Fluconazole

Funzela®

Antifungal

50 mg, 150 mg, 200 mg Tablet

FORMULATION
Each tablet contains:
Fluconazole ..... 50 mg
Each scored tablet contains
Fluconazole ..... 150 mg or 200 mg

PRODUCT DESCRIPTION
Fluconazole 50 mg is a plain, mottled pink, round biconvex tablet.
Fluconazole 150 mg is a mottled pink, biconvex tablet, bisected on one side and plain on the other side.
Fluconazole 200 mg is a plain, mottled pink, round biconvex tablet, bisected on one side and plain on the other side.

PHARMACODYNAMICS
Fluconazole, a synthetic broad spectrum bis-triazole antifungal agent, is a highly selective inhibitor of cytochrome P450-dependent enzymes and sterol C-14 alpha-demethylation. These actions result in impairment of ergosterol synthesis in fungal cell membrane, leading to growth inhibition, abnormal cell wall formation, and accumulation of intracellular lipids and membranous vesicles. Depending on the concentration, Fluconazole may be fungicidal or fungistatic.

ANTIMICROBIAL SPECTRUM OF ACTIVITY
Fluconazole has a relative selectivity for fungal cytochrome P450 system. It exhibits in vitro activity against *Cryptococcus neoformans* and *Candida* spp. and has demonstrated fungistatic activity in normal and immunocompromised animal models for systemic and intracranial fungal infections due to *Cryptococcus neoformans* and for systemic infections due to *Candida albicans*. Development of resistance to Fluconazole has not been studied; however, there have been reports of cases of superinfection with *Candida* spp. other than *Candida albicans*, which are often inherently nonsusceptible to Fluconazole.

Like other azole antifungal agents, most fungi show a higher apparent sensitivity to Fluconazole in vivo then in vitro. Activity has been demonstrated against fungal infections caused by *Aspergillus flavus* and *Aspergillus fumigatus* in mice. Fluconazole is active in animal models of endemic mycoses, including one model of *Blastomyces dermatitidis* pulmonary infections, one model of *Coccidioides immitis* intracranial infections and several models of *Histoplasma capsulatum* pulmonary infection.

Coadministration of Fluconazole and Amphotericin B in infected normal and immunosuppressed mice showed a small additive antifungal effect in systemic infection with *Candida albicans*, no interaction in intracranial infection with *Candida neoformans*, and antagonism of the two drugs in systemic infection with *Aspergillus fumigatus*.

PHARMACOKINETICS
The pharmacokinetic properties of Fluconazole are similar after intravenous or oral administration. Bioavailability of oral Fluconazole is >90% in healthy volunteers.

Peak plasma Fluconazole concentrations in fasted healthy volunteers occur between 1 and 2 hours with a terminal plasma elimination half-life of 30 hours after oral administration. A single oral 400 mg dose leads to a mean Cmax of 6.72 mcg/mL; after single oral doses of 50 to 400 mg, plasma concentrations and AUC are dose-proportional. A single 150 mg oral dose given to 10 lactating women resulted in a mean Cmax of 2.61 mcg/mL.

Steady-state concentrations are reached within 5 to 10 days after oral doses of 50 to 400 mg given once daily. Administration of a loading dose (day 1) of twice the usual daily dose results in plasma concentrations close to steady state by day 2. The apparent volume of distribution approximates that of total body water. Plasma protein binding is low (11 to 12%). Fluconazole penetrates into all body fluids studied after either single or multiple oral doses for up to 14 days. (See table below).

Tissue/Fluid Concentrations of Fluconazole

Tissue or fluid	Concentrations[1] (tissue/plasma ratio)
Cerebrospinal fluid[2]	0.5 - 0.9
Saliva	1
Sputum	1
Blister fluid	1
Urine	10
Normal skin	10
Nails	1
Blister skin	2
Vaginal tissue	1
Vaginal fluid	0.4 - 0.7

[1] Relative to plasma concentrations in subjects with normal renal function.
[2] Independent of degree of meningeal inflammation.

In healthy volunteers, Fluconazole is cleared primarily by renal excretion, with 80% of the dose appearing in the urine unchanged, and 11% as metabolites. Fluconazole's pharmacokinetics are markedly affected by reduction in renal function. There is an inverse relationship between elimination half-life and creatinine clearance. Dose may need to be reduced in patients with impaired renal function. A 3 hour hemodialysis session decreases plasma concentrations by 50%.

