SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE FINISHED PRODUCT

Difluvid 150mg Capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ACTIVE INGREDIENTS	PER CAPSULE (MG)
Fluconazole	150.00mg
Kindly refer to Section 6.1 for excipient.	

3. PHARMACEUTICAL FORM

Light turquoise opaque/light turquoise opaque capsule with "HOVID" printed on one end and "FL150" printed on the other end of the capsule. The capsule is filled with white to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

- Mucosal candidiasis. These include oropharyngeal, esophageal, non-invasive bronchopulmonary infections, candiduria, mucocutaneous and chronic oral atrophic candidiasis (denture sore mouth). Normal hosts and patients with compromised immune function may be treated. Prevention of relapse of oropharyngeal candidiasis in patients with AIDS.
- Genital candidiasis: Vaginal candidiasis, acute or recurrent; and prophylaxis to reduce the incidence of recurrent vaginal candidiasis (3 or more episodes a year). Candidal balanitis. Prevention of relapse of oropharyngeal candidiasis in patients with AIDS.
- Prevention of fungal infections in patients with malignancy who are predisposed to such infections as a result of cytotoxic chemotherapy or radiotherapy.
- Dermatomycosis including tinea pedis, tinea corporis, tinea cruris, tinea versicolor, and dermal candida infections.

4.2 Posology and Method of administration

Use in Adults

For prevention of relapse of oropharyngeal candidiasis in patients with AIDS, after the patient receives a full course of primary therapy, fluconazole may be administered at a 150 mg once weekly dose.

For the treatment of vaginal candidiasis, fluconazole 150 mg should be administered as a single oral dose. To reduce the incidence of recurrent vaginal candidiasis, a 150 mg once monthly may be used. The duration of therapy should be individualized, but ranges from 4-12 months. Some patients may require more frequent dosing. For candida balanitis, fluconazole 150 mg should be administered as a single oral dose.

The recommended dose for the prevention of candidiasis is 50 to 400 mg once daily, based on the patient's risk of fungal infection.

For dermal infections including tinea pedis, corporis, cruris and candida infections the recommended dosage is 150 mg once weekly. Duration of treatment is normally 2 to 4 weeks but tinea pedis may require treatment for up to 6 weeks. For tinea versicolor, the recommended dose is 300 mg once weekly for 2 weeks; a third weekly dose of 300 mg may be needed in some patients , whereas, in some patients, a single dose of 300 to 400 mg may be sufficient.

Use in Renal Impairment
Patient with Renal Impairment Fluconazole is predominantly excreted in the urine as unchanged drug. No adjustments in single-dose therapy are necessary. In multiple-dose therapy of patients with renal impairment, normal doses should be given on days 1 and 2 of treatment, and thereafter the dosage intervals of daily dose should be modified accordance with creatinine clearance below:

Creatinine Clearance (ml/min)	**Dosage Intervals/Daily Dose**
> 50	Normal dosage regimen
11 - 50	50% of normal daily dose
Patients with regular dialysis	One dose after every dialysis session

These are suggested dose adjustments based on pharmacokinetics following administration of single doses. Further adjustment may be needed depending on clinical condition.

Use in Children
There are limited data available on the use of fluconazole for genital candidiasis in children below 16 years old. Use at present is not recommended unless antifungal treatment is imperative and no suitable alternative agent exists.

Note: The information given here is limited. For further information, kindly consult your doctor or pharmacist.

Contraindication

- Fluconazole should not be used in patients with known sensitivity to the drug, any of the inert ingredients or to related azole compounds.
- Coadministration of terfenadine is contraindicated in patients receiving fluconazole at multiple doses of 400 mg per day or higher based upon results of a multiple dose interaction study.
- Coadmininstration of cisapride is contraindicated in patients receiving fluconazole.
- Fluconazole is generally unadvised in association with halofantrine.
- Fluconazole should not be administered in the following cases:
    - Hypersensitivity to fluconazole and/or other azole derivatives.
    - Pregnancy and lactation.
    - In combination with cisapride and pimozide.

Warnings and precautions

- Fluconazole has been associated with rare cases of serious hepatic toxicity including fatalities, primarily in patients with serious underlying medical conditions. Fluconazole hepatotoxicity has usually been reversible on discontinuation of therapy. Patients who develop abnormal liver function tests during fluconazole therapy should be monitored for the development of more serious hepatic injury. Fluconazole should be discontinued if clinical signs or symptoms consistent with liver disease

develop that may be attributable to fluconazole.

- Patients have rarely developed exfoliative cutaneous reactions, such as Stevens - Johnson Syndrome and toxic epidermal necrolysis, during treatment with fluconazole. AIDS patients are more prone to the development of severe cutaneous reactions to many drugs. If a rash, which is considered attributable to fluconazole, develops in a patient treated for a superficial infection, further therapy with this agent should be discontinued. Patients with invasive/systemic fungal infections who develop rashes should be monitored closely and fluconazole discontinued if bullous lesions and erythema multiforme develop.
- The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored.
- In rare cases, as with other azoles, anaphylaxis has been reported.
- Cases of torsade de pointes and QT prolongation have been reported rarely and caution is advised when giving fluconazole to patients with proarrhythmic conditions.

