SPORANOX®

itraconazole

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

SPORANOX® itraconazole 10 mg/mL oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml SPORANOX Oral Solution contains 10 mg itraconazole.

Excipient(s) with known effect:

Sorbitol (7.92 g in 40 mL of solution). Products containing sorbitol may have a laxative effect or cause diarrhoea.

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

3. PHARMACEUTICAL FORM

Oral solution.

SPORANOX Oral Solution is clear, yellow to slightly amber solution with an odour of cherry.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SPORANOX oral solution is indicated for the:

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

4.2 Dose and method of administration

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

Treatment of oral candidiasis

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

Treatment of oesophageal candidiasis

100 mg (1 measuring cup, i.e. 10 mL) daily for a minimum treatment of three weeks. Treatment should continue for 2 weeks following resolution of symptoms. Doses up to 200 mg (2 measuring cups, i.e. 20 mL) per day may be used based on the clinical response of the patient.

Treatment of fluconazole-resistant oral and/or oesophageal candidiasis

200 to 400 mg (2-4 measuring cups or 20-40 mL) daily in one or two intakes for 2 weeks. If there is no response after 2 weeks, treatment should be continued for another 2 weeks. The 400 mg daily dose should not be used for longer than 14 days if there are no signs of improvement.

Prophylaxis of fungal infections

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

For use in children, the elderly and in patients with renal or hepatic impairment (see **section 4.4**).

Special Populations

Paediatrics

Clinical data on the use of SPORANOX oral solution in paediatric patients are limited. The use of SPORANOX oral solution in paediatric patients is not recommended unless it is determined that the potential benefit outweighs the potential risks. See **section 4.4**.

Prophylaxis of fungal infections: there are no efficacy data available in neutropenic children. Limited safety experience is available with a dose of 5 mg/kg per day administered in two intakes. The incidence of adverse events such as diarrhoea, abdominal pain, vomiting, fever, rash and mucositis was higher in adults. However, it is not clear to what extent this is attributable to SPORANOX oral solution or chemotherapy.

Elderly

Clinical data on the use of SPORANOX oral solution in elderly patients are limited. It is advised to use SPORANOX oral solution 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**.

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**.

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.

4.3 Contraindications

- SPORANOX oral solution is contraindicated in patients who have shown hypersensitivity to itraconazole or the excipients.
- SPORANOX oral solution should only be given to pregnant women in life-threatening cases and when in these cases the potential benefit outweighs the potential harm to the foetus. Highly effective contraceptive precautions should be used by women of childbearing potential throughout SPORANOX therapy, and continued until the next menstrual period following the end of SPORANOX therapy.
- Co-administration of a number of CYP3A4 substrates is contraindicated with SPORANOX oral solution. Increased plasma concentrations of these drugs, caused by co-administration with itraconazole, may increase or prolong, both therapeutic and adverse effects to such an extent that a potentially serious situation may occur. For example,

increased plasma concentrations of some of these drugs can lead to QT prolongation and ventricular tachyarrythmias including, occurrences of torsades de pointes, a potentially fatal arrhythmia. Specific examples are listed in **section 4.5**.

- SPORANOX oral solution should not be administered to patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF except for the treatment of life-threatening or other serious infections (see **section 4.4**).

4.4 Special warnings and precautions for use

SPORANOX has a potential for clinically important interactions with other medicines (see **section 4.5**).

Congestive heart failure

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

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

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

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

Interaction potential

Co-administration of specific drugs with itraconazole may result in changes in efficacy of itraconazole and/or the co-administered 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 4.5.**

Cross-hypersensitivity

There is -limited information regarding cross-hypersensitivity between itraconazole and other azole antifungal agents. Caution should be used in prescribing SPORANOX oral solution to patients with hypersensitivity to other azoles.

Cystic fibrosis

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

Treatment of severely neutropenic patients

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

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.

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 it is recommended to have their sensitivity 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 is given.

Hepatic impairment

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

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

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 of half-life 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**)

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.

Peripheral neuropathy

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

Other azole antifungal agents

There is limited information regarding cross hypersensitivity between itraconazole and other azole antifungal agents. Caution should be used in prescribing SPORANOX oral solution to patients with hypersensitivity to other azoles.

Use in children

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

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

Toxicological studies have shown that itraconazole, when administered to rats, can produce bone toxicity. While such toxicity has not been reported in adult patients, the long-term effect of itraconazole in children is unknown (See **section 5.3 - Toxicology**).

Use in elderly patients

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

4.5 Interactions with other medicines and other forms of interactions

Itraconazole is a drug with a high interaction potential. The various types of interaction and associated general recommendations are described below. In addition, table 1 below is provided listing examples of drugs that may interact with itraconazole, organised per drug family for easy reference.

Itraconazole is mainly metabolised through CYP3A4. Other substances that either share this metabolic pathway or modify CYP3A4 activity may influence the pharmacokinetics of itraconazole. Co-administration of itraconazole with moderate or potent CYP3A4 inducers may decrease the bioavailability of itraconazole and hydroxy-itraconazole to such an extent that efficacy may be reduced. Co-administration with moderate or potent inhibitors of CYP3A4 may increase the bioavailability of itraconazole, which may result in increased or prolonged pharmacologic effects of itraconazole.

Itraconazole and its major metabolite, hydroxy-itraconazole are potent CYP3A4 inhibitors. Itraconazole is an inhibitor of the drug transporters P-glycoprotein and breast cancer resistance protein (BCRP). Itraconazole can inhibit the metabolism of drugs metabolised by CYP3A4 and can inhibit the drug transport by P-glycoprotein and/or BCRP, which may result in increased plasma concentrations of these drugs and/or their active metabolite(s) when they are administered with itraconazole. These elevated plasma concentrations may increase or prolong

both therapeutic and adverse effects of these drugs. For some drugs, co-administration with itraconazole may result in decreased plasma concentrations of the drug or of the active moiety of the drug. This may result in reduced efficacy of the drug.

Following cessation of medical treatment with itraconazole, plasma concentrations decrease below the detection limit 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 plasma concentrations decline slower. This is particularly important for consideration when initiating therapy with drugs whose metabolism is affected by itraconazole.

The following general recommendations apply, unless stated differently in table.

- 'Contraindicated': Under no circumstances is the drug to be co-administered with itraconazole. This applies to:
    - CYP3A4 substrates for which increased plasma concentrations may increase or prolong therapeutic and/or adverse effects to such an extent that a potentially serious situation may occur. (see *Contraindications*)
- 'Not recommended': It is recommended that the use of the drug be avoided, unless the benefits outweigh the potentially increased risks. If co-administration cannot be avoided, clinical monitoring is recommended, and the dosage of itraconazole and/or the co-administered drug adapted as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. This applies to:
    - Moderate or potent CYP3A4 inducers: not recommended from 2 weeks before and during treatment with itraconazole
    - CYP3A4/P-gp/BCRP substrates for which increased or decreased plasma concentrations result in significant risk: not recommended during and up to 2 weeks after treatment with itraconazole.
- '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 and the dosage of itraconazole and/or the co-administered drug adapted as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. This applies to:
    - Drugs that reduce gastric acidity (itra caps only)
    - Moderate or potent inhibitors of CYP3A4
    - CYP3A4/P-gp/BCRP substrates for which increased or decreased plasma concentrations result in a clinically relevant risk

The list of examples of interacting drugs in the table below is not comprehensive and therefore the label 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 drugs listed in this table are based on either drug interaction studies or case reports, or potential interactions based on the mechanism of interaction.

