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 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

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):

Analgesics; Anaesthetics		
Ergot alkaloids (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	

	(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	

	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)**

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% 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%; Hydroxyitraconazole Cmax ↓ 35%, AUC ↓ 37%	Not recommended
Nevirapine PO 200 mg OD	Itraconazole Cmax ↓ 38%, AUC ↓ 62%	Not recommended
Cobicistat, Darunavir (boosted), Elvitegravir (ritonavir-boosted), Fosamprenavir (ritonavir-boosted), Ritonavir, 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), H_2-receptor anatagonists (eg, cimetidine, ranitidine), 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

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 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

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

Riociguat, Tadalafil (pulmonary hypertension)	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Not recommended
Bosentan, Diltiazem, Guanafacine, Other Dihydropyridines (eg, amlodipine, isradipine, nefidipine, nimodipine), 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 Dexamethasone PO 4.5 mg	Dexamethasone IV: Cmax ↔, AUC ↑ 3.3-fold 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 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 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 ↑; 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 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 Mild renal or hepatic impairment: Concomitant use should be avoided 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 Moderate or severe hepatic impairment: Contraindicated 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 N-desethyloxybutynin Cmax ↔, AUC ↔ Following transdermal administration: 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). Contraindicated in CYP2D6 intermediate metabolisers (IMs) or extensive metabolisers (EMs) taking a strong or moderate CYP2D6 inibitor. Use with caution in CYP2D6 IMs and EMs. 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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