## Pharmaniaga Fluconazole Capsule

**DESCRIPTION**

***Pharmaniaga Fluconazole Capsule 150 mg***

Light blue/light blue, hard gelatin, size '2' capsule with Pharmaniaga icon and '150' markings.

***Pharmaniaga Fluconazole Capsule 100 mg***

Blue/white, hard gelatin, size '2' capsule with Pharmaniaga icon and "100" markings.

**COMPOSITION**

***Pharmaniaga Fluconazole Capsule 150 mg***

Each capsule contains: Fluconazole 150 mg

***Pharmaniaga Fluconazole Capsule 100 mg***

Each capsule contains: Fluconazole 100 mg

**PHARMACODYNAMICS**

Fluconazole is a triazole antifungal drug which is a potent and specific inhibitor of fungal sterol synthesis. It interferes with the cytochrome P-450 activity, which is necessary for the demethylation of 14-alpha-methylsterols to ergosterol. Ergosterol, the principal sterol in the fungal cell membrane, becomes depleted. This damages the cell membrane, producing alterations in membrane functions and permeability.

It is active against *Blastomyces dermatitidis*, *Candida* spp., *Coccidioides immitis*, *Cryptococcus neoformans, Epidermophyton* spp., *Histoplasma capsulatum, Microsporum* spp., and *Trichophyton* spp.

**PHARMACOKINETICS**

Fluconazole is well absorbed following oral administration, bioavailability from the oral route being 90% or more of that from the intravenous route. Mean peak plasma concentrations of 6.72 µg per mL have been reported in healthy subjects following a 400 mg oral dose. Peak concentrations are reached within 1 to 2 hours of oral administration. Plasma concentrations are proportional to the dose over a range of 50 to 400 mg. Multiple dosing leads to increases in peak plasma concentrations; steady-state concentrations are reached in 6 to 10 days but may be attained on day 2 if a loading dose is given.

Fluconazole is widely distributed and the apparent volume of distribution is close to that of total body water. Concentrations in breast milk, joint fluid, saliva, sputum, vaginal fluids and peritoneal fluid are similar to those achieved in plasma. Concentrations in the cerebrospinal fluid range from 50 to 90% of plasma concentrations, even in the absence of meningeal inflammation. Protein binding is only about 12%.

Eighty percent or more of fluconazole is excreted unchanged in the urine; about 11% is excreted as metabolites. The elimination half-life of fluconazole is about 30 hours and is increased in patients with impaired renal function. Fluconazole is removed by dialysis.

**INDICATIONS**

1. Genital candidiasis. Vaginal candidiasis, acute or reccurrent; and prophylaxis to reduce the incidence of reccurrent vaginal candidiasis (3 or more episodes a year). Candidal balanitis. Prevention of relapse of oropharyngeal candidiasis in patients with AIDS.

2. Cryptococcosis, including cryptococcal meningitis and infections of other sites {(e.g., pulmonary, cutaneous). Normal hosts and patients with AIDS, organ transplants or other causes of immunosuppression may be treated. Fluconazole can be used as maintenance therapy to prevent relapse of cryptococcal disease in patients with AIDS.

3. Systemic candidiasis, including candidemia, disseminated candidiasis and other forms of invasive candidal infection. These include infections of the peritoneum, endocardium, eye, pulmonary and urinary tracts. Patients with malignancy, in intensive care units, receiving cytotoxic or immunosuppressive therapy, or with other factors predisposing to candidal infection may be treated.

4. Mucosa 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.

5. Prevention of fungal infections in patients with malignancy who are predisposed to such infections as a result of cytotoxic chemotheraphy or radiotherapy.

6. Dermatomycosis including tinea pedis, tinea corporis, tinea cruris, tinea versicolor and dermal candida infections.

**CONTRAINDICATIONS**

Fluconazole is contraindicated in patients who have shown hypersensitivity to fluconazole or to related azole compounds.