Table 1: Examples of interacting drugs		
Example of Medicinal products within class	**Expected/Potential effect on drug levels (see footnotes for additional info)**	**Clinical comment (see codes above for additional info)**
Alpha Blockers		
Alfuzosin Silodosin Tamsulosin	Alfuzosin C_{max} (↑↑), AUC (↑↑)[a] Silodosin C_{max} (↑↑), AUC (↑↑)[a] Tamsulosin C_{max} (↑↑), AUC (↑↑)[a]	Not recommended during and for 2 weeks after treatment with itraconazole. Increased risk of alfuzosin/silodosin/tamsulosin-related adverse reactions[c].
Analgesics		
Alfentanil Buprenorphine (IV and sublingual) Oxycodone Sufentanil	Alfentanil AUC (↑↑ to ↑↑↑↑)[a] Buprenorphine C_{max} (↑↑), AUC (↑↑)[a] Oxycodone C_{max} ↑, AUC ↑↑ Sufentanil conc increase (extent unknown)[a,b]	Use with caution, monitor for adverse reactions related to the analgesic[c], dose reduction of alfentanil/buprenorphine/oxycodone/sufentanil may be necessary.
Fentanyl	Fentanyl IV AUC (↑↑)[a] Fentanyl other form. conc increase (extent unknown)[a,b]	Not recommended during and for 2 weeks after treatment with itraconazole. Increased risk of fentanyl-related adverse reactions[c].
Levacetylmethadol (levomethadyl)	Levacetylmethadol C_{max} (↑↑), AUC (↑↑↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of levacetylmethadol-related adverse reactions, such as QT prolongation and TdP.
Methadone	(R)-methadone C_{max} (↑), AUC (↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of methadone-related adverse reactions, such as potentially life-threatening respiratory depression, QT prolongation and TdP.
Antiarrhythmics		
Digoxin	Digoxin C_{max} ↑, AUC ↑	Use with caution, monitor for digoxin adverse reactions, dose reduction of digoxin may be necessary[c].
Disopyramide	Disopyramide conc increase (↑↑)[a,b]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of disopyramide-related adverse reactions, such as serious arrhythmias including TdP .
Dofetilide	Dofetilide C_{max} (↑), AUC (↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of dofetilide-related adverse reactions, such as serious ventricular arrhythmias including TdP.
Dronedarone	Dronedarone C_{max} (↑↑↑), AUC (↑↑↑↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of dronedarone-related adverse reactions, such as QT prolongation and cardiovascular death.
Quinidine	Quinidine C_{max} ↑, AUC ↑↑	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of quinidine-related adverse reactions, such as QT prolongation, TdP, hypotension, confusion and delirium.
Antibacterials		
Bedaquiline	Bedaquiline C_{max} (↔), AUC (↑) during 2 weeks of bedaquiline q.d. dosing[a]	Not recommended, coadministration for more than 2 weeks at any time during bedaquiline dosing is not recommended: increased risk of bedaquiline-related adverse reactions[c].
Ciprofloxacin Erythromycin	Itraconazole C_{max} ↑, AUC ↑	Use with caution, monitor for itraconazole adverse reactions, dose reduction of itraconazole may be necessary.

Table 1: Examples of interacting drugs		
Example of Medicinal products within class	**Expected/Potential effect on drug levels (see footnotes for additional info)**	**Clinical comment (see codes above for additional info)**
Clarithromycin	Clarithromycin conc increase (extent unknown)[a,b] Itraconazole C_{max} ↑, AUC ↑;	Use with caution, monitor for adverse reactions related to itraconazole and/or clarithromycin[c], dose reduction of itraconazole and/or clarithromycin may be necessary.
Delamanid Trimetrexate	Delamanid conc. increase (extent unknown)[a,b] Trimetrexate conc increase (extent unknown)[a,b]	Use with caution, monitor for delamanid/trimetrexate adverse reactions, dose reduction of delamanid/trimetrexate may be necessary[c].
Isoniazid Rifampicin	Isoniazid: itraconazole conc. (↓↓↓)[a,b] Rifampicin: itraconazole AUC ↓↓↓	Not recommended from 2 weeks before and during treatment with itraconazole, Itraconazole efficacy may be reduced.
Rifabutin	Rifabutin conc. increase (extent unknown)[a,b] Itraconazole: C_{max} ↓↓, AUC ↓↓	Not recommended from 2 weeks before, during and for 2 weeks after treatment with itraconazole. Itraconazole efficacy may be reduced and increased risk of rifabutin-related adverse reactions[c].
Telithromycin	In healthy subjects: telithromycin C_{max} ↑, AUC ↑ In severe renal impairment: telithromycin AUC (↑↑)[a] In severe hepatic impairment: telithromycin conc. increase (extent unknown)[a,b]	Contraindicated in patients with severe renal or hepatic impairment during and for 2 weeks after treatment with itraconazole, Increased risk of telithromycin-related adverse reactions, such as hepatotoxicity, QT prolongation and TdPs. Use with caution in other patients:, monitor for telithromycin adverse reactions, dose reduction of telithromycin may be necessary[c].
Anticoagulants and Antiplatelet Drugs		
Apixaban Edoxaban Rivaroxaban Vorapaxar	Apixaban C_{max} (↑), AUC (↑)[a] Edoxaban C_{max} (↑), AUC (↑)[a] Rivaroxaban C_{max} (↑), AUC (↑ to ↑↑)[a] Vorapaxar C_{max} (↑), AUC (↑)[a]	Not recommended during and for 2 weeks after treatment with itraconazole. Increased risk of apixaban/ edoxaban/rivaroxaban/vorapaxar-related adverse reactions[c].
Coumarins (eg, warfarin) Cilostazol	Coumarins (eg, warfarin) conc increase (extent unknown)[a,b] Cilostazol C_{max} (↑), AUC (↑↑)[a]	Use with caution, monitor for coumarins/cilostazol adverse reactions, dose reduction of coumarins/cilostazol may be necessary[c].
Dabigatran	Dabigatran C_{max} (↑↑), AUC (↑↑)[a]	Use with caution, monitor for dabigatran adverse reactions, dose reduction of dabigatran may be necessary[c].
Ticagrelor	Ticagrelor C_{max} (↑↑), AUC (↑↑↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of ticagrelor-related adverse reactions, such as bleeding.
Anticonvulsants		
Carbamazepine	Carbamazepine conc. (↑)[a,b] Itraconazole conc. (↓↓)[a,b]	Not recommended from 2 weeks before, during and for 2 weeks after treatment with itraconazole. Itraconazole efficacy may be reduced and increased risk for carbamazepine-related adverse reactions[c].
Phenobarbital Phenytoin	Phenobarbital: itraconazole conc. (↓↓↓)[a,b] Phenytoin: itraconazole AUC ↓↓↓	Not recommended from 2 weeks before and during treatment with itraconazole. Itraconazole efficacy may be reduced.
Antidiabetics		
Repaglinide Saxagliptin	Repaglinide C_{max} ↑, AUC ↑ Saxagliptin C_{max} (↑↑), AUC (↑↑)[a]	Use with caution, monitor for repaglinide/saxagliptin adverse reactions, dose reduction of repaglinide/saxagliptin may be necessary[c].

