AUSTRALIAN PRODUCT INFORMATION

ITRACAP®

(Itraconazole) capsules

1 NAME OF THE MEDICINE

Itraconazole

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ITRACAP capsules contain itraconazole 100 mg.

Excipients with known effect
sugars and sufites.

For the full list of excipients, see **Section 6.1 List of Excipients**.

3 PHARMACEUTICAL FORM

ITRACAP is available as size 0el hard gelatin white opaque capsules filled with off-white to cream colored pellets and imprinting with ITR on cap and 100 on body.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ITRACAP is indicated for use in adults for the treatment of:

- Superficial dermatomycoses not responding to topical treatment.
- Fungal keratitis which has failed to respond to topical treatment or where the disease is either progressing rapidly or is immediately sight threatening.
- Pityriasis versicolor not responding to any other treatment.
- Vulvovaginal candidiasis not responding to topical treatment.
- Oral candidiasis in immunocompromised patients.
- Onychomycosis caused by dermatophytes.
- Systemic mycoses, only in the following fungal infections:
    - Systemic aspergillosis, histoplasmosis, lymphocutaneous/cutaneous sporotrichosis.
    - Treatment and maintenance therapy in AIDS patients with disseminated or chronic pulmonary histoplasmosis infection.
    - Treatment of oropharyngeal and/or oesophageal candidiasis when first line systemic antifungal therapy is inappropriate or has proven ineffective.
    - Treatment of non-invasive candidiasis in non-neutropenic patients when first-line systemic antifungal therapy is inappropriate or has proven ineffective. This may be due to underlying pathology, insensitivity of the pathogen or drug toxicity.

4.2 DOSE AND METHOD OF ADMINISTRATION

It is essential that ITRACAP capsules are taken immediately after a meal for maximal absorption. The capsules must be swallowed whole. Treatment schedules are as follows:

Superficial dermatomycoses:

- Tinea corporis, tinea cruris: 1 capsule (100 mg) daily for 2 weeks
- Tinea pedis, tinea manus: 1 capsule (100 mg) daily for 4 weeks

Fungal keratitis:

- 2 capsules (200 mg) once daily for 3 weeks

Pityriasis versicolor:

- 2 capsules (200 mg) once daily for 1 week

Vulvovaginal candidiasis:

- 2 capsules (200 mg) morning and evening for 1 day or 2 capsules (200 mg) once daily for 3 days

Oral candidiasis in immunocompromised patients:

- 1 capsule (100 mg) or 2 capsules (200 mg) daily for 4 weeks. (see **section 4.4 Special warnings and precautions for use, Immunocompromised patients**).

Onychomycosis:

- 2 capsules (200 mg) once daily for 3 months OR
- Pulse therapy (see table below):

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

Table 1: Recommended clinical dose for onychomycosis

Site of Onychomycosis	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**	**Week 9**
Toenails with or without fingernail involvement	Pulse 1	Itraconazole free weeks			Pulse 2	Itraconazole free weeks			Pulse 3
Fingernails only	Pulse 1	Itraconazole free weeks			Pulse 2				

Systemic mycoses:

(Dosage recommendations vary according to the infection treated)

Table 2: Dosing recommendations for other systemic mycoses

INDICATION	DOSE	USUAL DURATION	REMARKS
Aspergillosis	200 mg once daily	2 - 5 months	Increase dose to 200 mg twice daily in cases of invasive or disseminated disease
Histoplasmosis	200 mg once daily. - 200 mg twice daily.	8 months	Continue as necessary in AIDS patients. Maintenance therapy: 200 mg once. daily.
Lymphocutaneous/Cutaneous Sporotrichosis	100 mg oncedaily.	3 months	Some patients may require 200 mg daily. (See section 5.1 Pharmacodynamic properties, *Clinical Trial, Sporotrichosis*)
Candidiasis	100 - 200 mg once daily.	3 weeks - 7 months	-

Special Populations

Elderly

Clinical data on the use of Itraconazole capsules in elderly patients are limited. It is advised to use ITRACAP capsules in these patients only if it is determined that the potential benefit outweighs the potential risks. In general, it is recommended that the dose selection for an elderly patient should be taken into consideration, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (See **section 4.4 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 insufficiency. The exposure of itraconazole may be lower in some patients with renal insufficiency. Caution should be exercised when this drug is administered in this patient population and adjusting the dose may be considered.

