | | Dyspnoea |
| **Gastrointestinal disorders** | | |
| *Common* | | Abdominal pain, Nausea |
| *Uncommon* | | Diarrhoea, Vomiting, Constipation, Dyspepsia, Flatulence |
| *Rare* | | Pancreatitis |
| **Hepato-biliary disorders** | | |
| *Uncommon* | | Hepatic function abnormal |
| *Rare* | | Serious hepatotoxicity (including some cases of fatal acute liver failure)*, Hyperbilirubinaemia |
| **Skin and subcutaneous tissue disorders** | | |
| *Uncommon* | | Urticaria, Rash, Pruritus |
| *Rare* | | Toxic epidermal necrolysis, Stevens-Johnson syndrome,Acute generalised exanthematous pustulosis, Erythema multiforme, Exfoliative dermatitis, Leukocytoclastic vasculitis, Alopecia, Photosensitivity |
| **Renal and urinary disorders** | | |
| *Rare* | | Pollakiuria |
| **Reproductive system and breast disorders** | | |
| *Uncommon* | | Menstrual disorders |
| *Rare* | | Erectile dysfunction |
| **General disorders and administration site conditions** | | |
| *Rare* | | Oedema |
| **Investigations** | | |
| *Rare* | | Blood creatine phosphokinase increased |

**see section 4.4*

*Description of selected adverse reactions*

The following is a list of ADRs associated with itraconazole that have been reported in clinical trials of Sporanox Oral Solution and Sporanox I.V., excluding the ADR term "Injection site inflammation", which is specific to the injection route of administration.

**Blood and lymphatic system disorders:** Granulocytopenia, Thrombocytopenia
**Immune system disorders:** Anaphylactoid reaction
**Metabolism and nutrition disorders:** Hyperglycaemia, Hyperkalaemia, Hypokalaemia, Hypomagnesaemia
**Psychiatric disorders:** Confusional state
**Nervous system disorders:** Peripheral neuropathy*, Dizziness, Somnolence
**Cardiac disorders:** Cardiac failure, Left ventricular failure, Tachycardia
**Vascular disorders:** Hypertension, Hypotension
**Respiratory, thoracic and mediastinal disorders:** Pulmonary oedema, Dysphonia, Cough
**Gastrointestinal disorders:** Gastrointestinal disorder
**Hepatobiliary disorders:** Hepatic failure*, Hepatitis, Jaundice
**Skin and subcutaneous tissue disorders:** Rash erythematous, Hyperhidrosis
**Musculoskeletal and connective tissue disorders:** Myalgia, Arthralgia

**Renal and urinary disorders:** Renal impairment, Urinary incontinence
**General disorders and administration site conditions:** Generalised oedema, Face oedema, Chest pain, Pyrexia, Pain, Fatigue, Chills
**Investigations:** Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Blood lactate dehydrogenase increased, Blood urea increased, Gamma-glutamyltransferase increased, Hepatic enzyme increased, Urine analysis abnormal

*Paediatric population*
The safety of Sporanox Capsules was evaluated in 165 paediatric patients aged 1 to 17 years who participated in 14 clinical trials (4 double-blind, placebo controlled trials; 9 open-label trials; and 1 trial had an open-label phase followed by a double-blind phase). These patients received at least one dose of Sporanox Capsules for the treatment of fungal infections and provided safety data.

Based on pooled safety data from these clinical trials, the commonly reported adverse drug reactions (ADRs) in paediatric patients were Headache (3.0%), Vomiting (3.0%), Abdominal pain (2.4%), Diarrhoea (2.4%), Hepatic function abnormal (1.2%), Hypotension (1.2%), Nausea (1.2%), and Urticaria (1.2%). In general, the nature of ADRs in paediatric patients is similar to that observed in adult subjects, but the incidence is higher in the paediatric patients.