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Example of Medicinal products within class	**Expected/Potential effect on drug levels (see footnotes for additional info)**	**Clinical comment (see codes above for additional info)**
Antihelminthics, antifungals and antiprotozoals		
Artemether-lumefantrine Quinine	Artemether C_{max} (↑↑), AUC (↑↑)[a] Lumefantrine C_{max} (↑), AUC (↑)[a] Quinine C_{max} ↔, AUC ↑	Use with caution, monitor for artemether-lumefantrine/quinine adverse reactions[c]. Refer to the label for specific actions to be taken.
Halofantrine	Halofantrine conc increase (extent unknown)[a,b]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of halofantrine-related adverse reactions, such as QT prolongation and fatal arrhythmias.
Isavuconazole	Isavuconazole C_{max} (↔), AUC (↑↑↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of isavuconazole-related adverse reactions, such as hepatic adverse reactions, hypersensitivity reactions and embryo-fetal toxicity.
Praziquantel	Praziquantel C_{max} (↑↑), AUC (↑)[a]	Use with caution, monitor for praziquantel adverse reactions, dose reduction of praziquantel may be necessary[c].
Antihistamines		
Astemizole	Astemizole C_{max} (↑), AUC (↑↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of astemizole-related adverse reactions, such as QT prolongation, TdP and other ventricular arrhythmias.
Bilastine Ebastine Rupatadine	Bilastine C_{max} (↑↑), AUC (↑)[a] Ebastine C_{max} ↑↑, AUC ↑↑↑ Rupatadine conc increase (↑↑↑↑)[a,b]	Use with caution, monitor for bilastine/ebastine/rupatadine adverse reactions[c], dose reduction of bilastine/ebastine/rupatadine may be necessary.
Mizolastine	Mizolastine C_{max} (↑), AUC (↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of mizolastine-related adverse reactions, such as QT prolongation.
Terfenadine	Terfenadine conc increase (extent unknown)[b]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of terfenadine-related adverse reactions, such as QT prolongation, TdP and other ventricular arrhythmias.
Antimigraine Drugs		
Eletriptan	Eletriptan C_{max} (↑↑), AUC (↑↑↑)[a]	Use with caution, monitor for eletriptan adverse reactions[c], dose reduction of eletriptan may be necessary.
Ergot alkaloids (such as dihydroergotamine, ergometrine, ergotamine, methylergometrine)	Ergot alkaloids conc increase (extent unknown)[a,b]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of ergot alkaloid-related adverse reactions, such as ergotism.
Antineoplastics		
Bortezomib Brentuximab vedotin Busulfan Erlotinib Gefitinib Imatinib Ixabepilone Nintedanib Panobinostat Pemigatinib Ponatinib Ruxolitinib Sonidegib Tretinoin (oral)	Bortezomib AUC (↑)[a] Brentuximab vedotin AUC (↑)[a] Busulfan C_{max} ↑, AUC ↑ Erlotinib C_{max} (↑↑), AUC (↑)[a] Gefitinib C_{max} ↑, AUC ↑ Imatinib C_{max} (↑), AUC (↑)[a] Ixabepilone C_{max} (↔), AUC (↑)[a] Nintedanib C_{max} (↑), AUC (↑)[a] Panobinostat C_{max} (↑), AUC (↑)[a]	Use with caution, monitor for adverse reactions related to the antineoplastic drug[c], dose reduction of the antineoplastic drug may be necessary.

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Example of Medicinal products within class	**Expected/Potential effect on drug levels (see footnotes for additional info)**	**Clinical comment (see codes above for additional info)**
Vandetanib	Pemigatinib C_{max} ↑, AUC ↑ Ponatinib C_{max} (↑), AUC (↑)[a] Ruxolitinib C_{max} (↑), AUC (↑)[a] Sonidegib C_{max} (↑), AUC (↑↑)[a] Tretinoin C_{max} (↑), AUC (↑)[a] Vandetanib C_{max} ↔, AUC ↑	
Idelalisib	Idelalisib C_{max} (↑), AUC (↑)[a] Itraconazole serum conc. increase (extent unknown)[a,b]	Use with caution, monitor for adverse reactions related to itraconazole and/or idelalisib[c], dose reduction of itraconazole and/or idelalisib may be necessary.
Axitinib Bosutinib Cabazitaxel Cabozantinib Ceritinib Cobimetinib Crizotinib Dabrafenib Dasatinib Docetaxel Entrectinib Glasdegib Ibrutinib Lapatinib Nilotinib Olaparib Pazopanib Sunitinib Talazoparib Trabectedin Trastuzumab emtansine Vinca alkaloids	Axitinib C_{max} (↑), AUC (↑↑)[a] Bosutinib C_{max} (↑↑↑), AUC (↑↑↑)[a] Cabazitaxel C_{max} (↔), AUC (↔)[a] Cabozantinib C_{max} (↔), AUC (↑)[a] Ceritinib C_{max} (↑), AUC (↑↑)[a] Cobimetinib C_{max} ↑↑, AUC ↑↑↑ Crizotinib C_{max} (↑), AUC (↑↑)[a] Dabrafenib AUC (↑)[a] Dasatinib C_{max} (↑↑), AUC (↑↑)[a] Docetaxel AUC (↔ to ↑↑)[a] Entrectinib C_{max} ↑, AUC ↑↑↑ Glasdegib C_{max} (↑), AUC (↑↑)[a] Ibrutinib C_{max} (↑↑↑↑), AUC (↑↑↑↑)[a] Lapatinib C_{max} (↑↑), AUC (↑↑)[a] Nilotinib C_{max} (↑), AUC (↑↑)[a] Olaparib C_{max} ↑, AUC ↑↑ Pazopanib C_{max} (↑), AUC (↑)[a] Sunitinib C_{max} (↑), AUC (↑)[a] Talazoparib C_{max} ↑, AUC ↑ Trabectedin C_{max} (↑), AUC (↑)[a] Trastuzumab emtansine conc increase (extent unknown)[a,b] Vinca alkaloid conc increase (extent unknown)[a,b]	Not recommended during and for 2 weeks after treatment with itraconazole. Increased risk of adverse reactions related to the antineoplastic drug[c]. Additionally: For cabazitaxel, even though the change in pharmacokinetic parameters did not reach statistical significance in a low-dose drug interaction study with ketoconazole, a high variability in the results was observed. For ibrutinib, refer to the label for specific actions to be taken.
Regorafenib	Regorafenib AUC (↓↓ by estimation of active moiety)[a]	Not recommended during and for 2 weeks after treatment with itraconazole. Regorafenib efficacy may be reduced.
Irinotecan	Irinotecan and its active metabolite conc increase (extent unknown)[a,b]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of irinotecan-related

