Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Sporanox I.V. 10 mg/mL concentrate and solvent for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of the SPORANOX IV concentrate contains 10 mg itraconazole. One ampoule with 25 mL contains 250 mg itraconazole (itraconazole trihydrochloride salt formed in situ). Each mL of the admixed solution contains 3.33 mg itraconazole. One single dose of 200 mg itraconazole corresponds to 60 mL of the admixed solution.

Excipients with known effect

One single dose of the 60 mL admixed solution contains:
8.0 g of hydroxypropyl-β (cyclodextrin)
520 mg of propylene glycol (E1520)
161 mg of sodium

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate and solvent for solution for infusion.

SPORANOX IV 10 mg/mL concentrate and solvent (0.9% Sodium Chloride Injection) for solution for infusion is presented in a procedure pack consisting of:
(a) 25 mL of SPORANOX IV 10 mg/mL concentrate for infusion, a colourless solution presented in a glass ampoule.
(b) 50 mL of 0.9% Sodium Chloride Injection solvent for solution for infusion, a colourless solution presented in a polypropylene bag.
(c) Extension line with 2-way stopcock and in-line filter.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

SPORANOX IV is indicated for the treatment of histoplasmosis.

SPORANOX IV is indicated only in the following systemic fungal infections when first-line systemic anti-fungal therapy is inappropriate or has proved ineffective. (This may be due to underlying pathology, insensitivity of the pathogen or drug toxicity).
SPORANOX IV is only indicated for the treatment of aspergillosis, candidosis and cryptococcosis (including cryptococcal meningitis): in immunocompromised patients with cryptococcosis and in all patients with cryptococcosis of the central nervous system.

Consideration should be given to national and/or local guidance regarding the appropriate use of antifungal agents.

4.2 Posology and method of administration

This product is supplied with an extension line with a 2-way stopcock and 0.2 µm in-line filter. The dedicated extension line including the in-line filter must be used to ensure the correct administration of the product.

SPORANOX IV is given on the first two days in a loading dose twice daily, followed by once daily dosing.

Day 1 and 2 of the treatment: 1-hour infusion of 200 mg (60 ml of the admixed solution) SPORANOX IV twice daily (see section 6.6).

From day 3 on: one 1-hour infusion of 200 mg (60 ml of the admixed solution) SPORANOX IV each day. Safety for periods longer than 14 days has not been established.

Paediatric population
The safety and efficacy of SPORANOX IV in children has not been established. Currently available data are described in section 4.4 and 5.2 but no recommendation on a posology can be made.
The use of SPORANOX IV in paediatric patients is not recommended unless it is determined that the potential benefit outweighs the potential risks (see section 4.4).

Use in elderly
Since clinical data of the use of SPORANOX IV in elderly patients are limited, it is advised to use SPORANOX IV in these patients only if 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).

Use in patients with renal impairment
Limited data are available on the use of intravenous itraconazole in patients with renal impairment.
Hydroxypropyl-β-cyclodextrin, a required component of Sporanox intravenous formulation, is eliminated through glomerular filtration. Therefore, in patients with severe renal impairment defined as creatinine clearance below 30 ml/min the use of SPORANOX IV is contraindicated (see section 4.3).

In patients with mild and moderate renal impairment, SPORANOX IV should be used with caution. Serum creatinine levels should be closely monitored and, if renal toxicity is suspected, consideration should be given to changing to the oral capsule formulation (see sections 4.4 and 5.2).

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

Method of administration
Precautions to be taken before handling or administering the medicinal product.
For instructions on handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications

SPORANOX IV is contraindicated in patients with a known hypersensitivity to itraconazole or to any of the excipients.

SPORANOX IV cannot be used when administration of Sodium Chloride Injection is contraindicated.

The excipient hydroxypropyl-β-cyclodextrin is eliminated through glomerular filtration. Therefore, SPORANOX IV is contraindicated in patients with severe renal impairment defined as creatinine clearance below 30 ml/min (see sections 4.4 and 5.2).

SPORANOX IV must not be used during pregnancy for non life-threatening indications (see section 4.6).

- Co-administration of a number of CYP3A4 substrates is contraindicated with SPORANOX IV (see sections 4.4 and 4.5). These include:

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			
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	Dronedarone	Nisoldipine	
Bepridil	Eplerenone	Quinidine	
Disopyramide	Ivabradine	Ranolazine	
Dofetilide	Lercanidipine	Sildenafil (pulmonary hypertension)	
Gastrointestinal Drugs, including Antidiarrheals, Intestinal Anti-inflammatory/Anti-infective Agents; Antiemetics and Antinauseants; Drugs for Constipation; Drugs for Functional Gastrointestinal Disorders			
Cisapride	Domperidone	Naloxegol	
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).		

