Colours used

Pantone Black

Colours not for Printing

Keylines

Space Pharma Code

Pharma Code Readable Direction

CANDIFORCE-100
(Itraconazole Capsules BP 100mg)

PRODUCT NAME
CANDIFORCE-100 (Itraconazole Capsules BP 100mg)

NAME AND STRENGTH OF ACTIVE INGREDIENTS
Each hard gelatin capsule contains: Itraconazole Ph. Eur. - 100 mg (As Itraconazole Pellets)

PRODUCT DESCRIPTION
Size "0el" hard gelatin white opaque capsules filled with off white to cream colored pellets.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamics Properties
Pharmacotherapeutic group: (Antimycotics for systemic use, triazole derivatives).
ATC code: J02A C02
Itraconazole, a triazole derivative, has a broad spectrum of activity.
In vitro studies have demonstrated that Itraconazole impairs the synthesis of ergosterol in fungal cells. Ergosterol is a vital cell membrane component in fungi. Impairment of its synthesis ultimately results in an antifungal effect.
In vitro studies demonstrate that Itraconazole inhibits the growth of a broad range of fungi pathogenic for humans at concentrations usually ≤ 1 μg/ml. These include:
dermatophytes (Trichophyton spp., Microsporum spp., *Epidermophyton floccosum*); yeasts (Candida spp., including *C. albicans*, *C. tropicalis*, *C. parapsilosis* and *C. krusei*, *Cryptococcus neoformans*, *Malassezia* spp., Trichosporon spp., Geotrichum spp.); Aspergillus spp.; Histoplasma spp., including *H. capsulatum*; *Paracoccidioides brasiliensis*; *Sporothrix schenckii*; Fonsecaea spp.; Cladosporium spp.; *Blastomyces dermatitidis*; *Coccidiodes immitis*; *Pseudallescheria boydii*; *Penicillium marneffei*; and various other yeasts and fungi.
Candida krusei, *Candida glabrata* and *Candida tropicalis* are generally the least susceptible Candida species, with some isolates showing unequivocal resistance to Itraconazole *in vitro*.
The principal fungus types that are not inhibited by Itraconazole are Zygomycetes (e.g. Rhizopus spp., Rhizomucor spp., Mucor spp. and Absidia spp.), Fusarium spp., *Scedosporium proliferans* and Scopulariopsis spp.
Azole resistance appears to develop slowly and is often the result of several genetic mutations. Mechanisms that have been described are overexpression of ERG11, which encodes the target enzyme 14α-demethylase, point mutations in ERG11 that lead to decreased target affinity and/or transporter overexpression resulting in increased efflux. Cross resistance between members of the azole class has been observed within Candida spp., although resistance to one member of the class does not necessarily confer resistance to other azoles. Itraconazole-resistant strains of *Aspergillus fumigatus* have been reported.
Pharmacokinetics Properties
General pharmacokinetic characteristics
Peak plasma concentrations of itraconazole are reached within 2 to 5 hours following oral administration. As a consequence of non-linear pharmacokinetics, itraconazole accumulates in plasma during multiple dosing. Steady-state concentrations are generally reached within about 15 days, with Cmax values of 0.5 μg/ml, 1.1 μg/ml and 2.0 μg/ml after oral administration of 100 mg once daily, 200 mg once daily and 200 mg b.i.d., respectively. The terminal half-life of itraconazole generally ranges from 16 to 28 hours after single dose and increases to 34 to 42 hours with repeated dosing. 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. Itraconazole mean total plasma clearance following intravenous administration is 278 ml/min. Itraconazole clearance decreases at higher doses due to saturable hepatic metabolism.
Absorption
Itraconazole is rapidly absorbed after oral administration. Peak plasma concentrations of the unchanged drug are reached within 2 to 5 hours following an oral capsule dose. The observed absolute bioavailability of itraconazole is about 55%. Oral bioavailability is maximal when the capsules are taken immediately after a full meal.
Absorption of itraconazole capsules is reduced in subjects with reduced gastric acidity, such as subjects taking medications known as gastric acid secretion suppressors (e.g., H_2-receptor antagonists, proton pump inhibitors) or subjects with achlorhydria caused by certain diseases. Absorption of itraconazole under fasted conditions in these subjects is increased when Itraconazole Capsules are administered with an acidic beverage (such as a non-diet cola).
Itraconazole exposure is lower with the capsule formulation than with the oral solution when the same dose of drug is given.
Distribution
Most of the itraconazole in plasma is bound to protein (99.8%) with albumin being the main binding component (99.6% for the hydroxy- metabolite). It has also a marked affinity for lipids. Only 0.2% of the itraconazole in plasma is present as free drug. Itraconazole is distributed in a large apparent volume in the body (> 700 L), suggesting its extensive distribution into tissues: Concentrations in lung, kidney, liver, bone, stomach, spleen and muscle were found to be two to three times higher than corresponding concentrations in plasma, and the uptake into keratinous tissues, skin in particular, is up to four times higher than in plasma. Concentrations in the cerebrospinal fluid are much lower than in plasma, but efficacy has been demonstrated against infections present in the cerebrospinal fluid.
Metabolism
Itraconazole is extensively metabolised by the liver into a large number of metabolites. In vitro studies have shown that CYP3A4 is the major enzyme involved in the metabolism of itraconazole. The main metabolite is hydroxy-itraconazole, which has in vitro antifungal activity comparable to Itraconazole; trough plasma concentrations of the hydroxy-itraconazole are about twice those of itraconazole.
Excretion
Itraconazole is excreted mainly as inactive metabolites in urine (35%) and faeces (54%) within one week of an oral solution dose. Renal excretion of itraconazole and the active metabolite hydroxy-itraconazole account for less than 1% of an intravenous dose. Based on an oral radiolabelled dose, faecal excretion of unchanged drug varies between 3 – 18% of the dose.
Special Populations
Hepatic Impairment:
Itraconazole is predominantly metabolised in the liver. Data are not available in cirrhotic patients during long-term use of itraconazole.
Renal Impairment:
Limited data are available on the use of oral itraconazole in patients with renal impairment.
Data are not available in renally impaired patients during long-term use of itraconazole. Dialysis has no effect on the half-life or clearance of itraconazole or hydroxy-itraconazole.
Paediatrics:
Limited pharmacokinetic data are available on the use of itraconazole in the paediatric population. Itraconazole apparent clearance and distribution volume seemed to be related to weight.

