For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

ITRACLAR/TRICUTIS

1. **Generic Name**

   Itraconazole Capsules I.P.

2. **Qualitative and quantitative Composition:**

   ITRACLAR/TRICUTIS 100

   Each hard gelatin capsule contains:

   Itraconazole I.P. ……..100 mg

   (As Pellets)

   Approved colours used in capsule shells.

   The excipients used are ready to use pellets of Itraconazole and starch.

   ITRACLAR/TRICUTIS 200

   Each hard gelatin capsule contains:

   Itraconazole I.P. ……..200 mg

   (As Pellets)

   Approved colours used in capsule shells.

   The excipients used are ready to use pellets of Itraconazole and starch.

3. **Dosage form and strength**

   Dosage form: Capsule

   Strength: 100 mg and 200 mg

4. **Clinical particulars**

4.1. Therapeutic indication

ITRACLAR/TRICUTIS 100

It is indicated for Systemic aspergillosis and candidas cryptococcosis, sporotrichosis, paracoccidioidomycosis, blastomycosis and other rarely occurring systemic or tropical mycoses.

ITRACLAR/TRICUTIS 200

It is indicated for treatment of onychomycosis of the toenail due to Trichophyton rubrum or T. mentagrophytes in non-immunocompromised patients.

4.2. Posology and method of administration

Posology

One capsule of ITRACLAR/TRICUTIS is therapeutically equivalent to one 100 mg capsule of conventional itraconazole capsules. The recommended dose for ITRACLAR/TRICUTIS is therefore half the recommended dose for conventional itraconazole capsules. ITRACLAR/TRICUTIS capsules and conventional itraconazole 100 mg capsules are not bioequivalent and therefore are not interchangeable.

A discussion of the relative pharmacokinetics of ITRACLAR/TRICUTIS compared with conventional itraconazole hard capsules is presented below.

Use in patients with hepatic impairment

Limited data are available on the use of oral itraconazole in patients with hepatic impairment. Caution should be exercised when the drug is administered in this patient population.

Use in patients with renal impairment

The oral bioavailability of itraconazole may be lower in patients with renal insufficiency. Caution should be exercised when this drug is administered in this patient population and adjusting the dose may be considered.

Use in the elderly

Clinical data on the use of itraconazole in elderly patients are limited. It is advised to use itraconazole 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.

The itraconazole treatment schedules in adults for each indication are given in the following tables:

NB. In some immunosuppressed patients, e.g. with neutropenia, AIDS or after organ transplantation, the bioavailability of itraconazole may be lowered. Doubling the dose may be indicated.

Itraconazole remains substantially longer in the skin than in the blood. Optimal healing is thus achieved 2-4 weeks after withdrawing itraconazole in cases of mycoses of the skin.

Superficial mycoses (of skin, mucosae, eyes)		
Indication	***Itraconazole 50 mg Capsule Dosage***	***Duration of treatment***
Pityriasis versicolor	*2 capsules once daily*	*7 days*
Tinea corporis, Tinea cruris	*1 capsule once daily*	*2 weeks*
Fungal keratitis	*2 capsules once daily*	*3 weeks*
Dermatomycosis of palms and soles (tinea manus, tinea pedis)	*1 capsule once daily*	*4 weeks*
Vulvovaginal candidiasis	*2 capsules morning and evening*	*1 day*
	2 capsules once daily	*3 days*
Oral candidiasis in immunocompromised patients	*1 capsule or 2 capsules daily*	*4 weeks*
Dermatomycosis of nails (onychomycosis)	*2 capsules once daily (or pulsed therapy – see following table)*	*12 weeks*

An alternative dosage regimen for dermatomycosis of nails (onychomycosis) is pulsed therapy. A pulse treatment consists of two capsules twice daily 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.