Co-administration of terfenadine is contraindicated in patients receiving fluconazole at multiple doses of 400 mg or higher based upon results of a multiple dose interaction study. Co-administration of cisapride is contraindicated in patients receiving fluconazole.

**ADVERSE REACTIONS/SIDE EFFECTS**

The most common side-effects associated with fluconazole are symptoms related to the gastrointestinal tract. These include nausea, abdominal pain, diarrhoea and flatulence. The second most commonly observed side-effect was rash.

Headache has been associated with fluconazole. In some patients, particularly those with serious underlying diseases such as AIDS and cancer, changes in renal and haematological function test results and hepatic abnormalities have been observed during treatment with fluconazole and comparative agents, but the clinical significance and relationship to treatment is uncertain. Exfoliative skin disorders; seizures, leukopenia including neutropenia and agranulocytosis, thrombocytopenia and alopecia have occurred under conditions where a causal association is uncertain.

In rare cases, as with other azoles, anaphylaxis has been reported.

If a rash develops in a patient treated for a superficial fungal infection which is considered attributable in fluconazole, further therapy with this agent should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and fluconazole discontinued if bullous lesions or erythema multiforme develop.

**PRECAUTIONS**

Hepatic injury: Fluconazole has been associated with rare cases of serious hepatic toxicity, including fatalities primarily in patients with serious underlying medical conditions. In cases of fluconazole associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of the patient has been observed.

Fluconazole hepatotoxicity has usually, but not always, been reversible on discontinuation of therapy. Patients who develop abnormal liver function tests during fluconazole therapy should be monitored for the development of more severe hepatic injury. Fluconazole should be discontinued if clinical signs and 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 fungal infection, further therapy with this agent should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and fluconazole discontinued if bullous lesions or erythema multiforme develop.

**Drug Interactions**

**Coumarin-type anticoagulants:** Prothrombin time may be increased in patients receiving concomitant fluconazole and coumarin-type anticoagulants.

**Phenytoin:** Fluconazole increases the plasma concentrations of phenytoin.

**Cyclosporine:** Fluconazole may significantly increase cyclosporine levels in renal transplant patients with or without renal impairment. Cyclosporine plasma concentration monitoring in patients receiving fluconazole is recommended.

**Rifampin:** Rifampin enhances the metabolism of concurrently administered fluconazole. Depending on clinical circumstances, consideration should be given to increasing the dose of fluconazole when it is administered with rifampin.

**Theophylline:** Fluconazole increases the serum concentrations of theophylline.

**Terfenadine:** Because of the occurrence of serious cardiac dysrhythmias secondary to prolongation of the QTc interval in patients receiving azole antifungals in conjunction with terfenadine, interaction studies have been performed. One study at a 200 mg daily dose of fluconazole failed to demonstrate a prolongation in QTc intervals. Another study at a 400 mg and 800 mg daily dose of fluconazole demonstrated that fluconazole taken in doses of 400 mg per day or greater significantly

increases plasma levels of terfenadine when taken concomitantly. The combined use of fluconazole at doses of 400 mg or greater with terfenadine is contraindicated. The coadministration of fluconazole at doses lower than 400 mg/day with terfenadine should be carefully monitored.

**Cisapride:** There have been reports of cardiac events, including torsade de pointes in patients to whom fluconazole and cisapride were coadministratered. The combined use of fluconazole with cisapride is contraindicated.

**Rifabutin:** There have been reports that an interaction exists when fluconazole is administered concomitantly 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.

**Tacrolimus:** There have been reports that 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 to whom fluconazole and tacrolimus were coadministered. Patients receiving tacrolimus and fluconazole concomitantly should be carefully monitored.

**Sulfonylureas:** Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulfonylureas (chlorpropamide, glibenclamide, glipizide and tolbutamide) in healthy volunteers, by reducing the metabolism of these agents and thereby increases their plasma concentration. Fluconazole and oral sulfonylureas may be coadministered to diabetic patients, but the possibility of a hypoglycaemic episode should be borne in mind.

