Candirid (Fluconazole)

کینڈی ریڈ (فلوکونازول)

1. NAME OF THE MEDICINAL PRODUCT:
Candirid (Fluconazole)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Candirid Capsules contains as its active ingredient fluconazole USP 150mg.

3. PHARMACEUTICAL FORM:
Capsule for oral use.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications
Therapy may be istitiuted before the results of the cultures and other laboratory studies are known, however, once these results become available, anti-infective therapy should be adjusted accordingly.

1. Cryptococcosis, including cryptococcal meningitis and infectious of other sites (e.g., pulmonary, cutaneous). Normal hosts and patients with AIDS, organ transplants or other causes or immunosuppression may be treated. Fluconazole can be used as maintenance therapy to prevent relopse of cryptococcal disease in patients with AIDS.
2. Systemic candidiasis, including candidemia, disseminated canddates and other forms of invasive candidal infection These include infections of the peritoneum, endocardium, eye and pulmonary and urinary tracts. Patients with malignancy, in intensive care units, receiving cytotoxicor immunosuppressive therapy, or with other factors predisposing to candidal infection may be treated.
3. 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 candidasis in patients with AIDS.
4. Genital candidiasis. Vaginal candidiasis, acute or recurrent; and prophylaxis to reduce the incidence of recurrents vaginal candidiasis (3 or more episodes a year). Candidal baianitis.
5. Prevention of fungal infections in patients with malignancy who are predisposed to such infections as a result of cytotoxic chemotherapy or radiotherapy.
6. Dermatomycosis including thea pedis. tinea corporis tinea cruris, tinea versicolor, tinea unguium (onychornycosis).and dermal candida infections
7. Deep endemic mycoses in immunocompetent patients, coccidioidomycosis, paracoccidioidomycosis, sportrichosis and histoplasmosis.

4.2 Posology and Methed of administration
The daily dose of fluconazole should be based on the nature and severity of the fungal infection. Most case 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 tests indicate that active fungal infection has subsided. An in adequate 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.

In Adults.

1. For cryptococcal meningitis and cryptococcal infections at other Sites, the usual dose is 400mg on the first day followed by 200mg-400mg 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 indefintely at daily dose of 200mg.
2. For candidemia, disseminated candidiasis and other invasive candidal infections, the usual dose is 400mg on the first day followed by 200mg daily. Depending on the clinical response, the dose may be increased to 400mg daily. Duration of treatment is based upon the clinical response.
3. For oropharyngeal candidiasis , the usual dose is 50 to 100mg once daily for 7-14 days. If necessary, treatment can be continued for longer periods in patients with severaly compromised immune function. For atrophic oral candidiasis associated with dentures, the usual dose is 50mg once daily for 14 days administered concurrently with local antiseptic measures to the denture.
   For other candidal infections of mucosa, except genital candidiasis (see below) (e.g. esophagitis, non-invasive) bronchopulmonary infections, candiduna, mucocutaneous candidiasis, etc.) the usual effective dose is 50 to 100mg daily. given for 14-30 days.
   For the prevention of relapse of oropharyngal candidiasis in patients with AIDS, after the patient receives a full course of primary therapy, fluconazole may be administered at a 150mg once weekly dose.
4. For the treatment of vaginal candidiasis, fluconazole 150mg should be admistered as a single oral dose.
   To reduce the incidence of recurrent vaginal candidasis, a 150mg once monthly dose may be used. The duration of therapy should be individualized, but ranges from 4-12, months,some should be individualized, but ranges from 4-12 months, some patients may required more frequent dosing. For Candida balanitis, fluconazole 150mg should be administered as a single oral dose.
5. For tinea unguium, the recommended dosages is 150mg once weekly. Treatment should be continued until infected nail is replaced (uninfected nail grows in). Regrowth of fingernails and toenails normaliy requrires 3 to 6 months and 6 to 1 months, respectively. However, growth rates may vary widely in individuals, and by age. After successful treatment of long-term chronic infections, nails ocassionally remain disfigured.