Pulsed therapy for onychomycosis									
Site of onychomycosis infection	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 7**	**Week 8**	**Week 9**
Toenails with or without fingernail involvement	2 capsules morning and evening	Itraconazole free weeks			2 capsules morning and evening	Itraconazole free weeks			2 capsules morning and evening
Fingernails only	2 capsules morning and evening	Itraconazole free weeks			2 capsules morning and evening	Itraconazole free weeks			

Systemic mycoses			
Systemic mycoses	**Itraconazole 50 mg Capsule Dosage**	**Duration of treatment**	**Notes**
Aspergillosis	2 capsules once daily	2 – 5 months	In invasive or disseminated disease, increase to 2 capsules twice daily (in the morning and in the evening)
Candidiasis	1 – 2 capsules once daily	3 weeks –7 months	In invasive or disseminated disease, increase to 2 capsules twice daily (in the morning and in the evening)
Histoplasmosis	2 capsules once daily or up to twice daily (in the morning and in the evening)	8 months	-
Sporotrichosis	1 capsule once daily	3 months	Some patients may require 2 capsules once daily

*The duration of the treatment should be adjusted depending on clinical efficacy.

Method of administration

Itraconazole capsule is for oral administration and can be taken with or without food.

4.3. Contraindications

- Itraconazole Capsules are contraindicated in patients with known hypersensitivity to itraconazole or to any of the excipients.

- Co-administration of a number of CYP3A4 substrates is contraindicated with Itraconazole capsules. Increased plasma concentrations of these drugs, caused by co- administration with itraconazole, may increase or prolong both therapeutic and adverse effects to such an extent that a potentially serious situation may occur. For example, increased plasma concentrations of some of these drugs can lead to QT prolongation and ventricular tachyarrhythmias including occurrences of torsade de pointes, a potentially fatal arrhythmia.
- 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.
- Itraconazole capsules must not be used during pregnancy except for life-threatening cases.
- Women of childbearing potential taking Itraconazole capsules should use contraceptive precautions. Effective contraception should be continued until the menstrual period following the end of Itraconazole capsules therapy.

4.4. Special warnings and precautions for use

Cross-hypersensitivity

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

Cardiac effects

In a reported healthy volunteer study with Itraconazole IV, a transient asymptomatic decrease of the left ventricular ejection fraction was observed; this resolved before the next infusion. The clinical relevance of these findings to the oral formulations is unknown.

Itraconazole has been shown to have a negative inotropic effect and Itraconazole capsules 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. This individual benefit/risk assessment should take into consideration factors such as the severity of the indication, the dosing regimen (e.g. total daily dose), and individual risk factors for congestive heart failure. These risk factors include cardiac disease, such as ischemic and valvular disease; significant pulmonary disease, such as chronic obstructive pulmonary disease; and renal failure and other edematous disorders. Such patients should be informed of the signs and symptoms of congestive heart failure, should be treated with caution, and should be monitored for signs and symptoms of congestive heart failure during treatment; if such signs or symptoms do occur during treatment, Itraconazole should be discontinued.

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 exercised when co-administering itraconazole and calcium channel blockers due to an increased risk of congestive heart failure.

Hepatic effects

Very rare cases of serious hepatotoxicity, including some cases of fatal acute liver failure, have occurred with the use of Itraconazole capsules. 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 were 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 drug is administered in this patient population. It is recommended that patients with impaired hepatic function be carefully monitored when taking itraconazole. It is recommended that the prolonged elimination half- life of itraconazole observed in the reported single oral dose clinical trial with itraconazole capsules in cirrhotic patients be considered when deciding to initiate therapy with other medications metabolised by CYP3A4.

In patients with elevated or abnormal liver enzymes or active liver disease, or who have experienced liver toxicity with other drugs, treatment with Itraconazole is strongly discouraged unless there is a serious or life threatening situation where the expected benefit exceeds the risk. It is recommended that liver function monitoring be done in patients with pre-existing hepatic function abnormalities or those who have experienced liver toxicity with other medications.

