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

ITRACLAR SB

1. Generic Name:

Itraconazole Capsules B.P. 50mg

2. Qualitative and quantitative composition:

Each hard gelatin capsule contains:
Itraconazole B.P. ……..50 mg
Excipients……..q.s.
Approved colours used in empty capsule shells.
The excipients used are Microcrystalline Cellulose, Betacyclodextrin, Sodium Lauryl sulphate, Talcum.

3. Dosage form and strength:

Dosage form: Powder-filled capsule
Strength: 50 mg

4. Clinical particulars:

4.1 Therapeutic indication:

Superficial mycoses

LOZANOC is indicated – if external treatment is not effective or not appropriate – for the treatment of the following fungal infections: dermatomycoses (e.g. tinea corporis, tinea cruris, tinea pedis, tinea manus, onychomycosis) and pityriasis versicolor.

Systemic mycoses

LOZANOC is indicated for the treatment of systemic mycoses, such as candidiasis, aspergillosis, and histoplasmosis.
Consideration should be given to official guidance on the appropriate use of antimycotic agents, and to the discussion of the pharmacodynamic properties (see *section 5.1 Pharmacodynamic Properties*).

4.2 Posology and method of administration:

ITRACLAR SB is for oral administration and can be taken with or without food.
One capsule of ITRACLAR SB is therapeutically equivalent to one 100 mg capsule of conventional itraconazole capsules. The recommended dose for ITRACLAR SB is therefore half the recommended dose for conventional itraconazole capsules. ITRACLAR SB capsules and conventional itraconazole 100 mg capsules are not bioequivalent and therefore are not interchangeable.
A discussion of the relative pharmacokinetics of ITRACLAR SB 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 ITRACLAR SB 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	***ITRACLAR SB 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	***ITRACLAR SB 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.

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
Coadministration of specific drugs with itraconazole may result in changes in efficacy of itraconazole and/or the coadministered drug, life-threatening effects and/or sudden death.

4.5 Drug-Interaction:
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.

Drugs that may decrease itraconazole plasma concentrations
Drugs that reduce the gastric acidity (e.g. acid neutralising medicines such as aluminum 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 coadministered 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 coadministration, 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 coadministered 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 coadministered 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 coadministration 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 coadministered with itraconazole.

Upon coadministration, 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 coadministration 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
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		
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
Coadministration of itraconazole with the NSAID meloxicam may decrease the plasma concentrations of meloxicam. It is recommended that meloxicam be used with caution when coadministered with itraconazole, and its effects or side effects be monitored. It is recommended that the dosage of meloxicam, if coadministered with itraconazole, be adapted if necessary.

Paediatric Population
Interaction studies have only been performed in adults.

4.6 Use in special populations

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 child bearing 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 reportingThe 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
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 intraconazole 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 side effects:
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:
http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

4.9 Overdose:

Symptoms and signs

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

Treatment

In the event of 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:

Pharmacotherapeutic classification: (Antimycotics for systemic use, triazole derivatives).
ATC code: J02A C02

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 MIC_{90} < 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 ITRACLAR SB capsules to conventional 100 mg itraconazole capsules, both taken with a full meal, the observed relative bioavailability (F_{rel}) of itraconazole of the ITRACLAR SB formulation was 181%. In this trial, the F_{rel} for the ITRACLAR SB 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 ITRACLAR SB 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 ITRACLAR SB 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:

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.

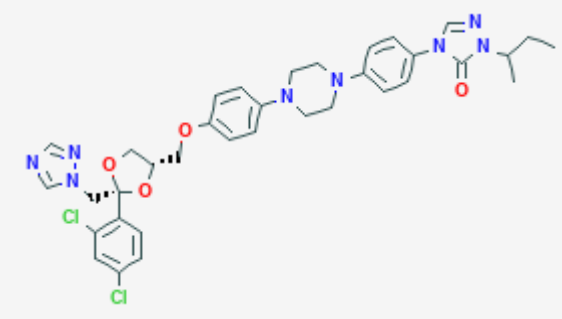
Toxicology

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 $C_{35}H_{38}Cl_2N_8O_4$ and molecular weight of 705.6 g/mol. The chemical structure is:



Itraconazole capsules are Blue cap and White body, size "0" hard gelatin capsules containing white to off-white coloured granular powder. The excipients used are Microcrystalline Cellulose, Betacyclodextrin, Sodium Lauryl sulphate, Talcum.

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 SB is packed in blister strips of 10 capsules.