**Reporting of suspected adverse reactions**
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:
HPRA Pharmacovigilance
Website: www.hpra.ie

**4.9 Overdose**

**Symptoms and signs**

In general, adverse events reported with overdose have been consistent with those reported for itraconazole use. (See section 4.8 *Undesirable effects*)

*Treatment*
In the event of an overdose, supportive measures should be employed. Itraconazole cannot be removed by haemodialysis.
No specific antidote is available.
It is advisable to contact a poison control centre to determine the latest recommendations for the management of an overdose.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic classification
Antimycotic for systemic use, triazole and tetrazole derivatives
ATC code: J02A C02

Mode of action
Itraconazole inhibits fungal 14α-demethylase, resulting in a depletion of ergosterol and disruption of membrane synthesis by fungi.

PK/PD relationship
The PK/PD relationship for itraconazole, and for triazoles in general, is poorly understood.

Mechanism(s) of resistance
Resistance of fungi to azoles appears to develop slowly and is often the result of several genetic mutations. Mechanisms that have been described are

- Over-expression of *ERG11*, the gene that encodes 14-alpha-demethylase (the target enzyme)
- Point mutations in *ERG11* that lead to decreased affinity of 14-alpha-demethylase for itraconazole

- Drug-transporter over-expression resulting in increased efflux of itraconazole from fungal cells (i.e., removal of itraconazole from its target)
- Cross-resistance. Cross-resistance amongst members of the azole class of drugs has been observed within *Candida* species though resistance to one member of the class does not necessarily confer resistance to other azoles.

Breakpoints

Breakpoints for itraconazole have been established in the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for antifungal agents, version 10.0, valid from 2020-02-04.

| **Candida and Aspergillus species** | **MIC breakpoint (mg/L)** | |
|---|---|---|
| | **≤ S (Susceptible)** | **> R (Resistant)** |
| *Candida albicans* | 0.06 | 0.06 |
| *Candida dubliniensis* | 0.06 | 0.06 |
| *Candida parapsilosis* | 0.125 | 0.125 |
| *Candida tropicalis* | 0.125 | 0.125 |
| *Aspergillus flavus*[1,2] | 1 | 1 |
| *Aspergillus fumigatus*[1,2] | 1 | 1 |
| *Aspergillus nidulans*[1,2] | 1 | 1 |
| *Aspergillus terreus*[1,2] | 1 | 1 |

There is currently insufficient evidence to set clinical breakpoints for *Candida glabrata*[3], *C. krusei*[3], *C. guilliermondi*[3], *Cryptococcus neoformans*, and Non-species related breakpoints for *Candida*.
There is currently insufficient evidence to set clinical breakpoints for *Aspergillus niger*[4,5] and Non species related breakpoints for *Aspergillus spp*[5].
[1] Monitoring of azole trough concentrations in patients treated for fungal infection is recommended.
[2]Area of technical uncertainty (ATU) is 2. Report as R with the following comment: "In some clinical situations (non-invasive infections forms) itraconazole can be used provided sufficient exposure is ensured".
[3] The epidemiological cut-off values (ECOFFs) for these species are in general higher than for *C. albicans*.
[4] The epidemiological cut-off values (ECOFFs) for these species are in general one two-fold dilution higher than for *A. fumigatus*.
[5] The MIC values for isolates of *A. niger* and *A. versicolor* are in general higher than those for *A. fumigatus*. Whether this translates into a poorer clinical response is unknown.
Interpretive breakpoints for itraconazole have not been established for *Candida* species and filamentous fungi, using Clinical and Laboratory Standards Institute (CLSI) methods, M60 Performance Standards Antifungal Susceptibility Testing of Yeasts. 2nd edition, 2020.