Table 1: Examples of interacting drugs		
Example of Medicinal products within class	**Expected/Potential effect on drug levels (see footnotes for additional info)**	**Clinical comment (see codes above for additional info)**
		adverse reactions, such as potentially life-threatening myelosuppression and diarrhea.
Mobocertinib	Mobocertinib C_{max} ↑↑, AUC ↑↑↑	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of mobocertinib-related adverse reactions[c].
Venetoclax	Venetoclax C_{max} (↑↑↑), AUC (↑↑↑)[a]	Contraindicated for chronic lymphocytic leukemia/small lymphocytic lymphoma patients during dose initiation/titration/ramp-up phase of venetoclax. Otherwise, not recommended during and for 2 weeks after treatment with itraconazole[c].
Antipsychotics, Anxiolytics and Hypnotics		
Alprazolam Aripiprazole Brotizolam Buspirone Cariprazine Haloperidol Midazolam (iv) Perospirone Quetiapine Ramelteon Risperidone Suvorexant Zopliclone	Alprazolam C_{max} ↔, AUC ↑↑ Aripiprazole C_{max} ↑, AUC ↑ Brotizolam C_{max} ↔, AUC ↑↑ Buspirone C_{max} ↑↑↑, AUC ↑↑↑↑ Cariprazine (↑↑)[a,b] Haloperidol C_{max} ↑, AUC ↑ Midazolam (iv) conc increase ↑↑[b] Perospirone C_{max} ↑↑↑, AUC ↑↑↑ Quetiapine C_{max} (↑↑), AUC (↑↑↑)[a] Ramelteon C_{max} (↑), AUC (↑)[a] Risperidone conc increase ↑[b] Suvorexant C_{max} (↑), AUC (↑↑)[a] Zopiclone C_{max} ↑, AUC ↑	Use with caution, monitor for adverse reactions related to the antipsychotic, anxiolytic or hypnotic drug[c], dose reduction of these drugs may be necessary.
Lurasidone	Lurasidone C_{max} (↑↑↑), AUC (↑↑↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of lurasidone-related adverse reactions, such as hypotension, circulatory collapse, severe extrapyramidal symptoms, seizures.
Midazolam (oral)	Midazolam (oral) C_{max} ↑ to ↑↑, AUC ↑↑ to ↑↑↑↑	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of midazolam-related adverse reactions, such as respiratory depression, cardiac arrest, prolonged sedation and coma.
Pimozide	Pimozide C_{max} (↑), AUC (↑↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of pimozide-related adverse reactions, such as cardiac arrhythmias, possibly associated with QT prolongation and TdP.
Sertindole	Sertindole conc increase (extent unknown)[a,b]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of sertindole-related adverse reactions, such as QT prolongation and TdP.
Triazolam	Triazolam C_{max} ↑ to ↑↑, AUC ↑↑ to ↑↑↑↑	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of triazolam-related adverse reactions, such as seizures, respiratory depression, angioedema, apnea and coma.
Antivirals		
Asunaprevir (boosted) Tenofovir disoproxil fumarate (TDF)	Asunaprevir C_{max} (↑↑↑), AUC (↑↑↑)[a] Tenofovir conc increase (extent unknown)[a,b]	Use with caution, however, refer to the label of the antiviral drug for specific actions to be taken.

Table 1: Examples of interacting drugs		
Example of Medicinal products within class	**Expected/Potential effect on drug levels (see footnotes for additional info)**	**Clinical comment (see codes above for additional info)**
Boceprevir	Boceprevir C_{max} (↑), AUC (↑↑)[a] Itraconazole conc increase (extent unknown)[a,b]	Use with caution, monitor for adverse reactions related to itraconazole and/or boceprevir[c], dose reduction of itraconazole may be necessary. Refer to the boceprevir label for specific actions to be taken.
Cobicistat	Cobicistat conc increase (extent unknown)[a,b] Itraconazole conc increase (extent unknown)[a,b]	Use with caution, monitor for adverse reactions related to itraconazole, dose reduction of itraconazole may be necessary.
Daclatasvir Vaniprevir	Daclatasvir C_{max} (↑), AUC (↑↑)[a] Vaniprevir C_{max} (↑↑↑), AUC (↑↑↑)[a]	Use with caution, monitor for daclatasvir/vaniprevir adverse reactions[c], dose reduction of daclatasvir/vaniprevir may be necessary.
Darunavir (boosted) Fosamprenavir (ritonavir-boosted)	Ritonavir-boosted darunavir: itraconazole C_{max} (↑↑), AUC (↑↑)[a] Ritonavir-boosted fosamprenavir: itraconazole C_{max} (↑), AUC (↑↑)[a]	Use with caution, monitor for itraconazole adverse reactions, dose reduction of itraconazole may be necessary.
Elvitegravir (boosted)	Elvitegravir C_{max} (↑), AUC (↑)[a] Itraconazole conc increase (extent unknown)[a,b]	Use with caution, monitor for adverse reactions related to itraconazole and/or elvitegravir (ritonavir-boosted) [c]. Dose reduction of itraconazole may be necessary; refer to the elvitegravir label for specific actions to be taken.
Efavirenz Nevirapine	Efavirenz: itraconazole C_{max} ↓, AUC ↓ Nevirapine: itraconazole C_{max} ↓, AUC ↓↓	Not recommended from 2 weeks before and during treatment with itraconazole. Itraconazole efficacy may be reduced.
Elbasvir/Grazoprevir	Elbasvir C_{max} ↔, AUC (↑)[a] Grazoprevir C_{max} ↔, AUC (↑↑)[a]	Use with caution, monitor for adverse reactions related to the co-administered drugs[c]. Refer to the elbasvir/grazoprevir label for specific actions to be taken.
Glecaprevir/Pibrentasvir	Glecaprevir C_{max} (↑↑), AUC (↑↑ to ↑↑↑) [a] Pibrentasvir C_{max} (↔ to ↑), AUC (↔ to ↑↑) [a]	Use with caution, monitor for adverse reactions related to the co-administered drugs[c]. Refer to the glecaprevir/pibrentasvir label for specific actions to be taken.
Indinavir	Itraconazole conc. ↑[b] Indinavir C_{max} ↔, AUC ↑	Use with caution, monitor for adverse reactions related to itraconazole and/or indinavir[c], dose reduction of itraconazole and/or indinavir may be necessary.
Maraviroc	Maraviroc C_{max} (↑↑), AUC (↑↑↑)[a]	Use with caution monitor for adverse reactions[c]. Dose reduction of maraviroc may be necessary.
Ombitasvir/Paritaprevir/Ritonavir with or without Dasabuvir	Itraconazole C_{max} (↑), AUC (↑↑)[a] Ombitasvir C_{max} (↔), AUC (↑) [a] Paritaprevir C_{max} (↑), AUC (↑↑) [a] Ritonavir C_{max} (↑), AUC (↑) [a] Dasabuvir C_{max} (↑), AUC (↑) [a]	Use with caution, monitor for adverse reations related to itraconazole and/or the antivirals [c]. dose reduction of itraconazole may be necessary. Refer to the label(s) of the coadministered drugs for specific actions to be taken.
Ritonavir	Itraconazole C_{max} (↑), AUC (↑↑)[a] Ritonavir C_{max} (↔), AUC (↑)[a]	Use with caution, monitor for adverse reactions related to itraconazole and/or ritonavir[c], Dose reduction of itraconazole may be necessary; refer to the ritonavir label for specific actions to be taken.
Saquinavir	Saquinavir (unboosted) C_{max} ↑↑, AUC ↑↑↑	Use with caution, monitor for adverse reactions related to itraconazole and/or saquinavir[c], Dose reduction of