4.4 Special warnings and precautions for use

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

Cardiac effects
In a healthy volunteer study with SPORANOX IV, a transient asymptomatic decrease of the left ventricular ejection fraction was observed; this resolved before the next infusion. A similar investigation was not performed in the target patient population.

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

SPORANOX should not be used in patients with congestive heart failure or with a history of congestive heart failure unless the benefit clearly outweighs the risk.

Physicians should carefully review the risks and benefits of SPORANOX therapy for patients with known 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.
Caution should be exercised when co-administering itraconazole and calcium channel blockers (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. Some of these cases involved patients with no pre-existing liver disease. Some of these cases have been observed within the first month of treatment, including some within the first week. Liver function monitoring should be considered in patients receiving SPORANOX treatment. Patients should be instructed to promptly report to their physician signs and symptoms suggestive of hepatitis such as anorexia, nausea, vomiting, fatigue, abdominal pain or dark urine. In these patients treatment should be stopped immediately and liver function testing should be conducted. Most cases of serious hepatotoxicity 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.

Paediatric population
Clinical data on the use of SPORANOX IV in paediatric patients are limited. The use of SPORANOX IV in paediatric patients is not recommended unless it is determined that the potential benefit outweighs the potential risks.

Use in elderly
Since clinical data of the use of SPORANOX IV in elderly patients are limited, it is advised to use SPORANOX IV in these patients only if 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).

Hepatic impairment
Studies have not been conducted with intravenous itraconazole in patients with hepatic impairment. Limited data are available on the use of oral itraconazole in patients with hepatic impairment. Caution should be exercised when the drug is administered to 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 sections 4.2 and 5.2).

Renal impairment
Hydroxypropyl-β-cyclodextrin, when administered intravenously, is eliminated through glomerular filtration. Therefore, in patients with severe renal impairment defined as creatinine clearance below 30 mL/min SPORANOX IV is contraindicated (see sections 4.3 and 5.2).
SPORANOX IV should be used with caution in patients with a lesser degree of renal failure. In patients with mild or moderate renal impairment, serum creatinine levels should be closely monitored and, if renal toxicity is suspected, consideration should be given to changing to the oral capsule formulation (see section 4.4).

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

Neuropathy
If neuropathy occurs that may be attributable to SPORANOX IV, the treatment should be discontinued.

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.

Interaction potential
Co-administration of specific drugs with itraconazole may result in changes in efficacy or safety of itraconazole and/or the co-administered drug. For example, the use of itraconazole with CYP3A4 inducing agents may lead to sub-therapeutic plasma concentrations of itraconazole and thus treatment failure. In addition, the use of itraconazole with some substrates of CYP3A4 can lead to increases in plasma concentrations of these drugs and to serious and/or potentially life threatening adverse events, such as QT prolongation and ventricular tachyarrhythmias including occurrences of torsade de pointes, a potentially fatal arrhythmia. The prescriber should refer to the co-administered medicinal product information for further information regarding serious or life-threatening adverse events that could occur in cases of increased plasma concentrations for that medication. For recommendations concerning the co-administration of medicinal products which are contraindicated, not recommended or recommended for use with caution in combination with itraconazole please refer to sections 4.3 and 4.5.

Excipients of SPORANOX IV
SPORANOX IV admixed solution contains 161 mg sodium per 60 mL, equivalent to 8% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

The SPORANOX IV admixed solution contains 8.0 g cyclodextrin per 60 mL. There is insufficient information on the effects of cyclodextrin in children <2 years old. Therefore, a case by case judgement should be made regarding the risk/benefit for the patient with SPORANOX IV (see section 4.2).

4.5 Interaction with other medicinal products and other forms of interactions

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. Please refer to the prescribing information of the interacting drug for more information.