INDICATIONS
CANDIFORCE-100 capsules are indicated for the following conditions:
- Gynecological indications:
  - Treatment of vulvovaginal candidosis.
- Dermatological/mucosal/ophthalmological indications:
  - Treatment of dermatomycosis, including highly keratinized regions as in plantartinea pedis and palmar tinea manus;
  - Treatment of pityriasis versicolor;
  - Treatment of oral candidosis;
- Treatment of onychomycosis, caused by dermatophytes and/or yeasts.
- Systemic mycoses, only in the following fungal infections:
  - Treatment of systemic aspergillosis and candidosis;
  - Cryptococcosis (including cryptococcal meningitis):
  - Treatment of immunocompromised patients with cryptococcosis and in all patients with cryptococcosis of the central nervous system, only when first line treatment is considered inappropriate or has proven ineffective;
  - For maintenance therapy of cryptococcal meningitis in AIDS patients, only when first line treatment is considered inappropriate or has proven ineffective.
  - Treatment of histoplasmosis;
  - Histoplasmosis, maintenance therapy only in AIDS patients;
  - Treatment of blastomycosis;
  - Treatment of sporotrichosis, including lymphocutaneous/cutaneous and extracutaneous;
  - Treatment of paracoccidioidomycosis;
  - Treatment of chromomycosis.

RECOMMENDED DOSAGE
For optimal absorption, administer **CANDIFORCE-100** immediately after a full meal. THE CAPSULES MUST BE SWALLOWED WHOLE.

Gynecological indication		
Indication	**Dose**	**Treatment Duration**
Treatment of vulvovaginal candidosis	200 mg twice daily or 200 mg once daily	1 day or 3 days
Dermatological/mucosal/ophthalmological indications		
Indication	**Dose**	**Treatment Duration**
Treatment of dermatomycosis	200 mg once daily or 100 mg once daily	7 days or 15 days
Treatment of dermatomycosis in highly keratinized regions as in plantar tinea pedis and palmar tinea manus	200 mg twice daily or 100 mg once daily	7 days or 30 days
Treatment of pityriasis versicolor	100 mg twice daily or 200 mg once daily	5-7 days
Treatment of oral candidosis	100 mg once daily	15 days
Onychomycosis, Caused by Dermatophytes and/or Yeasts		
Onychomycosis **Pulse treatment**	Dose and Treatment Duration	
	A pulse treatment consists of two capsules twice daily (200 mg twice daily) for one week. Two pulse treatments are recommended for fingernail infections, and three pulse treatments for toenail infections. Pulse treatments are always separated by a 3 week drug-free interval. Clinical response will become evident as the nail re-grows, following discontinuation of the treatment.	