Drug Interactions

- Anticoagulants: Bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria, and melena), have been reported, in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. Prothrombin time in patients receiving coumarin-type anticoagulant should be carefully monitored.
- Azithromycin: There was no significant pharmacokinetic interaction between fluconazole and Azithromycin.
- Benzodiazepines (Short Acting): Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. This effect on midazolam appears to be more pronounced following oral administration of fluconazole than with fluconazole administered intravenously. If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dosage, and the patients should be appropriately monitored.
- Cisapride: Cisapride increased risk of ventricular arythmia troubles notably torsades de pointes. The interaction between fluconazole and cisapride yielded significant increase in cisapride plasma levels and prolongation of QTc interval. Coadministration of cisapride is contraindicated in patients receiving fluconazole.
- Cyclosporin: Fluconazole slowly increase cyclosporin concentrations in renal transplant patients. Fluconazole did not affect cyclosporine levels in patients with bone marrow transplants. Cyclosporin plasma concentration monitoring in patients receiving fluconazole is recommended.
- Hydrochlorothiazide: Interaction between multiple-dose hydrochlorothiazide and fluconazole has increased plasma concentrations of fluconazole by 40%. An effect of this magnitude should not necessitate a change in the fluconazole dose regimen in subjects receiving concomitant diuretics, although the prescriber should bear it in mind.
- Oral Contraceptives: Multiple dose use of fluconazole at these doses is unlikely to have an effect on the efficacy of the combined oral contraceptive.
- Phenytoin: Concomitant administration of fluconazole and phenytoin may increase the levels of phenytoin to a clinically significant degree. If it is necessary to administer both drugs concomitantly, phenytoin levels should be monitored and the phenytoin dose adjusted to maintain therapeutic levels.
- Pimozide: Combination of fluconazole will increase the risk of ventricular arythmia troubles notably torsades de pointes.
- Rifabutin: An interaction exists when fluconazole is administered concurrently with rifabutin, leading

to increased serum levels of rifabutin. There have been reports of uveitis in patients to whom fluconazole and rifabutin were coadministered. Patients receiving rifabutin and fluconazole concomitantly should be carefully monitored.

- Rifampicin: Concomitant administration of fluconazole and rifampicin resulted in a 25% decrease in the AUC and a 20% shorter half-life of fluconazole. In patients receiving concomitant rifampicin, an increase of the fluconazole dose should be considered.
- Sulfonylureas: Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulfonylureas (chlorpropamide, glibenclamide, glipizide and tolbutamide) in healthy volunteers. Fluconazole and oral sulfonylureas may be coadministerd to diabetic patients, but the possibility of a hypoglycemic episode should be borne in mind.
- Tacrolimus: An interaction exists when fluconazole is administered concomitantly with tacrolimus, leading to increased serum levels of tacrolimus. There have been reports of nephrotoxicity in patients also. Patients receiving tacrolimus and fluconazole concomitantly should be carefully monitored.
- Terfenadine: Concomitant fluconazole and terfenadine causes palpitations, tachycardia, dizziness, and chest pain where the relationship of the adverse events to drug therapy or underlying medical condition was not clear. Because of the potential seriousness of such an interaction, it is recommended that terfenadine not be taken in combination with fluconazole.
- Theophylline: Patients who are receiving high dose theophylline or who are otherwise at increased risk for theophylline toxicity should be observed for signs of theophylline toxicity while receiving fluconazole, and therapy modified appropriately if signs of toxicity develop.
- Zidovudine: Increased levels of zidovudine most likely caused by the decreased conversion of zidovudine to its major metabolite. Patients receiving this combination of fluconazole and zidovudine should be monitored for the development of zidovudine-related adverse reaction.
- Use of fluconazole in combination with astemizole or other drugs metabolized by the cytochrome P-450 system may be associated with elevations in serum levels of these drugs.
- Oral fluconazole is coadministered with food, cimetidine, antacids or following total body irradiation for bone marrow transplantation. No clinically significant impairment of fluconazole absorption.

4.6 Pregnancy and lactation

PREGNANCY:

Use in pregnancy should be avoided except in patients with severe or potentially life-threatening fungal infections in whom fluconazole may be used if the anticipated benefit outweighs the possible risk to the fetus and adequate contraception is employed.

LACTATION:

Fluconazole is found in human breast milk at concentrations similar to plasma, hence its use in nursing mothers is not recommended.

Effects on ability to drive and use machines

Not applicable.