Doses of 200 to 400 mg once daily for up to 2 weeks in healthy volunteers were associated with small, inconsistent effects on testosterone and endogenous corticosteroid concentrations and the ACTH-stimulated cortisol response.

INDICATIONS
- For the treatment of the following infections caused by susceptible strains of microorganisms:
  - > Cryptococcosis including cryptococcal meningitis and infections at other sites,
  - > Systemic candidiasis, including candidemia, disseminated candidiasis and other forms of invasive candidal infection including infections of the peritoneum, endocardium, eye, respiratory and urinary tracts,
  - > Mucosal candidiasis including oropharyngeal, esophageal, non-invasive bronchopulmonary infections, candiduria, mucocutaneous and denture sore mouth,
  - > Genital candidiasis including vaginal candidiasis (acute or recurrent), candidal balanitis
  - > Deep endemic mycoses, including coccidioidomycosis, paracoccidioidomycosis, blastomycosis, sporotrichosis, and histoplamosis in immunocompetent patients,
  - > Superficial fungal infections such as dermatomycosis and onychomycosis including tinea pedis, tinea capitis, tinea corporis, tinea cruris, tinea versicolor, and dermal candida infections.
- For the prophylaxis of transplant patients, patients with malignancy who are receiving cytotoxic chemotherapy, immunosupressive therapy or radiation therapy, and other patients who are at risk of developing candida infections and serious fungal infections such as coccidioidomycosis and cryptococcal infections.
- For the prophylaxis of HIV/AIDS patients who are at risk of developing candida infections and serious fungal infections such as coccidioidomycosis and cryptococcal infections.

DOSAGE AND ADMINISTRATION
Since Fluconazole has > 90% bioavailability, oral and intravenous dosing are the same. The intravenous route should be considered for patients who cannot tolerate or are unable to take Fluconazole orally.

Recommended Dosing Regimen for Adults

Infection/Condition	Adult Dosage
Cryptococcal meningitis & cryptococcal infections at other sites	400 mg on the 1st day, then 200 to 400 mg once daily. Recommended duration of treatment for initial therapy of cryptococcal meningitis is usually 6 to 8 weeks up to 10 to 12 weeks after CSF becomes culture negative.
Oropharyngeal candidiasis	50 to 100 mg once daily for 7 to 14 days
Denture-associated atrophic oral candidiasis	50 mg once daily for 14 days (together with local antiseptic measures to the denture)
Esophageal candidiasis	50 to 100 mg once daily for 14 to 30 days. Dose may be increased to 400 mg once daily if necessary.
For other candida infections of the mucosa (except genital candidiasis)	50 to 100 mg once daily for 14 to 30 days.
Systemic candida infections	400 mg on the 1st day, then 200 mg once daily. Dose may be increased to 400 once mg daily. Treatment should be continued for a minimum of 4 weeks and for at least 2 weeks after symptoms have resolved.
Vaginal candidiasis and candidal balanitis	150 mg single dose
Recurrent vulvovaginal candidiasis	150 mg on the 1st day, then 150 mg on the 4th day; maintenance regimen is 100 to 150 mg once a week for 6 months
Dermatologic infections including tinea pedis, corporis, and cruris; candida infections	150 mg once a week or 50 mg once daily for 2 to 6 weeks
Tinea versicolor and tinea captis	50 mg once daily for 2 to 4 weeks
Tinea unguium (onychomycosis)	150 mg once a week; treatment should be continued until regrowth of toenails or fingernails and usually ranges from 3 to 6 months for fingernails and 6 to 12 months for toenails, depending on the patients condition
Deep endemic mycoses	200 to 800 mg once daily; treament duration depends on the condition being treated but usually ranges from 11 to 24 months for coccidioidomycosis, 2 to 17 months for paracoccidioidomycosis, 1 to 16 months for sporotrichosis and 3 to 17 months for histoplasmosis
Suppression of relapse of cryptococcal meningitis & cryptococccal infections at other sites in patients with AIDS (after the patient receives a full course of primary therapy)	100 to 200 mg once daily for an indefinite period of time
Prevention of oropharyngeal candidiasis relapse in patients with AIDS (after the patient receives a full course of primary therapy)	100 to 200 mg once a week; duration of treatment is usually 4 to 9 months
Prevention of fungal infections in paberts with HIV	100 to 200 once daily; duration of treatment will depend on the patientis condition
Prevention of fungal infections in transplant patients, patients undergoing chemotherapy, immunotherapy or radiotherapy and other patients who are at high risk of systemic fungal infections	400 mg once daily depending on the patient's condition

Recommended Dosing Regimen for Children
Usual recommended dose: 3 to 12 mg/kg body weight once daily.
Do not exceed 600 mg once daily in children.