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 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 co-administration, 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

Medicinal products Per Orale [PO] Single Dose unless otherwise stated) within class	**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)**
Anti-bacterials for Systemic Use; Anti-mycobacterials		
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 C_{max} ↓ 71%, AUC ↓ 74%	Not recommended
Ciprofloxacin PO 500 mg BID	Itraconazole C_{max} ↑ 53%, AUC ↑ 82%	Use with caution
Erythromycin 1 g	Itraconazole C_{max} ↑ 44%, AUC ↑ 36%	Use with caution
Clarithromycin PO 500 mg BID	Itraconazole C_{max} ↑ 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 C_{max} ↓ 83%, AUC ↓ 93% Hydroxyitraconazole C_{max} ↓ 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 C_{max} ↓ 37%, AUC ↓ 39%; Hydroxyitraconazole C_{max} ↓ 35%, AUC ↓ 37%	Not recommended
Nevirapine PO 200 mg OD	Itraconazole C_{max} ↓ 38%, AUC ↓ 62%	Not recommended
Cobicistat, Darunavir (boosted),	Although not studied directly, these drugs are expected to increase the concentrations of itraconazole.	Use with caution

Elvitegravir (ritonavir-boosted), Fosamprenavir (ritonavir-boosted), Ritonavir, Saquinavir (ritonavir-boosted)		
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 antagonists (e.g., cimetidine, ranitidine), Proton pump inhibitors (e.g., lansoprazole, omeprazole, rabeprazole)	Itraconazole C_{max} ↓, 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

Medicinal products (PO Single Dose unless otherwise stated) within class	**Expected/Potential effect on drug levels**	**Clinical comment**
	(↑ = increase; ↔ = no change; ↓ = decrease)	**(see above for additional info and also sections 4.3 and 4.4)**
Analgesics; Anaesthetics		
Ergot alkaloids (e.g., dihydroergotamine, ergometrine, ergotamine, methylergometrine)	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Contraindicated
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: C_{max} ↑ 45%, AUC ↑ 2.4-fold	Use with caution
Oxycodone IV 0.1 mg/kg	Oxycodone IV: AUC ↑ 51%	Use with caution
Anti-bacterials for Systemic Use; Anti-mycobacterials; 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 delamanid.	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 C_{max} ↓ 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 C_{max} ↔, 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 C_{max} ↑ 2.5-fold, AUC ↑ 6.2-fold Carebastine C_{max} ↔, AUC ↑ 3.1-fold	Not recommended
Bilastine, Rupatadine	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
Axitinib, Bosutinib,	Although not studied	Not recommended

Cabazitaxel, Cabozantinib, Ceritinib, Crizotinib, Dabrafenib, Dasatinib, Docetaxel, Everolimus, Ibrutinib, Lapatinib, Nilotinib, Pazopanib, Regorafenib, Sunitinib, Temsirolimus, Trabectedin, Trastuzumab emtansine, Vinca alkaloids (e.g., vinflunine, vinorelbine)	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)	
Cobimetinib 10 mg	Cobimetinib C_{max} ↑ 3.2-fold, AUC ↑ 6.7-fold	Not recommended
Olaparib 100 mg	Olaparib C_{max} ↑ 40%, AUC ↑ 2.7-fold	Not recommended
Alitretinoin (oral), Bortezomib, Brentuximab vedotin, Erlotinib, Idelalisib, Imatinib, Nintedanib, Panobinostat, Ponatinib, Ruxolitinib, Sonidegib,	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs	Use with caution
Busulfan 1 mg/kg Q6h	Busulfan C_{max} ↑, AUC ↑	Use with caution
Gefitinib 250 mg	Gefitinib 250 mg C_{max} ↑, AUC ↑ 78%	Use with caution
Antithrombotic Agents		
Dabigatran, Ticagrelor	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Contraindicated
Apixaban, Rivaroxaban, Vorapaxar	Although not studied directly, itraconazole is likely to increase the concentrations of these drugs.	Not recommended
Cilostazol, Coumarins (e.g., 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, Simeprevir, Tenofovir alafenamide 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 C_{max} ↔, 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, 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 C_{max} ↑ 5.8-fold, AUC ↑ 6.5-fold	Contraindicated
Quinidine 100 mg	Quinidine C_{max} ↑ 59%, AUC ↑ 2.4-fold	Contraindicated
Felodipine 5 mg	Felodipine C_{max} ↑ 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, Guanfacine, Other Dihydropyridines (e.g., amlodipine, isradipine, nifedipine, nimodipine), Verapamil	Although not studied directly, itraconazole is likely to increase the concentrations of bosentan.	Use with caution
Digoxin 0.5 mg	Digoxin C_{max} ↑ 34%, AUC ↑ 68%	Use with caution
Nadolol 30 mg	Nadolol C_{max} ↑ 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 C_{max} ↑ 65%, AUC ↑ 4.2-fold; Budesonide (other formulations) concentration ↑	Use with caution
Dexamethasone IV 5 mg Dexamethasone PO 4.5 mg	Dexamethasone IV: C_{max} ↔, AUC ↑ 3.3-fold Dexamethasone PO: C_{max} ↑ 69%, AUC ↑ 3.7-fold	Use with caution
Fluticasone INH 1 mg BID	Fluticasone INH concentration ↑	Use with caution
Methylprednisolone 16 mg	Methylprednisolone PO C_{max} ↑ 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	Use with caution

