SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE FINISHED PRODUCT

Inox Capsule 100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ACTIVE INGREDIENTS	PER CAPSULE (MG)
Itraconazole	100mg

Kindly refer to Section 6.1 for excipient.

3. PHARMACEUTICAL FORM

Opaque blue and pink transparent capsule printed with "INOX100" and "hovid".

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Treatment of the following conditions:-

Systemic Mycoses: Systemic aspergillosis and candidiasis, cryptococcosis (including cryptococcal meningitis), histoplasmosis, sporotrichosis, paracoccidioidomycosis, blastomycosis and other rarely occurring systemic or topical mycoses.

Dermatological/Opthalmological: Onychomycosis, Pityriasis versicolor, dermatomycosis and oral candidiasis. Gynaecological: Vulvovaginal candidosis.

4.2 Posology and Method of administration

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

Indications	Dose	Duration
Gynaecological indications • Vulvovaginal candidosis	200mg b.i.d. or 200mg o.d.	1 day or 3 days
Dermatological/ ophthalmological indications: • Pityriasis versicolor	200mg o.d.	7 days
• Dermatomycosis	200mg o.d. or 100mg o.d.	7 days or 15 days
Highly keratinized regions as in plantar tinea pedis and palmar tinea manus require 200mg twice daily for 7 days or 100mg daily for 30 days.		
• Oral candidosis	100mg o.d.	15 days
In some immunocompromised patients, e.g. neutropenic, AIDS or organ transplant patients, the oral bioavailability of itraconazole may be decreased. Therefore, the doses may need doubling.		

• Onychomycosis (Continuous Treatment) OR	200mg o.d.	3 months
• Onychomycosis (Pulse Treatment)	200mg b.i.d.	1 week

A pulse treatment consists of 200mg b.i.d. for 1 week. Two pulse treatments are recommended for fingernail infections, and three pulse treatment 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 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				

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.

Indication	**Dose**	**Merdian Duration**	**Remarks**
Aspergillosis	200mg o.d.	2-5 months	In increase dose to 200mg b.i.d. in case of invasive or disseminated disease.
Candidosis	100-200mg o.d.	3 weeks - 7 months	
Non-meningeal cryptococcosis	200mg o.d.	2 months - 1 year	Maintenance therapy (meningeal cases) 200mg o.d.
Cryptococcal meningitis	200mg b.i.d.		
Histoplasmosis	200mg o.d. - 200mg b.i.d.	8 months	
Sporotrichosis	100mg o.d.	3 months	
Paracoccidioidomycosis	100mg o.d.	6 months	
Chromomycosis	100-200mg o.d.	6 months	
Blastomycosis	100mg o.d. - 200mg b.i.d.	6 months	

4.3 Contraindication

- Itraconazole is contraindicated in patients with known hypersensitivity to the drug.
- It is contraindicated in pregnant women except for the treatment of systemic mycoses where the potential advantages must be weighed against the potential harm to the foetus. Adequate contraceptive precautions should be taken by women of childbearing potential during itraconazole therapy and for one menstrual cycle after stopping therapy.
- Terfenadine, astemizole, mizolastine, cisapride, dofetilide, quinidine, pimozide, CYP3A4 metabolised HMG-CoA reductase inhibitors such as simvastatin and lovastatin, triazolam and oral midazolam are contraindicated with itraconazole.

4.4 Warnings and precautions

Itraconazole has been shown to have a negative inotropic effect and associated with reports of congestive heart failure. It 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, and individual risk factors for congestive heart failure. These risk factors include cardiac disease, such as ischemic and valvular disease; and significant pulmonary disease, such as chronic obstructive pulmonary disease; and renal failure and other edematous disorders. These patients should be informed of the congestive heart failure signs and symptoms, should be treated with caution and the signs and symptoms during treatment should be monitored. Itraconazole should be discontinued if the signs and symptoms do occur during treatment.