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

Onychomycosis **Continuous treatment**	Dose	Treatment Duration
Toenails with or without fingernail involvement	200 mg once daily	3 months

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

Systemic Mycoses			
Indication	**Dose**	**Median Treatment Duration[1]**	**Remarks**
Treatment of aspergillosis	200 mg once daily	2 - 5 months	Increase dose to 200 mg twice daily in case of invasive or disseminated disease.
Treatment of candidosis	100 - 200 mg once daily	3 weeks – 7 months	Increase dose to 200 mg twice daily in case of invasive or disseminated disease.
Treatment of non-meningeal cryptococcosis	200 mg once daily	2 months - 1 year	
Treatment of cryptococcal meningitis	200 mg twice daily	2 months - 1 year	
Cryptococcal meningitis (maintenance therapy only in AIDS patients)	200 mg once daily	Until immune recovery[2]	
Treatment of histoplasmosis	200 mg once daily - 200 mg twice daily	8 months	
Histoplasmosis (maintenance therapy only in AIDS patients)	200 mg once or twice daily	Until immune recovery[2]	
Treatment of blastomycosis	100 mg once daily -200 mg twice daily	6 months	
Treatment of lymphocutaneous and cutaneous sporotrichosis	100 mg or 200 mg once daily (localized lesions) or 200 mg twice daily (extensive lesions)	3 months to 6 months	
Treatment of extracutaneous sporotrichosis	200 mg twice daily	12 months	
Treatment of paracoccidioidomycosis	100 mg once daily	6 months	Data on the efficacy of Itraconazole Capsules at this dosage for treatment of paracoccidioidomycosis in patients with AIDS is not available.
Treatment of chromomycosis	200 mg once daily	6 months	

[1] The duration of treatment should be adjusted depending on the clinical response.
[2] The duration of treatment should be based upon the status of the immune recovery.

Special populations
Pediatrics
The data on the use of Itraconazole Capsules 100mg in paediatric patients is limited. The use of **CANDIFORCE-100** in pediatric patients is not recommended unless it is determined that the potential benefit outweighs the potential risks.
Elderly
The data on the use of Itraconazole Capsules 100mg in elderly patients is limited. It is advised to use **CANDIFORCE-100** 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.
Hepatic Impairment
Limited data are available on the use of oral itraconazole in patients with hepatic impairment. Caution should be exercised when this drug is administered in this patient population.
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.
Method of administration: For oral use. The capsule must be swallowed whole. To be taken immediately after meal.
CONTRAINDICATIONS
- Itraconazole Capsules are contra-indicated in patients with known hypersensitivity to Itraconazole or to any of the excipients.
- Coadministration of a number of CYP3A4 substrates is contraindicated with Itraconazole Capsules. Increased plasma concentrations of these drugs, caused by coadministration 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.

WARNING 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
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 Capsules 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 oedematous 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 Capsules 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 Capsules 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 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 Capsules 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.
Paediatrics
The use of Itraconazole Capsules in paediatric patients is not recommended unless it is determined that the potential benefit outweighs the potential risks.
Elderly
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
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 non-meningeal) 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.
Disorders of Carbohydrate Metabolism
Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
Cross-resistance
In systemic 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 Capsules 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. Drugs that are contraindicated, not recommended or recommended for use with caution in combination with Itraconazole are listed in section *Interaction with other medicinal products and other forms of interaction.*

INTERACTION WITH OTHER MEDICAMENTS
Itraconazole is mainly metabolized 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 H_2-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 non-diet 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 coadministration, it is recommended that the antifungal activity be monitored and the Itraconazole dose increased as deemed necessary.
Coadministration 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.
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*),
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
Antiarrhythmics	disopyramide, dofetilide, dronedarone, quinidine		digoxin
Antibacterials		rifabutin[a]	
Anticoagulants and Antiplatelet Drugs		rivaroxaban	coumarins, cilostazol, dabigatran
Anticonvulsants		carbamazepine[a]	
Antidiabetics			repaglinide, saxagliptin
Antihelmintics and Antiprotozoals	halofantrine		praziquantel
Antihistamines	astemizole, mizolastine, terfenadine		ebastine
Antimigraine Drugs	ergot alkaloids, such as dihydroergotamine, ergometrine (ergonovine), ergotamine, methylergometrine (methylergonovine)		eletriptan
Antineoplastics	irinotecan	dasatinib, nilotinib, trabectedin	bortezomib, busulphan, docetaxel, erlotinib, ixabepilone, lapatinib, trimetrexate, vinca alkaloids
Antipsychotics, Anxiolytics and Hypnotics	lurasidone, oral midazolam, pimozide, sertindole, triazolam		alprazolam, aripiprazole, brotizolam, buspirone, haloperidol, midazolam IV, perospirone, quetiapine, ramelteon, risperidone
Antivirals			maraviroc, indinavir[b], ritonavir[b], saquinavir
Beta Blockers			nadolol
Calcium Channel Blockers	bepridil, felodipine, lercanidipine, nisoldipine		other dihydropyridines, including verapamil
Cardiovascular Drugs, Miscellaneous	ivabradine, ranolazine	aliskiren	
Diuretics	eplerenone		
Gastrointestinal Drugs	cisapride,		aprepitant, domperidone
Immunosuppres-sants		everolimus	budesonide, ciclesonide, ciclosporin, dexamethasone, fluticasone, methylprednisolone, rapamycin (also known as sirolimus), tacrolimus, temsirolimus
Lipid Regulating Drugs	lovastatin, simvastatin		atorvastatin
Respiratory Drugs		salmeterol	
SSRIs, Tricyclics and Related Antidepressants			reboxetine
Urological Drugs		vardenafil	fesoterodine. imidafenacin, sildenafil, solifenacin, tadalafil, tolterodine
Other	colchicine, in subjects with renal or hepatic impairment	colchicine	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.