	concentrations of nasally-administered fluticasone.	
Drugs Used in Diabetes		
Repaglinide 0.25 mg	Repaglinide C_{max} ↑ 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 Anti-inflammatory/Anti-infective 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 C_{max} ↑ 2.7-fold, AUC ↑ 3.2-fold	Contraindicated
Aprepitant, Loperamide, Netupitant	Although not studied directly, itraconazole is likely to increase the concentrations of aprepitant.	Use with caution
Immunosuppressants		
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 cyclosporine.	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 C_{max} ↑ 14.5->20-fold, AUC ↑ > 14.8 - >20-fold Lovastatin acid C_{max} ↑ 11.5-13-fold, AUC ↑ 15.4-20-fold	Contraindicated
Simvastatin 40 mg	Simvastatin acid C_{max} ↑ 17-fold, AUC ↑ 19-fold	Contraindicated
Atorvastatin	Atorvastatin acid: C_{max} ↔ to ↑2.5-fold, AUC ↑ 40% to 3-fold	Not recommended
Psychoanaleptics; Psycholeptics (e.g., 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) C_{max} ↑ 2.5 to 3.4-fold, AUC ↑ 6.6 to 10.8-fold	Contraindicated
Triazolam 0.25 mg	Triazolam C_{max} ↑, AUC ↑	Contraindicated
Alprazolam 0.8 mg	Alprazolam C_{max} ↔, AUC ↑ 2.8-fold	Use with caution
Aripiprazole 3 mg	Aripiprazole C_{max} ↑ 19%, AUC ↑ 48%	Use with caution
Brotizolam 0.5 mg	Brotizolam C_{max} ↔, AUC ↑ 2.6-fold	Use with caution
Buspirone 10 mg	Buspirone C_{max} ↑ 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 C_{max} ↑ 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 C_{max} ↑ 3.6-fold, AUC ↑ 4.3-fold Lumacaftor C_{max} ↔, 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 Gynaecologicals		
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	Contraindicated

	drugs.	
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 function: 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 C_{max} ↑ 2-fold, AUC ↑ 2-fold N-desethyloxybutynin C_{max} ↔, AUC ↔ Following transdermal administration: Although not studied directly, itraconazole is likely to increase the concentrations of oxybutynin following transdermal administration.	Use with caution
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	Contraindicated in CYP2D6 poor metabolisers (PM).

	concentrations of eliglustat.	Contraindicated in CYP2D6 intermediate metabolisers (IMs) or extensive metabolisers (EMs) taking a strong or moderate CYP2D6 inhibitor. 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 IV 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 shows reproduction toxicity (see section 5.3).
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. Itraconazole has been shown to cross the placenta in a rat model.

Women of childbearing potential
Women of childbearing potential receiving SPORANOX IV should use contraceptive precautions. Effective contraception should be continued until the next menstrual period following the end of SPORANOX IV therapy.

Breast-feeding
A very small amount of itraconazole is excreted in human milk and must not be administered to lactating women.
Breast-feeding is to be discontinued prior to taking itraconazole.

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 Oral Solution treatment identified from clinical trials and/or from spontaneous reporting were dizziness, headache, dysgeusia, dyspnoea, cough, abdominal pain, diarrhoea, vomiting, nausea, dyspepsia, rash, and pyrexia. 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 (Special warnings and precautions for use) for additional information on other serious effects.

Tabulated list of adverse reactions
The ADRs in the table below were derived from double-blind and open-label clinical trials with SPORANOX Oral Solution involving 889 patients for the treatment of oropharyngeal and oesophageal candidiasis, and from spontaneous reporting.

The table below presents ADRs by System Organ Class. Within each System Organ Class, the ADRs are presented by incidence, using the following convention:

Very common (³ 1/10); Common (³ 1/100 to < 1/10); Uncommon (³ 1/1 000 to < 1/100); Rare (³ 1/10 000 to < 1/1 000); Very rare (< 1/10 000), Not known (cannot be estimated from the available data).