Infection	Pediatric Dosage
Oropharyngeal candidiasis	6 mg/kg body weight on the 1st day, then 3 mg/kg body weight once daily for at least 2 weeks to decrease likelihood of relapse.
Esophageal candidiasis	6 mg/kg body weight on the 1st day, then 3 mg/kg body weight once daily. Doses may be increased to 12 mg/kg body weight/day. Minimum treatment duration is 3 weeks and at least 2 weeks after the symptoms resolve.
Systemic candida infections	6 to 12 mg/kg body weight daily; duration of treatment will depend on the organism being treated and the patient's condition
Cryptococcal meningitis & cryptococcal infections at other sites	12 mg/kg body weight on the 1st day, then 6 mg/kg body weight once daily. Dose may be increased to 12 mg/kg body weight per day. Recommended duration of treatment for initial therapy of cryptococcal meningitis is 10 to 12 weeks after CSF becomes culture negative.
Suppression of cryptococcal meningitis in patients with AIDS	6 mg/kg body weight once daily for 6 months or longer

For children less than 4 weeks, the same Fluconazole dose as above should be given. However, the dosage regimen is changed as follows:

Age Group	Recommended Dosing Regimen
Infants less than 2 weeks old	Fluconazole dose to be given once every 3 days
Infants 2 to 4 weeks old	Fluconazole dose to be given every other day

The following dose equivalency scheme should generally provide equivalent exposure in pediatric and adult patients:

Pediatric Patients	Adult Patients
3 mg/kg body weight	100 mg
6 mg/kg body weight	200 mg
12 mg/kg* body weight	400 mg

*Some older children may have clearances similar to those of adults. Absolute doses exceeding 600 mg/day are not recommended in children.

Dosage in Patients with Impaired Renal Function
No dosage adjustment is necessary for patients with renal impairment who are to receive a single dose of Fluconazole. For patients who need multiple doses of Fluconazole, an initial loading dose of 50 to 400 mg is required followed by a daily dose based on creatinine clearance as shown in the following table:

Creatinine clearance (mL/min)	Percentage of recommended dose
> 50	100%
11 - 50	50%
Patients undergoing regular dialysis	One recommended dose after each dialysis

These are suggested dose adjustments based on Fluconazole pharmacokinetics after administration of multiple doses in patients with renal impairment. Further dose adjustment may be needed depending on the patient's clinical condition.

When serum creatinine is the only measure of renal function available, use the following formula to estimate the creatinine clearance.

Males: $\frac{\text{Weight (kg) x (140 - age)}}{72 \text{ x serum creatinine (mg/dL)}}$ = Ccr

Females: 0.85 x above value

CONTRAINDICATIONS
Known hypersensitivity to Fluconazole, other azole antifungals, and to any of its excipients.

WARNINGS AND PRECAUTIONS
Serious adverse hepatic effects have been reported with Fluconazole. Although these are rare, these should be considered when giving Fluconazole therapy. If signs and symptoms of liver disease develops, treatment should be discontinued immediately; if abnormal liver function tests occur, the patient should be carefully monitored for the possibility of more severe liver injury.

Overgrowth of nonsusceptible strains of Candida have been reported in some patients receving Fluconazole. When this occurs, patients may require an alternative anti-fungal therapy.

Anaphylaxis has occurred rarely in patients taking Fluconazole.

Rare but serious exfoliative skin disorders such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported during treatment with Fluconazole which rarely resulted in a fatal outcome in patients with serious underlying diseases (predominantly AIDS & malignancy). It is recommended that in patients with superficial fungal infection, Fluconazole treatment be discontinued at the first sign of rash. Patients with serious underlying disease who develop rashes should be closely observed and Fluconazole treatment should be discontinued when bullous lesions or erythema multiforme progresses.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Evidence of mutagenicity was not seen when Fluconazole was used in vitro.