Table 1: Examples of interacting drugs		
Example of Medicinal products within class	**Expected/Potential effect on drug levels (see footnotes for additional info)**	**Clinical comment (see codes above for additional info)**
	Itraconazole (with boosted saquinavir) C_{max} (↑), AUC (↑↑)[a]	itraconazole may be necessary; refer to the saquinavir label for specific actions to be taken.
Beta Blockers		
Nadolol	Nadolol C_{max} ↑↑, AUC ↑↑	Use with caution, monitor for nadolol adverse reactions[c]. Dose reduction of nadolol may be necessary.
Calcium Channel Blockers		
Bepridil	Bepridil conc increase (extent unknown)[a,b]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of bepridil-related adverse reactions, such as new arrhythmias and TdP type ventricular tachycardia.
Diltiazem	Diltiazem & Itraconazole conc increase (extent unknown)[a,b]	Use with caution, monitor for adverse reactions related to itraconazole and/or diltiazem[c], dose reduction of itraconazole and/or diltiazem may be necessary.
Felodipine Lercanidipine Nisoldipine	Felodipine C_{max} ↑↑↑, AUC ↑↑↑ Lercanidipine AUC (↑↑↑↑)[a] Nisoldipine C_{max} (↑↑↑↑), AUC (↑↑↑↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of dihydropyridine-related adverse reactions, such as hypotension and peripheral edema.
Other dihydropyridines Verapamil	Dihydropyridine conc increase (extent unknown)[a,b] Verapamil conc increase (extent unknown)[a,b]	Use with caution, monitor for dihydropyridine/verapamil adverse reactions[c], dose reduction of dihydropyridine/verapamil may be necessary.
Cardiovascular Drugs, Misc		
Aliskiren Riociguat Sildenafil (pulmonary hypertension) Tadalafil (pulmonary hypertension)	Aliskiren C_{max} ↑↑↑, AUC ↑↑↑ Riociguat C_{max} (↑), AUC (↑↑)[a] Sildenafil/Tadalafil conc increase (extent unknown but effect may be greater than reported under Urological Drugs)[a,b]	Not recommended during and for 2 weeks after treatment with itraconazole[c]. Increased risk of adverse reactions related to the cardiovascular drug.
Bosentan Guanfacine	Bosentan C_{max} (↑↑), AUC (↑↑)[a] Guanfacine C_{max} (↑), AUC (↑↑)[a]	Use with caution, monitor for bosentan/guanfacine adverse reactions[c], dose reduction of bosentan/guanfacine may be necessary.
Ivabradine	Ivabradine C_{max} (↑↑), AUC (↑↑↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of ivabradine-related adverse reactions, such as atrial fibrillation, bradycardia, sinus arrest and heart block.
Ranolazine	Ranolazine C_{max} (↑↑), AUC (↑↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of ranolazine-related adverse reactions, such as QT prolongation and renal failure.
Contraceptives*		
Dienogest Ulipristal	Dienogest C_{max} (↑), AUC (↑↑)[a] Ulipristal C_{max} (↑↑), AUC (↑↑↑)[a]	Use with caution, monitor for contraceptive adverse reactions[c], refer to the dienogest/ulipristal label for specific actions to be taken.
Diuretics		
Eplerenone	Eplerenone C_{max} (↑), AUC (↑↑↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of eplerenone-related adverse reactions, such as hyperkalemia and hypotension.
Finerenone	Finerenone C_{max} (↑↑), AUC (↑↑↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of finerenone-related adverse reactions[c].

Table 1: Examples of interacting drugs		
Example of Medicinal products within class	**Expected/Potential effect on drug levels (see footnotes for additional info)**	**Clinical comment (see codes above for additional info)**
Gastrointestinal Drugs		
Aprepitant Loperamide Netupitant	Aprepitant AUC (↑↑↑)[a] Loperamide C_{max} ↑↑, AUC ↑↑ Netupitant C_{max} (↑), AUC (↑↑)[a]	Use with caution, monitor for aprepitant/loperamide/netupitant adverse reactions[c], Dose reduction of aprepitant/loperamide/ may be necessary. Refer to the netupitant label for specific actions to be taken.
Cisapride	Cisapride conc increase (extent unknown)[a,b]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of cisapride-related adverse reactions, such as serious cardiovascular events including QT prolongation, serious ventricular arrhythmias and TdP.
Domperidone	Domperidone C_{max} ↑↑, AUC ↑↑	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of domperidone-related adverse reactions, such as serious ventricular arrhythmias and sudden cardiac death.
Drugs that reduce gastric acidity	Itraconazole: C_{max} ↓↓, AUC ↓↓	Use with caution: Drugs that reduce gastric acidity: e.g. acid neutralising medicines such as aluminum hydroxide, or acid secretion suppressors such as H_2- receptor antagonists and proton pump inhibitors. When co-treatment with acid neutralising medicines (e.g. aluminum hydroxide) these should be administered at least 2 hours before or 2 hours after the intake of Sporanox capsules. (See **PRECAUTIONS**.)
Naloxegol	Naloxegol C_{max} (↑↑↑), AUC (↑↑↑↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of naloxegol-related adverse reactions, such as opioid withdrawal symptoms.
Saccharomyces boulardii	*S. boulardii* colonisation decrease (extent unknown)	Not recommended during and for 2 weeks after treatment with itraconazole. *S. boulardii* efficacy may be reduced.
Immunosuppressants		
Budesonide Ciclesonide Cyclosporine Dexamethasone Fluticasone Methylprednisolone Tacrolimus Temsirolimus	Budesonide (inhalation) C_{max} ↑, AUC ↑↑; Budesonide (other form.) conc increase (extent unknown)[a,b] Ciclesonide (inhalation) C_{max} (↑↑), AUC (↑↑)[a] Cyclosporine (iv) conc increase ↔ to ↑[b] Cyclosporine (other form.) conc increase (extent unknown)[a,b] Dexamethasone C_{max} ↔ (iv) ↑ (oral), AUC ↑↑ (iv, oral) Fluticasone (inhalation) conc increase ↑↑[b] Fluticasone (nasal) conc increase (↑)[a,b] Methylprednisolone (oral) C_{max} ↑ to ↑↑, AUC ↑↑ Methylprednisolone (iv) AUC ↑↑ Tacrolimus (iv) conc increase ↑[b] Tacrolimus (oral) C_{max} (↑↑), AUC (↑↑)[a] Temsirolimus (iv) C_{max} (↑↑), AUC (↑↑)[a]	Use with caution monitor for immunosuppressant adverse reactions[c], Dose reduction of the immunosuppressant drug may be necessary.