- Calcium channel blockers can have negative inotropic effects which may be additive to those of itraconazole; itraconazole can inhibit the metabolism of calcium channel blockers. Therefore, caution should be used when co-administering, itraconazole and calcium channel blockers.
- Itraconazole has the potential for clinically important drug interactions.
- Decreased gastric acidity: Absorption of itraconazole is impaired when the gastric acidity is decreased. In patients also receiving acid neutralizing medicines (eg aluminium hydroxide) these should be administered at least 2 hours after the intake of itraconazole. In patients with achlorhydria such as certain AIDS patient and patients on acid secretion suppressors (eg H_2-antagonists, proton pump inhibitors), it is advisable to administer itraconazole with a cola beverage.
- It is advisable to monitor liver function in patients receiving continuous treatment of more than one month and promptly in patients developing symptoms suggestive of hepatitis such as anorexia, nausea, vomiting, fatigue, abdominal pain or dark urine. If abnormal, treatment should be stopped. In patients with raised liver enzymes or an active liver disease, or who have experienced liver toxicity with other drugs, treatment should not be started unless the expected benefit exceeds the risk of hepatic injury. In such cases, liver enzyme monitoring is necessary.
- Hepatic impairment: Itraconazole is predominantly metabolized in the liver. The terminal half-life of itraconazole in cirrhotic patients is somewhat prolonged. The oral bioavailability in cirrhotic patients is somewhat decreased. It is advised to monitor the itraconazole plasma concentrations and to adapt the dose when necessary.
- Renal impairment: The bioavailability of itraconazole may be lower in patients with renal insufficiency. Monitoring of the itraconazole plasma concentrations and a dose adaptation is advisable.
- The treatment should be discontinued if neuropathy occurs that may be attributable to itraconazole.

- Caution should be used in prescribing itraconazole to patients with hypersensitivity to other azoles even though there is no information regarding cross hypersensitivity between itraconazole and other azole antifungal agents.

Use in children and elderly:
Since the clinical data on the use of itraconazole in paediatric and geriatric patients is limited, it should not be used in these patients unless the potential benefit outweighs the potential risks.

4.5 Drug Interactions

- Interaction studies have been performed with rifampicin, rifabutin and phenytoin. The bioavailability of itraconazole and hydroxyl-itraconazole was decreased in these studies to such an extent that efficacy may be largely reduced. Therefore, the combination of itraconazole with these potent enzyme inducers is not recommended. No formal study data are available for other enzyme inducers, such as carbamazepine, phenobarbital and isoniazid but similar effects should be anticipated.
- As itraconazole is mainly metabolised through CYP3A4, potent inhibitors of this enzyme such as clarithromycin, erythromycin, indinavir and ritonavir may increase the bioavailability of itraconazole.
- Itraconazole can inhibit the metabolism of drugs metabolised by the cytochrome 3A family and result in an increase and/or prolongation of their effects, including side effects. Thus, drugs such as terfenadine, astemizole, mizolastine, cisapride, triazolam and oral midazolam, dofetilide, quinidine, pimoxide, CYP3A4 metabolised HMG-CoA reductase inhibitors (simvastatin and lovastatin) should not be used during treatment with itraconazole.
- Calcium channel blockers can have negative inotropic effects which may be additive to those of itraconazole; itraconazole can inhibit the metabolism of calcium channel blockers. Therefore, caution should be taken when co-administering itraconazole and calcium channel blockers.
- Drugs whose plasma levels, effects or side effects should be monitored. Their dosage, if co-administrated with itraconazole should be reduced if necessary.
  - Oral anticoagulants
  - HIV Protease Inhibitors such as ritonavir, indinavir, saquinavir
  - Certain Antineoplastic Agents such as vinca alkaloids, busulphan, docetaxel and trimetrexate
  - CYP3A4 metabolised Calcium Channel Blockers such as dihydropyridines and verapamil
  - Certain immunosuppressive agents: cyclosporine, tacrolimus, rapamycin (also known as sirolimus);
  - Others: digoxin, carbamazepine, buspirone, alfentanil, alprazolam, brotizolam, midazolam IV, rifabutin, methylprednisolone, ebastine and reboxetine.
- No interaction of itraconazole with AZT (zidovudine) and fluvastatine has been observed. No inducing effects of itraconazole on the metabolism of ethinyloestradiol and norethisterone were observed.
- *In vitro* studies have shown that there are no interactions on the plasma protein binding between itraconazole and imipramine, propranolol, diazepam, cimetidine, indomethacin, tolbutamide and sulfamethazine.

4.6 Pregnancy and lactation

Adequate and well-controlled studies on the use of itraconazole in pregnant women are not available. Therefore, itraconazole should only be given in life threatening cases of systemic mycosis and when in these cases, the potential benefit outweighs the potential harm to the foetus.
A very small amount of itraconazole is excreted in human milk. The expected benefits of itraconazole therapy should be weighted against the potential risk of breast feeding. In case of doubt, the patient should not breast-feed.

4.7 Effects on ability to drive and use machines

None known.

4.8 Main Side/ Adverse Effects

The most frequently reported adverse effects were of gastro-intestinal origin, such as dyspepsia, abdominal pain, nausea and constipation. Less frequently reported adverse effect include headache, reversible increases in hepatic enzymes, menstrual disorders, dizziness and allergic reactions (such as pruritus, rash, urticaria and angio-oedema). Isolated cases of peripheral neuropathy and of Steven-Johnsons syndrome have also been reported.

