IN IMPAIRED RENAL FUNCTION
See Dosage and Administration.

IN IMPAIRED HEPATIC FUNCTION
Patients who develop abnormal liver function should be monitored. Immunocompromised patients who develop rash during **FLUCONAZOLE** therapy should be monitored and the drug discontinued if lesions progress.

Side Effects
FLUCONAZOLE is generally well tolerated. Commonly reported side effects are nausea, vomiting, abdominal pain, headache, skin rash and diarrhoea. Mild transient, reversible Increase in liver enzymes like ALT, AST, alkaline phosphatase and serum billirubin, etc. may be seen. Serious hepatotoxicity is rarely seen, Clinical adverse reactions have been more frequently reported in HIV infected patients than in nonHIV infected patients, however, the patterns were similar, In rare cases, anaphylaxis has been reported.

Overdosage
In the event of overdosage, supportive measures and symptomatic treatment with gastric lavage if necessary, may be adequate.
FLUCONAZOLE is excreted largely in the urine, forced diuresis would probably increase the elimination rate. A three hour session of haemodialysis decreases plasma levels by approximately 50 percent

Storage :
Store below 30°C.
Protect from light and moisture.
Keep the medicine out of reach of children.

Dosage :
As directed by the physician.

Presentation
1 capsules

Marketed by:

PYXUS PHARMACEUTICALS PVT. LTD.
A/707, Mondeal Heights, Beside Novotel Hotel,
Nr. Iscon Square, S.G. Highway, Ahmedabad,
Gujarat- 380015 (India).

For the use only of a Registered Medical Practitioner or a Hospital or a Laboretory.

FLUCONAZOLE

Fluconazole Capsules BP 150 mg

Composition :
Each hard gelatin capsule contains :
Fluconazole BP ..... 150 mg
Excipients ..... Q.S.
Approved colours used in empty hard gelatin capsule shells.

Therapeutic class : Antifungal

Pharmacology
Fluconazole is a bis-trizole antifungal structurally related to imidazole derivative antifungals. The nitrogen of the azolering of the triazole binds to the haem moiety of the fungal cytochrome P-450 enzyme lanosterol 14 alpha demethylase which falls conversion of lanosterol to ergosterol that to a cascade of abnormalities in membrane permeabillity, membrane bound enzyme activity and coordination of chitin synthesis.

Pharmacokinetics
The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral routes. In normal volunteers, the bioavailabillity of orally administered fluconazole is over 90% compared with intravenous administration. Bioequivalence was established between the 100 mg capsule and both suspension strengths when administered as a single 200 mg dose. Peak plasma concentrations (C) in fasted normal volunteers occur between 1 and 2 hours with a terminal plasma elimination half-life of approximately 30 hours (range:20-50 hours) alter oral administration. Steady-state concentrations are reached within 5-10 days following oral dose of 50-400 mg. once given once daily administration of a loading (on day 1) of twice the usual daily dose results in plasma concentrations close to steady-state by the second day. The apparent volume of distribution of fluconazole approximates that of total body water. Plasma protein binding is low (11-12%). Following either single-or muitiple-oral doses for up to 14 days. Fluconazole penetrates into all body fluids studied (see table below). In normal volunteers, saliva concentrations of fluconazole were equal to slightly greater than plasma concentrations regardless of dose, route, or duration of dosing.

Tissue of Fluid	Ratio of Fluconazole Tissue (Fluid)/Plasma concentration*
Cerebrospinal fluid**	0.5 - 0.9
Saliva	1
Sputum	1
Blister fluid	1
Urine	10
Normal skin	1
Nails	1
Blister skin	2
Vaginal tissue	1
Vaginal fluid	0.4 - 0.7

*Relative to concurrent concentrations in plasma in subjects with normal renal function

** Independent of degree of meningeal inflammation.

In normal volunteers, fluconazole is cleared primarily by renal excretion, *with approximately 80% of the administered dose appearing in the urine as unchanged drug. About 11% of the dose is excreted in the urine as metabolites.

Pharmcokinetice in Children
In children, the following pharmacokinetic data {Mean(%cv)} have been reported :

Age studied	Dose (mg/kg)	Half-life	C_{max} (µg/mL)
9 months-13 years	Single - oral 2mg/kg	25.0	2.9 (22%) N=16
9 months-13 years	Single - oral 8mg/kg	19.5	9.8 (20%) N=15
5-15 years	Multiple IV 2mg/kg	17.4	5.5 (25%) N=5
5-15 years	Multiple IV 4mg/kg	15.2	11.4 (44%) N=6
5-15 years	Multiple IV 8mg/kg	17.6	14.1 (22%) N=8

Clearance corrected for body weight was not affected by age in these studies. Mean clearance in adults is reported to be 0.23 (17%) mL/min/kg.