Adverse Drug Reactions	
Blood and lymphatic system disorders	
Uncommon	Leukopenia, Thrombocytopenia
Immune system disorders	
Uncommon	Hypersensitivity*
Not Known	Serum sickness, Angioneurotic oedema, Anaphylactic reaction
Metabolism and nutrition disorders	
Uncommon	Hypokalaemia
Not Known	Hypertriglyceridaemia
Nervous system disorders	
Common	Dizziness, Headache, Dysgeusia
Uncommon	Peripheral neuropathy*, Paraesthesia, Hypoaesthesia
Eye disorders	
Uncommon	Visual disturbances (including diplopia and blurred vision)
Ear and labyrinth disorders	
Uncommon	Tinnitus
Not Known	Transient or permanent hearing loss*
Cardiac disorders	
Uncommon	Cardiac failure
Not Known	Congestive heart failure*
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea, Cough
Gastrointestinal disorders	
Common	Abdominal pain, Diarrhoea, Vomiting, Nausea, Dyspepsia
Uncommon	Constipation
Not Known	Pancreatitis
Hepatobiliary disorders	
Uncommon	Hepatic failure*, Hyperbilirubinaemia
Not Known	Serious hepatotoxicity (including some cases of fatal acute liver failure)*
Skin and subcutaneous tissue disorders	
Common	Rash
Uncommon	Urticaria, Pruritus
Not Known	Toxic epidermal necrolysis, Stevens-Johnson syndrome, Acute generalised exanthematous pustulosis, Erythema multiforme, Exfoliative dermatitis, Leukocytoclastic vasculitis, Alopecia, Photosensitivity
Musculoskeletal and connective tissue disorders	

Uncommon	Myalgia, Arthralgia
Reproductive system and breast disorders	
Uncommon	Menstrual disorders
General disorders and administration site conditions	
Common	Pyrexia
Uncommon	Oedema
Investigations	
Not Known	Blood creatine phosphokinase increased

***** see section 4.4.

Description of selected adverse reactions
The following is a list of additional ADRs associated with itraconazole that have been reported in clinical trials of SPORANOX Capsules and SPORANOX IV, excluding the ADR term "Injection site inflammation", which is specific to the injection route of administration.

Infections and infestations: Sinusitis, Upper respiratory tract infection, Rhinitis
Blood and lymphatic system disorders: Granulocytopenia
Immune system disorders: Anaphylactoid reaction
Metabolism and nutrition disorders: Hyperglycaemia, Hyperkalaemia, Hypomagnesaemia
Psychiatric disorders: Confusional state
Nervous system disorders: Somnolence, Tremor
Cardiac disorders: Left ventricular failure, Tachycardia
Vascular disorders: Hypertension, Hypotension
Respiratory, thoracic and mediastinal disorders: Pulmonary oedema, Dysphonia
Gastrointestinal disorders: Gastrointestinal disorder, Flatulence
Hepatobiliary disorders: Hepatitis, Jaundice, Hepatic function abnormal
Skin and subcutaneous tissue disorders: Rash erythematous, Hyperhidrosis
Renal and urinary disorders: Renal impairment, Pollakiuria, Urinary incontinence
Reproductive system and breast disorders: Erectile dysfunction
General disorders and administration site conditions: Generalised oedema, Face oedema, Chest pain, 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 oral solution was evaluated in 250 paediatric patients aged 6 months to 14 years who participated in five open-label clinical trials. These patients received at least one dose of SPORANOX oral solution for prophylaxis of fungal infections or for treatment of oral thrush or systemic fungal infections and provided safety data.
Based on pooled safety data from these clinical trials, the very common reported ADRs in paediatric patients were Vomiting (36.0%), Pyrexia (30.8%), Diarrhoea (28.4%), Mucosal inflammation (23.2%), Rash (22.8%), Abdominal pain (17.2%), Nausea (15.6%), Hypertension (14.0%), and Cough (11.2%). 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
In general, adverse events reported with overdose have been consistent with adverse drug reactions already listed in this SmPC for itraconazole (see section 4.8).

Treatment
In the event of an overdose, supportive measures should be employed. Itraconazole cannot be removed by haemodialysis. No specific antidote is available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotic for systemic use, triazole derivative.
ATC code: J02A C02

Mechanism of action
Itraconazole inhibits fungal 14-alpha-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 and is complicated by limited understanding of antifungal pharmacokinetics.

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 not yet been established for fungi using EUCAST methods.

Using CLSI methods, breakpoints for itraconazole have only been established for *Candida* species from superficial mycotic infections. The CLSI breakpoints are: susceptible £0.125 mg/L and resistant ≥1 mg/L.