Reduced gastric acidity

Absorption of itraconazole from Itraconazole capsules is impaired when gastric acidity is reduced. In patients with reduced gastric acidity, whether from disease (e.g. patients with achlorhydria) or from concomitant medication (e.g. patients taking drugs that reduce gastric acidity), it is advisable to administer Itraconazole capsules with an acidic beverage (such as non-diet cola). The antifungal activity should be monitored and the itraconazole dose increased as deemed necessary.

Paediatric population

Clinical data on the use of Itraconazole Capsules in paediatric patients is limited. The use of Itraconazole capsules in paediatric patients is not recommended unless it is determined that the potential benefit outweighs the potential risks.

Use in 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 drug therapy.

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.

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. The hearing loss usually resolves when treatment is stopped, but can persist in some patients.

Immunocompromised patients

In some immunocompromised patients (e.g., neutropenic, AIDS or organ transplant patients), the oral bioavailability of Itraconazole capsules may be decreased.

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 nonmeningeal) and who are considered at risk for relapse, the treating physician should evaluate the need for a maintenance treatment.

Neuropathy

If neuropathy occurs which may be attributable to Itraconazole capsules, the treatment should be discontinued.

Cross-resistance

In systemic candidosis, if fluconazole-resistant strains of Candida species are suspected, it cannot be assumed that these are sensitive to itraconazole, hence their sensitivity should be tested before the start of Itraconazole therapy.

Interchangeability

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

Interaction Potential

Co-administration of specific drugs with itraconazole may result in changes in efficacy of itraconazole and/or the co-administered drug, life-threatening effects and/or sudden death.

4.5. Drugs interactions

Itraconazole is mainly metabolised through CYP3A4. Other substances that either share this metabolic pathway or modify CYP3A4 activity may influence the pharmacokinetics of itraconazole. Similarly, itraconazole may modify the pharmacokinetics of other substances that share this metabolic pathway. Itraconazole is a potent CYP3A4 inhibitor and a P- glycoprotein inhibitor. When using concomitant medication, it is recommended that the corresponding label be consulted for information on the route of metabolism and the possible need to adjust dosages.

<u>Drugs that may decrease itraconazole plasma concentrations</u>

Drugs that reduce the gastric acidity (e.g. acid neutralising medicines such as aluminium hydroxide, or acid secretion suppressors such as H2-receptor antagonists and proton pump inhibitors) impair the absorption of itraconazole from itraconazole capsules. It is recommended that these drugs be used with caution when co-administered with itraconazole capsules:

- It is recommended that itraconazole be administered with an acidic beverage (such as nondiet cola) upon co-treatment with drugs reducing gastric acidity.
- It is recommended that acid neutralising medicines (e.g. aluminum hydroxide) be administered at least 1 hour before or 2 hours after the intake of Itraconazole capsules.

- Upon co-administration, it is recommended that the antifungal activity be monitored and the itraconazole dose increased as deemed necessary.
- Co-administration of itraconazole with potent enzyme inducers of CYP3A4 may decrease the bioavailability of itraconazole and hydroxy-itraconazole to such an extent that efficacy may be largely reduced. Examples include:

Antibacterials: isoniazid, rifabutin (see also under Drugs that may have their plasma concentrations increased by itraconazole), rifampicin.
Anticonvulsants: carbamazepine, (see also under Drugs that may have their plasma concentrations increased by itraconazole), phenobarbital, phenytoin.
Antivirals: efavirenz, nevirapine.
Herbal medicines: Hypericum perforatum (St John's Wort).

Therefore, administration of potent enzyme inducers of CYP3A4 with itraconazole is not recommended. It is recommended that the use of these drugs be avoided from 2 weeks before and during treatment with itraconazole, unless the benefits outweigh the risk of potentially reduced itraconazole efficacy. Upon co-administration, it is recommended that the antifungal activity be monitored and the itraconazole dose increased as deemed necessary.

Drugs that may increase itraconazole plasma concentrations

Potent inhibitors of CYP3A4 may increase the bioavailability of itraconazole.