Reports have been received of oedema, congestive heart failure and pulmonary oedema. Cases of hypokalaemia, hepatitis and hair loss have been observed especially in patients receiving prolonged (=approximately 1 month) continuous treatment.

4.9 Overdose

No data is available. In the event of accidental overdose, supportive measures should be employed. Within the first hour after ingestion, gastric lavage may be performed. Activated charcoal may be given if considered appropriate. Itraconazole cannot be removed by haemodialysis. No specific antidote is available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Itraconazole is a triazole derivative. It is active against infections with dermatophytes (*Trichophyton spp*, *Microsporum spp*, and *Epidermophyton floccosum*), yeast (*Cryptococcus neoformans*, *Pitryrosporum spp*, *Candida spp*, including *C. albicans*, *C. glabrata* and *C. krusel*), *Aspergillus spp*, *Histoplasma spp*, *Paracoccidioides brasiliensis*, *Sporothrix schenckii*, *Fonsecaea spp*, *Cladosporium spp*, *Blastomyces dermatitidis* and various other yeasts and fungi. *In vitro* studies have demonstrated that itraconazole impairs the synthesis of ergosterol, a vital cell membrane component in fungi. Impairment of its synthesis ultimately results in an antifungal effect.

5.2 Pharmacokinetic properties

Itraconazole is absorbed from the gastrointestinal tract when administered orally. The bioavailability is maximal when the capsules are taken immediately after a full meal. Peak plasma levels are reached 3 to 4 hours following an oral dose. Elimination from plasma is biphasic with a terminal half life of 1 to 1.5 days. During chronic administration, steady state is reached after 1-2 weeks. Steady state plasma concentrations of itraconazole 3-4 hours after drug intake are 0.4µg/ml (100 mg o.d.), 1.1µg/ml (200mg o.d.) and 2.0µg/ml (200mg b.i.d.).

The plasma protein binding of Itraconazole is 99.8%. Concentrations of itraconazole in whole blood are 60% of those in plasma. Uptake in keratinous tissues, especially the skin is up to 4 times higher than in plasma elimination of itraconazole is related to epidermal regeneration. In contrast to the plasma levels which become undetectable within 7 days of stopping therapy, therapeutic levels in the skin persist for 2 to 4 weeks after a 4 weeks treatment is discontinued.

Itraconazole levels have been detected in the nail keratin as early as 1 weekafter start of treatment and persist for at least 6 months after the end of a 3 months course of therapy. Itraconazole is also present

in sebum and to a lesser extent in sweat.
Itraconazole is extensively distributed into tissues that are prone to fungal invasion. Concentrations in lung, kidney, liver, bone, stomach, spleen and muscle were found to be two to three times higher than the corresponding plasma concentrations.
Therapeutic levels in vaginal tissue are maintained for another 2 days after discontinuation of a 3 day course with 200mg daily, and for another 3 days afters discontinuation of a 1 day course with 200mg b.i.d.
Itraconazole is extensively metabolized by the liver into a large number of metabolites. Hydroxyl-itraconazole is one of the metabolites which has a comparable antifungal activity *in vitro* to itraconazole. Faecal excretion of the parent drug varies between 3 to 18% of the dose. Renal excretion of the parent drug is less than 0.3% of the dose. About 35% of a dose is excreted as metabolites in the urine within 1 week.

5.3 Preclinical Safety Data
NOT APPLICABLE

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
No excipients

6.2 Incompatibilities
NOT APPLICABLE

6.3 Shelf life
3 years from date of manufacture

6.4 Special precaution for storage
Store below 30˚C. Protect from light and moisture.

6.5 Nature and contents of container

Descriptions of each packaging material for Inox Capsule are as below:

1	Material description	:	Rigid PVDC film
	Colour of film	:	Glass clear transparent
2	Glass clear transparent	:	Inox Capsule aluminium foil
	Specification	:	Foil property: Silver plain hard tempered 20 micron aluminium foil with high slip primer on dull surface and heat seal on bright surface.
3	Material description	:	Inox Capsule Insert
4	Material description	:	Inox Capsule (7 x 4) Unit Box

6.6 Instructions for use and handling <and disposal>

NOT APPLICABLE

7. MARKETING AUTHORISATION HOLDER

Name: HOVID Bhd.
Address : 121, Jalan Tunku Abdul Rahman,
(Jalan Kuala Kangsar)
30010 Ipoh, Perak, Malaysia

Manufacturer Name :

Name	:	HOVID Bhd.
Address	:	Lot 56442, 7 ½ Miles, Jalan Ipoh / Chemor, 31200 Chemor, Perak., Malaysia.

8. NUMBER (S) IN THE NATIONAL REGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

HOV/MAL/22

9. DATE OF FIRST AUTHORISATION

November 2016

10. DATE OF REVISION OF THE TEXT

June 2019