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
Aspergillusspp.[2]
Blastomyces dermatitidis[1]
Candida albicans
Candida parapsilosis
Cladosporium spp.
Coccidioides immitis[1]
Cryptococcus neoformans
Epidermophyton floccosum

Fonsecaea spp.[1]
Geotrichumspp.
Histoplasmaspp.
Malassezia(formerly Pityrosporum) spp.
Microsporum spp.
Paracoccidioides brasiliensis[1]
Penicillium marneffei[1]
Pseudallescheria boydii
Sporothrix schenckii
Trichophytonspp.
Trichosporonspp.
Species for which acquired resistance may be a problem
Candida glabrata[3]
Candida krusei
Candida tropicalis[3]
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.

Paediatric Population
The tolerability and safety of itraconazole oral solution was studied in the prophylaxis of fungal infections in 103 neutropenic paediatric patients aged 0 to14 years (median 5 years) in an open-label uncontrolled phase III clinical study. Most patients (78%) were undergoing allogenic bone marrow transplantation for haematological malignancies. All patients received 5 mg/kg/day of itraconazole oral solution as a single or divided dose. Due to the design of the study, no formal conclusion with regard to efficacy could be derived. The most common adverse events considered definitely for possibly related to itraconazole were vomiting, abnormal liver function, and abdominal pain.

5.2 Pharmacokinetic properties

Itraconazole
General pharmacokinetic characteristics
Peak plasma concentrations are reached within 2.5 hours following administration of the oral solution. 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} and AUC values 4 to 7-fold higher than those seen after a single dose. Steady-state C_{max} values of about 2 µg/mL are reached after oral administration of 200 mg once daily. 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 administration of the Oral Solution. Peak plasma concentrations of itraconazole are reached within 2.5 hours following administration of the Oral Solution under fasting conditions. The observed absolute bioavailability of itraconazole under fed conditions is about 55% and increases by 30% when the Oral Solution is taken in fasting conditions. Itraconazole exposure is greater with the Oral Solution than with the Capsule formulation 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, 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.

Elimination
Itraconazole is excreted mainly as inactive metabolites in urine (35%) and in 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 significantly reduction in average C_{max} (47%) and a two-fold increase in the elimination half-life (37 ± 17 versus 16 ± 5 hours) of itraconazole were noted in cirrhotic subjectscompared 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 (uraemia: n=7; haemodialysis: 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 haemodialysis 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 sections 4.2 and 4.4).

Paediatric Population
Two pharmacokinetic studies have been conducted in neutropenic children aged 6 months to 14 years in which itraconazole oral solution was administered 5 mg/kg once or twice daily. The exposure to itraconazole was somewhat higher in older children (6 to 14 years) compared to younger children. In all children, effective plasma concentrations of itraconazole were reached within 3 to 5 days after initiation of treatment and maintained throughout treatment.

Hydroxypropyl- β -Cyclodextrin
The oral bioavailability of hydroxypropyl-β-cyclodextrin given as a solubilizer of itraconazole in oral solution is on average lower than 0.5% and is similar to that of hydroxypropyl-β-cyclodextrin alone. This low oral bioavailability of hydroxypropyl-β-cyclodextrin is not modified by the presence of food and is similar after single and repeated administrations.

5.3 Preclinical safety data

Itraconazole
Acute oral toxicity studies with itraconazole in mice, rats, guinea-pigs and dogs indicate a wide safety margin (3- to 16-fold of Maximum Recommended Human Dose [MRHD] based on mg/m^2).

Itraconazole is not a primary carcinogen in rats or mice up to 20 and 80 mg/kg, respectively.

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), 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. Itraconazole was found to cause a dose-related increase in maternal toxicity, embryotoxicity and teratogenicity in rats and mice at high doses. A global lower bone mineral density was observed in juvenile dogs after chronic itraconazole administration, (no toxicity was observed up to 20 mg/kg (2-fold of MRHD based on mg/m^2), and in rats, a decreased bone plate activity, thinning of the zona compacta of the large bones, and an increased bone fragility was observed.

Hydroxypropyl-β-cyclodextrin
Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity, and toxicity to reproduction and development. In a rat carcinogenicity study (at 80 mg/kg dose (2-fold of MRHD based on mg/m^2)), hydroxypropyl-β-cyclodextrin produced adenocarcinomas in the large intestine and exocrine pancreatic adenocarcinomas. These findings were not observed in a similar mouse carcinogenicity study. The clinical relevance of the large intestine adenocarcinomas is low and the mechanism of exocrine pancreatic adenocarcinomas induction not considered relevant to humans.