There was no evidence of carcinogenicity in studies done in mice and rats receiving Fluconazole dosages of 2.5 to 10 mg/kg daily for 24 months. However, there was an increase in adenomas in male rats receiving Fluconazole of 5 or 10 mg/kg daily.

Reproduction studies in male and female rats given Fluconazole dosages of up to 75 mg/kg once daily did not show any evidence of impaired fertility. However, onset of parturition is slightly delayed.

Use in children: A different dosing regimen is recommended for infants less than 4 weeks (refer to Dosage and Administration section).

Adverse effects reported in neonates and infants receiving 3 to 6 mg/kg daily are transient increases in serum transaminase concentrations, vomiting, and eosinophilia. Severe thrombophlebitis have also occurred in one neonate after IV fluconazole administration.

Use in elderly patients: Since elderly patients are more likely to have impaired renal function, dosage should be modified as necessary. However, dosage adjustments based on age alone is not necessary.

DRUG INTERACTION

* Fluconazole Drug Interactions			
Precipitant Drug	**Object Drug**	**↓**	**Description**
Cimetidine	Fluconazole	↑	Cimetidine resulted in a reduction in Fluconazole AUC and Cmax.
Hydrochloro-thiazide	Fluconazole	↓	Concomitant use resulted in a significant increase in Fluconazole Cmax and AUC, which can be attributed to reduced renal clearance.
Rifampicin	Fluconazole	↑	A single oral Fluconazole dose after chronic Rifampicin resulted in a decrease in AUC and a shorter half-life of Fluconazole.
Aztemizole	Fluconazole	↑	Concomitant administration with Fluconazole causes elevations in serum levels of these drugs. Caution should be exercised.
Fluconazole	Rifabutin	↑	Concomitant use resulted in a significant increase in Rifabutin serum levels
Fluconazole	Antihistamines, nonsedating	↑	Although Terfenadine levels were not affected by Fluconazole, Terfenadine metabolite ALIC increased.
Fluconazole	Contraceptives, oral (OC)	**	Concurrent use with an OC containing ethinyl estradiol/levonorgestrel produced an overall mean increase in the levels of the OC components, however, in some cases there were decreases up to 47% and 33% of ethinyl estradiol and levonorgestrel levels, respectively.
Fluconazole	Cyclosporine	↑	Significant increases in Cyclosporin Cmax, Cmin, and AUC values occurred following Fluconazole use.
Fluconazole	Phenytoin	↑	Coadministration resulted in an increase of Phenytoin AUC values.
Fluconazole	Theophylline	↑	Theophylline AUC, Cmax, and half-life were significantly increased and clearance was decreased.
Fluconazole	Sulfonylureas	↑	Fluconazole resulted in significant increases in Cmax and AUC of Tolbutamide, Glibenclamide, and Glipizide. Several subjects experienced symptoms consistent with hypoglycemia; some required oral glucose treatment.
Fluconazole	Warfarin	↑	A single warfarin dose after 14 days of Fluconazole resulted in an increase in the PT response (area under the prothrombin time-time curve). Of 13 subjects, 1 experienced a twofold increase in PT response.
Fluconazole	Zidovudine	↑	Significant increase in Zidovudine AUC after Fluconazole administration.
Fluconazole	Cisapride	↑	Fluconazole significantly increased the AUC and Cmax of Cisapride after both single and multiple dosing. Fluconazole also significantly increased the QTc interval in subjects receiving Cisapride 20 mg four times a day x 5 days
Fluconazole	Tacrolimus	↑	Concomitant use resulted in a significant increase in Tacrolimus serum levels

* ↑-Object drug increased ↓-Object drug decreased **-Undetermined

DRUG/LABORATORY INTERACTIONS
Mild, transient increases in serum concentrations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, -glutamyltransferase, and bilirubin have been reported. The patient's liver function should be closely monitored for signs of severe hepatotoxicity.

PREGNANCY AND LACTATION
Pregnancy: (Pregnancy Category C) Reproduction studies in pregnant rabbits receiving Fluconazole doses of up to 75 mg/kg once daily during organogenesis revealed impaired maternal weight gain and abortions, although no adverse fetal effects were seen. In a different study involving rats, Fluconazole doses of up to 25 mg/kg once daily were associated with maternal weight gain and placental weight increase. When dosages were increased to 320 mg/kg once daily, fetal abnormalities (e.g., wavy ribs, cleft palate and abnormal craniofacial ossification) and embryolethality were observed.