4.3 CONTRAINDICATIONS

Co-administration of a number of CYP3A4 substrates is contraindicated with itraconazole 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 and ventricular tachyarrhythmias including occurrences of Torsades de Pointes, a

potentially fatal arrhythmia. (see **section 4.5 Interactions with Other medicines and other forms of interactions – Table 3** for specific examples).

Co-administration of the following drugs is contraindicated with Itraconazole capsule: terfenadine, astemizole, Aliskiren, bepridil, felodipine, lercanidipine, domperidone, disopyramide, dronedarone, methadone, lurasidone, quetiapine, dabigatran, ticagrelor, apixaban, rivaroxaban, halofantrine, isavuconazole, naloxegol, lomitapide, avanafil, darifenacin, dapoxetine, eliglustat, irinotecan, venetoclax (in patients with chronic lymphotic leukaemia during dose initiation/titration/ramp-up phase of venetoclax), ivabradine, ranolazine, eplerenone, sildenafil (pulmonary hypertension), Ombitasvir/Paritaprevir/Ritonavir (with or without Dasabuvir), nisoldipine, mizolastine, cisapride, dofetilide, levacetylmethadol (levomethadyl), quinidine, pimozide, sertindole, CYP3A4-metabolised HMG-CoA reductase inhibitors such as simvastatin and lovastatin, oral midazolam, triazolam and ergot alkaloids such as dihydroergotamine, ergometrine (ergonovine), ergotamine, eletriptan 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), vardenafil (in patients older than 75 years, colchicine (in subjects with renal or hepatic impairment), vorapaxar, edoxaban, 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 3 for specific examples)**.

Itraconazole capsules are contraindicated in patients with a known hypersensitivity to the drug or its excipients.

Itraconazole 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 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 for two months 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.

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 itraconazole capsules with a cola beverage. (See **section 4.5 Interactions with other medicines and other forms of interactions**). The antifungal activity should be monitored and the itraconazole dose increased as deemed necessary.

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.

Cardiac Dysrhythmias
Life-threatening cardiac dysrhythmias and/or sudden death have occurred in patients using drugs such as methadone, pimozide or quinidine concomitantly with itraconazole and/or other CYP3A4 inhibitors. Concomitant administration of these drugs with itraconazole is contraindicated (see sections **4.3 Contraindications** and **4.5 Interactions with other medicines and other forms of interactions**).

Use in patients with 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 CHF. 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 evidence of ventricular dysfunction such as CHF or with a history of CHF 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 CHF. 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 CHF. Caution should be exercised and the patient monitored for the signs and symptoms of CHF. 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. Concomitant administration of Itraconazole with felodipine is contraindicated.

Cases of CHF, peripheral oedema, and pulmonary oedema have been reported in the post-marketing period among patients being treated for onychomycosis and/or systemic fungal infections (see section **4.8 Adverse effects** (**undesirable effects**)).

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 populations***).

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 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 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.

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 drugs, treatment with itraconazole is strongly discouraged unless there is serious or life-threatening situation where the expected benefit exceeds the risk.

It is recommended that liver function monitoring be done in patients with pre-existing hepatic function abnormalities or those who have experienced liver toxicity with other medications. (See section **5.2 Pharmacokinetic properties - Special Populations, Hepatic impairment**).

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.

Several cases of hypokalaemia have been reported. Serum potassium should be monitored in patients at risk during high-dose itraconazole therapy. Itraconazole cannot be removed by haemodialysis.

Immunocompromised patients
In some immunocompromised patients (e.g. neutropenic, AIDS or organ transplant patients) the oral bioavailability of itraconazole capsules may be decreased. Impaired absorption in AIDS and neutropenic patients may lead to low itraconazole blood levels and lack of efficacy. Therefore, the dose should be adjusted based on the clinical response in these patients (see section **4.2 Dose and method of administration**) and therapeutic blood level monitoring may be necessary.