Indications
FLUCONAZOLE is indicated for mucosal candidiasis: e.g. oropharyngeal, oesophageal, mucocutaneous and chronic oral atrophic candidiasis, vaginal candidiasis etc.
systemic candidiasis : Candidaemla, disseminated candidiasis, infection of peritoneum, endocardium, pulmonary and urinary tract.
Cryptococcosis : Cryptococcal meningitis, primary as well as maintenance therapy.
Prevention of fungal infection in patients with malignancy,AIDS, in intensive care units and patients on immunosuppressive drugs.

Dosage and Administration
FLUCONAZOLE may be administered either orally or by intravenous infusion at a rate of approximately 5 - 10 ml/min. On transferring the patient from the intravenous to oral route or vice versa, is no need to change the daily dose.
Adults
Oropharyngeal candidiasis : 200 mg on the first day, followed by 100 mg once daily for 14 days.
Oesophageal candidiasis : 200 mg on the first day, followed by 100 mg once daily for 21 days.
Veginal candidiasis : 150 mg single dose
Mucosal candidiasis : 50-100 mg daily for 14-30 days.
Systemic candidiasis : 400 mg on first day, then 200-400 mg once daily.
Cryptococcal meningitis : 400 mg loading dose, followed by 200 mg daily for 10-12 weeks after CSF become culture negative
Maintenance to prevent relapse of cryptococcai meningitis: 100-200 mg daily.
Prophylaxis in immunocompromised: 50-400 mg once daily started several days before onset of neutropenia and continued for-7days afterneutmphit count > 1000 cell/mm^3.
Children
Mucosal candidiasis:
<2 weeks : 3 mg/kg every 72 hrs
2-4 weeks : 3 mg/kg every 48 hrs
over 4 weeks : 3 mg/kg daily
Systemic candidiasis:
<2 weeks : 6-12 mg/kg every 72 hrs
2-4 weeks : 6-12 mg/kg every 48 hrs
over 4 weeks : 6-12 mg/kg daily

Store below 30°C. Protect from light and moisture.
Keep the medicine out of reach of children.

Prophylaxis in immunocompromised:
<2 weeks : 3-12 mg/kg every 72 hrs
2-4 weeks : 3-12 mg/kg every 48 hrs
over 4 weeks : 3-12 mg/kg daily
In impaired renal function:
FLUCONAZOLE is excreted predominantly in urine as unchanged drug. hence in patients with impaired renal function, dosage of fluconazole must be modified in response to the degree of impairment and should be based on the patients measured or estimated creatinine clearance.

The recommended dosage are :

Creatinine clearance (mL/min)	Dosage Interval(mL/min) daily dose
>50	24 hrs / 100%
21-50	48 hrs / 50%?
10-20	72 hrs / 25%
Patients receiving regular haemodialysis	100 percent dose after every dialysis

Compatibillity of intravenous infusion : Although further dilution is unnecessary, **FLUCONAZOLE** intravenous infusion is compatible with the following administration fluids :
- Dextrose 20 per cent
- Ringer's solution
- Hartmann's solution
- Potassium chloride in dextrose
- Sodium bicarbonate
- Normal saline (0.9 per cent)

Mixing with any other drug prior to infusion is not recommended

Contraindications
Hypersensitivity to **FLUCONAZOLE** or any of its excipients of related azole compounds.

Warnings and Precautions
DRUG INTERACTIONS
Anticoagulants : Fluconazole has been shown to prolong prothrombin times of coumarin drugs, hence requires careful monitoring.
Cyclosporin : Concomitant administration of fluconazole and cyclosporin may result in increase in cyclosporin level.
Phenytoin : **FLUCONAZOLE** significantly increases phenytoin levels and AUC resulting in phenytoin toxicity.
Oral hypoglycaemics : Concomitant administration of **FLUCONAZOLE** and oral hypoglycaemics such as sulphonylurea in diabetic patients results in increased plasma concentration and reduced metabolism of antidiabetic agents.
Rifampicin : Concomitant administration of **FLUCONAZOLE** and rifampicin decrease AUC for **FLUCONAZOLE** by 20 per cent.
Theophylline : **FLUCONAZOLE** may increase serum concentrations of theophlline. Careful monitoring is recommended if the two drugs are coadministered.

PREGNANCY
There are no adequate and wellcontrolled studies in pregnant women **FLUCONAZOLE** should be used in pregnancy only if the benefits outweigh risks.

NURSING MOTHERS
Since the drug is secreted in breast milk, it should not be used in lactating women.

PAEDIATRIC USE
See Dosage and Administration.