Examples include:

- Antibacterials: ciprofloxacin, clarithromycin, erythromycin,
- Antivirals: ritonavir-boosted darunavir, ritonavir-boosted fosamprenavir, indinavir (see also under drugs that may have their plasma concentrations increased by itraconazole), ritonavir (see also under drugs that may have their plasma concentrations increased by itraconazole) and telaprevir,

It is recommended that these drugs be used with caution when co-administered with itraconazole capsules. It is recommended that patients who must take itraconazole concomitantly with potent inhibitors of CYP3A4 be monitored closely for signs or symptoms of increased or prolonged pharmacologic effects of itraconazole, and the itraconazole dose be decreased as deemed necessary. When appropriate, it is recommended that itraconazole plasma concentrations be measured.

Drugs that may have their plasma concentrations increased by itraconazole

Itraconazole and its major metabolite, hydroxy-itraconazole, can inhibit the metabolism of drugs metabolised by CYP3A4 and can inhibit the drug transport by P-glycoprotein, 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. CYP3A4-metabolised drugs known to prolong the QT interval may be contraindicated with itraconazole, since the combination may lead to ventricular tachyarrhythmias including occurrences of torsade de pointes, a potentially fatal arrhythmia.

Once treatment is stopped, itraconazole plasma concentrations decrease to an almost undetectable concentration within 7 to 14 days, depending on the dose and duration of treatment. In patients with hepatic cirrhosis or in subjects receiving CYP3A4 inhibitors, the decline in plasma concentrations may be even more gradual. This is particularly important when initiating therapy with drugs whose metabolism is affected by itraconazole.

The interacting drugs are categorized as follows:

- 'Contraindicated': Under no circumstances is the drug to be co-administered with itraconazole, and up to two weeks after discontinuation of treatment with itraconazole.
- 'Not recommended': It is recommended that the use of the drug be avoided during and up to two weeks after discontinuation of treatment with itraconazole, unless the benefits outweigh the potentially increased risks of side effects. If co-administration cannot be avoided, clinical monitoring for signs or symptoms of increased or prolonged effects or side effects of the interacting drug is recommended, and its dosage be reduced or interrupted as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured.
- 'Use with caution': Careful monitoring is recommended when the drug is co-administered with itraconazole.

Upon co-administration, it is recommended that patients be monitored closely for signs or symptoms of increased or prolonged effects or side effects of the interacting drug, and its dosage be reduced as deemed necessary. When appropriate, it is recommended that plasma concentrations be measured.

Examples of drugs that may have their plasma concentrations increased by itraconazole presented by drug class with advice regarding co-administration with itraconazole:

Drug Class	**Contraindicated**	**Not Recommended**	**Use with Caution**
Alpha Blockers		Tamsulosin	
Analgesics	Levacetylmethadol (levomethadyl), methadone	Fentanyl	Alfentanil, buprenorphine IV and sublingual, oxycodone, sufentanil
Antiarrhythmics	Disopyramide, dofetilide, dronedarone, quinidine		Digoxin
Antibacterials	Telithoromycin, in subjects with severe renal impairment or severe hepatic impairment	Rifabutin[a]	Telithromycin
Anticoagulants and Antiplatelet Drugs	Dabigatran, ticagrelor	Apixaban, rivaroxaban	Coumarins, cilostazol
Anticonvulsants		Carbamazepine[a]	
Antidiabetics			Repaglinide, saxagliptin
Antihelmintics and Antiprotozoals	Halofantrine		Praziquantel

