NEW ZEALAND DATA SHEET

ITRAZOLE

1. Product Name

Itrazole 100 mg capsules

2. Qualitative and Quantitative Composition

Each capsule contains 100 mg of itraconazole.

Excipient with known effect: Sugar

Allergen Declaration: Sugar

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Capsule: Size 00, hard gelatin capsule with a red opaque cap and red opaque body printed axially with “MYLAN” over “IE 100” in white ink on cap and body, and containing white to off-white coloured pellets.

4. Clinical Particulars

4.1 Therapeutic indications

Itrazole capsule is indicated for the treatment of:

- vulvovaginal candidiasis.
- pityriasis versicolor,
- dermatomycosis – including highly keratinised regions as in plantar tinea pedis and palmer tinea manus,
- fungal keratitis,
- oral candidiasis,
- onychomycosis caused by dermatophytes and/or yeasts,
- systemic mycoses, only in the following fungal infections:
    - systemic aspergillosis and candidiasis,
    - histoplasmosis,
    - histoplasmosis, maintenance therapy only in AIDS patients
    - sporotrichosis (including lymphocutaneous/cutaneous and extracutaneous),
    - paracoccidioidomycosis,
    - chromomycosis,
    - blastomycosis.

4.2 Dose and method of administration

Treatment schedules are as follows:

Indication	Dose	Duration
Vulvovaginal candidiasis	200 mg twice daily or 200 mg once daily	1 day 3 days
Pityriasis versicolor	100 mg twice daily 200 mg once daily	5-7 days
Dermatomycosis	100 mg once daily or 200 mg once daily	15 days or 7 days
Dermatomycosis in highly keratinised regions as in plantar tinea pedis and palmar tinea manus	200 mg twice daily or 100 mg once daily	7 days or 30 days
Oral candidiasis	100 mg once daily	15 days
Fungal keratitis	200 mg once daily	21 days The duration of treatment should be adjusted to clinical response.

Onychomycosis

Pulse treatment (see table below):

A pulse treatment consists of two capsules (200 mg) twice daily for one week. Two pulse treatments are recommended for fingernail infections and three pulse treatments for toenail infections. Pulse treatments are always separated by a 3-week treatment-free interval. Clinical response will become evident as the nail regrows, following discontinuation of the treatment.

Site of onychomycosis	Week 1	Weeks 2, 3, 4	Week 5	Weeks 6, 7, 8	Week 9
Toenails with or without fingernail involvement	Pulse 1	Itraconazole-free	Pulse 2	Itraconazole-free	Pulse 3
Fingernails only	Pulse 1	Itraconazole-free	Pulse 2	Itraconazole-free	-

Continuous Treatment: 200 mg once daily for 3 months.

Elimination of itraconazole from skin and nail tissue is slower than from plasma. Optimal clinical and mycological response is thus reached 2 to 4 weeks after the cessation of treatment for skin infections and 6 to 9 months after the cessation of treatment for nail infections.

Systemic mycoses

Dosage recommendations for systemic mycoses vary according to the infection treated and are as follows:

Indication	Dose	Median duration[1]	Remarks
Aspergillosis	200 mg once daily	2-5 months	Increase dose to 200 mg twice daily in case of invasive or disseminated disease

Candidiasis	100 to 200 mg once daily	3 weeks - 7 months	Increase dose to 200 mg twice daily in case of invasive or disseminated disease
Histoplasmosis	200 mg once daily to 200 mg twice daily	8 months	
Histoplasmosis (maintenance therapy only in AIDS patients)	200 mg once or twice daily	*Until immune recovery*[2]	
Lymphocutaneous and cutaneous sporotrichosis	100 mg or 200 mg once daily (localised lesions) Or 200 mg twice daily (extensive lesions)	3 months to 6 months	
Extracutaneous sporotrichosis	200 mg twice daily	12 months	
Paracoccidioido-mycosis	100 mg once daily	6 months	
Chromomycosis	200 mg once daily	6 months	
Blastomycosis	100 mg once daily to 200 mg twice daily	6 months	

[1] The duration of treatment should be adjusted depending on the clinical response.

[2] The duration of treatment should be based upon the status of the immune recovery.

