AUSTRALIA PRODUCT INFORMATION

SPORANOX® (itraconazole)

Oral Solution

1. NAME OF THE MEDICINE

Itraconazole

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SPORANOX oral solution contains itraconazole 10 mg/mL.

Excipients with known effect: saccharin

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

3. PHARMACEUTICAL FORM

Oral liquid, solution.

SPORANOX oral solution is clear, slightly amber to yellow solution, with a cherry odour.

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

SPORANOX oral solution should be taken on an empty stomach at least 1 hour before food.

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 mg (2 measuring cups, 20 mL) daily in one or two intakes for 2 weeks. If there is no response after 2 weeks the dose should be increased to 400 mg/day for a further 2 weeks.

Prophylaxis of fungal infections:

5 mg/kg per day administered as a twice daily dose until recovery of neutrophils for up to 8 weeks (see section **5.1 – Pharmacodynamics – Clinical trials – Antifungal prophylaxis in neutropenia**).

Instructions for use:

The bottle comes with a child-resistant cap and should be opened by pushing the plastic screw cap down whilst turning it counter clockwise.

Dosage adjustment in:

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 Special Warnings and Precautions for Use**.

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 4.4 Special Warnings and Precautions for Use**.

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. See **section 4.4 Special Warnings and Precautions for Use**.

4.3 CONTRAINDICATIONS

- Co-administration of a number of CYP3A4 substrates is contraindicated with SPORANOX Capsules. Increased plasma concentration of these drugs, caused by co-administration with itraconazole, may increase or prolong both therapeutic and adverse effect to such an extent that a potentially serious situation may occur. Increased plasma concentrations of some of these drugs can lead to QT prolongation. (see **section 4.5 Interactions with Other Medicines and Other Forms of Interactions** – **Table 1** for specific examples)
- Co-administration of the following drugs is contraindicated with SPORANOX oral solution: terfenadine, astemizole, mizolastine, bepridil, felodipine, lercanidipine, nisoldipine, cisapride, domperidone, disopyramide, dofetilide, dronedarone, quinidine, levacetylmethadol (levomethadyl), methadone, pimozide, sertindole, lurasidone, ticagrelor, halofantrine, isavuconazole, naloxegol, lomitapide, avanafil, dapoxetine, eliglustat, irinotecan, ivabradine, ranolazine, eplerenone, CYP3A4-metabolised HMG-CoA reductase inhibitors such as simvastatin and lovastatin, oral midazolam, triazolam and ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine), fesoterodine (in subjects with moderate to severe renal impairment, or moderate to severe hepatic impairment), solifenacin (in subjects with severe renal impairment or moderate to severe hepatic impairment), colchicine (in subjects with renal or hepatic impairment), telithromycin (in subjects with severe renal impairment or severe hepatic impairment). (see **section 4.5 Interactions with Other Medicines and Other Forms of Interactions** – **Table 1** for specific examples).

- SPORANOX oral solution is contraindicated in patients with a known hypersensitivity to the drug or its excipients. There is no information regarding cross hypersensitivity between itraconazole and other azole antifungal agents. Caution should be used in prescribing itraconazole to patients with hypersensitivity to other azoles.
- 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 Special Warnings and Precautions for Use**).
- Itraconazole is contraindicated in pregnant women except for the treatment of life-threatening cases of systemic mycoses, where the potential benefits outweigh the potential harm to the foetus. Highly effective contraceptive precautions should be taken by women of childbearing potential throughout itraconazole therapy, and continued until the next menstrual period following the completion of itraconazole therapy.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use with caution in the following circumstances

Peripheral neuropathy:

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

Use in patients with cystic fibrosis

Variability in therapeutic levels of itraconazole was observed and the therapeutic levels of itraconazole were not achieved in some patients. 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 candidasis 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 Contraindications** and **section 4.5 Interactions with Other Medicines and Other Forms of Interactions**). The hearing loss usually resolves when treatment is stopped, but can persist in some patients.

Cross-resistance

In systemic candidiasis, if fluconazole-resistant strains of Candida species are suspected, it cannot be assumed that these are sensitive to itraconazole, hence it is recommended to 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 of the drug is given.

