1. Name of the medicinal product

FLUCONAZOLE CAPSULES BP 200 MG

2. Qualitative and quantitative composition

SR. NO.	NAME OF THE INGREDIENTS	PHARMACOPEIAL SPECIFICATION	LABLE CLAIM	OVERAGES %	QTY. / CAPSULE	PURPOSE
ACTIVE INGREDIENTS						
1.	Fluconazole	BP	200 mg	0.00%	200.000 mg	API
INACTIVE INGREDIENTS						
2.	Colloidal silicon Dioxide	USP	-	0.00 %	10.000 mg	Glidant
3.	Anhydrous lactose	BP	-	0.00 %	230.000 mg	Diluent
4.	Croscarmellose Sodium	BP	-	0.00%	20.000 mg	Disintegrant
5.	Sodium starch glycolate	BP	-	0.00 %	40.000mg	Disintegrant
6.	Empty hard gelatin capsule blue/red size '0'	INHOUSE	-	0.00 %	1.000 nos	Encapsulation

3. Pharmaceutical form

Oral capsule

4. Clinical particulars

4.1 Therapeutic indications

Fluconazole is an antifungal type of antibiotic. It treats serious fungal infections found throughout the body. These include oral candidiasis or thrush infections of the mouth or throat, vaginal yeast infections, candidal infection of the urinary tract, meningitis, and others.

4.2 Posology and method of administration

Single Dose
Vaginal candidiasis: The recommended dosage of Fluconazole Capsule for vaginal candidiasis is 100 mg as a single oral dose.
Multiple Dose
Oropharyngeal candidiasis: The recommended dosage of Fluconazole Capsule for oropharyngeal candidiasis is 200 mg on the first day, followed by 100 mg once daily.
Esophageal candidiasis: The recommended dosage of Fluconazole Capsule for esophageal 200 mg on the first day, followed by 100 mg once daily. Doses up to 400 mg/day may be used, based on medical judgment of the patient's response to therapy.

Systemic Candida infections: 400 mg daily have been used.
Urinary tract infections and peritonitis: Daily doses of 50-200 mg
Cryptococcal meningitis: The recommended dosage for treatment of acute cryptococcal meningitis is 400 mg on the first day, followed by 200 mg once daily. A dosage of 400 mg once daily may be used, based on medical judgment of the patient's response to therapy.
The recommended Fluconazole Capsule daily dosage for the prevention of candidiasis of patients undergoing bone marrow transplantation is 400 mg, once daily.
Dosage and Administration in Children
The following dose equivalency scheme should generally provide equivalent exposure in pediatric and adult patients:

Pediatric Patients	**Adults**
3 mg/kg	100 mg
6 mg/kg	200 mg
12* mg/kg	400 mg
* Some older children may have clearances similar to that of adults. Absolute doses exceeding 600 mg/day are not recommended.	

candidiasis is Method of administration: For oral use.

4.3 Contraindications

- Fluconazole are contraindicated in patients who have shown hypersensitivity to fluconazole or to any of its excipients.
- There is no information regarding cross-hypersensitivity between fluconazole and other azole antifungal agents. Caution should be used in
- prescribing fluconazole to patients with hypersensitivity to other azoles.
- Coadministration 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.
- Coadministration of cisapride is contraindicated in patients receiving fluconazole.

4.4 Special warnings and precautions for use

- **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-i-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.
- **Hypersensitivity:** In rare cases, anaphylaxis has been reported.
- **Dermatologic:** Patients have rarely developed exfoliative skin disorders during treatment with Fluconazole. In patients with serious underlying diseases (predominantly AIDS and malignancy), these have rarely resulted in a fatal outcome. Patients who develop rashes during treatment with fluconazole should be monitored closely and the drug discontinued if lesions progress.

- **Cardiovascular system:** Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. Fluconazole capsule should be administered with caution to patients with these potentially proarrhythmic conditions. Coadministration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 are contraindicated.
- **Halofantrine:** Halofantrine has been shown to prolong QTc interval at the recommended therapeutic dose and is a substrate of CYP3A4. The concomitant use of fluconazole and halofantrine is therefore not recommended

4.5 Interaction with other medicinal products and other forms of interaction

Coumarin-type anticoagulants: Prothrombin time may be increased in patients receiving concomitant Fluconazole and coumarin-type anticoagulants. In post-marketing experience, as with other azole antifungals, 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. Careful monitoring of prothrombin time in patients receiving Fluconazole and coumarin-type anticoagulants is recommended.
Phenytoin: Fluconazole increases the plasma concentrations of phenytoin. Careful monitoring of phenytoin concentrations in patients receiving Fluconazole and phenytoin is recommended.
Cyclosporine: Fluconazole may significantly increase cyclosporine levels in renal transplant patients with or without renal impairment. Careful monitoring of cyclosporine concentrations and serum creatinine is recommended in patients receiving Fluconazole and cyclosporine.
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. Careful monitoring of serum theophylline concentrations in patients receiving Fluconazole and theophylline is recommended. 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.