In patients with Renal Impairment
Fluconazole is predominantly excreted in the urine as unchanged drug no adjustments in single dose therapy are necessary. In patients (including children) with impaired renal function who will receive multiple doses of fluconazole, an initial loading dose of 50mg to 400mg should be given. After the loading dose, the daily dose (according to indication) should be based on the following table:

Creatinine Clearance	Present of Recommended of
>50	100%
50(no dialysis)	50%
Regular dialysis	100% after each dialysis

4.3 Contra-Indications
Fluconazole should not be used in patients with known sensitivity to the drug or to related azole compounds. Coadministration of terfenadine is contraindicated in patients receiving fluconazole at multiple doses of 400mg per day if higher based upon results of cisapride is contraindicated in Interaction study, Coadministration of cisapride is contraindicated in patients receiving fluconazole (see section 4.5 - interaction with other Medicaments and other forms of interaction.)

4.4 Special Warnings and Special Precautions for Use
Fluconazole Should be discontinued it clinical signs or symptoms toxicity including fatalities, primarily in patients with serious uriderlying medical conditions. In cases of fluconazole associated hepatotoxicity, no obvious relationship to total daily dose duration of therapy, sex or age of patients has been observed. 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 live 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 to may prone to the development of severe cutaneous reactions to many drugs. If a rash, which is considered attributable to fluconazole, develops in 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 buillous lesions or erythema multiforme develop. The coadministration of fluconazole at doses lower than 400mg per day with terfenadine should be carefully monitored (see section 4.5 - Interaction with Other Medicaments and Other Forms of interaction). In rare cases, as with other azoles, anaphylaxis has been reported.

4.5 Interaction with Other Medicaments and Other Forms of Interaction.
Anticoagulants: In an interaction study, fluconazole increased the prothrombin time (12%) after warfarin administration in healthy males in post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematura, 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 anticoagulants should be carefully monitored.
Benzodiazepines (Short Acting): Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. This effects 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: There have been reports of cardiac events including torsade de pointes in patients to whom fluconazole and cisapride were coadministered. Coadministration of cisapride is contraindicated in Patients receiving fluconazole.
Cyclosporin: A kinetic study in renal transplant patients found fluconazole 200mg daily to slowly increase cyclosporin concentrations. However, in another multiple dose study with 100mg daily, fluconazole did not affect cyclosporin levels in patients with bone marrow transplants. Cyclosporin plasma concentration monitoring in patients receiving fluconazole is recommended.
Hydrochlorothiazide: In a kinetic interaction study, coadministration of multiple-dose hydrochlorothiazide to healthy volunters receiving fluconazole increased plasma concentrations of volunters receiving 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 Contraceives: Two kinetic studies with combined oral contraceptive have been performed using multiple doses of fluconazole, There were no relevant effect on either hormone level in the 50mg fluconazole study, while at 200mg daily, the AUCs of ethinyl estradiol and levonorgestrel were increased 40% and 24% respectively. This multiple dose use of fluconazole at these doses is unlikely to have an effect on the efficiency of the combined oral contraceptive.
Phenytoin: Conncomitant administrstion 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.
Rifampcin: 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.
Rifabutin: Concomitant administration of fluconazole and rifampicn resulted in a 5% decrease in the AUC and a 0% shorter half-life of fluconazole. In patients receiving concomitant rifampicn, 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 (chlorproprnide, glibenclamide, glipizide and tolbutamide) in healthy volunteers. Fluconazole and oral sulfonylureas may be coadministered to diabetic patients, but the possibility of a hypoglycernic episode should be borne in mind.
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 hepatotoxicity in patients to whom fluconazole and tacrolimus were coadministered. Patients receiving tacrolimus and fluconazole concomitantly should be carefully monitored.
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 200mg daily dose of flucinazole failed to demonstrate a prolongation in Qtc interval. Another study at a 400mg and 800mg daily dose of fluconazole demonstrated that fluconazole taken in doses of 400mg per day or greater significantly increases plasma levels of terfendine when taken concomitantly. The combined use of fluconazole at dose of 400mg or greater with terfenadine is contraindicated (see section 4.3 - Contra-indications). The coadministration of fluconazole at doses lower than 400mg per day with terfenadine should be carefully monitored.
Theophylline: In a placebo controlled interaction study. The administration of fluconazole 200mg for 14 days resulted in an 18% decrease in the mean plasma clearance rate of 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.
Zidouvdine: Two kinetic studies resulted in increased levels of zidovudine most likely caused by the decreased conversion of zidouvdine to its major metabolite, One study determind zidouvdine levels in AIDS or ARC patients before and following fluconazole 200mg daily for 15 days. There was a significant increase in zodouvdine 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 200mg every eight hours either with or without fluconazole 400mg daily for seven days. The AUC of zidovudine significantly increased (72%) during coadministration with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine related adverse reactions.
The use of fluconazole in patients concurrently taking astemizole or other drugs metabolized by the patients concurrently taking asternizole or associated with elevations in serum levels of these drugs. In the absence of definitive information, caution should be used when coadministering fluconazole. Patients would be carefully monitored. Interaction studies have shown that when oral fluconazole is coadministering with food, cimetidine, antacids or following total body irradiation for bone marrow transplantation, no clinically significant impairment of fluconazole absorption occurs.
Physicians should be aware that drug-drug interaction studies with other medications have been conducted. but such interactions may occur.