Table 1: Examples of interacting drugs		
Example of Medicinal products within class	**Expected/Potential effect on drug levels (see footnotes for additional info)**	**Clinical comment (see codes above for additional info)**
Everolimus Sirolimus (rapamycin)	Everolimus C_{max} (↑↑), AUC (↑↑↑↑)[a] Sirolimus C_{max} (↑↑), AUC (↑↑↑↑)[a]	Not recommended during and for 2 weeks after treatment with itraconazole[c]. Increased risk of everolimus/ sirolimus-related adverse reactions.
Voclosporin	Voclosporin C_{max} (↑↑↑), AUC (↑↑↑↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of voclosporin-related adverse reactions[c].
Lipid Regulating Drugs		
Atorvastatin	Atorvastatin C_{max} ↔ to ↑↑, AUC ↑ to↑↑	Use with caution, monitor for atorvastatin adverse reactions[c], Dose reduction of atorvastatin may be necessary.
Lomitapide	Lomitapide C_{max} (↑↑↑↑), AUC (↑↑↑↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of lomitapide-related adverse reactions, such as hepatotoxicity and severe gastrointestinal reactions.
Lovastatin Simvastatin	Lovastatin C_{max} ↑↑↑↑, AUC ↑↑↑↑ Simvastatin C_{max} ↑↑↑↑, AUC ↑↑↑↑	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of lovastatin/ simvastatin-related adverse reactions, such as myopathy, rhabdomyolysis and liver enzyme abnormalities.
Nonsteroidal Anti-Inflammatory Drugs		
Meloxicam	Meloxicam C_{max} ↓↓, AUC ↓	Use with caution, monitor for reduced efficacy of meloxicam, dose adaption of meloxicam may be necessary.
Respiratory Drugs		
Salmeterol	Salmeterol C_{max} (↑), AUC (↑↑↑↑)[a]	Not recommended during and for 2 weeks after treatment with itraconazole. Increased risk of salmeterol-related adverse reactions[c].
SSRIs, Tricyclics and Related Antidepressants		
Reboxetine Venlafaxine	Reboxetine C_{max} (↔), AUC (↑)[a] Venlafaxine C_{max} (↑), AUC (↑)[a]	Use with caution, monitor for reboxetine/venlafaxine adverse reactions[c], dose reduction of reboxetine/venlafaxine may be necessary.
Urologic Drugs		
Avanafil	Avanafil C_{max} (↑↑), AUC (↑↑↑↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk avanafil-related adverse reactions, such as priapism, visual problems and sudden loss of hearing.
Dapoxetine	Dapoxetine C_{max} (↑), AUC (↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk for dapoxetine-related adverse reactions, such as orthostatic hypotension and ocular effects.
Darifenacin Vardenafil	Darifenacin C_{max} (↑↑↑), AUC (↑↑↑ to ↑↑↑↑)[a] Vardenafil C_{max} (↑↑), AUC (↑↑↑↑)[a]	Not recommended during and for 2 weeks after treatment with itraconazole. Increased risk of darifenacin/vardenafil-related adverse reactions[c].
Dutasteride Imidafenacin Oxybutynin Sildenafil (erectile dysfunction) Tadalafil (erectile dysfunction and benign prostatic hyperplasia) Tolterodine Udenafil	Dutasteride conc increase (extent unknown)[a,b] Imidafenacin C_{max} ↑, AUC ↑ Oxybutynin conc increase ↑[b] Sildenafil C_{max} (↑↑), AUC (↑↑ to ↑↑↑↑)[a] Tadalafil C_{max} (↑), AUC (↑↑)[a]	Use with caution, monitor for urologic drug adverse reactions[c], dose reduction of the urologic drug may be necessary; refer to the dutasteride label for specific actions to be taken. (For sildenafil and tadalafil, see also *Cardiovascular Drugs, Miscellaneous Drugs and other substances*.)

Table 1: Examples of interacting drugs		
Example of Medicinal products within class	**Expected/Potential effect on drug levels (see footnotes for additional info)**	**Clinical comment (see codes above for additional info)**
	Tolterodine C_{max} (↑ to ↑↑), AUC (↑↑)[a] in poor metabolisers of CYP2D6 Udenafil C_{max} (↑), AUC (↑↑)[a]	
Fesoterodine	Fesoterodine C_{max} (↑↑), AUC (↑↑)[a]	Contraindicated in patients with moderate to severe renal or hepatic impairment, during and for 2 weeks after treatment with itraconazole. Increased risk of fesoterodine-related adverse reactions, such as severe anticholinergic effects. Use with caution in other patients: monitor for fesoterodine adverse reactions[c], dose reduction of fesoterodine may be necessary.
Solifenacin	Solifenacin C_{max} (↑), AUC (↑↑)[a]	Contraindicated in patients with severe renal or moderate to severe hepatic impairment, during and for 2 weeks after treatment with itraconazole. Increased risk of solifenacin-related adverse reactions, such as anticholinergic effects and QT prolongation. Use with caution in other patients, monitor for solifenacin drug adverse reactions[c], dose reduction of solifenacin may be necessary.
Miscellaneous Drugs and Other Substances		
Alitretinoin (oral) Cabergoline Cannabinoids Cinacalcet	Alitretinoin C_{max} (↑), AUC (↑)[a] Cabergoline C_{max} (↑↑), AUC (↑↑)[a] Cannabinoids conc increase, extent unknown but likely (↑↑)[a] Cinacalcet C_{max} (↑↑), AUC (↑↑)[a]	Use with caution, monitor for alitretinoin/ cabergoline/cannabinoids/cinacalcet drug adverse reactions, dose reduction of alitretinoin/ cabergoline/cannabinoids/cinacalcet may be necessary[c].
Valbenazine	Valbenazine C_{max} (↑), AUC (↑↑)[a]	Use with caution, monitor for valbenazine related adverse reactions, dose reduction of valbenazine is necessary.
Colchicine	Colchicine C_{max} (↑), AUC (↑↑)[a]	Contraindicated in patients with renal or hepatic impairment, during and for 2 weeks after treatment with itraconazole. Increased risk of colchicine-related adverse reactions, such as decreased cardiac output, cardiac arrhythmias, respiratory distress and bone marrow depression. Not recommended in other patients, during and for 2 weeks after treatment with itraconazole. Increased risk of colchicine-related adverse reactions[c].
Eliglustat	CYP2D6 EMs: Eliglustat C_{max} (↑↑), AUC (↑↑)[a] Higher increases are expected in CYP2D6 IMs/PMs and upon coadministration with a CYP2D6 inhibitor.	Contraindicated in CYP2D6 EMs taking a strong or moderate CYP2D6 inhibitor / CYP2D6 IMs and PMs, during and for 2 weeks after treatment with itraconazole. Increased risk of eliglustat-related AEs such as prolongation of the PR, QTc, and/or QRS cardiac interval, and cardiac arrhythmias. Use with caution in CYP2D6 EMs, monitor for eliglustat adverse reactions[c], dose reduction of eliglustat may be necessary.
Ergot alkaloids	Ergot alkaloids conc increase (extent unknown)[a,b]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of ergot alkaloid-related adverse reactions, such as ergotism. (see also *Antimigraine Drugs*)

Table 1: Examples of interacting drugs		
Example of Medicinal products within class	**Expected/Potential effect on drug levels (see footnotes for additional info)**	**Clinical comment (see codes above for additional info)**
Galantamine	Galantamine C_{max} (↑), AUC (↑)[a]	Use with caution, monitor for galantamine adverse reactions [c]. Dose reduction of galantamine may be necessary.
Ivacaftor	Ivacaftor C_{max} (↑↑), AUC (↑↑↑)[a]	Use with caution, monitor for ivacaftor adverse reactions[c], dose reduction of ivacaftor may be necessary.
Lumacaftor/Ivacaftor	Ivacaftor C_{max} (↑↑), AUC (↑↑)[a] Lumacaftor C_{max} (↔), AUC (↔)[a] Itraconazole conc decrease, extent unknown but likely ↓↓↓	Not recommended from 2 weeks before, during and for 2 weeks after treatment with itraconazole. Itraconazole efficacy may be reduced and increased risk of ivacaftor-related adverse reactions[c].
Vasopressin Receptor Antagonists		
Conivaptan Tolvaptan	Conivaptan C_{max} (↑↑), AUC (↑↑↑↑)[a] Tolvaptan C_{max} (↑↑), AUC (↑↑↑)[a]	Not recommended during and for 2 weeks after treatment with itraconazole. Increased risk of conivaptan/ tolvaptan-related adverse reactions[c].
Mozavaptan	Mozavaptan C_{max} ↑, AUC ↑↑	Use with caution, monitor for mozavaptan adverse reactions[c], dose reduction of mozavaptan may be necessary.