Use in patients with hepatic impairment

Itraconazole is predominantly metabolised in the liver. Patient with impaired hepatic function should be carefully monitored when taking itraconazole and when deciding to initiate therapy with other medications metabolised by CYP3A4. Dose adjustments may be considered in these patients. (See **section 5.2 Pharmacokinetic Properties – Special population**).

Patients with pre-existing abnormalities of hepatic function (raised liver enzymes, an active liver disease or patients who have experienced liver toxicity with other drugs) who require itraconazole should be monitored, regardless of the duration of therapy.

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

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

Use in patients with 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.

Use in the elderly

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. 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.

Paediatric use

Clinical data on the use of SPORANOX oral solution in paediatric patients are limited. The use of SPORANOX oral solution inpaediatric patients is not recommended unless it is determined that 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 nausea, diarrhoea, abdominal pain, vomiting, fever, rash, pyrexia, hypertension, cough 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 **Toxicology**).

Instructions to the patient

Patients should be instructed to take SPORANOX oral solution at least one hour before food. For the treatment of oral and/or oesophageal candidiasis the solution should be swished around the oral cavity (approximately 20 seconds) and swallowed. There should be no rinsing after swallowing.

Patients should be instructed to report any signs and symptoms that may suggest liver dysfunction so that the appropriate laboratory testing can be done. Such signs and symptoms may include unusual fatigue, anorexia, nausea and/or vomiting, jaundice, dark urine or pale stool. see **section 4.8 Adverse Effects (Undesirable Effects)**.

Toxicology

(See **section 5.3 Preclinical Safety Data – Toxicology**).

Effects on laboratory test

No data available

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, a table is provided listing examples of drugs that may interact with itraconazole, organized per drug family for easy reference. This list of examples is not comprehensive and therefore the label of each drug that is coadministered 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 coadministration.

Itraconazole is mainly metabolized through CYP3A4. Other substances that either share this metabolic pathway or modify CYP3A4 activity may influence the pharmacokinetics of

itraconazole. Coadministration 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. Coadministration 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 metabolized 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, coadministration 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 the table below.

- 'Contraindicated': Under no circumstances is the drug to be coadministered 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 **section 4.3 Contraindications**)
- 'Not recommended': It is recommended that the use of the drug be avoided, unless the benefits outweigh the potentially increased risks. If coadministration cannot be avoided, clinical monitoring is recommended, and the dosage of itraconazole and/or the coadministered 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 coadministered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely and the dosage of itraconazole and/or the coadministered drug adapted as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. This applies to:
    - Drugs that reduce gastric acidity (SPORANOX capsules 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

Examples of interacting drugs are listed in the table below. 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		
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].

Medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see codes above for additional info)
Ciprofloxacin Erythromycin	Itraconazole C_{max} ↑, AUC ↑	Use with caution, monitor for itraconazole adverse reactions, dose reduction of itraconazole may be necessary.
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 Rivaroxaban Vorapaxar	Apixaban 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/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 ↑	Use with caution, monitor for repaglinide/saxagliptin adverse reactions,

Medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see codes above for additional info)
	Saxagliptin C_{max} (↑↑), AUC (↑↑)[a]	dose reduction of repaglinide/saxagliptin may be necessary[c].
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	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]	Use with caution, monitor for adverse reactions related to the antineoplastic drug[c], dose reduction of the antineoplastic drug may be necessary.

Medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see codes above for additional info)
Panobinostat Ponatinib Ruxolitinib Sonidegib Vandetanib	Ixabepilone C_{max} (↔), AUC (↑)[a] Nintedanib C_{max} (↑), AUC (↑)[a] Panobinostat C_{max} (↑), AUC (↑)[a] Ponatinib C_{max} (↑), AUC (↑)[a] Ruxolitinib C_{max} (↑), AUC (↑)[a] Sonidegib 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 Ibrutinib Lapatinib Nilotinib Olaparib Pazopanib Sunitinib 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] 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] Trabectedin C_{max} (↑), AUC (↑)[a] Trastuzumab emtasine 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 adverse reactions, such as potentially life-threatening myelosuppression and diarrhea.
Antipsychotics, Anxiolytics and Hypnotics		

Medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see codes above for additional info)
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, apnoea 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.

