1.1 Name of the medicinal product:

EDEN FLUCONAZOLE 150MG CAPSULES (Fluconazole 150mg Capsules)

1.2 Qualitative and quantitative composition:
Each Capsule Contains:
Fluconazole USP 150mg
Excipients Q.S.
Approved Colour Used in Empty Capsule Shell.

Sr. No.	Ingredients	Specifi-cation	Label Claim / Capsule (In mg)	Over ages added (In %)	Qty. / Capsule (In mg)	Reason for Function
1.	Fluconazole	USP	150.00	NA	150.00	Medicament
2.	Colloidal anhydrous silica	BP	NA	NA	02.50	Glidant
3.	Lactose monohydrate	BP	NA	NA	38.50	Diluent
4.	Sodium Starch Glycolate (Primojel)	USP	NA	NA	08.00	Disintegrant
5.	Purified Talc	BP	NA	NA	10.00	Glidant
6.	Magnesium Stearate	BP	NA	NA	01.00	Lubricant
7.	EHG Capsule Size`2` Cap- Green Body-white	In-House	NA	NA	1 Capsule = 63 mg	Capsule Shell
	Net Content/Capsule (In mg)				**210.00**	
	Weight of Empty Hard Gelatin Capsule Shell (In mg)				**63.00**	
	Average Weight of Filled Capsule (In mg)				**273.00**	

1.3 Pharmaceutical form: Hard Gelatin Capsules
Description: Green coloured cap and white coloured body of capsule Size "2", containing white powder.

1.4 Clinical Particulars
4.1 Therapeutic indications
EDEN FLUCONAZOLE 150MG CAPSULES (Fluconazole Capsules 150 mg) is indicated for the treatment of:
1. Vaginal candidiasis (vaginal yeast infections due to Candida).
2. Oropharyngeal and esophageal candidiasis. In open noncomparative studies of relatively small numbers of patients, Fluconazole Capsules 150 mg was also effective for the treatment of Candida urinary tract infections, peritonitis, and systemic Candida infections including candidemia, disseminated candidiasis, and pneumonia.
3. Cryptococcal meningitis: Fluconazole Capsule 150 mg is prescribed in AIDS patients with cryptococcal meningitis.
Prophylaxis
EDEN FLUCONAZOLE 150MG CAPSULES (Fluconazole Capsules 150 mg) is also indicated to decrease the incidence of candidiasis in patients undergoing bone marrow transplantation who receive cytotoxic chemotherapy and/or radiation therapy.
Specimens for fungal culture and other relevant laboratory studies (serology, histopathology) should be obtained prior to therapy to isolate and identify causative organisms. Therapy may be instituted 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.

4.2 Posology and method of administration

Route: Oral

Vaginal candidiasis

The recommended dosage of fluconazole for vaginal candidiasis is 150 mg as a single oral dose.

Multiple Dose

The daily dose of fluconazole for the treatment of infections other than vaginal candidiasis should be based on the infecting organism and the patient's response to therapy. Treatment should be continued until clinical parameters or laboratory tests indicate that active fungal infection has subsided.

Oropharyngeal candidiasis

The recommended dosage of fluconazole for oropharyngeal candidiasis is 200 mg on the first day, followed by 100 mg once daily. Clinical evidence of oropharyngeal candidiasis generally resolves within several days, but treatment should be continued for at least 2 weeks to decrease the likelihood of relapse.

Systemic Candida infections

For systemic Candida infections including candidemia, disseminated candidiasis, and pneumonia, optimal therapeutic dosage and duration of therapy have not been established. In open, noncomparative studies of small numbers of patients, doses of up to 400 mg daily have been used.

Urinary tract infections and peritonitis

For the treatment of Candida urinary tract infections and peritonitis, daily doses of 50 to 200 mg have been used in open, noncomparative studies of small numbers of patients.

Special populations

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 50 mg to 400 mg should be given.