Special population

Paediatric

Clinical data on the use of itraconazole capsules in paediatric patients are limited. The use of itraconazole capsules in paediatric patients is not recommended unless it is determined that the potential benefit outweighs the potential risks (see section 4.4).

Elderly

Clinical data on the use of itraconazole capsules in elderly patients are limited. It is advised to use itraconazole capsules in these patients only if it is determined that the potential benefit outweighs the potential risks. In general, it is recommended that the dose selection for an elderly patient should be taken into consideration, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other medicine 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 medicine 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 medicine is administered in this patient population and adjusting the dose may be considered.

Method of administration

For optimal absorption, it is essential to administer itraconazole capsules immediately after a full meal. The capsules must be swallowed whole.

4.3 Contraindications

- Itrazole capsules are contraindicated in patients who have shown hypersensitivity to itraconazole or to any of the excipients listed in section 6.1.
- Itrazole capsules are contraindicated in pregnant women except for the treatment of life-threatening cases systemic mycoses, where the potential advantages must be weighed against the potential harm to the foetus. Highly effective contraceptive precautions should be used by women of childbearing potential throughout itraconazole therapy, and continued until the next menstrual period following the end of itraconazole therapy.
- Co-administration of a number of CYP3A4 substrates is contraindicated with itraconazole. Increased plasma concentrations of these medicines, 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 medicines can lead to QT prolongation and ventricular tachyarrythmias including occurrences of Torsades de Pointes, a potentially fatal arrhythmia (see section 4.5).
- Itrazole capsules should not be administered to patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF except for the treatment of life-threatening or other serious infections (see section 4.4).
- Co-administration of the following medicines is contraindicated with Itrazole capsule: 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).

4.4 Special warnings and precautions for use

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

Peripheral neuropathy

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

Decreased gastric acidity

Absorption of itraconazole from itraconazole capsules is impaired when the gastric acidity is decreased. In patients also receiving acid neutralising medicines (e.g. aluminium hydroxide), these should be administered at least 2 hours after the intake of itraconazole. In patients with achlorhydria, such as certain AIDS patients and patients on acid secretion suppressors (e.g. H_2-antagonists, proton-pump inhibitors), it is advisable to administer itraconzaole capsules with a cola beverage (see section 4.5). The antifungal activity should be monitored.

Other azole antifungal agents

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

Congestive heart failure

In a study with itraconazole 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. Itraconazole 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.

Itraconazole 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 itraconazole, 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. Itraconazole 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.

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.

Patients with pre-existing abnormalities of hepatic function (raised liver enzymes, an active liver disease, or patients who have experienced liver toxicity with other medicines) 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 itraconazole. 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 medicines. 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 itraconazole 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.

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.

Limited data are available on the use of oral itraconazole in patients with hepatic impairment. Caution should be exercised when the medicine 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 metabolized by CYP3A4.

In patients with elevated or abnormal liver enzymes or active liver disease, or who have experienced liver toxicity with other medicines, treatment should not be started unless the expected benefit exceeds the risk of hepatic injury. In such cases liver enzyme monitoring is necessary. 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 medicine is administered in this patient population and adjusting the dose may be considered.

Immunocompromised patients

In some immunocompromised patients (e.g. neutropenic, AIDS or organ transplant patients) the oral bioavailability of itraconazole capsules may be decreased. Therefore, the dose should be adjusted based on the clinical response in these patients.

Patients with immediately life-threatening systemic fungal infections

Due to the pharmacokinetic properties itraconazole capsules are not recommended for initiation of treatment in patients with immediately life-threatening systemic fungal infections.

Patients with AIDS

In patients with AIDS who have received treatment for a systemic fungal infection with itraconazole and who are considered at risk for relapse, the treating physician should evaluate the need for a maintenance therapy.

Cystic fibrosis

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

Hearing loss

Transient or permanent hearing loss has been reported in patients receiving treatment with itraconazole. Several of these reports included concurrent administration of quinidine which is contraindicated (see sections 4.3 and 4.5). The hearing loss usually resolves when treatment is stopped, but can persist in some patients.

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 have their sensitivity tested before the start of itraconazole therapy.

Interchangeability

It is not recommended that itraconazole capsules and itraconazole oral solution be used interchangeably. This is because medicine exposure is greater with the oral solution than with the capsules when the same dose is given.