Drug Class	Contraindicated	Not Recommended	Use with Caution
Antihistamines	Astemizole, mizolastine, terfenadine	Ebastine	Bilastine
Antimigraine Drugs	Ergot alkaloids, such as dihydroergotamine, ergometrine (ergonovine), ergotamine, methylergometrine (methylergonovine)	Eletriptan	
Antineoplastics	Irinotecan	Axitinib, dabrafenib, dasatinib, ibrutinib, lapatinib, nilotinib, sunitinib, trabectedin	Bortezomib, busulphan, docetaxel, erlotinib, gefitinib, imatinib, ixabepilone, lapatinib, ponatanib, trimetrexate, vinca alkaloids
Antipsychotics, Anxiolytics and Hypnotics	Lurasidone, oral midazolam, pimozide, quetipine sertindole, triazolam		Alprazolam, aripiprazole, brotizolam, buspirone, haloperidol, midazolam IV, perospirone, quetiapine, ramelteon, risperidone
Antivirals		Simeprevir	Maraviroc, indinavir[b], ritonavir[b], saquinavir
Beta Blockers			nadolol
Calcium Channel Blockers	Bepridil, felodipine, lercanidipine, nisoldipine		Other dihydropyridines, including verapamil
Cardiovascular Drugs, Miscellaneous	Alikisiren, ivabradine, ranolazine	Sildenafil, for the treatment of pulmonary hypertension	Bosentan, riociguat
Diuretics	Eplerenone		

Drug Class	Contraindicated	Not Recommended	Use with Caution
Gastrointestinal Drugs	Cisapride, domperidone		Aprepitant
Immunosuppressants		Ciclesonide, everolimus, temsirolimus	Budesonide, ciclosporin, dexamethasone, fluticasone, methylprednisolone, rapamycin (also known as sirolimus), tacrolimus
Lipid Regulating Drugs	Atorvastatin, lovastatin, simvastatin		
Respiratory Drugs		Salmeterol	
SSRIs, Tricyclics and Related Antidepressants			Reboxetine
Urological Drugs	Darifenacin, 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		Fesoterodine, imidafenacin, oxybutynin, sildenafil, for the treatment of erectile dysfunction, solifenacin, tadalafil, tolterodine
Other	Colchicine, in subjects with renal or hepatic impairment	Colchicine, conivaptan	Alitretinoin (oral formulation), cinacalcet, mozavaptan, tolvaptan

[a]See also under *Drugs that may decrease itraconazole plasma concentrations*
[b]See also under *Drugs that may increase itraconazole plasma concentrations*

Drugs that may have their plasma concentrations decreased by itraconazole

Co-administration of itraconazole with the NSAID meloxicam may decrease the plasma concentrations of meloxicam. It is recommended that meloxicam be used with caution when

co-administered with itraconazole, and its effects or side effects be monitored. It is recommended that the dosage of meloxicam, if co-administered with itraconazole, be adapted if necessary.

Paediatric Population

Interaction studies have only been performed in adults.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

Itraconazole capsules must not be used during pregnancy except for life-threatening cases where the potential benefit to the mother outweighs the potential harm to the foetus.

In animal studies itraconazole has shown reproduction toxicity.

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.

Reported epidemiological data on exposure to Itraconazole during the first trimester of pregnancy mostly in patients receiving short-term treatment for vulvovaginal candidosis.

Did not show an increased risk for malformations as compared to control subjects not exposed to any known teratogens.

Women of childbearing potential

Women of childbearing potential taking Itraconazole capsules should use contraceptive precautions. Effective contraception should be continued until the next menstrual period following the end of Itraconazole therapy.

Lactation

A very small amount of itraconazole is excreted in human milk. The expected benefits of Itraconazole therapy should be weighed against the risks 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 and use machines have been performed. When driving vehicles and operating machinery the possibility of adverse reactions such as dizziness, visual disturbances and hearing loss, which may occur in some instances, must be taken into account.

4.8. Undesirable effects

Summary of the safety profile

The most frequently reported adverse drug reactions (ADRs) with Itraconazole capsules treatment identified from reported clinical trials and/or from spontaneous reporting were headache, abdominal pain, and nausea. The most serious ADRs were serious allergic reactions, cardiac failure/congestive heart failure/pulmonary oedema, pancreatitis, serious hepatotoxicity (including some cases of fatal acute liver failure), and serious skin reactions.