Children:

The recommended dosage of fluconazole for mucosal candidiasis is 3 mg/kg once daily. A loading dose of 6 mg/kg may be used on the first day to achieve steady-state levels more rapidly. For the treatment of systemic candidiasis and cryptococcal infections, the recommended dosage is 6 to 12mg/kg once daily, depending on the severity of the disease.

Elderly:

Where there is no evidence of renal impairment, normal dosage recommendations should be adopted. For patients with renal impairment (creatinine clearance <50 ml/min).

4.3 Contraindications

Fluconazole should not be used in patients with known sensitivity to the drug, any of the inert ingredients or to related azole compounds. Coadministration of terfenadine is contraindicated in patients receiving fluconazole at multiple doses of 400 mg/day or higher based upon results of a multiple-dose interaction study. Coadministration of other drugs known to prolong the QT interval and which are metabolized via the enzyme CYP3A4 such as cisapride, astemizole, erythromycin, pimozide and quinidine are contraindicated in patients receiving Fluconazole.

4.4 Special warnings and precautions for use

-Fluconazole should be administered with caution to patients with liver dysfunction. 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 patient 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 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.

-The coadministration of fluconazole at doses lower than 400 mg/day with terfenadine should be carefully monitored.

- In rare cases, as with other azoles, anaphylaxis has been reported.
- Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. Fluconazole causes QT prolongation via the inhibition of Rectifier Potassium Channel current (Ikr). The QT prolongation caused by other medicinal products (such as amiodarone) may be amplified via the inhibition of cytochrome P450 (CYP) 3A4.
- Fluconazole should be administered with caution to patients with these potentially proarrhythmic conditions.
- Fluconazole should be administered with caution to patients with renal dysfunction.

4.5 Interaction with other medicinal products and other forms of interaction
Concomitant use of the following other medicinal product is contraindicated:
Cisapride: There have been reports of cardiac events including torsade de pointes in patients to whom fluconazole and cisapride were coadministered. Acontrolled study found that concomitant treatment with fluconazole 200 mg once daily and cisapride 20 mg four times a day yielded a significant increase in cisapride plasma levels and prolongation of QTc interval. Concomitant treatment with fluconazole and cisapride is contraindicated in patients receiving fluconazole.
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. 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.
Astemizole: Concomitant administration of fluconazole with astemizole may decrease the clearance of astemizole. Resulting increased plasma concentrations of astemizole can lead to QT prolongation and rare occurrences of Torsade de Pointes. Coadministration of fluconazole and astemizole is contraindicated.
Pimozide: Although not studied in vitro or in vivo, concomitant administration of fluconazole with pimozide may result in inhibition of pimozide metabolism. Increased pimozide plasma concentrations can lead to QT prolongation and rare occurrences of torsade de pointes. Coadministration of Fluconazole and pimozide is contraindicated.
Quinidine: Although not studied in vitro or in vivo, concomitant administration of fluconazole with quinidine may result in inhibition of quinidine metabolism. Use of quinidine has been associated with QT prolongation and rare occurrences of Torsades de Pointes. Coadministration of fluconazole and quinidine is contraindicated.
Erythromycin: Concomitant use of fluconazole and erythromycin has the potential to increase the risk of cardiotoxicity (prolonged QT interval, torsade de pointes) and consequently sudden heart death. Coadministration of fluconazole and erythromycin is contraindicated

4.6 Pregnancy and Lactation
Pregnancy:
Use in pregnancy should be avoided except in patients with severe or potentially life-threatening fungal infections in whom fluconazole may be used if the anticipated benefit outweighs the possible risk to the fetus. Effective contraceptive measures should be considered in women of child-bearing potential and should continue throughout the treatment period and for approximately 1 week (5 to 6 half-lives) after the final dose.
Lactation
Fluconazole passes into breast milk to reach concentrations similar to those in plasma. Breast-feeding may be maintained after a single dose of 150 mg fluconazole. Breast-feeding is not recommended after repeated use or after high dose fluconazole. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for fluconazole and any potential adverse effects on the breast-fed child from fluconazole or from the underlying maternal condition.