Interaction potential

Co-administration of specific medicines with itraconazole may result in changes in efficacy of itraconazole and/or the co-administered medicine, life-threatening effects and/or sudden death. Medicines 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 itraconazole capsules to patients with hypersensitivity to other azoles.

Special population

Use in children

The efficacy and safety of itraconazole capsules have not been established in children. Since clinical data for the use of itraconazole in children is limited, the use of itraconazole capsules is not recommended unless it is determined that the potential benefit outweighs the potential risks.

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).

Use in the elderly

Clinical data on the use of Itraconazole capsules in elderly patients is limited. Use itraconazole capsules 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 medicine therapy.

Instructions to the patient

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).

Toxicology

(See section 5.3 Preclinical Safety Data – Toxicology).

Effects on laboratory test

No data available

4.5 Interaction with other medicines and other forms of interaction

Itraconazole is a medicine with high interaction potential. The various types of interaction and associated general recommendations are described below. In addition, a table is provided listing examples of medicines that may interact with itraconazole, organized per medicine family for each reference. The list of examples is not comprehensive and therefore the data sheet of each medicine 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 co-administration.

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. 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.

Absorption of itraconazole from the capsule formulation is reduced in subjects with reduced gastric acidity. Medicines that reduce gastric acidity impair the absorption of itraconazole from itraconazole capsules. To counteract this effect it is recommended to administer itraconazole capsules with an acidic beverage (such as non-diet cola) upon coadministration with medicines that reduce gastric acidity (see section 4.4).

Itraconazole and its major metabolite, hydroxy-itraconazole are potent CYP3A4 inhibitors. Itraconazole is an inhibitor of drug transporter P-glycoprotein and breast cancer resistance protein (BRCP). Itraconazole can inhibit the metabolism of medicines metabolized by CYP3A4 and can inhibit the medicine transport by P-glycoprotein and/or BCRP, which may result in increased plasma concentrations of these medicines 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 medicines. For some medicines, coadministration with itraconazole may result in decreased plasma concentrations of the medicine or of the active moiety of the medicine. This may result in reduced efficacy of the medicine.

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 medicines whose metabolism is affected by itraconazole.

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

- 'Contraindicated': Under no circumstances is the medicine 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).
- 'Not recommended': It is recommended that the use of the medicine 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 medicine 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 medicine is coadministered with itraconazole. Upon coadministration, it is recommended that patients be monitored closely and the dosage of itraconazole and/or the coadministered medicine adapted as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured. This applies to:
    - Medicines that reduce gastric acidity (itraconazole 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 medicines are listed in the table below. The medicines listed in this table

are based on either medicine interaction studies or case reports, or potential interactions based on the mechanism of interaction.

Medicinal products within class	Expected/Potential effect on medicine 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)	Alfentanil AUC (↑↑ to ↑↑↑↑)[a] Buprenorphine C_{max} (↑↑), AUC (↑↑)[a]	Use with caution, monitor for adverse reactions related to the analgesic[c], dose reduction of alfentanil/buprenorphine/oxycodone/sufentanil
Oxycodone Sufentanil	Oxycodone C_{max} ↑, AUC ↑↑ Sufentanil conc. increase (extent unknown)[a,b]	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.
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[c], dose reduction of delamanid/trimetrexate may be necessary.
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 [c], 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.
Anticoagulants and Antiplatelet Medicines		
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[c], dose reduction of dabigatran may be necessary
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[c], dose reduction of repaglinide/saxagliptin may be necessary
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 data sheet 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[c], dose reduction of praziquantel may be necessary.
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 Medicines		
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) Vandetanib	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] 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 ↑	Use with caution, monitor for adverse reactions related to the antineoplastic medicine[c], dose reduction of the antineoplastic medicine may be necessary.
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 medicine[c]. Additionally: For cabazitaxel, even though the change in pharmacokinetic parameters did not reach statistical significance in a low-dose medicine interaction study with ketoconazole, a high variability in the results was observed. For ibrutinib, refer to the data sheet 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 diarrhoea.
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 Zopiclone	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 medicine[c], dose reduction of these medicines 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 data sheet of the antiviral medicine for specific actions to be taken.
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 data sheet 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 data sheet 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 medicines[c]. Refer to the elbasvir/grazoprevir data sheet 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 medicines[c]. Refer to the glecaprevir/pibrentasvir data sheet 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 reactions related to itraconazole and/or the antivirals[c]. dose reduction of itraconazole may be necessary. Refer to the data sheet (s) of the coadministered medicines 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 data sheet 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 data sheet 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 Medicines, 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 medicines)[a,b]	Not recommended during and for 2 weeks after treatment with itraconazole[c]. Increased risk of adverse reactions related to the cardiovascular medicine.
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 data sheet 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].
Gastrointestinal Medicines		
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 data sheet 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.
Medicines that reduce gastric acidity	Itraconazole: C_{max} ↓↓, AUC ↓↓	Use with caution: Medicines 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 itraconazole capsules (see section 4.4).
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 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	Use with caution monitor for immunosuppressant adverse reactions[c], dose reduction of the immunosuppressant medicine may be necessary.