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) Telaprevir	Ritonavir-boosted darunavir: itraconazole C_{max} (↑↑), AUC (↑↑)[a] Ritonavir-boosted fosamprenavir: itraconazole C_{max} (↑), AUC (↑↑)[a] Telaprevir: 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]	Use with caution, monitor for adverse reactions related to itraconazole and/or ritonavir[c], Dose reduction of itraconazole may

Medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see codes above for additional info)
	Ritonavir C_{max} (↔), AUC (↑)[a]	be necessary; refer to the ritonavir label for specific actions to be taken.
Saquinavir	Saquinavir (unboosted) C_{max} ↑↑, AUC ↑↑↑ Itraconazole (with boosted saquinavir) C_{max} (↑), AUC (↑↑)[a]	Use with caution, monitor for adverse reactions related to itraconazole and/or saquinavir[c], Dose reduction of itraconazole may be necessary; refer to the saquinavir label for specific actions to be taken.
Simeprevir	Simeprevir C_{max} (↑↑), AUC (↑↑↑)[a]	Not recommended during and for 2 weeks after treatment with itraconazole.
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]	Use with caution, monitor for contraceptive adverse reactions[c], refer to the

Medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see codes above for additional info)
	Ulipristal C_{max} (↑↑), AUC (↑↑↑)[a]	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 hyperkalaemia and hypotension.
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 neutralizing medicines such as aluminium hydroxide, or acid secretion suppressors such as H_2- receptor antagonists and proton pump inhibitors. When co-treatment with acid neutralizing medicines (e.g. aluminium hydroxide) these should be administered at least 2 hours before or 2 hours after the intake of SPORANOX capsules. (See **section 4.4 Special Warnings and Precautions for Use**.)
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* colonization 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	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)	Use with caution monitor for immunosuppressant adverse reactions[c], Dose reduction of the immunosuppressant drug may be necessary.

Medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see codes above for additional info)
Methylprednisolone Tacrolimus Temsirolimus	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]	
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.
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.

Medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see codes above for additional info)
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] Tolterodine C_{max} (↑ to ↑↑), AUC (↑↑)[a] in poor metabolisers of CYP2D6 Udenafil 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*.)
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].
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

Medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see codes above for additional info)
		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*)
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. The clinical relevance of such a potential interaction remains unknown.

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: ↔;

Medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see codes above for additional info)

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

Potential interactions that have been excluded

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

No interaction of itraconazole with zidovudine (AZT) and fluvastatin has been observed. The results of a study in which eight HIV-infected patients were treated with zidovudine, 8±0.4 mg/kg/day, with or without itraconazole, 100 mg b.i.d. showed that the pharmacokinetics of zidovudine are not significantly affected during co-administration with itraconazole.

No inducing effects of itraconazole on the metabolism of ethinyloestradiol and norethisterone were observed.

Absorption from SPORANOX oral solution is not affected by co-administration of H2-antagonists, in contrast to the effect seen with SPORANOX capsules.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

See **section 5.3 Preclinical Safety Data - Genotoxicity, carcinogenicity & effects on fertility**.

Use in pregnancy - Category B3

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

SPORANOX oral solution is contraindicated in pregnancy except in life-threatening cases where the potential benefit to the mother outweighs the potential harm to the foetus (see **section 4.3 Contraindications**).

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

Epidemiological data on exposure to SPORANOX during the first trimester of pregnancy (mostly in patients receiving short-term treatment for vulvovaginal 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.

Use in lactation

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

4.7 EFFECTS OF ABILITY TO DRIVE OR 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 effects such as dizziness, visual disturbances and hearing loss, which may occur in some instances, must be taken into account. See **section 4.8 Adverse Effects (Undesirable Effects)**.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

With the use of SPORANOX oral solution, the most frequently reported adverse effects were of gastrointestinal origin, such as diarrhoea, nausea, abdominal pain and vomiting. Less frequently reported adverse experiences include headache, reversible increases in hepatic enzymes, dizziness and allergic reactions (such as pruritis, rash, urticaria and angio-oedema).