Hydrochlorothiazide: In a kinetic interaction study, co-administration of multiple-dose hydrochlorothiazide to healthy volunteers receiving fluconazole 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:** Two kinetic studies with a combined oral contraceptive have been performed using multiple doses of fluconazole. There were no relevant effects on either hormone level in the 50 mg fluconazole study, while at 200 mg daily, the AUCs of ethinyl estradiol and levonorgestrel were increased 40% and 24%, respectively. Thus, multiple dose use of fluconazole at these doses is unlikely to have an effect on the efficacy of the combined oral contraceptive.

Zidovudine: Two kinetic studies resulted in increased levels of zidovudine most likely caused by the decreased conversion of zidovudine to its major metabolite. One study determined zidovudine levels in AIDS or ARC patients before and following fluconazole 200 mg daily for 15 days. There was a significant increase in zidovudine AUC (20%). A second randomized, two-period, two treatment cross over study examined zidovudine levels in HIV infected patients. On two occasions, 21 days apart, patients received zidovudine 200 mg every eight hours either with or without fluconazole 400 mg daily for seven days. The AUC of zidovudine significantly increased (74%) during co-administration with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine - related adverse reactions.

**PREGNANCY AND LACTATION**

***Use During Pregnancy***

There have been reports of spontaneous abortion and congenital abnormalities in infants whose mothers were treated with 150 mg of fluconazole as a single or repeated dose in the first trimester.

Use in pregnancy should be avoided except in patients with severe or potentially life-threatening fungal infections in whom Pharmaniaga Fluconazole Capsule 100 mg and 150 mg may be used if the anticipated benefit outweighs the possible risk to the foetus. If this drug is used during pregnancy, or if the patient becomes pregnancy while taking the drug, the patient should be informed of the potential hazard to the foetus.

Effective contraceptive measures should be considered in women of child-bearing potential and for approximately 1 week (5 to 6 half-lives) after the final dose.

There have been reports of multiple congenital abnormalities in infants whose mothers were treated with high-dose (400mg/day to 800mg/day) fluconazole therapy for coccidioidomycosis (an approved indication). The relationship between fluconazole use and these events is unclear. Adverse fetal effects have been seen in animals only at high-dose levels associated with maternal toxicity. There were no fetal effects at 5mg/kg or 10mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25mg/kg and 50mg/kg and higher doses. At doses ranging from 80 mg/kg (approximately 20-60 times the recommended human dose) to 320 mg/kg, embryolethality in rats were increased and fetal abnormalities included wavy ribs, cleft palate and abnormal craniofacial ossification. Case reports describe a distinctive and a rare pattern of birth defects among infants whose mothers received high dose (400 - 800 mg/day) fluconazole during most or all of the first trimester of pregnancy. The features seen in these infants include brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital health disease.

**Use During Lactation**

Fluconazole is found in human breast milk at concentrations similar to plasma. Breast-feeding may be maintained after a single dose of 150mg fluconazole. Breast-feeding is not recommended after repeated use or after-dose fluconazole.

**EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

No studies have been performed on the effects of Fluconazole on the ability to drive or use machines.

Patients should be warned about the potential for dizziness or seizures while taking Fluconazole and should be advised not to drive or operate machines if any of these symptoms occur.

**DOSAGE AND ADMINISTRATION**

The daily dose of fluconazole should be based on the nature and severity of the fungal infection. Most cases of vaginal candidiasis respond to single dose therapy. Therapy for those types of infections requiring multiple dose treatment should be continued until clinical parameters or laboratory test indicate that active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection. Patients with AIDS and cryptococcal meningitis or recurrent oropharyngeal candidiasis usually require maintenance therapy to prevent relapse.

**Adult**

1. 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 dose may be used. The duration of therapy should be individualised, 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.