Tabulated list of adverse reactions

The ADRs in the table below were derived from open-label and double-blind clinical trials with itraconazole capsules involving 8499 patients in the treatment of dermatomycoses or onychomycosis, and from spontaneous reporting. The table below presents adverse drug reactions by System Organ Class. Within each System Organ Class, the adverse drug reactions are presented by incidence, using the following convention:

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

Adverse Drug Reactions	
Infections and infestations	
Uncommon	Sinusitis, Upper respiratory tract infection, Rhinitis
Blood and lymphatic system disorders	
Rare	Leukopenia
Immune system disorders	
Uncommon	Hypersensitivity
Rare	Anaphylactic Reaction, Angioneurotic Oedema, Serum Sickness
Metabolism and nutrition disorders	
Rare	Hypertriglyceridemia
Nervous system disorders	
Common	Headache
Rare	Hypoaesthesia, Paraesthesia, Dysgeusia
Eye disorders	
Rare	Visual Disturbance (including diplopia and blurred vision)
Ear and labyrinth disorder	
Rare	Tinnitus, Transient or permanent Hearing Loss*
Cardiac disorders	
Rare	Congestive Heart Failure*
Respiratory, thoracic and mediastinal disorders	
Rare	Dyspnoea
Gastrointestinal disorders	
Common	Abdominal Pain, Nausea
Uncommon	Vomiting, Diarrhoea, Constipation, Dyspepsia, Flatulence
Rare	Pancreatitis
Hepatobiliary disorders	
Uncommon	Hepatic function abnormal
Rare	Serious hepatotoxicity (including some cases of fatal acute liver failure)*, Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	
Uncommon	Urticaria, Rash, Pruritus

Adverse Drug Reactions	
Rare	Toxic Epidermal Necrolysis, Stevens-Johnson Syndrome, Acute generalised exhanthematous pustulosis, Erythema Multiforme, Exfoliative Dermatitis, Leukocytoclastic Vasculitis, Alopecia, Photosensitivity
Renal and urinary disorders	
Rare	Pollakiuria
Reproductive system and breast disorders	
Uncommon	Menstrual Disorders
Rare	Erectile Dysfunction
General disorders and administration site conditions	
Rare	Oedema
Investigations	
Rare	Blood creatine phosphokinase increased

Description of selected adverse reactions

The following is a list of ADRs associated with itraconazole that have been reported in clinical trials of itraconazole oral solution and itraconazole I.V., excluding the ADR term "Injection site inflammation", which is specific to the injection route of administration.

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: Peripheral neuropathy*, Dizziness, Somnolence, Tremor

Cardiac disorders: Cardiac failure, Left ventricular failure, Tachycardia

Vascular disorders: Hypertension, Hypotension

Respiratory, thoracic and mediastinal disorders: Pulmonary oedema, Dysphonia, Cough

Gastrointestinal disorders: Gastrointestinal disorder

Hepatobiliary disorders: Hepatic failure*, Hepatitis, Jaundice

Skin and subcutaneous tissue disorders: Rash erythematous, Hyperhidrosis

Musculoskeletal and connective tissue disorders: Myalgia, Arthralgia

Renal and urinary disorders: Renal impairment, Urinary incontinence.

General disorders and administration site conditions: Generalised oedema, Face oedema, Chest pain, Pyrexia, Pain, Fatigue, Chills

Investigations: Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Blood lactate dehydrogenase increased, Blood urea increased, Gamma-glutamyltransferase increased, Hepatic enzyme increased, Urine analysis abnormal.

Paediatric population

The reported 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 reported pooled safety data from these clinical trials, the commonly reported adverse drug 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.

Reporting of adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com.

4.9. Overdose

Symptoms and signs

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

Treatment

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

5. Pharmacological properties

5.1. Mechanism of Action

Itraconazole inhibits fungal 14α-demethylase, resulting in a depletion of ergosterol and disruption of membrane synthesis by fungi.

5.2. Pharmacodynamic properties

Pharmacokinetic/pharmacodynamic relationship

The pharmacokinetic/pharmacodynamic relationship for itraconazole, and for triazoles in general, is poorly understood and is complicated by limited understanding of antifungal pharmacokinetics.