Adverse experiences reported in association with the use of SPORANOX 100 mg capsules:

Common (>1%)	
Body as a whole	dizziness, headache
Hepatobiliary disorders	reversible increases in hepatic enzymes
Gastrointestinal disorders	nausea, vomiting, diarrhoea, abdominal pain, constipation, dyspepsia
Uncommon (<1%)	
Infections and Infestations	sinusitis, upper respiratory tract infection, rhinitis
Gastrointestinal disorders	flatulence
Hepatobiliary disorders	hepatic function abnormal
Renal and urinary disorders	pollakiuria
Reproductive System and breast disorders	erectile dysfunction
Rare (<0.1%)	
Body as a whole	allergic reactions such as pruritus, rash, urticaria and angio-oedema.
Endocrine disorders	menstrual disorder
Very rare (<0.01%)	
Hepatobiliary disorders	hepatitis (especially during prolonged treatment)

The following is a list of additional adverse effects associated with itraconazole that have been reported in clinical trials of SPORANOX oral solution and/or SPORANOX IV. The adverse effects are related to the active substance and are not specifically formulation dependent.

Blood and Lymphatic System Disorders	Granulocytopenia, Thrombocytopenia
Immune System Disorders	Anaphylactoid reaction
Metabolism and Nutrition Disorders	Hyperglycaemia, Hyperkalaemia, Hypokalaemia , Hypomagnesaemia
Psychiatric Disorders	Confusional state
Nervous System Disorders	Neuropathy peripheral, Dizziness, Somnolence
Cardiac Disorders	Cardiac failure, Left ventricular failure, Tachycardia
Vascular Disorders	Hypertension, Hypotension
Respiratory, Thoracic and Mediastinal Disorders	Pulmonary oedema, Dysphonia, Cough
Gastrointestinal Disorders	Gastrointestinal disorder
Hepatobiliary Disorders	Hepatic failure , Hepatitis, Jaundice
Skin and Subcutaneous Tissue Disorders	Rash erythematous, Hyperhidrosis
Musculoskeletal and Connective Tissue Disorders	Myalgia, Arthralgia
Renal and Urinary Disorders	Renal impairment, Urinary incontinence
General Disorders and Administration Site Conditions	Generalized oedema, Face oedema, Chest pain, Pyrexia, Pain, Fatigue, Chills
Investigations	Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Blood lactate dehydrogenase increased, Blood urea increased, Gamma-glutamyltransferase increased, Hepatic enzyme increased, Urine analysis abnormal

POSTMARKETING DATA

Adverse drug effects from spontaneous reports during the worldwide postmarketing experience with SPORANOX (all formulations) that meet threshold criteria are included in the table below. The adverse drug effects are ranked by frequency, using 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.

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

Blood and Lymphatic System Disorders	Very rare: leukopenia and neutropenia, thrombocytopenia
Immune system disorders	Very rare: Serum sickness, angioneurotic oedema, anaphylactic, anaphylactoid and allergic reactions
Metabolism and Nutrition Disorders	Very rare: Hypertriglyceridemia, hypokalaemia
Nervous System Disorders	Very rare: Peripheral neuropathy, paraesthesia, hypoaesthesia, headache, dizziness, tremor
Eye Disorders	Very rare: Visual disturbances, including vision blurred and diplopia
Ear and Labyrinth Disorder	Very rare: Tinnitus, transient or permanent hearing loss
Cardiac Disorders	Very rare: Congestive heart failure
Respiratory, Thoracic and Mediastinal Disorders	Very rare: Pulmonary oedema, dyspnoea

Gastrointestinal Disorders	Very rare: Pancreatitis, abdominal pain, vomiting, dyspepsia, nausea, diarrhoea, constipation, dysgeusia
Hepato-biliary disorders	Very rare: Serious hepatotoxicity (including some cases of fatal acute liver failure), hepatitis, reversible increases in hepatic enzymes
Skin and Subcutaneous Tissue Disorders	Very rare: Toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, erythema multiforme, exfoliative dermatitis, leukocytoclastic vasculitis, urticaria, alopecia, photosensitivity, rash, pruritus
Musculoskeletal and connective tissue disorders	Very rare: Myalgia, arthralgia
Renal and Urinary Disorders	Very rare: Pollakiuria, urinary incontinence
Reproductive System and Breast Disorders	Very rare: Menstrual disorders, erectile dysfunction
General Disorders and Administration Site Conditions	Very rare: Oedema, pyrexia
Investigations	Very rare: Blood creatine phosphokinase increased

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at **http://www.tga.gov.au/reporting-problems**.