* CYP3A4 inhibitors (including itraconazole) may increase systemic contraceptive hormone concentrations.
EMs: extensive metabolisers; IMs: intermediate metabolisers, PMs: poor metabolisers; TdP: Torsade de Pointes
Note:
Average increase:
↑: <100% (i.e. <2-fold);
↑↑: 100-400% (i.e. ≥2-fold to <5-fold);
↑↑↑: 400-900% (i.e. ≥5-fold and <10-fold);
↑↑↑↑: ≥10-fold;
Average decrease:
↓: <40%;
↓↓: 40-80%;
↓↓↓: >80%;
No effect: ↔;

For the effect (middle column) the name of the parent drug is stated, even when the effect is related to the active moiety or the active metabolite of a prodrug.

[a] For drugs with arrows between brackets, the assessment was based on the mechanism of interaction and clinical drug interaction information with ketoconazole or other strong CYP3A4 inhibitors and/or inhibitors of P-glycoprotein or BCRP, modelling techniques, case reports and/or in vitro data. For the other drugs listed, the assessment was based on clinical drug interaction information with itraconazole.

[b] Pharmacokinetic parameters were not available.

[c] Please consult the corresponding label for information on drug-related adverse events

Paediatric Population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B3.

Teratogenic effects: Itraconazole was found to cause a dosage-related increase in maternal toxicity, embryotoxicity and teratogenicity in rats at dosage levels of approximately 40-160 mg/kg/day and in mice at dosage levels of approximately 80 mg/kg/day. In rats, the

teratogenicity consisted of major skeletal defects and in mice it consisted of encephaloceles and/or macroglossia.

Itraconazole must not be used during pregnancy except for life-threatening cases where the potential benefit to the mother outweighs the potential harm to the foetus (see **section 4.3**).

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 casual relationship with SPORANOX has not been established.

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

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

Breast-feeding

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

Fertility

Refer to **section 5.3 – Carcinogenesis, mutagenicity, impairment of fertility** section for information relevant to itraconazole and hydroxyl-beta-cyclodextrin.

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, which may occur in some instances, must be taken into account (See **section 4.8**).

4.8 Undesirable effects

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of itraconazole based on the comprehensive assessment of the available adverse event information. A causal relationship with itraconazole cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical Trial Data

The safety of SPORANOX oral solution was evaluated in 889 patients who participated in six double-blind and four open-label clinical trials. Of the 889 patients treated with SPORANOX oral solution, 624 patients were treated with SPORANOX oral solution during the double-blind trials. All 889 patients received at least one dose of SPORANOX oral solution for the treatment of oropharyngeal and esophageal candidiasis and provided safety data. Adverse drug reactions (ADRs) reported for ≥1% of patients treated with SPORANOX oral solution in these clinical trials are shown in **Table 1**.

Table 2: Adverse Drug Reactions Reported by ≥1% of Patients Treated with SPORANOX Oral Solution in 10 Clinical Trials	
System Organ Class Adverse Drug Reaction	**SPORANOX Oral Solution %** **(N=889)**
Nervous System Disorders	
Headache	3.6
Dysgeusia	1.5
Dizziness	1.1
Respiratory, Thoracic and Mediastinal Disorders	
Cough	1.8
Gastrointestinal Disorders	
Diarrhoea	9.1
Nausea	8.2
Vomiting	5.2
Abdominal Pain	4.5
Dyspepsia	1.0
Skin and Subcutaneous Tissue Disorders	
Rash	2.5
General Disorders and Administration Site Conditions	
Pyrexia	5.2

Adverse drug reaction that occurred in <1% of patients treated with SPORANOX oral solution in these clinical trials are listed in **Table 2**.

Table 3: Adverse Drug Reactions Reported by <1% of Patients Treated with SPORANOX Oral Solution in 10 Clinical Trials
System Organ Class Adverse Drug Reactions
Blood and Lymphatic System Disorders
Leukopenia
Thrombocytopenia
Immune System Disorders
Hypersensitivity
Metabolism and Nutrition Disorders
Hypokalemia
Nervous System Disorder
Hypoesthesia
Neuropathy peripheral
Paresthesia
Ear and Labyrinth Disorders
Tinnitus
Cardiac Disorders
Cardiac failure
Gastrointestinal Disorders
Constipation
Hepatobiliary Disorders
Hepatic failure
Hyperbilirubinemia
Skin and Subcutaneous Tissue Disorders
Pruritus
Urticaria

System Organ Class Adverse Drug Reactions
Musculoskeletal and Connective Tissue Disorders Arthralgia Myalgia
Reproductive System and Breast Disorders Menstrual disorder
General Disorders and Administrative Site Conditions Oedema

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 Disorders:
Granulocytopenia

Immune System Disorders:
Anaphylactoid reaction

Metabolism and Nutrition Disorders:
Hyperglycaemia, Hyperkalaemia, Hypomagnesemia

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

Paediatrics

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 paediatric patients.

Post-marketing data

Adverse drug reactions first identified during the post-marketing experience with SPORANOX (all formulations) are included in **Table 3**. In this table, the frequencies are provided according to the following convention:

Very common	(≥ 1/10)
Common	(≥1/100 and < 1/10)
Uncommon	(≥1/1,000 and < 1/100)
Rare	(≥1/10,000 and < 1/1000)
Very rare	(<1/10,000), including isolated reports.

Table 4: Adverse Reactions Identified During Post-Marketing Experience with SPORANOX by Frequency Category Estimated from Spontaneous Reporting Rates

Immune System Disorders	
Very rare	Serum sickness, Angioneurotic oedema, Anaphylactic reaction
Endocrine Disorders	
Very rare	Pseudoaldosteronism
Metabolism and Nutrition Disorders	
Very rare	Hypertriglyceridemia
Nervous System Disorders	
Very rare	Tremor
Eye Disorders	
Very rare	Visual disturbances (including diplopia and vision blurred)
Ear and Labyrinth Disorders	
Very rare	Transient or permanent hearing loss
Cardiac Disorders	
Very rare	Congestive heart failure
Respiratory, Thoracic and Mediastinal Disorders	
Very rare	Dyspnoea
Gastrointestinal Disorders	
Very rare	Pancreatitis
Hepatobiliary Disorders	
Very rare	Serious hepatotoxicity (including some cases of fatal acute liver failure)
Skin and Subcutaneous Tissue Disorders	
Very rare	Toxic epidermal necrolysis, Stevens-Johnson syndrome, Acute generalized exanthematous pustulosis, Erythema multiforme, Exfoliative dermatitis, Leukocytoclastic vasculitis, Alopecia, Photosensitivity
Investigations	
Very rare	Blood creatine phosphokinase increased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https//nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Symptoms and Signs

In general, adverse events reported with overdose have been consistent with those reported for itraconazole use.