8.4 Storage and handing instructions:

- Store below 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

Package leaflet: Information for the user
ITRACLAR SB
Itraconazole Capsules

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

9.1 What ITRACLAR SB is and what it is used for

ITRACLAR SB capsules contain a medicine called itraconazole. This belongs to a group of medicines called 'antifungals'.
ITRACLAR SB capsules are used for infections caused by fungi or yeasts in adults. They are used for:

- Infections of the mouth or vagina causing 'thrush'
- Skin infections
- Infections affecting other parts of the body

Patches of skin may take a few weeks to completely clear up after you have finished your treatment with itraconazole capsules. Finger and toe nails may take several months to completely clear up. This is because your skin or nail will only look normal after new skin or nail has grown, even though the medicine has killed the fungus that caused the infection.

9.2 What you need to know before you take ITRACLAR SB

Do not take ITRALAR SB:
If you are **allergic** to itraconazole or any of the other ingredients of this medicine.

- you are **pregnant** or could become pregnant unless your doctor has told you to (see 'Pregnancy and breastfeeding' below)

Do not take this medicine if any of the above applies to you. If you are not sure, talk to your doctor or pharmacist before taking itraconazole capsules.
Warnings and precautions
Talk to your doctor or pharmacist before taking Itraconazole capsules:

- if you have ever had **kidney** problems. Your dose of itraconazole capsules may have to be changed
- If you have ever had **liver** problems such as yellow skin (jaundice). Your dose of itraconazole capsules may have to be changed. If after taking this medicine you have a severe lack of appetite, feel sick (nausea), are sick (vomiting), feel unusually tired, get stomach pain, muscle weakness, yellowing of the skin or whites of the eyes, unusually dark urine, pale stools or hair loss, stop taking itraconazole capsules and tell your doctor straight away

- If you have ever had a **heart** problem including heart failure (also called congestive heart failure or CHF). Itraconazole capsules could make it worse. If after taking this medicine you get any of the following:
  - shortness of breath
  - unexpected weight gain
  - swelling of your legs or tummy
  - feel unusually tired
  - wake up short of breath at night

Stop taking itraconazole capsules and tell your doctor straight away. These may be signs of heart failure

- if you have Acquired Immunodeficiency Syndrome (AIDS) or your immune system is not working as well as it should
- if you have had an allergic reaction to another antifungal product in the past
- Itraconazole capsules are not normally given to the elderly. However, your doctor may prescribe them in special cases.

Children and adolescents:

Itraconazole capsules are not normally given to children under the age of 12. However, your doctor may prescribe them in special cases.

Blood tests:

If your itraconazole capsules course is for more than one month, your doctor may want to check your liver by testing your blood.

Other medicines and Itraconazole capsules

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.This includes medicines that you buy without a prescription or herbal medicines.

In particular, do not take this medicine and tell your doctor if you are taking any of the following:

- Medicines for hay fever or allergy called terfenadine, astemizole or mizolastine
- Medicines to lower cholesterol called atorvastatin, lovastatin or simvastatin
- Medicines for an irregular heart beat called quinidine, disopyramide, dronedarone or dofetilide
- Medicines used to treat angina (crushing chest pain) and high blood pressure called bepridil, felodipine, lercanidipine, ivabradine, ranolazine and nisoldipine
- Medicines for migraine headaches called dihydroergotamine and ergotamine
- Medicines for the treatment of drug abuse called levacetylmethadol and methadone
- Cisapride - for digestive problems
- Colchicine (in patients with kidney and liver problems as well) – for gout
- Eplerenone – a diuretic
- Ergometrine (ergonovine) and methylergometrine (methylergonovine) - used after giving birth
- Halofantrine – for malaria
- Irinotecan – for cancer
- Dabigatran – a medicine to thin blood
- Ticagrelor – a medicine to thin blood
- Quetiapine – for conditions affecting thoughts, feelings and behaviour
- Aliskiren – for high blood pressure
- Darifenacin – for urge incontinence and/or increased urinary frequency
- Midazolam (by mouth) or triazolam - for anxiety or to help you sleep
- Pimozide, lurasidone and sertindole - for conditions affecting thoughts, feelings and behaviour

Do not start taking itraconazole capsules and tell your doctor if you are taking any of the above.
Also, upon completing your course of Itraconazole capsules, do not take any of the medicines listed above for 2 weeks.
Tell your doctor if you are taking, any of the following medicines as they are not recommended with itraconazole capsules unless your doctor feels it necessary.