The prevalence of acquired resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

The *in vitro* susceptibility of fungi to itraconazole depends on the inoculum size, incubation temperature, growth phase of the fungi, and the culture medium used. For these reasons, the minimum inhibitory concentration of itraconazole may vary widely. Susceptibility in the table below is based on $MIC_{90}$ < 1 mg itraconazole/L. There is no correlation between *in vitro* susceptibility and clinical efficacy.

| **Commonly susceptible species** |
|---|
| Aspergillus spp.[2] |
| *Blastomyces dermatitidis*[1] |
| *Candida albicans* |
| *Candida parapsilosis* |
| *Candida dubliniensis* |
| Cladosporium spp. |
| *Coccidioides immitis*[1] |
| *Cryptococcus neoformans* |
| *Epidermophyton floccosum* |
| Fonsecaea spp.[1] |
| Geotrichum spp. |
| Histoplasma spp. |

| |
|---|
| Malassezia (formerly Pityrosporum*)* spp. |
| Microsporum spp. |
| *Paracoccidioides brasiliensis*[1] |
| *Talaromyces* (formerly *Penicillium*) *marneffei*[1] |
| *Pseudallescheria boydii* |
| *Sporothrix schenckii* |
| Trichophyton spp. |
| Trichosporon spp. |
| **Species for which acquired resistance may be a problem** |
| *Candida glabrata*[3] |
| *Candida krusei* |
| *Candida guillermondi* |
| **Inherently resistant organisms** |
| Absidia spp. |
| Fusarium spp. |
| Mucor spp. |
| Rhizomucor spp. |
| Rhizopus spp. |
| *Scedosporium proliferans* |
| Scopulariopsis spp. |

[1] These organisms may be encountered in patients who have returned from travel outside Europe.
[2] Itraconazole-resistant strains of *Aspergillus fumigatus* have been reported.
[3] Natural intermediate susceptibility.

**5.2 Pharmacokinetic properties**

*General pharmacokinetic characteristics:*
Peak plasma concentrations of itraconazole are reached within 2 to 5 hours following administration of the oral administration. As a consequence of non-linear pharmacokinetics, itraconazole accumulates in plasma during multiple dosing. Steady-state concentrations are generally reached within about 15 days, with $C_{max}$ values of 0.5 microgram/ml, 1.1 microgram/ml and 2.0 microgram/ml after oral administration of 100 mg once daily, 200 mg once daily and 200 mg b.i.d., respectively. The terminal half-life of itraconazole generally ranges from 16 to 28 hours after single dose and increases to 34 to 42 hours with repeated dosing. Once treatment is stopped, itraconazole plasma concentrations decrease to an almost undetectable concentration within 7 to 14 days, depending on the dose and duration of treatment. Itraconazole mean total plasma clearance following intravenous administration is 278 ml/min. Itraconazole clearance decreases at higher doses due to saturable hepatic metabolism.

*Absorption:*
Itraconazole is rapidly absorbed after oral administration. Peak plasma concentrations of the unchanged drug are reached within 2 to 5 hours following an oral capsule dose. The observed absolute oral bioavailability of itraconazole is about 55%. Oral bioavailability is maximal when the capsules are taken immediately after a full meal.

Absorption of itraconazole capsules is reduced in subjects with reduced gastric acidity, such as subjects taking medications known as gastric acid secretion suppressors (e.g., $H_2$-receptor antagonists, proton pump inhibitors) or subjects with achlorhydria caused by certain diseases (see section 4.4 and section 4.5). Absorption of itraconazole under fasted conditions in these subjects is increased when Sporanox Capsules are administered with an acidic beverage (such as a non-diet cola). When Sporanox Capsules were administered as a single 200 mg dose under fasted conditions with non-diet cola after ranitidine pretreatment, a $H_2$-receptor antagonist, itraconazole absorption was comparable to that observed when Sporanox Capsules were administered alone. (See section 4.5.)