4.9 OVERDOSE

Symptoms

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

Treatment

Itraconazole is not removed by dialysis.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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

Microbiology

In vitro Susceptibility Tests, Dilution or diffusion techniques:

Either quantitative (MIC) or breakpoint, should be used following a regulatory updated, recognised and standardised method (eg, Clinical and Laboratory Standard Institute [CLSI formerly NCCLS]). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

For itraconazole, breakpoints have only been established for *Candida* spp. from superficial mycotic infections (CLSI M27-A2, using laboratory controlled *Candida parapsilosis* ATCC 22019, *Candida krusei* ATCC 6258). The proposed MIC breakpoints are as follows:

- Susceptible: A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antifungal compound in the blood reaches the concentrations usually achievable.
- Susceptibility that is "dose- or delivery-dependent" (S-DD): This category implies possible clinical applicability in body sites where the medicine is physiologically concentrated or in situations where high dosage of medicine can be used.
    - Note that itraconazole MIC values for Candida species; Cryptococcus neoformans; Blastomyces dermatidis; Coccidioides immitis; Histroplasma capsulatum; and Geotricum species were reported as ≤ 1 µg/mL.
    - Itraconazole MIC values for Aspergillus flavus, Aspergillus fumigatus Trichosporon species, Fonsecaea pedrosoi, and Trichophyton species were reported as ≤ 1 µg/mL, although interpretive breakpoints have not been established for the filamentous fungi.
- Resistant: A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antifungal compound in the blood reaches the concentrations usually achievable; other therapy should be select.
    - Candida krusei, Candida glabrata and Candida tropicalis are generally the least susceptible Candida species, with some isolates showing unequivocal resistance to itraconazole in vitro.
    - The principal fungus types that are not inhibited by itraconazole are Zygomycetes (e.g. Rhizopus spp., Rhizomucor spp., Mucor spp. and Absidia spp.), Fusarium spp., Scedosporium spp. and Scopulariopsis spp.
    - Azole resistance appears to develop slowly and is often the result of several genetic mutations. Mechanisms that have been described are overexpression of ERG11, which encodes the target enzyme 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.

Correlation between in vitro MIC results and clinical outcomes:

Susceptibility of a microorganism *in vitro* does not predict successful therapy. Host factors are often more important than susceptibility test results in determining clinical outcomes, and resistance *in vitro* should often predict therapeutic failure. Correlation between minimum inhibitory concentration (MIC) results *in vitro* and clinical outcome has yet to be established for azole antifungal agents.

Clinical trials

Oral Candidiasis:

Two randomised, double-blind studies using fluconazole as a comparator were conducted in Group IV HIV-positive adults with culture proven oral candidiasis. In one study, itraconazole 100 mg b.i.d. (n = 135) was compared to fluconazole 100 mg o.d. (n = 132) each given for 7 days. Maintenance therapy of itraconazole 100 mg b.i.d. or fluconazole 100 mg o.d. one day per week was given for 12 weeks. At day 7, 86% of evaluable patients (n = 124) receiving itraconazole had a global evaluation of cured or markedly improved, 41% had a negative culture and 64% had a negative microscopic result. For evaluable patients receiving fluconazole (n = 112) the results were 87%, 32% and 49% respectively. The median time to relapse in the maintenance period using the Kaplan-Meier analysis of survival was greater

than 108 and 94 days respectively. The global evaluation and time to relapse for itraconazole 100 mg b.i.d. and fluconazole 100 mg o.d. were equivalent. In the other double-blind study, itraconazole 100 mg b.i.d. (n = 68 evaluable patients) for 7 days was compared to itraconazole 100 mg b.i.d. (n = 68 evaluable patients) and fluconazole 100 mg o.d. (n = 78 evaluable patients) each for 14 days. A therapeutic response of 84%, 91% and 91% at day 15 was observed. The time to relapse and the relapse rate were similar. The mean symptom scores for soreness and burning, dysphagia, plaques, erythema and extent of lesions were almost identical.

Oesophageal (with and without oral) Candidiasis:

Two randomised, double-blind, double-dummy studies comparing itraconazole oral solution with fluconazole in the treatment of oesophageal candidiasis with or without oral candidiasis were conducted. The first study compared itraconazole 100 mg b.i.d. (n = 58 evaluable patients) with fluconazole 50 mg for 7 days (n = 55 evaluable patients) in patients with AIDS. Pulse therapy of either itraconazole 100 mg b.i.d. or fluconazole 50 mg once weekly was continued for a further 12 weeks. In patients with oesophagitis a clinical response was seen in 93% of patients receiving itraconazole and 89% receiving fluconazole while in patients with oral candidiasis a clinical response was seen in 88% and 89% respectively. The median time to relapse was greater than 3 months by the Kaplan-Meier survival curve.