- Medicines for the treatment of cancer called axitinib, dabrafenib, dasatinib, ibrutinib, lapatinib, nilotinib, sunitinib or trabectedin
- Colchicine – for gout
- Ebastine – for allergy
- Eletriptan – for migraine headaches
- Everolimus – usually given after an organ transplant
- Fentanyl – a strong painkiller
- Rivaroxaban – a medicine to thin blood
- Salmeterol – for asthma and other breathing problems
- Tamsulosin - for urinary incontinence in men
- Vardenafil – for erection problems
- Ciclesonide - usually given after an organ transplant
- Temsirolimus - usually given after an organ transplant

Also, upon completing your course of Itraconazole capsules, do not take any of the medicines listed above for 2 weeks.
Do not take any of following medicines 2 weeks before and while you are taking Itraconazole capsules unless your doctor tells you otherwise:
Medicines for tuberculosis called rifampicin, rifabutin or isoniazid

- Medicines for epilepsy called phenytoin, carbamazepine or phenobarbital
- Medicines to treat viral infections called efavirenz or nevirapine
- St. John's Wort (a herbal medicine)

Tell your doctor before taking, or if you are already taking any of the above. They may stop itraconazole capsules from working properly. Your doctor may need to alter the dose of itraconazole capsules or your other medicine:

- Strong painkillers called alfentanil, buprenorphine (by injection or under your tongue) and oxycodone
- Medicines for indigestion, stomach ulcers or heartburn can affect the stomach producing acid.
  There must be enough acid in your stomach to make sure that your body can use the medicine. For this reason you should wait two hours after taking itraconazole capsules before taking any of these other medicines. If you take medicines that stop the production of stomach acid, you should take itraconazole capsules with a drink of cola (not diet cola)
- Medicines used for anxiety or to help you sleep (tranquillisers), such as buspirone, alprazolam or brotizolam
- Medicines used in the treatment of cancer such as bortezomib, busulphan, docetaxel, erlotinib, ixabepilone, trimetrexate and a group of medicines known as 'vinca alkaloids'
- Medicines for conditions affecting thoughts, feelings and behaviour called aripiprazole, haloperidol, perospirone, ramelteon and risperidone
- Medicines to thin the blood (anticoagulants) such as warfarin
- Medicines for HIV infection such as ritonavir, darunavir, indinavir, fosamprenavir and saquinivir. (They are called 'antiviral protease inhibitors'). Also maraviroc

- Medicines for bacterial infections called ciprofloxacin, clarithromycin or erythromycin
- Medicines that act on the heart and blood vessels called nadolol, digoxin and cilostazol or 'calcium channel-blockers' such as dihydropyridines and verapamil
- Medicines for inflammation, asthma or allergies (given by mouth or injection) called methylprednisolone, fluticasone, budesonide or dexamethasone
- Medicines that are usually given after an organ transplant called ciclosporin, tacrolimus or rapamycin (also known as sirolimus)
- Medicines to treat and overactive bladder – fesoterodine, imidafenacin, solifenacin or tolterodine
- Alitretioin (by mouth) – for eczema
- Aprepitant and domperidone – to stop you feeling and being sick
- Atorvastatin – to lower cholesterol
- Cinacalcet – for an over active parathyroid gland
- Mozavaptan or tolvaptan – for low sodium blood levels
- Praziquantel – for treatment of worms
- Reboxetine - for depression
- Repaglinide or saxagliptin - for diabetes
- Meloxicam – to reduce inflammation and pain
- Midazolam - to help you relax or sleep when given into a vein
- Sildenafil and tadalafil – for erection problems

Tell your doctor before taking, or if you are already taking any of the above. They may need to alter the dose of itraconazole capsules or your other medicine.

Itraconazole capsules with food and drink:

Always take itraconazole capsules straight after a meal as this helps your body to use the medicine.

Pregnancy, breast-feeding and fertility:

- Do not take itraconazole capsules if you are pregnant unless your doctor has told you to. You should use contraception to make sure that you do not become pregnant when taking this medicine
- The medicine in itraconazole capsules stays in your body for some time after you have stopped taking them. After your treatment has finished, you must use contraception up until your next period (menstrual bleed). Ask your doctor for advice on what type of contraception to use
- If you become pregnant after starting a course of itraconazole capsules, stop taking them and tell your doctor straight away
- Do not breast-feed if you are taking Itraconazole capsules, as small amounts of the medicine could pass into your milk. Ask your doctor for advice.
  Ask your doctor for or pharmacist for advice before taking this medicine if you are pregnant or breast-feeding

Driving and using machines:

Itraconazole capsules can sometimes cause dizziness, blurred/double vision or hearing loss. If you have these symptoms do not drive or use machines.

Itraconazole capsules contains sucrose:

This medicine contains the sugar sucrose. If your doctor has told you that you are intolerant of some sugars, contact them before taking this medicine.

9.3 How to take ITRACLAR SB

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.
Method and route of administration:
- Always take itraconazole capsules straight after a meal as this helps your body to use the medicine
- Swallow the capsules whole with some liquid
- There must be enough acid in your stomach to make sure that your body can use the medicine.