Itraconazole exposure is lower with the capsule formulation than with the oral solution when the same dose of drug is given. (See section 4.4)

*Distribution:*
Most of the itraconazole in plasma is bound to protein (99.8%) with albumin being the main binding component (99.6% for the hydroxy-metabolite). It has also a marked affinity for lipids. Only 0.2% of the itraconazole in plasma is present as free drug. Itraconazole is distributed in a large apparent volume in the body (**>** 700 L), suggesting extensive distribution into tissues:

Concentrations in lung, kidney, liver, bone, stomach, spleen and muscle were found to be two to three times higher than corresponding concentrations in plasma, and the uptake into keratinous tissues, skin in particular, is up to four times higher. Concentrations in the cerebrospinal fluid are much lower than in plasma, but efficacy has been demonstrated against infections present in the cerebrospinal fluid.

*Metabolism:*
Itraconazole is extensively metabolised by the liver into a large number of metabolites. *In vitro* studies have shown that CYP3A4 is the major enzyme involved in the metabolism of itraconazole. The main metabolite is hydroxy-itraconazole which has *in vitro* antifungal activity comparable to itraconazole; trough plasma concentrations of this metabolite are about twice those of itraconazole.

*Excretion:*
Itraconazole is excreted mainly as inactive metabolites in urine (35%) and faeces (54%) within one week of an oral solution dose. Renal excretion of itraconazole and the active metabolite hydroxy-itraconazole account for less than 1% of an intravenous dose. Based on an oral radiolabelled dose, faecal excretion of unchanged drug ranges from 3 to 18% of the dose.

As re-distribution of itraconazole from keratinous tissues appears to be negligible, elimination of itraconazole from these tissues is related to epidermal regeneration. Contrary to plasma, the concentration in skin persists for 2 to 4 weeks after discontinuation of a 4-week treatment and in nail keratin – where itraconazole can be detected as early as 1 week after start of treatment – for at least six months after the end of a 3-month treatment period.

Special Populations
*Hepatic impairment*
Itraconazole is predominantly metabolised in the liver. A pharmacokinetic study was conducted in 6 healthy and 12 cirrhotic subjects who were administered a single 100-mg dose of itraconazole as a capsule. A statistically significant reduction in mean $C_{max}$ (47%) and a twofold increase in the elimination half-life (37 ± 17 hours vs. 16 ± 5 hours) of itraconazole were noted in cirrhotic subjects compared with healthy subjects. However, 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. (See sections 4.2 and 4.4.)

*Renal impairment*
Limited data are available on the use of oral itraconazole in patients with renal impairment.

A pharmacokinetic study using a single 200-mg dose of itraconazole (four 50-mg capsules) was conducted in three groups of patients with renal impairment (uremia: n=7; hemodialysis: n=7; and continuous ambulatory peritoneal dialysis: n=5). In uremic subjects with a mean creatinine clearance of 13 ml/min. × 1.73 $m^2$, the exposure, based on AUC, was slightly reduced compared with normal population parameters. This study did not demonstrate any significant effect of hemodialysis or continuous ambulatory peritoneal dialysis on the pharmacokinetics of itraconazole ($T_{max}$, $C_{max}$, and $AUC_{0-8h}$). Plasma concentration-versus-time profiles showed wide intersubject variation in all three groups.

After a single intravenous dose, the mean terminal half-lives of itraconazole in patients with mild (defined in this study as CrCl 50-79 ml/min), moderate (defined in this study as CrCl 20-49 ml/min), and severe renal impairment (defined in this study as CrCl <20 ml/min) were similar to that in healthy subjects, (range of means 42-49 hours vs 48 hours in renally impaired patients and healthy subjects, respectively.) Overall exposure to itraconazole, based on AUC, was decreased in patients with moderate and severe renal impairment by approximately 30% and 40%, respectively, as compared with subjects with normal renal function.

Data are not available in renally impaired patients during long-term use of itraconazole. Dialysis has no effect on the half-life or clearance of itraconazole or hydroxy-itraconazole. (See also section 4.2).