In the other study, 126 immunocompromised patients (92% HIV positive) with endoscopy-confirmed oesophageal candidiasis and a positive fungal culture were treated with either 100 mg itraconazole or fluconazole for 7 days after which treatment could be increased to 200 mg. All patients were given a 200 mg dose of either drug on the first day followed by 100 mg daily thereafter. Patients continued treatment for 2 weeks following resolution of symptoms and were then followed for a further 4 weeks. A total of 18 (16%) patients (6 itraconazole, 12 fluconazole) had their dose increased to 200 mg daily due to lack of clinical response. Clinical response was seen in 94% of 53 evaluable patients receiving itraconazole and 91% of 57 evaluable patients receiving fluconazole. Mycological cures were obtained in 92% evaluable itraconazole patients and 78% evaluable fluconazole patients. The median time to relapse was comparable for the 2 groups, around 26 days. In these two studies, itraconazole oral solution and fluconazole capsules were demonstrated to be equivalent in the treatment of oesophageal candidiasis.

Oral and oesophageal candidiasis resistant to fluconazole:

Three open-label studies were conducted in patients with either oral or oesophageal candidiasis not responding to fluconazole. In the first study, 60 patients, of whom 40 were evaluable for efficacy, received itraconazole 100 mg b.i.d. for 14 days and 200 mg b.i.d. for a further 14 days if sufficient improvement had not occurred. A global assessment of cure at day 14 was seen in 60% of patients. Clinical cure at day 14 was 68% overall and 52% by intent to treat analysis. In the second study, 83 patients (65 evaluated for efficacy) received itraconazole 100 mg q.i.d. for 14 days. In patients who responded at 7 days the dose was reduced to itraconazole 200 mg for another 7 days. A maintenance phase of itraconazole 200 mg daily or 200 mg 3 times weekly was then continued for up to 6 months. Clinical response (cure or improved) at day 14 was 83% and 70% at study end point. Relapse occurred in 36% of patients at a mean time of 216 days. In the third study, adult HIV positive patients (n = 74) with oral candidiasis resistant to fluconazole received itraconazole 100 mg b.i.d. for 14 days and if not cured then treatment was continued for another 14 days. Follow up was for 6 weeks. Clinical improvement at the end of treatment was seen in 74% of evaluable patients and 70% by intent to treat analysis. The mean time to relapse was 13 days.

Antifungal prophylaxis in neutropenia:

Data on antifungal prophylaxis in neutropenia with itraconazole oral solution is currently limited to patients with haematological malignancy undergoing treatment with chemotherapy or allogeneic stem cell transplant. Commencement of prophylaxis treatment should be prior to the development of neutropenia.

The prophylactic antifungal activity of itraconazole 5 mg/kg was studied in 3 main randomised trials on neutropenic patients with haematological malignancy. In the pivotal double-blind, placebo-controlled trial, patients received itraconazole 2.5 mg/kg b.i.d. (n = 201) or placebo (n = 204). Oral itraconazole solution was started together with chemotherapy, except for bone marrow transplant patients in whom prophylaxis was commenced between 7 days prior to and 3 days after re-infusion of marrow until neutrophil count was restored to >1.0 x 10^9/L for a maximum of 8 weeks. Treatment was continued for a maximum of 8 weeks until neutrophil recovery or until another trial endpoint (e.g. deep fungal infections, superficial fungal infections, rescue IV amphotericin B) was reached. All patients also received both nystatin (500,000 IU q.i.d.) and ciprofloxacin (500 mg b.i.d.). Incidence of all fungal infections was significantly lower in the itraconazole group (23.9% vs 33.3%). Incidence of proven deep fungal infections including aspergillosis was 5 in the itraconazole group and 9 in the placebo group (p = 0.291, one-tailed analysis). There was no statistical difference between treatments in the use of IV amphotericin B as rescue medication.