Medicines for indigestion, stomach ulcers or heartburn can affect the stomach producing acid. For this reason, you should wait two hours after taking itraconazole capsules before taking any of these other medicines.
If you do take medicines that stop the production of stomach acid, you should take itraconazole capsules with a drink of cola
Frequency and duration of treatment:
Your doctor will tell you how many itraconazole capsules to take and for how long. The recommended dose is:
Yeast infection of the vagina (thrush)
- Take 2 capsules in the morning and two capsules 12 hours later for one day only

Yeast infection of the mouth (oral thrush)
- Take 1 capsule each day for 15 days

Fungal infections of the skin
The dosage depends on your infection.
Your doctor might tell you to take:
- 2 capsules each day for 7 days, or
- 1 capsule each day for 15 days, or
- 1 capsule each day for 30 days

Fungal infections in other parts of the body
Your doctor will tell you how many itraconazole capsules to take and for how long depending on your infection.
If you take more Itraconazole capsules than you should:
Immediately consult your doctor or pharmacist if you take more Itraconazole capsules than you should.
If you forget to take Itraconazole capsules:
Take the missed dose as soon as you remember it. However, if it is almost time for the next dose, skip the missed dose and continue your regular dosing schedule. Do not take a double dose to make up for a forgotten dose.
If you stop taking Itraconazole capsules
Keep taking Itraconazole capsules as long as your doctor has told you. Do not stop your treatment just because you feel better.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.
Stop using itraconazole capsules and tell your doctor straight away if you notice or suspect any of the following. You may need urgent medical treatment.
Sudden signs of allergy such as rash, hives (also known as nettle rash or urticaria), severe irritation of your skin, swelling of the face, lips, tongue or other parts of the body. These may be signs of a severe allergic reaction. This only happens in a small number of people

- Severe skin disorders with peeling and/or rashes with small pustules (with a fever) or blistering of the skin, mouth, eyes and genitals, with fever, chills, aching muscles and generally feeling unwell. (the precise frequency of how often these may occur is not known)
- A tingling sensation, numbness or weakness in your limbs (the precise frequency of how often this may occur is not known)
- Severe lack of appetite, feeling sick (nausea), being sick (vomiting), unusual tiredness, stomach pain, muscle weakness, yellowing of your skin or whites of your eyes (jaundice), unusually dark urine, pale stools or hair loss. These may be signs of a liver problem (This only happens in a small number of people)
- Shortness of breath, unexpected weight gain, swelling of your legs or abdomen, feeling unusually tired or waking up short of breath at night. These may be signs of heart failure. Shortness of breath can also be a sign of fluid on the lungs (this occurs rarely).

Tell your doctor or pharmacist if you notice any of the following side effects:

Common (may affect up to 1 in 10 people)
- Stomach ache, feeling sick (nausea)
- Headache

Uncommon (may affect up to 1 in 100 people)
- Problems with periods
- Sinusitis, runny nose, coughs and colds
- Constipation, diarrhoea, wind, being sick (vomiting), indigestion

Rare (may affect up to 1 in 1000 people)
- Increases in liver function tests (shown by blood tests)
- Unexpected passing of urine or need to urinate (pass water) more often
- Problems with sight including blurred vision and double vision
- Change in taste
- Certain blood disorders which may increase the risk of infections
- Ringing in your ears
- Hearing loss (may be permanent)
- Severe upper stomach pain, often with nausea and vomiting (inflammation of the pancreas)
- Swelling due to fluid under the skin
- Unusual hair loss or thinning (alopecia)
- Red, itchy, flaking or peeling skin
- High levels of triglycerides in the blood (shown by blood tests)
- Sensitivity of the skin to light
- Erection difficulties

9.5 How to store ITRACLAR SB

- Store below 30°C.
- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.
- Do not use this medicine if you notice visible signs of deterioration.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

9.6 Contents of the pack and other information

What ITRACLAR SB contains

- The active substance is **Itraconazole**

Itraconazole Capsules B.P. 50mg

Each hard gelatin capsule contains:
Itraconazole B.P. ……..50 mg
Excipients……..q.s.
Approved colours used in capsule shells.
The excipients used are Microcrystalline Cellulose, Betacyclodextrin, Sodium Lauryl sulphate, Talcum.

10. Details of manufacturer

MANUFACTURED BY:
Synokem Pharmaceuticals Ltd.
Plot No. 56-57, Sector 6A, I.I.E (SIDCUL),
Ranipur (BHEL), Hardiwar – 249403, Uttarakhand.

11. Details of permission or licence number with date

Mfg Lic No. 27/UA/2018 issued on 29.04.2021

12. Date of revision

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ITRACLAR SB 50 mg/JUN-21/01/PI