Mechanism(s) of resistance

Resistance of fungi to azoles appears to develop slowly and is often the result of several genetic mutations. Mechanisms that have been described are:

- Over-expression of ERG11, the gene that encodes 14-alpha-demethylase (the target enzyme
- Point mutations in ERG11 that lead to decreased affinity of 14-alpha-demethylase for itraconazole
- Drug-transporter over-expression resulting in increased efflux of itraconazole from fungal cells (i.e., removal of itraconazole from its target)

- Cross-resistance. Cross-resistance amongst members of the azole class of drugs has been observed within Candida species though resistance to one member of the class does not necessarily confer resistance to other azoles.

Breakpoints

Breakpoints for itraconazole have not yet been established for fungi using EUCAST methods.

Using CLSI methods, breakpoints for itraconazole have only been established for Candida species from superficial mycotic infections. The CLSI breakpoints are: susceptible ≤0.125 μg/mL, susceptible, dose-dependent 0.25-0.5 mg/mL and resistant ≥1 μg/mL. Interpretive breakpoints have not been established for the filamentous fungi.

The prevalence of acquired resistance may vary geographically and with time for selected species, and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable. The *in vitro* susceptibility of fungi to itraconazole depends on the inoculum size, incubation temperature, growth phase of the fungi, and the culture medium used. For these reasons, the minimum inhibitory concentration of itraconazole may vary widely. Susceptibility in the table below is based on MIC90 < 1mg itraconazole/L. There is no correlation between *in vitro* susceptibility and clinical efficacy.

Commonly susceptible species
Aspergillus spp.[2]
Blastomyces dermatitidis[1]
Candida albicans
Candida parapsilosis
Cladosporium spp.
Coccidioides immitis[1]
Cryptococcus neoformans
Epidermophyton floccosum
Fonsecaea spp. [1]
Geotrichum spp.
Histoplasma spp.
Malassezia (formerly Pityrosporum*)* spp.
Microsporum spp.
Paracoccidioides brasiliensis[1]
Penicillium marneffei[1]
Pseudallescheria boydii
Sporothrix schenckii
Trichophyton spp.
Trichosporon spp.
Species for which acquired resistance may be a problem
Candida glabrata[3]
Candida krusei
Candida tropicalis[3]

Inherently resistant organisms
Absidia spp.
Fusarium spp.
Mucor spp.
Rhizomucor spp.
Rhizopus spp.
Scedosporium proliferans
Scopulariopsis spp.

[1] These organisms may be encountered in patients who have returned from travel outside Europe.
[2] Itraconazole-resistant strains of Aspergillus fumigatus have been reported.
[3] Natural intermediate susceptibility.

5.3. Pharmacokinetic properties

The pharmacokinetics of itraconazole have been investigated in healthy subjects after single and multiple dosing.

SUBA Technology:

SUBA is a technology developed to enhance the bioavailability of poorly soluble drugs. SUBA uses a "solid dispersion" in a polymer to increase the absorbency of drugs in the gastrointestinal tract to enhance the bioavailability.

Advantages of SUBA Technology:

- No requirement of acidic environment for dissolution.
- Targeted drug release directly at the site of absorption (Duodenum)
- No interaction with food
- No interaction with gastric acid lowering agents
- Less intra and inter subject variability
- Improved clinical efficacy

Absorption

Itraconazole is rapidly absorbed after oral administration. Peak plasma concentrations of the unchanged drug are reached within 2 – 6 hours following an oral dose.

In a clinical trial comparing single doses of itraconazole capsules to conventional 100 mg itraconazole capsules, both taken with a full meal, the observed relative bioavailability (Frel) of itraconazole of the itraconazole formulation was 181%. In this trial, the F_{rel} for the itraconazole capsule formulation when taken in the fasted versus the fed state was 124%, whereas for the conventional 100 mg capsule formulation the F_{rel} was 156%. In a replicate-designed clinical trial comparing two single doses of itraconazole capsules to two single doses of conventional 100 mg itraconazole capsules, both taken with a full meal, within-subject variability in total exposure was considerably lower for the itraconazole formulation than for the conventional 100 mg itraconazole formulation, with values of 27.8% and 51.2% for $AUC_{0\text{-}tlast}$ and 22.2% and 47.4% for $AUC_{0\text{-}inf}$, respectively. There was no overlap in the 90% CI ranges obtained for the two formulations at each AUC measure, therefore the difference in within-subject variability, in the order of 50%, was statistically significant at the 90% level.