However, there are no adequate and well controlled studies in pregnant women to date. Use in pregnancy only if the potential benefit justifies possible risk to the fetus.

Lactation: Fluconazole is excreted in human breast milk in concentrations similar to that found in plasma; therefore, avoid use in breastfeeding women.

UNDESIRABLE EFFECTS
Fluconazole is generally well tolerated. Most common adverse effects are abdominal pain, diarrhea, flatulence, nausea, vomiting, and taste disturbance. Other reported adverse effects include headache, dizziness, leukopenia, thrombocytopenia, hyperlipidemia, and raised liver enzyme concentrations.

Since Fluconazole is used in patients with serious underlying diseases, there are some instances where causal relationship of the adverse event to the treatment is hard to establish.

Gastrointestinal effects. Gastrointestinal effects are the most common adverse reactions reported with Fluconazole use. These reactions are usually mild to moderate in nature and do not usually require discontinuation of therapy. These adverse effects are nausea, vomiting, abdominal pain, and diarrhea. Rarely, there have been reports of flatus, bloating, dry mouth, hiccups, heartburn, and anorexia.

In patients with vulvovaginal candidiasis receiving single dose of Fluconazole, abdominal pain, nausea, diarrhea, dyspepsia, and dysgeusia have been reported.

Dermatologic and Hypersensitivity Reactions. Rare reports of anaphylaxis have occurred. Rash (including diffuse rash with eosinophilia) and pruritus were also reported. Stevens-Johnson syndrome has also occurred and may be a fatal.

In patients with serious diseases such as autoimmune deficiency syndrome (AIDS) or malignancy, exfoliative skin disorders have occurred. In patients with vulvovaginal candidiasis receiving single dose Fluconazole, angioedema and anaphylaxis were reported rarely.

Hepatic Effects. Rare but serious hepatotoxicity (e.g., necrosis, clinical hepatitis, cholestasis, fulminant hepatic failure) have been reported. Although these events may be reversible, there have been reports of death, especially involving patients with serious underlying conditions.

Nervous System Effects. Dizziness and headache have occurred. Somnolence, delirium/coma, dysesthesia, psychiatric disturbances, malaise, paresthesia of hands and feet, fatigue, and seizure have been reported rarely.

Hematologic Effects. Eosinophilia, anemia, leukopenia, neutropenia, and thrombocytopenia have been reported. Although thrombocytopenia may be reversible after drug discontinuation, there were reports of severe cases necessitating treatment.

Endocrine Effects. Endocrine effects of Fluconazole have not been studied. However, there have been reports of alterations on testosterone and endogenous corticosteroid concentrations, as well as changes in ACTH-stimulated cortisol response.

Other Adverse Effects. There have been rare reports of fever, edema, pleural effusion, oliguria, hypotension, arthralgia/myalgia, and finger stiffness. Alopecia was also reported, occurring in both genders after 3 months of therapy. Alopecia may respond to either drug discontinuation or dose reduction. Fluconazole may also cause hair loss on the face, axillary, pubic, leg and chest area.

OVERDOSAGE & MANAGEMENT
Death, often following clonic seizures, occurred at 1.5 hours to 3 days after administration of 1 to 2 grams of Fluconazole. In one patient with human immunodeficiency virus (HIV) infection, hallucinations and paranoid behavior were reported after ingestion of 8.2 g of Fluconazole. The patient required hospitalization and the condition resolved after 48 hours.

If acute overdosage occurs, supportive and symptomatic treatment should be initiated as necessary. The stomach may be emptied by gastric lavage. Fluconazole is also removed by hemodialysis and plasma Fluconazole concentration usually decreases to 50% after 3-hours of hemodialysis.

STORAGE
Store at temperatures not exceeding 30°C.
Protect from light.
Do not freeze.

AVAILABILITY:
Fluconazole (Funzela®) 50 mg, 200 mg Tablet - in box of 20 tablets (in blister pack)

Fluconazole (Funzela®) 150 mg - box of 1's and box of 10's (in blister pack)

CAUTION:
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

Manufactured by :
AMHERST LABORATORIES, INC.
UNILAB Pharma Campus,
Barangay Mamplasan, Biñan, Laguna
Philippines
For:
BIOFEMME, INC.
2nd Flr. Bonaventure Plaza Bldg., Ortigas Ave.
Greenhills, San Juan City, Philippines