	(↑↑)[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 Medicines		
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 Medicines		
Meloxicam	Meloxicam C_{max} ↓↓, AUC ↓	Use with caution, monitor for reduced efficacy of meloxicam, dose adaption of meloxicam may be necessary.
Respiratory Medicines		
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 Medicines		
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] Tolterodine C_{max} (↑ to ↑↑), AUC (↑↑)[a] in poor metabolisers of CYP2D6 Udenafil C_{max} (↑), AUC (↑↑)[a]	Use with caution, monitor for urologic medicine adverse reactions[c], dose reduction of the urologic medicine may be necessary; refer to the dutasteride data sheet for specific actions to be taken. (For sildenafil and tadalafil, see also *Cardiovascular Medicines, Miscellaneous Medicines 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 medicine adverse reactions[c], dose reduction of solifenacin may be necessary.
Miscellaneous Medicines 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 medicine 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 Adverse reactions 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 medicines*).
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 medicine is stated, even when the effect is related to the active moiety or the active metabolite of a prodrug.
[a] For medicines with arrows between brackets, the assessment was based on the mechanism of interaction and clinical medicine 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 medicines listed, the assessment was based on clinical medicine interaction information with itraconazole.
[b] Pharmacokinetic parameters were not available.
[c] Please consult the corresponding data sheet for information on medicine-related adverse reactions

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 AZT (zidovudine) and fluvastatin has been observed.

The results from a study in which eight HIV-infected individuals 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 concomitant administration of itraconazole.

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

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Fertility

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.

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.

Itraconazole capsules are 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).

There is limited information on the use of itraconazole 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 itraconazole has not been established.

Epidemiological data on exposure to itraconazole 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

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

Breastfeeding

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 twice daily), 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 itraconazole therapy should therefore be weighed against the potential risk of breastfeeding. In case of doubt the patient should not breastfeed.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive or to use machinery 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 medicine cannot be directly compared to rates in the clinical trials of another medicine and may not reflect the rates observed in clinical practice.

Clinical trial data

In clinical studies involving short periods of treatment with itraconazole the overall incidence of adverse experiences is about 7%. In patients receiving prolonged (approximately 1 month) continuous treatment especially, the incidence of adverse experiences was higher (about 15%).

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, hyperbilirubinemia
Renal and urinary disorders	pollakiuria
Reproductive System and breast disorders	erectile dysfunction
Immune System disorders	hypersensitivity

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 itraconazole oral solution and/or intraconazole 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 edema, 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 edema, Face edema, 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

Paediatrics

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

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

Post-marketing data

Adverse medicine effects from spontaneous reports during the worldwide post-marketing experience with itraconazole (all formulations) that meet threshold criteria are included in the table below. The adverse medicine 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 medicine 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

Endocrine Disorder	Very rare: Pseudoaldosteronism
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 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://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

Symptoms and signs

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

Treatment

In the event of accidental overdosage, supportive measures should be employed. Itraconazole cannot be removed by haemodialysis.

For further advice on management of overdose please contact the National Poisons Information Centre (**0800 POISON** or **0800 764 766**).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic classification: Antimycotics for systemic use, triazole derivatives.
ATC code: J02AC02

Mechanism of action

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 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, interpretive breakpoints have not been established by CLSI for *Candida* spp. and the 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, C.lisitaniae, 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, 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.