Reproductive toxicology
Itraconazole was found to cause a dose-related increase in maternal toxicity, embryotoxicity, and teratogenicity in rats and mice at 40, 80 and 160 mg/kg (0.5-, 1- and 4-fold of MRHD based on mg/m^2). 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 dose (4-fold of MRHD based on mg/m^2).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropyl-β (cyclodextrin)
Propylene glycol (E1520)
Hydrochloric acid concentrated
Sodium hydroxide (for pH adjustment)
Water for injections.

0.9% Sodium Chloride Injection

Sodium Chloride, Water for Injections

6.2 Incompatibilities

Itraconazole has the potential to precipitate when SPORANOX IV is diluted in solutions other than the 50 mL 0.9% sodium chloride injection supplied.

6.3 Shelf life

Sporanox I.V. (as packaged): 2 years

0.9% Sodium Chloride Injection: 3 years

Admixed Solution: 24 hours

6.4 Special precautions for storage

SPORANOX IV:
Do not store above 25°C. Store in the original container.

0.9% Sodium Chloride Injection:
Do not store above 25°C. Do not freeze.

Admixed solution:
Protect from direct sunlight.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless the dilution of the admixture has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

SPORANOX IV: 25 mL siliconised type I colourless glass ampoule with 25 mL containing 250 mg itraconazole.

0.9% Sodium Chloride: Flexible polypropylene infusion bag, equipped with a flexible inlet and outlet port, and containing 52 to 56 mL of 0.9% Sodium Chloride Injection.

Extension line: Polyvinylchloride tubing with 2-way stopcock and in-line filter.

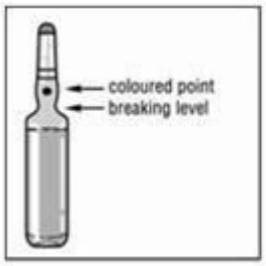
6.6 Special precautions for disposal and other handling

Itraconazole has the potential to precipitate when 25 mL of SPORANOX IV concentrate are diluted in solutions other than 50 mL 0.9% Sodium Chloride Injection. The full amount of 25 mL of SPORANOX IV concentrate from the ampoule must be diluted into the Sodium Chloride Infusion Bag, which is intended to be used exclusively in combination with SPORANOX IV concentrate. Only the components of unit sales pack (e.g., saline bag, an extension line with a 2-way stopcock and 0.2 µm in-line filter, and SPORANOX IV ampoule) must be used. SPORANOX IV cannot be co-administered with other drugs or fluids (see section 6.2).
Prior to starting the admixing process, the SPORANOX IV concentrate, and the solvent (Sodium Chloride) must be visually inspected. Only clear solutions free from foreign particles should be used for the preparation of the admixture.

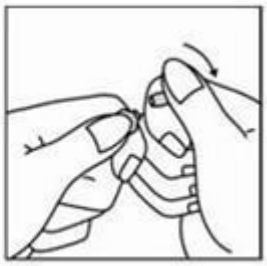
The full amount of SPORANOX IV concentrate must be injected into the Sodium Chloride bag in a slow single action (up to 60 seconds). During the admixing process opalescence may appear but will clear after gently mixing. When visually inspecting the bag after admixing and prior to administration, product intrinsic aggregates may be observed. These aggregates do not affect the quality of the product. The dedicated extension line with the 0.2 µm in-line filter must be used to prevent aggregates from reaching the recipient's circulation.

SPORANOX IV should be prepared for administration according to the following instructions:

Opening ampoule:
Break the ampoule as shown







Opening sodium chloride bag:

Tear outer wrap at notch and remove infusion bag.

Flush procedure before the infusion
Before the infusion, the catheter should be flushed to avoid compatibility problems between residual amounts of other drugs and itraconazole.

- Fill the extension line provided with the kit containing the 0.2 mm in-line filter with sterile 0.9% sodium chloride solution and connect directly to the indwelling intravenous catheter.

- Flush the extension line provided with the kit and indwelling intravenous catheter with sterile 0.9% sodium chloride solution.