5.1 Pharmacokinetic Properties
The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral route. After oral administration fluconazole is well absorbed and plasma levels (and systemic bioavailability) are over 90% of the levels achieved after intravenous administration. Oral absorption is not affected by concomitant food intake. Peak plasma concentration in the fasting state occur betwen 0.5 and 1.5 hours post dose with a plasma elimination half-life of approximately 30 hours. Plasma concentrations are proportional to dose. Ninety percent steady state levels are reached by day 4-5 with multiple once daily dosing.
Administration of loading dose (on day 1) of twice the usual daily dose enables plasma levels to approximate to 90% steady state levels by day. The apparent volume of distribution approximates to total body water. Plasma protein binding is low (11-12%).
Fluconazole achieves good penetration in all body fluids Studies. The levels of fluconazole in saliva and sputum are similar to plasma levels. In patients with fungal meningitis, fluconazole levels in the CSF are approximately 80% the corresponding plasma levels.
High skin concentration of fluconazole, above serum concentration, seat. Fluconazole accumulates in the stratum corneum. At a dose of 50mf once daily, the concentration of fluconazole after 12 days was 73 ug/g. At the 150mg once-a-week dose, the concentration of fluconazole in stratum corneum on day 7 was 34 ug/g and 7 days after the second dose was still 7.1 ug/g.
Concentration of fluconazole in nails after 4 months of 150mg once-a-week dosing was 4.05 ug/g in health and 1.8 ug/g in diseased nails and, fluconazole was still measurable in nail samples 6 month after the end of therapy.
The major route of excretion is renal, with approximately 80% of the administered dose appearing the urine as unchanged drug. Fluconazole clearance is proportional to creatinine clearance. There is no evidence of c irculating metabolites.
The long plasma elimination half-life provides the basis for single dose therapy for vaginal candidiasis, once daily and once weekly dosing for other indications.
A study compares the saliva and plasma concentrations of a single fluconazole 100mg dose administered in a capsule or in an oral suspension by rinsing and retaining mouth for minutes and swallowing, The maximum concentration of fluconazole in saliva after the suspension was observed 5 minutes after ingestion and was 18 times higher than the maximum saliva concentration after the capsule which occured 4 hours after ingestion. After about 4 hours, the saliva concentrations of fluconazole were similar. The mean AUC (0.96) in saliva was significantly greater after the suspension compared to the capsule. There was no significant difference in the elimination rate from salivas or there plasma pharmacokinetic parameters for the two formulations.

6. PHARMACEUTICAL PARTICULARS

6.1 Active Ingredients
Fluconazole is a bis-triazole, having the following chemical name: 2-(2.4-difiuorophenyl)- 1,3, bis-(1 H-1, 4-triazol-lyl)-2-propanol, It has a molecular weight of 306.3

6.2 List of Excipients
Capsules
Fluconazole capsules contain lactose, maize starch, colloidal silicon dioxide, magnesium stearate and sodium laury sulphate as excipients.

6.3 Special Precautions for Storage
Store the medicine between 15-30°C at dry place.

6.4 Nature and Contents of Container
Capsules
One Capsule in PVC-ALU blister pack.

6.5 Instructions for Use/ Handling
As directed by the physician.

تاکید: صرف رجسٹرڈ میڈیکل پریکٹشنر کے نسخہ پر فروخت کریں۔
خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
دوا بچوں کی پہنچ سے دور رکھیں۔ گرمی اور دھوپ بچائیں۔
دوا کا ۱۵ سے ۳۰ ڈگری سینٹی گریڈ درجہ حرارت کے درمیان خشک جگہ پر رکھیں۔

ORTA SINCE 1954
Manufactured By:
ORTA LABORATORIES (PVT.) LTD.
ISO 9001: 2008 CERTIFIED COMPANY
24 Km. Multan Road, Off. Defence Road,
Mohlanwal, Lahore - Pakistan.

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