PREGNANCY AND LACTATION
Pregnancy
CANDIFORCE-100 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.
Women of child bearing potential
Women of childbearing potential taking **CANDIFORCE-100** should use contraceptive precautions. Effective contraception should be continued until the next menstrual period following the end of **CANDIFORCE-100** therapy.
Lactation
A very small amount of itraconazole is excreted in human milk. The expected benefits of Candiforce-100 therapy should be weighed against the risks of breast feeding. In case of doubt, the patient should not breast feed.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
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.

UNDESIRABLE EFFECTS
The most frequently reported adverse drug reactions (ADRs) with Itraconazole Capsule treatment are 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 table below presents ADRs by System Organ Class. Within each System Organ Class, the ADRs 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).

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	Serum sickness, Angioneurotic oedema, Anaphylactic reaction
Metabolism and nutrition disorders	
Rare	Hypertriglyceridaemia
Nervous system disorders	
Common	Headache
Rare	Paraesthesia, Hypoaesthesia, Dysgeusia
Eye disorders	
Rare	Visual disturbance (including diplopia and blurred vision)
Ear and labyrinth disorder	
Rare	Transient or permanent hearing loss, Tinnitus
Cardiac disorders	
Rare	Congestive heart failure
Respiratory, thoracic and mediastinal disorders	
Rare	Dyspnoea
Gastrointestinal disorders	
Common	Abdominal pain, Nausea
Uncommon	Diarrhoea, Vomiting, 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 exanthematous pustulosis, Erythema multiforme, Exfoliative dermatitis, Leukocytoclastic vasculitis, Alopecia, Photosensitivity
Renal and urinary disorders	
Rare	Pollakiuria
Reproductive system and breast disorders	
Uncommon	Menstrual disorder
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, 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 safety of Itraconazole Capsules was evaluated in paediatric patients. These patients received at least one dose of Itraconazole Capsules for the treatment of fungal infections and provided safety data.
Based on pooled safety data, the commonly reported adverse drug reactions (ADRs) in paediatric patients were Headache, Vomiting, Abdominal pain, Diarrhoea, Hepatic function abnormal, Hypotension, Nausea and Urticaria. 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.

OVERDOSE AND TREATMENT
Symptoms and signs
In general, adverse events reported with overdose have been consistent with those reported for Itraconazole use.
Treatment
In the event of over dosage, supportive measures should be employed. Activated charcoal may be given if considered appropriate. Itraconazole cannot be removed by haemodialysis. No specific antidote is available.
INCOMPATIBILITIES
None
SHELF LIFE
36 months from the date of manufacture.
SPECIAL PRECAUTIONS FOR STORAGE
Store below 30°C. Protect from light & moisture.
Keep medicines out of reach of children.
DOSAGE FORM AND PACKAGING AVAILABLE
10 Capsules are packed in Alu/PVC-PVDC blister.3 such blisters are packed in a carton along with a package insert.
DATE OF REVISION: February'2023

Manufactured by:
Cohance Lifesciences Limited
FDF Unit-I, Plot No. A-19/C, A-23A,
& A-23B, Road No. 18, IDA,
Nacharam Village, Uppal Mandal,
Medchal – Malkajgiri District –500076,
Telangana State, India.

Mankind
Manufactured for:
MANKIND PHARMA LTD.
208, Okhla Industrial Estate, Phase-3
New Delhi-110020 (INDIA)

XXXXXXXXXXXXXXXX

Mankind Artwork Code

XXXXXXXX/XX

Plant code

Front Page

Back Page