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

Histoplasmosis

In five open-label, non-comparative studies in patients (n = 136) with histoplasmosis exposed to treatment and maintenance therapy with itraconazole: sixty-one patients (45%) were HIV infected and 8 patients (6%) had other causes of immunosuppression. Ninety-eight patients (72%) had disseminated disease and 42 patients (31%) had other forms of histoplasmosis. Overall, 135 of the 136 patients (approx. 100%) responded. Five patients (4%) relapsed while on treatment. Efficacy was demonstrated for the oral treatment and maintenance therapy of histoplasmosis, both in immunocompromised and non-immunocompromised patients at the recommended dose of 200 - 400 mg/day for 8 months.

Onychomycosis

In three double-blind, placebo-controlled studies (n = 214 total), conducted in the US, patients with onychomycosis of the toenails received 200 mg once daily for 12 consecutive weeks. Results of these studies demonstrated mycological cure in 54% of patients, defined as simultaneous occurrence of negative KOH plus negative culture. Thirty-five (35) percent of patients were considered an overall success (mycological cure plus clear or minimal nail involvement with significantly decreased signs); 14% of patients demonstrated mycological cure plus clinical cure (clearance of all signs, with or without residual nail deformity). The mean time to overall success was approximately 10 months. Twenty-one (21) percent of the overall success group has a relapse (worsening of the global score or conversion of KOH or culture from negative to positive).

Intermittent (Pulse) Treatment of Onychomycosis

Onychomycosis of the toe nail: In a double-blind study (n= 129 total) there was no significant difference in clinical and mycological success and overall response between itraconazole 200 mg twice daily one week per month (pulse) for 3 months and continuous treatment of itraconazole 200 mg once daily for 3 months. In an open study (n = 50 total) there was no significant difference in clinical and mycological success and overall response between a 3 pulse and 4 pulse regimen.

Onychomycosis of the fingernail: In a double-blind, placebo controlled study (n = 71 total) a treatment of itraconazole 200 mg twice daily one week per month was more effective than placebo. The clinical and mycological success for itraconazole pulse treatment in compliant patients was 77% and 73% respectively and for placebo was nil and 12%. In an open study 84% of patients receiving 2 pulse treatments (n = 48) and 91% receiving 3 pulse treatments (n = 68) showed a clinical success and 77% and 85% respectively showed a mycological cure at endpoint.

Aspergillosis

In nine open-label studies of patients (n = 719) with systemic aspergillosis and treated with itraconazole, an overall response rate of 63% was observed. This varied according to the clinical syndrome, e.g. pulmonary aspergilloma (60%), bronchopulmonary (78%), invasive (62%) and extra-pulmonary (62%). In eight patients with cerebral aspergillosis the response rate was 13%. In a randomised, double-blind, comparator trial against amphotericin B in patients with proven or highly suspected aspergillosis, 6 of 8 patients receiving itraconazole responded and 2 of 5 patients responded on amphotericin B. The numbers are too small to assert any difference between treatments. The recommended dose for systemic aspergillosis is 200 mg/day for 2 - 5 months, with a dose of 200 mg twice daily for invasive or disseminated disease.

Sporotrichosis

In four open-label, non-comparative studies of patients (n = 124) with sporotrichosis, 115 of 124 patients (93%) treated with itraconazole demonstrated a complete or marked remission rate. The recommended dosage is 100 - 200 mg/day for 3 months. Treatment duration may be longer in patients with lymphatic/lymphocutaneous and extracutaneous sporotrichosis.

Candidiasis

In three open-label studies of patients (n = 143) with systemic candidiasis and treated with itraconazole, patients with urinary and pulmonary candidiasis responded with high efficacy, although the numbers with these conditions were small. An 85% response rate was observed in patients with oral and oesophageal candidiasis who had underlying cancer and were receiving chemotherapy and/or antibiotics or who had HIV/AIDS. In non-neutropenic patients with non-invasive candidiasis the response rate was 76%. The recommended dose is 100 - 200 mg/day for 3 weeks to 7 months.