2. For the 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.

3. For cryptococcal meningitis and cryptococcal infections of other sites, the usual dose is 400 mg on the first day followed by 200 mg - 400 mg once daily. Duration of treatment for cryptococcal infections will depend on the clinical and mycological response, but is usually at least 6-8 weeks for cryptococcal meningitis.

For the prevention of relapse of cryptococcal meningitis in patients with AIDS, after the patient receives a full course of primary therapy, fluconazole may be administered indefinitely at a daily dose of 200 mg.

4. The recommended fluconazole dosage for the prevention of candidiasis is 50 mg to 400 mg once daily, based on the patient's risk for developing fungal infection. For patients at high risk of systemic infection e.g., patients who are anticipated to have profound or prolonged neutropenia, the recommended daily dose is 400 mg once daily. Fluconazole administration should start several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 1000 cells per $mm^3$.

5. For oropharyngeal candidiasis, the usual dose is 50 to 100 mg once daily for 7-14 days. If necessary, treatment can be continued for longer periods in patients with severely compromised immune function. For atrophic oral candidiasis associated with dentures, the usual dose is 50 mg once daily for 14 days administered concurrently with local antiseptic measures to the denture. For other candidal infections of mucosa except genital candidiasis (e.g. esophagitis, non-invasive bronchopulmonary infections, candiduria, mucocutenaous candidiasis, etc.) the usual effective dose is 50 to 100 mg daily, given for 14-30 days. For

the 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.

6. For dermal infections including tines pedis, corporis, cruris and candida infections the recommended dosage is 150 mg once weekly or 50 mg once daily. Duration of treatment is normally 2 to 4 weeks but tines pedis may require treatment for up to 6 weeks. For tines versicolor, the recommended dosage 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 - 400 mg may be sufficient. An alternate dosing regimen is 50 mg once daily for 2 to 4 weeks. For tines unguium, the recommended dosage is 150 mg once weekly. Treatment should be continued until infected nail is replaced (uninfected nail grows in). Regrowth of fingernails and toenails normally require 3 to 6 months and 6 to 12 months, respectively. However, growth rates may vary widely in individuals and by age. After successful treatment of long term chronic infections, nail occasionally remain disfigured.

**Elderly patients**
Where there is no evidence of renal impairment, normal dosage recommendations should be adopted. For patients with renal impairment (creatinine clearance < 50 mL/min) the dosage schedule should be adjusted as described in the following.

**Patients 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 in accordance with creatinine clearance below.

| Creatinine Clearance (mL/min) | Dosage Interval/daily dose |
|---|---|
| > 50 | normal dosage regimen |
| 11—50 | ½ normal daily dose |
| Patients receiving regular dialysis | 1 dose after every dialysis session |

**Children**
Not recommended.

**OVERDOSAGE**
There has been one reported case of overdosage with fluconazole. A 42 years old patient infected with human immunodeficiency virus developed hallucinations and exhibited paranoid behaviour after reportedly ingesting 8200 mg of fluconazole. The patient was admitted to the hospital, and his condition resolved within 48 hours. In the event of overdose, symptomatic treatment (with supportive measures and gastric lavage if clinically indicated) should be instituted.

Fluconazole is largely excreted in urine. Forced volume diuresis would probably increase the elimination rate. A three - hour haemodialysis session decreases plasma levels by approximately 50%.

**ROUTE OF ADMINISTRATION**
Oral

**STORAGE CONDITION**
Store below 30°C.
Protect from light.

**SHELF LIFE**
Product should not be used beyond the expiry date imprinted on the product packaging.

**PRESENTATION**
***Pharmaniaga Fluconazole Capsule 100 mg***
Blister pack of 30's.

***Pharmaniaga Fluconazole Capsule 150 mg***
Blister pack of 10's.

Date of revision: 08th November 2021

**PRODUCT REGISTRATION HOLDER/ MANUFACTURER:**
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PRP 0422.5/PRP 0421.5 081121