4.6 Pregnancy, Fertility and Breast Feeding

Administered as a single or repeated dose in the first trimester, show no undesirable effects in the foetus. There have been reports of multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in infants whose mothers were treated for at least three or more months with high doses (400-800 mg daily) of fluconazole for coccidioidomycosis. The relationship between fluconazole use and these events is unclear. Fluconazole in standard doses and short-term treatments should not be used in pregnancy unless clearly necessary.
Fluconazole passes into breast milk to reach concentrations lower than those in plasma. Breast-feeding may be maintained after a single use of a standard dose 200 mg fluconazole or less. Breast-feeding is not recommended after repeated use or after high dose fluconazole.

4.7 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.

4.8 Undesirable effects

Dark yellow or brown urine, dizziness, skin rash, redness, blistering, peeling, or loosening of skin, including inside the mouth, stomach pain, unusual bruising or bleeding, yellowing of the eyes or skin. Side effects that usually do not require medical attention (report to your prescriber or health care professional if they continue or are bothersome):
diarrhea, headache, loss of appetite, nausea, vomiting.

4.9 Overdose

Symptoms: Hallucination and paranoid behaviour have been concomitantly reported.
Treatment: In the event of overdose, symptomatic treatment (with supportive measures and gastric lavage if necessary) may be adequate. Fluconazole is largely excreted in the urine; forced volume diuresis would probably increase the elimination rate. A three-hour haemodialysis session decreases plasma levels by approximately 50%.

5. Pharmacological properties

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives; **ATC Code:** J02AC01.
Mechanism of action:
Fluconazole is a highly selective inhibitor of fungal cytochrome P-450 sterol C-14 alpha-demethylation. Mammalian cell demethylation is much less sensitive to fluconazole inhibition. The subsequent loss of normal sterols correlates with the accumulation of 14-alpha¬methyl sterols in fungi and may be responsible for the fungistatic activity of fluconazole.

5.2 Pharmacokinetic properties

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 concentrations in the fasting state occur between 0.5 and 1.5 hours post-dose. Plasma concentrations are proportional to dose.
Distribution: 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 studied. 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 concentrations are achieved in the stratum corneum, epidermis-dermis and eccrine sweat. Concentration of fluconazole in nails after 4 months of 150 mg once-a¬week dosing was 4.05 pg/g in healthy and 1.8 pg/g in diseased nails; and, fluconazole was still

measurable in nail samples 6 months after the end of therapy. Biotransformation: Fluconazole is metabolised only to a minor extent. Of a radioactive dose, only 11% is excreted in a changed form in the urine. Fluconazole is a selective inhibitor of the isozymes CYP2C9 and
CYP3A4. Fluconazole is also an inhibitor of the isozyme CYP2C19.
Excretion: Plasma elimination half-life for fluconazole is approximately 30 hours. The major route of excretion is renal, with approximately 80% of the administered dose appearing in the urine as unchanged medicinal product. 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.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the human exposure indicating little relevance to clinical use.
Carcinogenesis: Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5, or 10 mg/kg/day (approximately 2-7 times the recommended human dose). Male rats treated with 5 and 10 mg/kg/day had an increased incidence of hepatocellular adenomas.
Mutagenesis: Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of Salmonella typhimurium, and in the mouse lymphoma L5178Y system. Cytogenetic studies in vivo (murine bone marrow cells, following oral administration of fluconazole) and in vitro (human lymphocytes exposed to fluconazole at 1000 μg/ml) showed no evidence of chromosomal mutations.
Reproductive toxicity: Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10, or 20 mg/kg or with parenteral doses of 5, 25, or 75 mg/kg.
There were no foetal effects at 5 or 10 mg/kg; increases in foetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg to 320 mg/kg embryolethality in rats was increased and foetal abnormalities included wavy ribs, cleft palate, and abnormal cranio-facial ossification.
Oestrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole.

6. Pharmaceutical particulars

6.1 List of excipients

- Colloidal Silicon Dioxide
- Anhydrous lactose
- Sodium starch glycolate
- Croscarmellose sodium
- Empty Hard Gelatin Capsule Blue/Blue Size “0”

6.2 Incompatibilities

None

6.3 Shelf life

33 months

6.4 Special precautions for storage

Store in dry place below 30^0C. Protect from light.

6.5 Nature and contents of container

10 X 1 X 10 Capsules Alu-Alu pack, packed in printed and laminated carton

6.6 Special precautions for disposal and other handling

Not Applicable

7. Marketing authorization holder

West Coast Pharmaceutical Works LTD, Ahmedabad

8. Marketing authorization number(s)

Not Applicable

9. Date of first authorization/renewal of the authorization

Not Applicable

10. Date of revision of the text

November , 2023