5.2 Pharmacokinetic properties

The oral bioavailability of itraconazole capsules is maximal and appears to be more consistent when they are taken immediately after a meal. However, there is a marked intersubject variability. The observed absolute oral bioavailability of itraconazole was 55%. If administered in the fasting state, C_{max} and AUC are about 30-40% lower than after a meal. Peak plasma levels are reached 3 to 5 hours following an oral dose. Elimination from plasma is biphasic with a terminal half-life of 1.5 to 2 days. During chronic administration, steady state is reached after 10-14 days. Mean steady state plasma concentrations of itraconazole 3-4 hours after medicine intake are 0.4 microgram/mL (100 mg once daily), 1.1 micrograms/mL (200 mg once daily) and 2.0 micrograms/mL (200 mg twice daily). Itraconazole clearance decreases at higher doses due to saturable hepatic metabolism.

The plasma protein binding of itraconazole is 99.8%. Concentrations of itraconazole in whole blood are 60% of those in plasma. Steady state itraconazole levels in the skin vary according to the distribution of sebaceous glands, ranging from one third of plasma levels in the skin of the palms to double plasma levels in the skin of the back. Itraconazole is eliminated from keratinous tissues by the shedding of cells during normal regeneration. Itraconazole is undetectable in the plasma within 7 days of stopping therapy, but levels at or above the MIC_{90} for dermatophytes persist in the skin for one or two weeks after discontinuation of a 4-week treatment. Itraconazole is present at high concentrations in sebum but levels in sweat are negligible.

Absorption

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 the capsules are administered with an acidic beverage (such as a non-diet cola). When itraconazole capsules were administered as a single 200 mg dose under fasted conditions with non-diet cola after ranitidine pretreatment, a H_2-receptor antagonist, itraconazole absorption was comparable to that observed when itraconazole capsules were administered alone (see section 4.5).

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

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

In vitro studies have shown that CYP3A4 is the major enzyme involved in the metabolism of itraconazole. Itraconazole is extensively metabolized 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. Serum antifungal medicine levels measured by bioassay were about 3 times those of itraconazole assayed by high performance liquid chromatograph.

Excretion

Faecal excretion of the parent medicine varies between 3-18% of the dose. Renal excretion of the parent medicine is less than 0.03% of the dose. About 35% of a dose is excreted as metabolites in the urine within 1 week.

Special populations

Hepatic Impairment

Itraconazole is predominantly metabolized 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. 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).

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 x 50 mg capsules) was conducted in three groups of patients with renal impairment (uremia: n=7; hemodialysis: n=7; and continuous ambulatory peritoneal dialysis: n=5). In uremic hemodialysis 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 (hemodialysis / 51.7-111 ng.h/mL (continuous ambulatory peritoneal dialysis)

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

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

Data are not available in renally impaired patients during long-term use of itraconazole. Dialysis has no effect on the half-life or clearance of itraconazole or hydroxy-itraconazole (see sections 4.2 and 4.4).

Paediatrics

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

5.3 Preclinical safety data

Genotoxicity

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

Carcinogenesis and mutagenicity,

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.

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

Capsule contents:

- Sugar spheres

- Hypromellose
- Silica, colloidal hydrated
- Sorbitan stearate.

Capsule shell:

- Gelatin
- Titanium dioxide (E171)
- Red iron oxide (E172)
- White printing ink S-1-7078.

White printing ink S-1-7078:

- Shellac
- Titanium dioxide (E171)
- Isopropyl alcohol
- Propylene glycol
- n-Butyl alcohol
- Ammonium hydroxide
- Simeticone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

PVC/PVDC- aluminium blister pack. Pack-sizes of 4, 6, 7, 8, 14, 15, 18, 28, 30, 50, 60, 84, 100, 140, 150, 280, 300 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicine should be disposed of in accordance with local requirements.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
PO Box 11-183
Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

28 September 2006

10. Date of Revision of the Text

1 October 2024

Summary Table of Changes

Section	Summary of change
4.6, 4.8	Minor editorial change
4.8	Addition of Pseudoaldosteronism as a post marketing adverse effect Update ADR reporting website
5.1	Updated "*in vitro* Susceptibility Tests, Dilution or Diffusion Techniques" section