*Paediatrics*
Limited pharmacokinetic data are available on the use of itraconazole in the paediatric population. Clinical pharmacokinetic studies in children and adolescents aged between 5 months and 17 years were performed with itraconazole capsules, oral solution or intravenous formulation. Individual doses with the capsule and oral solution formulation ranged from 1.5 to 12.5 mg/kg/day, given as once-daily or twice-daily administration. The intravenous formulation was given either as a 2.5 mg/kg single infusion, or a 2.5 mg/kg infusion given once daily or twice daily. For the same daily dose, twice daily dosing compared to single daily dosing yielded peak and trough concentrations comparable to adult single daily dosing. No significant age dependence was observed for itraconazole AUC and total body clearance, while weak associations between age and

itraconazole distribution volume, $C_{max}$ and terminal elimination rate were noted. Itraconazole apparent clearance and distribution volume seemed to be related to weight.

**5.3 Preclinical safety data**

Itraconazole*:*
Itraconazole has been tested in a standard battery of non-clinical safety studies.

Itraconazole is not a primary carcinogen in rats up to 13 mg/kg/day (males) and 52 mg/kg/day (females), or in mice up to 80 mg/kg/day (1-fold of MRHD based on mg/m$^2$/day).

Nonclinical data on itraconazole revealed no indications for gene toxicity, primary carcinogenicity or impairment of fertility. At high doses, of 40 and 80 mg/kg/day in rats (1- and 2-fold of MRHD based on mg/m$^2$/day), effects were observed in the adrenal cortex, liver and the mononuclear phagocyte system but appear to have a low relevance for the proposed clinical use. A global lower bone mineral density was observed in juvenile dogs after chronic itraconazole administration, (no toxicity was observed up to 20 mg/kg/day (2-fold of MRHD based on mg/m$^2$/day), and in rats, a decreased bone plate activity, thinning of the zona compacta of the large bones, and an increased bone fragility was observed.

Reproductive toxicology
Itraconazole was found to cause a dose-related increase in maternal toxicity, embryotoxicity, and teratogenicity in rats from 40 mg/kg/day (1-fold of MRHD based on mg/m$^2$/day) and mice at from 80 mg/kg/day (1-fold of MRHD based on mg/m$^2$/day). In rats, the teratogenicity consisted of major skeletal defects; in mice, it consisted of encephaloceles and macroglossia. No teratogenic effects were found in rabbits up to 80 mg/kg/day dose (4-fold of MRHD based on mg/m$^2$/day).

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Sugar spheres (consisting of sucrose and maize starch)
Hypromellose 2910 5mPa.s
Macrogol 20 000

*Capsule shell:*
Titanium dioxide (E171)
Indigotin disulphonate sodium (E132)
Gelatin
Erythrosine (E127)

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

3 years.

**6.4 Special precautions for storage**

Do not store above 30°C.
Store in the original package.

**6.5 Nature and contents of container**

a) Tristar Blister-Plastic foil consisting of three layers.

Polyvinylchloride on the outside, low density polyethylene in the middle, and polyvinylidene chloride on the inside.
Aluminium foil (thickness 20µm) coated on the inner side with colourless heatseal lacquer PVC mixed polymers with acrylates 6 g/m$^2$.

b) Polyvinylchloride blister "genotherm" glass clear, thickness 250µm.

Aluminium foil (thickness 20µm) coated on the inner side with colourless heatseal lacquer PVC mixed polymers with acrylates 6 $g/m^2$.

Pack sizes: 4, 15 or 60 capsules.
Not all pack sizes may be marketed.

**6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product**

No special requirements.

**7 MARKETING AUTHORISATION HOLDER**

Janssen Sciences Ireland UC
Barnahely
Ringaskiddy
Cork
P43 FA46
Ireland

**8 MARKETING AUTHORISATION NUMBER**

PA22612/012/002

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

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Date of last renewal: 16 December 2006

**10 DATE OF REVISION OF THE TEXT**

March 2025