Treatment

In the event of accidental overdosage, supportive measures should be employed. Activated charcoal may be given if considered appropriate. Itraconazole cannot be removed by haemodialysis. No specific antidote is available.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PREPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic classification: (Antimycotics for systemic use, triazole and tetrazole derivatives).

ATC code: J02A C02

Mechanism of actions

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

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

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

5.2 Pharmacokinetic properties

Peak plasma concentrations of itraconazole are reached within 2 to 5 hours following 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 µg/ml, 1.1 µg/ml and 2.0 µg/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 **sections 4.4** and **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 pre-treatment, 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, 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 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 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 (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 also **sections 4.2** and **4.4**.

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.

Hydroxypropyl-ß-Cyclodextrin

The oral bioavailability of hydroxypropyl-β-cyclodextrin given as a solubiliser 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

Carcinogenesis, mutagenicity, impairment of fertility

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

occurrence of squamous cell carcinoma in the lung is extremely uncommon in untreated rats, the increase in this study was not statistically significant.

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

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

Toxicology

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

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

Microbiology

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

For itraconazole, interpretive breakpoints have not been established for the *Candida* spp. and filamentous fungi.

EUCAST breakpoints for itraconazole have been established for *Aspergillus flavus*, *A. fumigatus*, *A. nidulans* and *A. terreus*, and are as follows: susceptible ≤ 1 mg/L, resistant > 1 mg/L. EUCAST breakpoints for itraconazole have been established for *Candida albicans* and *C. dubliniensis*, and are as follows: susceptible ≤0.06 mg/L, resistant >0.06 mg/L. EUCAST breakpoints for itraconazole have been established for *Candida parapsilosis* and *C. tropicalis*, and are as follows: susceptible ≤0.125 mg/L, resistant >0.125 mg/L. Interpretive breakpoints have not been established by EUCAST for *Candida glabrata*, *C. krusei*, *C. guilliermondii*, *Cryptococcus neoformans*, *Aspergillus niger,* and Non-species related breakpoints for *Candida* and *Aspergillus*.

In vitro studies demonstrate that itraconazole inhibits the growth of a broad range of fungi pathogenic for humans at concentrations usually ≤ 1 µg/ml. These include:

Aspergillus spp., *Blastomyces dermatitidis*, *Cladosporium* spp., *Coccidioides immitis*, *Cryptococcus neoformans*, *Geotrichum* spp., *Histoplasma* spp., including *H. capsulatum*, *Paracoccidioides brasiliensis*, *Talaromyces* (formerly *Penicillium) marneffei*, *Sporothrix schenckii* and *Trichosporon* spp. Itraconazole also displayed activity *in vitro* against *Epidermophyton floccosum*, *Fonsecaea* spp., *Malassezia* spp., *Microsporum* spp., *Pseudallescheria boydii*, *Trichophyton* spp. and various other yeasts and fungi.

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

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

Hydroxypropyl-beta-Cyclodextrin

Single and repeated dose toxicity studies in mice, rats and dogs indicate a wide safety margin after oral and intravenous administration of hydroxypropyl-beta-cyclodextrin. Most effects were adaptive in nature (histological changes in the urinary tract, softening of faeces related to the osmotic water retention in the large intestine, activation of the mononuclear phagocyte system) and showed good reversibility.

Slight liver changes occurred at doses of about 30 times the proposed human dose of hydroxypropyl-beta-cyclodextrin.

Oral treatment of juvenile Beagle dogs with hydroxypropyl-beta-cyclodextrin at 1200 mg/kg for a period of up to 13 weeks with a 4-week recovery period was clinically well tolerated with no effects noted when compared to control animals at laboratory or histopathology examination.

Carcinogenicity and Mutagenicity

No primary carcinogenicity activity was evidenced in the mouse carcinogenicity study. In the rat carcinogenicity study, an increased incidence of neoplasms in the large intestine (at 5000 mg/kg/day) and in the exocrine pancreas (from 500 mg/kg/day) were seen. Based on a human equivalent dose calculation normalised for body surface area, the recommended clinical dose of SPORANOX oral solution contains approximately 1.7 times the amount of hydroxypropyl-beta-cyclodextrin as was in the 500 mg/kg/day dose administered in rats in this carcinogenicity study.

The slightly higher incidence of adenocarcinomas in the large intestines was linked to the hypertrophic/hyperplastic and inflammatory changes in the colonic mucosa brought about by hydroxypropyl-beta-cyclodextrin -induced increased osmotic forces and is considered to be of low clinical relevance. Development of the pancreatic tumors is related to the mitogenic action of cholecystokinin in rats. This finding was not observed in the mouse carcinogenicity study, nor in a 12-month toxicity study in dogs or in a 2-year toxicity study in female cynomolgus monkeys. There is no evidence that cholecystokinin has a mitogenic action in man. However, the clinical relevance of these findings is not applicable.

Hydroxypropyl-beta-cyclodextrin has no antifertile, no direct embryotoxic and no teratogenic effect, and is not mutagenic. The chemical structure of hydroxypropyl-beta-cyclodextrin does not raise suspicion for genotoxic activity. Tests on DNA-damage, gene mutations and chromosome aberrations *in vitro* and *in vivo* did not reveal any genotoxic activity.

Reproductive Toxicology

Hydroxypropyl-beta-cyclodextrin has no direct embryotoxic and no teratogenic effect.

Fertility

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydroxypropyl-beta-cyclodextrin

Sorbitol

Propylene glycol

Hydrochloric acid

Cherry flavour 1

Cherry flavour 2

Caramel flavour

Saccharin sodium

Sodium hydroxide

Purified water.

6.2 Incompatibilities

In the absence of compatibility studies this medicinal product must not be mixed with other medicinal products.

6.3 Shelf Life

2 years

Discard 3 months after opening the bottle.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal and other handling

SPORANOX Oral Solution is supplied in bottles with a child-proof cap, and should be opened as follows: push the plastic screw cap down while turning it counter clockwise.

A measuring cup is supplied with the SPORANOX Oral Solution. Use the measuring cup just as it sits on the bottle. Make sure that the side with the graduations (the side that holds less) is uppermost; that is the side you have to fill. When the arrow on the side points up, the correct side is uppermost.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Janssen-Cilag (New Zealand) Ltd

Auckland, NEW ZEALAND

Telephone: 0800 800 806

Fax: (09) 588 1398

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9. DATE OF FIRST APPROVAL

25 May 1998

10. DATE OF REVISION OF THE TEXT

18 Sep 2023

Summary table of changes

Section changes	Summary of new information
4.8	Addition of Pseudoaldosteronism as a post marketing adverse effect
5.3	Update naming for *Penicillium marneffei* to *Talaromyces* (formerly *Penicillium) marneffei*