4.7 Effects on ability to drive and use machines
When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or seizures may occur.

4.8 Undesirable effects
Common side effects
These common side effects of fluconazole happen in more than 1 in 100 people. There are things you can do to help cope with them:

-Headache
-Stomach pain
-Diarrhoea
-Feeling or being sick (nausea or vomiting)
-Rash
Serious side effects
-Irregular heartbeat
-Eyes and skin turns yellow
Serious allergic reaction
- Fast breathing or uneasy to breathe
- Choking or gasping for air

4.9 Overdose
There have been reports of overdose with fluconazole accompanied by hallucination and paranoid behavior.
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. A 3-hour hemodialysis session decreases plasma levels by approximately 50%.

5 Pharmacological properties
5.1 Pharmacodynamic properties
Fluconazole is a triazole antifungal agent. Its primary mode of action is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of fluconazole.
Fluconazole has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems. Susceptibility in vitro, fluconazole displays antifungal activity against clinically common Candida species (including C. albicans, C. parapsilosis, C. tropicalis). C. glabrata shows reduced susceptibility to fluconazole while C. krusei and C. auris are resistant to fluconazole. The MICs and epidemiological cutoff value (ECOFF) of fluconazole for C. guilliermondii are higher than for C. albicans. Fluconazole also exhibits activity in vitro against Cryptococcus neoformans and Cryptococcus. gattii as well as the endemic moulds Blastomyces, dermatiditis, Coccidioidesimmitis, Histoplasma capsulatum and Paracoccidioides brasiliensis.

5.2 Pharmacokinetic properties
Absorption: 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. Ninety percent steady state levels are reached by day 4-5 with multiple once daily dosing. Administration of a loading dose (on day 1) of twice the usual daily dose enables plasma levels to approximate to 90% steady-state levels by day 2.
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. Fluconazole accumulates in the stratum corneum. At a dose of 50 mg once daily, the concentration of fluconazole after 12 days was 73 µg/g and 7 days after cessation of treatment the concentration was still 5.8 µg/g. At the 150 mg once-a-week dose, the concentration of fluconazole in stratum corneum on day 7 was 23.4 µg/g and 7 days after the second dose was still 7.1 µg/g.
Metabolism: 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 moderate inhibitor of the isozymes CYP2C9 and CYP3A4. Fluconazole is also a strong inhibitor of the isozyme CYP2C19.
Elimination: 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. Fluconazole clearance is proportional to creatinine clearance. There is no evidence of

circulating 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.

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.
The onset of parturition was slightly delayed at 20 mg/kg orally and dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg and 40 mg/kg intravenously. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal survival at these dose levels. These effects on parturition are consistent with the species specific 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 anhydrous silica, Lactose monohydrate, Sodium Starch Glycolate, Purified Talc, Magnesium Stearate & EHG Capsule Size`2` having Cap & Body – Green/White.

6.2 Incompatibilities
Not applicable

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store in a cool, dry & dark place.
Keep all medicines out of reach of children.

6.5 Nature and contents of container
Primary packing: 10 capsules are packed in ALU-ALU blister.
Secondary packing: Such 1 blister is packed in an inner carton along with leaflet.
Tertiary packing: Such 10 inner cartons are packed in an outer carton. Shrink individual outer carton. Such 40 shrinks are packed in 5 Ply corrugated box sealed with BOPP tape & strap with strapping roll.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7 Applicant / Manufacturer

Applicant

Applicant name and address	**M/s. EDEN U-K PHARM LTD.** J116, Daminja Avenue Housing Estate, Fegge Onitsha, Anambra State
Contact person's phone number	
Contact person's email	

Manufacturer

Manufacturer name and address	**M/s. IMPULSE PHARMA PVT. LTD.** J-201, J-202/1 , MIDC Tarapur, Boisar, Dist. Palghar - 401506, Maharashtra State, India.
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