Inadequate plasma concentrations were frequently found in patients whose antineoplastic therapy predisposed them to very poor oral absorption and frequent vomiting. In this case, antiemetics can be co-administered and it is particularly important that itraconazole capsules be administered with meals.

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 having received treatment for a systemic fungal infection such as sporotrichosis, blastomycosis, histoplasmosis or cryptococcosis (meningeal or non-meningeal) with itraconazole and who are considered at risk for relapse, the treating physician should evaluate the need for a maintenance treatment.

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

Disorders of Carbohydrate Metabolism
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

Cross-resistance
In systemic 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.

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 (see section **4.3 Contraindications** and **section 4.5 Interactions with other medicines and other forms of interactions**).

Monitoring and Laboratory Tests
Plasma levels 3 to 4 hours after dosing with itraconazole should be monitored in patients requiring treatment for more than one month, in patients with systemic mycoses who have factors predisposing to poor absorption (such as achlorhydria, renal insufficiency, neutropenia, AIDS) or in those who are taking drugs which may alter itraconazole absorption or metabolism (such as rifampicin and phenytoin).

Due to the presence of an active metabolite, monitoring of plasma levels by bioassay will indicate plasma levels roughly 3 times higher than will monitoring by high-performance liquid chromatography, unless solvent conditions for the HPLC assay are adjusted to allow simultaneous detection of both the parent drug and this metabolite (hydroxy-itraconazole).

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 section 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 therapy.

Paediatric use
The efficacy and safety of itraconazole have not been established in children. Since clinical data on the use of itraconazole in children is limited, itraconazole capsules should not be used in these patients unless 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 Preclinical Safety Data, *Toxicology***).

Instructions to the patient
Patients should be instructed to take itraconazole capsules with food. The capsules must be swallowed whole. 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**).

Effects on laboratory tests
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 Product information 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.

Absorption of itraconazole from the capsule formulation is reduced in subjects with reduced gastric acidity. Drugs 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 drugs that reduce gastric acidity. (see **section 4.4 Special Warnings and Precautions for Use**).

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 table.

- '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 (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 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 3: Examples of interacting drugs

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

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

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

Medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see above for additional info)
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]	Contraindicated.
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]	Contraindicated.
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 Product Information for specific actions to be taken.

Medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see above for additional info)
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 and cardiac disorders, including QT c interval shortening.
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 Drugs		
Eletriptan	Eletriptan C_{max} (↑↑), AUC (↑↑↑)[a]	Contraindicated.

Medicinal products within class	**Expected/Potential effect on drug levels (see footnotes for additional info)**	**Clinical comment (see above for additional info)**
Ergot alkaloids (such as dihydroergotamine, ergometrine, ergonovine, 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 Cmax ↑, AUC ↑ Imatinib Cmax (↑), AUC (↑)a Ixabepilone Cmax (↔), AUC (↑)a Nintedanib Cmax (↑), AUC (↑)a Panobinostat Cmax (↑), AUC (↑)a Pemigatinib Cmax (↑), AUC (↑)a Ponatinib Cmax (↑), AUC (↑)a Ruxolitinib Cmax (↑), AUC (↑)a Sonidegib Cmax (↑), AUC (↑↑)a Tretinoin Cmax (↑), AUC (↑)a Vandetanib Cmax ↔, AUC ↑	Use with caution, monitor for adverse reactions related to the antineoplastic drug[c], dose reduction of the antineoplastic drug 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.

Medicinal products within class	**Expected/Potential effect on drug levels (see footnotes for additional info)**	**Clinical comment (see above for additional info)**
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 Cmax (↑), AUC ↑↑↑) Glasdegib Cmax (↑), 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 (↑)[a] Trabectedin Cmax (↑), AUC (↑)[a] Trastuzumab emtansine conc increase (extent unknown)[a,b] Vinca alkaloid conc increase (extent unknown)[a,b]	Not recommended during and for 2 weeks after treatment with itraconazole. Increased risk of adverse reactions related to the antineoplastic drug[c]. Additionally: For cabazitaxel, even though the change in pharmacokinetic parameters did not reach statistical significance in a low-dose drug interaction study with ketoconazole, a high variability in the results was observed. For ibrutinib/ertrecotnib, refer to the Product Information 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.
Mobocertinib	Mobocertinib C_{max} ↑↑, AUC ↑↑↑	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of mobocertinib-related adverse reactions[c].

Medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see above for additional info)
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
Antipsychotics, Anxiolytics and Hypnotics		
Alprazolam Aripiprazole Brotizolam Buspirone Cariprazine Haloperidol Midazolam (iv) Perospirone 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 ↑↑↑ 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.
Quetiapine	Quetiapine Cmax (↑↑), AUC (↑↑↑)[a]	Contraindicated
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.

Medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see above for additional info)
Sertindole	Sertindole conc increase (extent unknown)[a,b]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of sertindole-related adverse reactions, such as QT prolongation and TdP.
Triazolam	Triazolam C_{max} ↑ to ↑↑, AUC ↑↑ to ↑↑↑↑	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of triazolam-related adverse reactions, such as seizures, respiratory depression, angioedema, apnea and coma.
Antivirals		
Asunaprevir (boosted) Tenofovir disoproxil fumarate (TDF)	Asunaprevir C_{max} (↑↑↑), AUC (↑↑↑)[a] Tenofovir conc increase (extent unknown)[a,b]	Use with caution, however, refer to the Product information of the antiviral drug 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 Product information 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 Cmax (↑), 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 Product informationcfor specific actions to be taken.

Medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see above for additional info)
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 Product Information for specific actions to be taken.
Glecaprevir/ Pibrentasvir	Glecaprevir C_{max} (↑ ↑), AUC (↑ ↑ to ↑ ↑ ↑)[a] Pibrentasvir C_{max} (↔ to ↑), AUC	Use with caution, monitor for adverse reactions related to the co-administered drugsc. Refer to the glecaprevir/pibrentasvir Product Information 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]	Contraindicated.
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 Product Information 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 Product Information 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.

Medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see above for additional info)
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	Aliskiren Cmax ↑↑↑, AUC ↑↑↑	Contraindicated.
Riociguat Tadalafil (pulmonary hypertension)	Riociguat C_{max} (↑), AUC (↑↑)[a] 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.
Sildenafil (pulmonary hypertension)	Sildenafil conc increase (extent unknown but effect may be greater than reported under Urological Drugs)[a,b]	Contraindicated
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.

Medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see above for additional info)
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*		
DienogestU lipristal	Dienogest C_{max} (↑), AUC (↑↑)[a] Ulipristal C_{max} (↑↑), AUC (↑↑↑)[a]	Use with caution, monitor for contraceptive adverse reactions[c], refer to the dienogest/ulipristal Product information 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 Cmax (↑↑), AUC (↑↑↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increases risk of finerenone-related adverse reactions[c]
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 Product information 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.