Main Side/ Adverse Effects

- Increased risk of exfoliative skin disorders, including Stevens-Johnson syndrome, agranulocytosis, and thrombocytopenia.
- Adverse effects reported with fluconazole most commonly affect the gastrointestinal tract and include abdominal pain, diarrhea, flatulence, nausea and vomiting, and taste disturbance.

- Other adverse effects include headaches, dizziness, leucopenia, thrombocytopenia, hyperlipidaemias, and raised liver enzyme values. Serious hepatotoxicity has been reported in patients with severe underlying disease such as AIDS or malignancy. Anaphylaxis and angioedema have been reported rarely.
- Skin reactions are rare but exfoliative cutaneous reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome has occurred, more commonly in patients with AIDS.

4.9 Overdose

Overdosage with fluconazole in patient infected with human immunodeficiency virus developed hallucinations and exhibited paranoid behaviour after ingesting 8200 mg of fluconazole. The condition will resolve within 48 hours.

Treatment:

Symptomatic treatment (with supportive measures and gastric lavage if necessary) may be adequate. Fluconazole is largely excreted in the urine and forced volume diuresis would probably increase the elimination rate. A three-hour hemodialysis session decreases plasma levels by approximately 50%.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

- Fluconazole, a triazole antifungal agent, is a potent and specific inhibitor of fungal sterol synthesis. Both orally and intravenously administered fluconazole was active in a variety of animal fungal infection models. Activity has been demonstrated against opportunistic mycoses, such as infections with Candida spp, including systemic candidiasis in immunocompromised animals: with Cryptococcus neoformans, including intracranial infections; with Microsporum spp; and with Trichophyton spp. Fluconazole has also been shown to be active in animal models of endemic mycoses, including infections with Blasctomyces dermatitides; with Coccidioides immitis, including intracranial infection; and with Histoplasma capsulatum in normal and immunosuppressed animals.
- There have been reports of cases of superinfection with Candida species other than C.albicans, which are often inherently not susceptible to fluconazole (e.g., Candida krusei). Such cases may require alternative antifungal therapy.
- Fluconazole is highly specific for fungal cytochrome P-450 dependent enzymes. Fluconazole 50 mg daily given up to 28 days has been shown not to affect testosterone plasma concentrations in males or steroid concentrations in females of child-bearing age. Fluconazole 200 to 400 mg daily has no clinically significant effect on endogenous steroid levels or on ACTH stimulated response in healthy male volunteers. Interaction studies with antipyrine indicate that single or multiple doses of fluconazole 50 mg do not affect its metabolism.

Pharmacokinetic properties

Fluconazole is well absorbed after oral doses, bioavailability from the oral route being 90% or more of that from the intravenous route. Peak concentrations are needed within 0.5 to 1.5 hours of oral administration. Plasma concentrations are proportional to dose. Steady-state concentration are needed by day 4-5 with multiple once daily dosing, but may be obtained on day 2 if a loading dose is given.

Fluconazole is widely distributed throughout the body, with good penetration into the cerebrospinal fluid (CSF) in patients with fungal meningitis which is approximately 80% of the corresponding plasma levels, the eye, and peritoneal fluid. The apparent volume of distribution is close to that total body water.

Concentrations in breast milk, joint fluid, saliva, sputum, vaginal fluids, and peritoneal fluid are similar to those achieved in plasma. The plasma protein binding of fluconazole is low (11-12%).

Fluconazole is cleared primarily by renal excretion. About 80% of the administered dose is excreted unchanged in the urine and about 11% as metabolites. The elimination half-life of fluconazole is about 30 hours and is increased in patients with renal impairment. Fluconazole is removed by dialysis.

Preclinical Safety Data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

List of excipients

Lactose Monohydrate
Pregelatinized Starch
Microcrystalline Cellulose
Sodium Lauryl Sulphate
Colloidal Silicon Dioxide
Sodium Starch Glycolate
Magnesium Stearate

Incompatibilities

Not applicable.

Shelf life

3 years from date of manufacture

Special precaution for storage

Store below 30˚C. Protect from light and moisture.

Nature and contents of container

Immediate Container/Packaging

Blister Pack

Type

Push-through blister pack; the package consists of a clear thermoformable plastic (PVC) material and a heat-sealed, lacquered backing material.

Rigid Polyvinylchloride (PVC) Film

Description	:	Polyvinylchloride (PVC) Film
Appearance	:	Glass clear transparent film

Aluminium blister foil

Description	:	Aluminium foil with high slip primer on bright surface and heat seal on matt surface/Aluminium foil with high slip primer on matt surface and heat seal agent on bright surface
Appearance	:	Bright surface/Matt surface each side

Secondary Packaging Components

Outer Container/Packaging
Type: Unit box
Material: Paper carton

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 NATIONALREGISTER OF FINISHED PHARMACEUTICAL PRODUCTS

HOV/MAL/035

9. DATE OF FIRST AUTHORISATION

December 2016

9. DATE OF REVISION OF THE TEXT

May 2020