Distribution

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 seven 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 four-week treatment. Itraconazole is present at high concentrations in sebum but levels in sweat are negligible.

Metabolism

Itraconazole is extensively metabolised by the liver into a large number of metabolites. One of the main metabolites is hydroxyl-itraconazole, which has in vitro antifungal activity comparable to itraconazole. Plasma concentrations of the hydroxy-itraconazole are about twice those of itraconazole.

As shown in *in vitro* studies, CYP3A4 is the major enzyme that is involved in the metabolism of itraconazole.

Excretion

Itraconazole is excreted as inactive metabolites to about 35% in urine within one week and to about 54% with faeces. Renal excretion of the parent drug accounts for less than 0.03% of the dose, whereas faecal excretion of unchanged drug varies between 3-18% of the dose. Itraconazole clearance decreases at higher doses due to saturable hepatic metabolism. The mean elimination half-life of itraconazole is about 40 hours after repeated dosing.

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

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 hypercholesterolemia, 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.

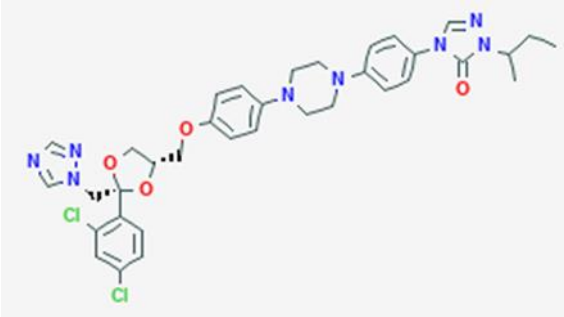
Toxicology

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.

7. Description

Itraconazole is chemically 2-butan-2-yl-4-[4-[4-[4-[[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy] phenyl]piperazin-1-yl]phenyl]-1,2,4-triazol-3-one with molecular formula of C35H38Cl2N8O4 and molecular weight of 705.6 g/mol. The chemical structure is:



ITRACLAR/TRICUTIS 100

Itraconazole capsules are Pink cap and Clear body, size "0" hard gelatin capsules containing creamish white coloured pellets. The excipients used are ready to use pellets of Itraconazole and starch.

ITRACLAR/TRICUTIS 200

Itraconazole capsules are Cream coloured cap and Cream coloured body, opaque, size "00" hard gelatin capsules containing white and creamish white coloured spherical pellets. The excipients used are ready to use pellets of Itraconazole and starch.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable.

8.2. Shelf-life

Do not use later than the date of expiry.

8.3. Packaging information

ITRACLAR/TRICUTIS is packed in blister strips of 10 capsules.

8.4. Storage and handing instructions

Store protected from light and moisture, at a temperature not exceeding 30°C.

- Capsules should be swallowed whole & not chewed or crushed.
- Keep medicines out of reach of children.
- For optimal absorption, Itraconazole capsules should be taken immediately after a full meal.
- Capsules should be swallowed whole & not chewed or crushed.
- Warning: Terfenadine or Astemizole should not be taken simultaneously when the patient is on this medication.

9. **Patient Counselling Information**

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. **Details of manufacturer**

Synokem Pharmaceuticals Ltd.

Plot No. 56-57, Sector 6-A, I.I.E., SIDCUL,

Ranipur, Distt.: Haridwar (Uttarakhand)

11. **Details of permission or licence number with date**

Mfg Lic No. 27/UA/2018 issued on 11.06.2024.

12. **Date of revision**

DEC 2025

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ITRACLAR/TRICUTIS 100, 200 mg/DEC-2025/02/PI