Admixing SPORANOX IV Concentrate and 0.9% Sodium Chloride Injection

- Each component must be at room temperature.
- Admix only in the **infusion bag** provided. Using aseptic technique and an additive delivery needle of appropriate length (not supplied with the kit), draw up all concentrate from the ampoule and subsequently add the SPORANOX IV concentrate to the infusion bag by puncturing the resealable additive port and inject.
- Add the entire volume (25 mL) of SPORANOX IV concentrate to the bag in a slow single action (up to 60 seconds). During the admixing process some opalescence may appear. This is a normal phenomenon for the product and will disappear after the full content of the 25 mL of SPORANOX IV has been diluted into the Sodium Chloride infusion bag and after gentle mixing. Withdraw needle after injecting the SPORANOX IV concentrate into the bag.
- Gently mix the content of the bag once the SPORANOX IV concentrate is completely transferred to the bag. The admixture will become clear but product intrinsic aggregates (described as fibrous to flake-like, non-crystalline, white particles) may be observed. These aggregates do not affect the quality of the product.
- The admixture should be used immediately and should be protected from direct sunlight. During administration, exposure to normal room light is acceptable (see sections 6.3 and 6.4).

Infusion

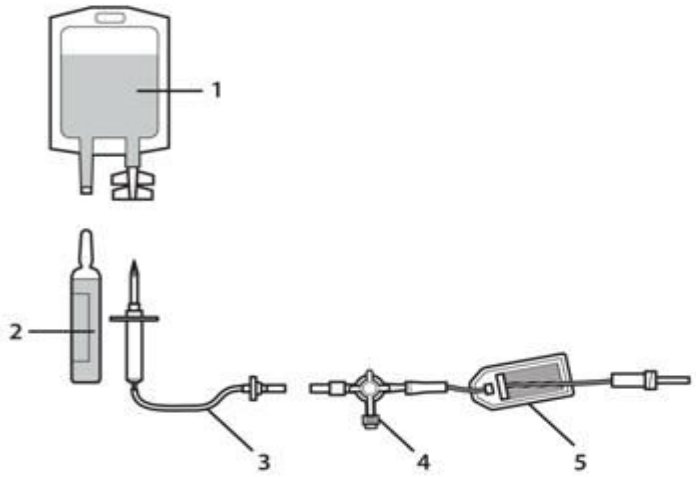
- The admixed solution is intended for single-dose infusion only. No administration should occur if the solution is a milky white colour that does not disappear after gentle mixing, or contains foreign matter, or if the infusion bag is damaged. The infusion bag should now contain 25 mL SPORANOX IV concentrate and 50 mL 0.9% Sodium Chloride Injection.
- Note: An infusion line with drip chamber is not supplied with the kit. Close the flow control device (e.g., rotary clamp) on the infusion line. Remove the breakable part of the outlet port. Using aseptic technique, push the pin of the infusion line in the flexible port of the infusion bag.
- Slowly release the flow control device and fill the drip chamber to half full by squeezing (pumping) it.
- Open the flow control device until all air has been expelled from the infusion line.
- Connect the infusion line to the two-way stopcock of the extension line.
- The SPORANOX infusion is now ready for intravenous infusion to the patient.
- Adjust the infusion rate to 1 mL/min (approximately 25 drops/min) by means of a flow control device (e.g. rotary clamp or infusion pump).
- Administer **60 mL** of the solution to the patient over approximately one hour.
- Stop the infusion when 60 mL is administered.
- Note that 200 mg of itraconazole has been administered.
- Flush the line as per the flushing procedure described below.

Flush procedure after the infusion

After the infusion a complete flush procedure must be started to clean the catheter. This is done to avoid compatibility problems between residual amounts of itraconazole and other drugs which later could be administered through the same catheter.

- Flush the extension line and catheter with 15 – 20 mL of sterile 0.9% sodium chloride solution at the level of the 2-way stop cock, just before the 0.2 mm in-line filter.

- Perform the flush in a continuous run of 30 seconds to 15 minutes.
- After flushing, disconnect and discard the bag,the infusion line and the extension line.
- Do not re-sterilise or re-use the SPORANOX infusion set.



- To avoid precipitation, other medication should only be administered via the catheter after flushing.
- If using a multi-lumen catheter, other medication may not be administered until the Sporanox I.V. infusion has been completed and the catheter has been flushed.

1. Sodium chloride infusion bag
2. Sporanox IV ampoule
3. Infusion line with drip chamber (not provided)
4. & 5. Extension line with 2-way stopcock and in-line filter

7 MARKETING AUTHORISATION HOLDER

Janssen Sciences Ireland UC
Barnahely
Ringaskiddy
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P43 FA46
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8 MARKETING AUTHORISATION NUMBER

PA22612/012/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 August 2003

Date of last renewal: 21 July 2009

10 DATE OF REVISION OF THE TEXT

May 2021