Medicinal products within class	**Expected/Potential effect on drug levels (see footnotes for additional info)**	**Clinical comment (see above for additional info)**
Drugs that reduce gastric acidity	Itraconazole: C_{max} ↓↓, AUC ↓↓	Use with caution: Drugs that reduce gastric acidity: e.g. acid neutralizing medicines such as aluminum hydroxide, or acid secretion suppressors such as H2- 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 itraconazole 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 Ciclosporin 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] Ciclosporin (iv) conc increase ↔ to ↑[b] Ciclosporin (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) Cmax (↑↑), AUC (↑↑)a Temsirolimus (iv) Cmax (↑↑), AUC (↑↑)a	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 above for additional info)
Everolimus Sirolimus (rapamycin)	Everolimus C_{max} (↑↑), AUC (↑↑↑↑)[a] Sirolimus C_{max} (↑↑), AUC (↑↑↑↑)[a]	Not recommended during and for 2 weeks after treatment with itraconazole. Increased risk of everolimus/ sirolimus-related adverse reactions[c].
Voclosporin	Voclosporin Cmax (↑↑↑), AUC (↑↑↑↑)a	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of voclosporin-related adverse reactions[c]
Lipid Regulating Drugs		
Atorvastatin	Atorvastatin C_{max} ↔ to ↑↑, AUC ↑ to↑↑	Use with caution, monitor for atorvastatin adverse reactions[c]. Dose reduction of atorvastatin may be necessary.
Lomitapide	Lomitapide C_{max} (↑↑↑↑), AUC (↑↑↑↑)[a]	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of lomitapide-related adverse reactions, such as hepatotoxicity and severe gastrointestinal reactions.
Lovastatin Simvastatin	Lovastatin C_{max} ↑↑↑↑, AUC ↑↑↑↑ Simvastatin C_{max} ↑↑↑↑, AUC ↑↑↑↑	Contraindicated during and for 2 weeks after treatment with itraconazole. Increased risk of lovastatin/ simvastatin-related adverse reactions, such as myopathy, rhabdomyolysis and liver enzyme abnormalities.
Nonsteroidal Anti-Inflammatory Drugs		
Meloxicam	Meloxicam C_{max} ↓↓, AUC ↓	Use with caution, monitor for reduced efficacy of meloxicam, dose adaption of meloxicam may be necessary.
Respiratory Drugs		
Salmeterol	Salmeterol C_{max} (↑), AUC (↑↑↑↑)[a]	Not recommended during and for 2 weeks after treatment with itraconazole. Increased risk of salmeterol-related adverse reactions[c].
SSRIs, Tricyclics and Related Antidepressants		
Reboxetine Venlafaxine	Reboxetine C_{max} (↔), AUC (↑)[a] Venlafaxine C_{max} (↑), AUC (↑)[a]	Use with caution, monitor for reboxetine/venlafaxine adverse reactions[c], dose reduction of reboxetine/venlafaxine may be necessary.
Urologic Drugs		

Medicinal products within class	**Expected/Potential effect on drug levels (see footnotes for additional info)**	**Clinical comment (see above for additional info)**
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]	Contraindicated.
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 metabolizers 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 product information 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.

Medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see above for additional info)
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[c], dose reduction of alitretinoin/ cabergoline/cannabinoids/cinacalcet may be necessary.
Valbenazine	Valbenazine Cmax (↑), 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].

Medicinal products within class	Expected/Potential effect on drug levels (see footnotes for additional info)	Clinical comment (see above for additional info)
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 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 Cmax (↑↑), 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 metabolizers; IMs: intermediate metabolizers, PMs: poor metabolizers; TdP: Torsade de pointes
Note:
Average increase:
↑: <100% (i.e. <2-fold);
↑↑: 100-400% (i.e. ≥2-fold to <5-fold);
↑↑↑: 400-900% (i.e. ≥5-fold and <10-fold);
↑↑↑↑: ≥10-fold;

Average decrease:
↓: <40%;
↓↓: 40-80%;
↓↓↓: >80%; No effect: ↔;

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

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

[b] Pharmacokinetic parameters were not available.

[c] Please consult the corresponding Product Information for information on drug-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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on 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 – 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 Contraindications).

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 taking itraconazole should use highly effective contraception during treatment and for 2 months following the end of treatment. A reliable method of barrier contraception must always be used in combination with other methods of contraception.

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 itraconazole capsules 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 ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive or use machines have been performed. When driving vehicles and operating machinery the possibility of adverse reactions such as dizziness, visual disturbances and hearing loss, which may occur in some instances, must be taken into account. See **section 4.8 Adverse Effects (Undesirable effects**).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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
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, oedema
Endocrine disorders	menstrual disorder
Blood and lymphatic system disorders	Leukopenia
Immune system disorders	Serum sickness, Angioneurotic oedema, Anaphylactic reaction
Adverse Drug Reactions	Hypertriglyceridaemia
Nervous system disorder	Tremor, Paraesthesia, Hypoaesthesia, Dysgeusia
Eye Disorders	Visual disturbance (including diplopia and blurred vision)
Ear and labyrinth disorder	Transient or permanent hearing loss, Tinnitus
Cardiac disorders	Congestive heart failure, Tinnitus
Respiratory, thoracic and mediastinal disorders	Dyspnoea
Gastrointestinal disorders	Pancreatitis
Hepatobiliary disorders	Serious hepatotoxicity (including some cases of fatal acute liver failure), Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	Toxic epidermal necrolysis, Stevens-Johnson syndrome, Acute generalised exanthematous pustulosis, Erythema multiforme, Exfoliative dermatitis, Leukocytoclastic vasculitis, Alopecia, Photosensitivity
Investigations	Blood creatine phosphokinase increased
Immune system disorders	Serum sickness, Angioneurotic oedema, Anaphylactic reaction