The second double-blind, double-dummy trial compared itraconazole 2.5 mg/kg b.i.d. (n = 281) to oral amphotericin B 500 mg q.i.d. (n = 276). Prophylaxis treatment with itraconazole oral solution was commenced on the first day of chemotherapy. Treatment was continued for a maximum of 8 weeks until neutrophil recovery or until another trial endpoint was reached. There were no differences between itraconazole and amphotericin B treatments in the incidence of invasive aspergillosis or proven deep fungal infections. No difference between treatments was observed in the usage of rescue antifungal medications. The third open-label study compared itraconazole 2.5 mg/kg b.i.d. (n = 218, with 288 episodes of neutropenia) with fluconazole 100 mg o.d. (n = 227, with 293 episodes of neutropenia). Prophylaxis treatment with itraconazole oral solution commenced on the first day of chemotherapy. Treatment was continued until neutrophil recovery or until another endpoint was reached. Although not statistically significant, 4 cases of aspergillosis (primary parameter) occurred in the fluconazole group compared to none in the itraconazole group. The number of breakthrough deep Candida infections was 2 and 1, and the number of breakthrough superficial infections was 4 and 11, for the itraconazole and the fluconazole groups, respectively.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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

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

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

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

Distribution

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

Metabolism

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

Excretion

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

Special population

Hepatic Impairment

A pharmacokinetic study using a single 100mg dose of itraconazole (one 100mg capsule) was conducted in 6 healthy and 12 cirrhotic subjects. No statistically significant differences in AUC were seen between these two groups. A statistically significant reduction in mean C_{max} (47%) and a twofold increase in the elimination half-life (37 ± 17 hours) of itraconazole were noted in cirrhotic subjects compared with healthy subjects. Patients with impaired hepatic functions should be carefully monitored when taking itraconazole. The prolonged elimination half-life of itraconazole observed in hepatic impairment patients (37.2 ± 17 h) should be considered when deciding to initiate therapy with other medications metabolised by CYP3A4. (See **section 4.4 Special Warnings and Precautions for Use - Use in patients with hepatic impairment**)

Renal Impairment

A pharmacokinetic study using a single 200mg dose of itraconazole (four 50mg capsules) was conducted in three groups of patients with renal impairment (uremic: n=7; haemodialysis: n=7, and continuous ambulatory peritoneal dialysis: n=5). In uremic / haemodialysis and continuous ambulatory peritoneal dialysis subjects, C_{max} were reduced compared with normal population parameters and listed below.

- C_{max} 132-417 (normal) / 50.9-505 ng.h/mL (uremic)
- C_{max} 18.2-341 (haemodialysis / 51.7-111 ng.h/mL (continuous ambulatory peritoneal dialysis)

Plasma concentration-versus-time profiles showed wide inter-subject variation in all three groups.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity, carcinogenicity & effects on fertility

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

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

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

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

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

Toxicology

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Hydroxypropylbetadex

Sorbitol solution (70 per cent) (non-crystallising)

Propylene glycol

Hydrochloric acid

654536 Cherry Flavour (ARTG PI No. 107587)

654595 Cherry Flavour (ARTG PI No. 107586)

Caramel

Saccharin sodium

Sodium hydroxide

Purified water

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

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.

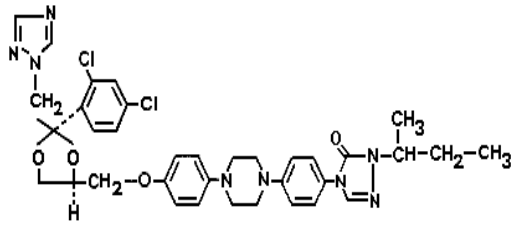
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Itraconazole is a synthetic triazole antifungal agent. It has three chiral centres and is a 1:1:1:1 racemic mixture of four diastereomers (two enantiomeric pairs).

Chemical structure:



$C_{35}H_{38}Cl_2N_8O_4$

CAS: 84625-61-6

7. MEDICINE SCHEDULE (POISON STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

JANSSEN-CILAG Pty Ltd

1-5 Khartoum Road

Macquarie Park NSW 2113 Australia

Telephone: 1800 226 334

NZ Office: Auckland New Zealand

Telephone: 0800 800 806

9. DATE OF FIRST APPROVAL

06 February 1998

10. DATE OF REVISION

26 May 2021

Summary table of changes

Section changed	Summary of new information
2	Inclusion of excipients with known effect.
6.1	Editorial changes to excipient listing