Very rare (<0.01%)

Hepatobiliary disorders	hepatitis (especially during prolonged treatment)

Not known:

Endocrine disorders	Pseudoaldosteronism

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 itraconazole 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	Hyperglycemia, Hyperkalemia, Hypokalemia, Hypomagnesemia
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

Postmarketing data

Adverse drug reactions from spontaneous reports during the worldwide postmarketing experience with itraconazole (all formulations) that meet threshold criteria are included in the table below. The adverse drug reactions 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 reactions 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 disorders	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, Bradycardia
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

Other reported events include granulocytopenia, hypersensitivity, Upper respiratory tract infection, hyperglycemia, hypomagnesimia, confusional state, cardiac failure, left ventricular failure, tachycardia, hypotension, dysphonia, gastrointestinal disorder, hepatic failure, hyperbilirubinemia, rash erythematous, hyperhidrosis, renal impairment, generalized oedema, face oedema, chills, 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.

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 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. In the event of accidental overdosage, supportive measures should be employed.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antimycotic for systemic use, triazole and tetrazole derivatives, ATC code: J02A C02.

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, 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 ≤1µg/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.

<u>Correlation between *in vitro* MIC results and clinical outcomes:</u>
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 b.i.d. one week per month (pulse) for 3 months and continuous treatment of itraconazole 200 mg o.d. 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 b.i.d. 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 (amphotericin) 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

Absorption

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 drug intake are 0.4 microgram/mL (100 mg o.d.), 1.1 micrograms/mL (200 mg o.d.) and 2.0 micrograms/mL (200 mg b.i.d.).

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.

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. Serum antifungal drug levels measured by bioassay were about 3 times those of itraconazole assayed by high performance liquid chromatograph.

Excretion

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 a 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 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; 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.

5.3 PRECLINICAL SAFETY DATA

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

Carcinogenicity
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.

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

Hypromellose, macrogol 20,000, sucrose, maize starch in a hard gelatin capsule. The capsules are printed with TekPrint SW-9008 Black Ink.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

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. Protect from light and moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

They are supplied in PVC/PE/PVDC/Al blister packs of 4, 6, 15, 28 and 60 capsules.

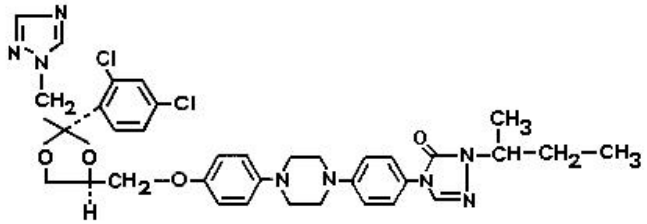
Not all pack sizes may be marketed.

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

Chemical structure



Chemical Name: (±)-cis-4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one.

Molecular Formula: $C_{35}H_{38}Cl_2N_8O_4$

Molecular Weight: 705.64

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). It is a white to slightly yellowish powder, insoluble in water at pH 1-12, very slightly soluble in alcohol and freely soluble in dichloromethane.

CAS number

84625-61-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 Prescription Only Medicine

8 SPONSOR

Arrotex Pharmaceuticals Pty Ltd
15-17 Chapel Street
Cremorne, VIC 3121
Australia
www.arrotex.com.au

9 DATE OF FIRST APPROVAL

9 August 2016

10 DATE OF REVISION

7 January 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.3	Updated section to include contraindications with itraconazole.
4.4	Added Cardiac dysrhythmias, Disorders of carbohydrate metabolism, Interaction potential and Monitoring and laboratory Tests.
4.8	Updated section to include adverse drug reactions.
All	Minor editorial changes.