1.3Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. **Name of the medicinal product:** KESFLUCAN 200MG CAPSULES (**FLUCONAZOLE CAPSULES 200 MG**)

2. **Qualitative and Quantitative composition:**

Composition:

Each hard gelatin capsule contains:

Fluconazole USP	200 mg
Excipients	q.s.

Approved colours used in empty hard gelatin capsule shells.

3. **Pharmaceutical Form:** Capsules for Oral Administration.

Clinical Particulars:

4.1 Therapeutic Indications:

Fluconazole capsule is indicated in the following fungal infections.

Fluconazole is an antifungal medication used for a number of fungal infections.

Fluconazole capsule is indicated in adults for the treatment of:

ATC code: J02AC01

- Cryptococcal meningitis.
- Coccidioidomycosis.
- Invasive candidiasis.
- Mucosal candidiasis including oropharyngeal, oesophageal candidiasis, candiduria and chronic mucocutaneous candidiasis.
- Chronic oral atrophic candidiasis (denture sore mouth) if dental hygiene or topical treatment are insufficient.
- Vaginal candidiasis, acute or recurrent; when local therapy is not appropriate.
- Candidal balanitis when local therapy is not appropriate.
- Dermatomycosis including tinea pedis, tinea corporis, tinea cruris, tinea versicolor and dermal candida infections when systemic therapy is indicated.
- Tinea unguinium (onychomycosis) when other agents are not considered appropriate.

Fluconazole capsule is indicated in adults for the prophylaxis of:

• Relapse of cryptococcal meningitis in patients with high risk of recurrence.

• Relapse of oropharyngeal or oesophageal candidiasis in patients infected with HIV who are at high risk of experiencing relapse.

• To reduce the incidence of recurrent vaginal candidiasis (4 or more episodes a year).

• Prophylaxis of candidal infections in patients with prolonged neutropenia (such as patients with haematological malignancies receiving chemotherapy or patients receiving Hematopoietic Stem Cell Transplantation.

Fluconazole capsule is indicated in term newborn infants, infants, toddlers, children, and adolescents aged from 0 to 17 years old:

Fluconazole capsule is used for the treatment of mucosal candidiasis (oropharyngeal, oesophageal), invasive candidiasis, cryptococcal meningitis and the prophylaxis of candidal infections in immunocompromised patients. Fluconazole capsule can be used as maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of reoccurrence.

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.

Consideration should be given to official guidance on the appropriate use of antifungals.

4.2 Posology and method of administration:

The dose should be based on the nature and severity of the fungal infection. Treatment of infections requiring multiple dosing should be continued until clinical parameters or laboratory tests indicate that active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection.

Indication		Posology	Duration of treatment
Cryptococcosis	Treatment of cryptococcal meningitis	Loading dose: 400 mg on Day 1 Subsequent dose: 200 mg to 400 mg daily	Usually at least 6 to 8 weeks. In life threatening infections the daily dose can be increased to 800 mg
	Maintenance therapy to prevent relapse of cryptococcal meningitis in patients with high risk of recurrence	200 mg daily	Indefinitely at a daily dose of 200 mg
Coccidioidomycosis		200 mg to 400 mg	11 months up to 24 months or longer depending on the patient. 800 mg daily may be considered for some infections and especially for meningeal disease
Treatment of mucosal candidiasis	Oropharyngeal candidiasis	Loading dose: 200 mg to 400 mg on Day 1 Subsequent dose: 100 mg to 200 mg daily	7 to 21 days (until oropharyngeal candidiasis is in remission). Longer periods may be used in patients with severely compromised immune function
	Oesophageal candidiasis	Loading dose: 200 mg to 400 mg on Day 1 Subsequent dose: 100 mg to 200 mg daily	14 to 30 days (until oesophageal candidiasis is in remission). Longer periods may be used in patients with severely compromised immune function

	Candiduria	200 mg to 400mg daily	7 to 21 days. Longer periods may be used in patients with severely compromised immune function.
	Chronic atrophic candidiasis	50 mg daily	14 days
	Chronic mucocutaneous candidiasis	50 mg to 100 mg daily	Up to 28 days. Longer periods depending on both the severity of infection or underlying immune compromisation and infection
Prevention of relapse of mucosal candidiasis in infected with HIV at high risk of experiencing relapse	Oropharyngeal candidiasis	100 mg to 200 mg daily or 200 mg 3 times per week	An indefinite period for patients with chronic immune suppression
	Oesophageal candidiasis	100 mg to 200 mg daily or 200 mg 3 times per week	An indefinite period for patients with chronic immune suppression
Dermatomycosis tinea pedis, tinea corporis, tinea cruris, candida infections		150 mg once weekly or 50 mg once daily	2 to 4 weeks, tinea pedis may require treatment for up to 6 weeks
Prophylaxis of candidal infections in patients with prolonged neutropeni		200 mg to 400 mg	Treatment should start several days before the anticipated onset of neutropenia and continue for 7 days after recovery from neutropenia after the neutrophil count rises above 1000 cells per mm^3

* including Fixed Drug Eruption

Paediatric population

The pattern and incidence of adverse reactions and laboratory abnormalities recorded during paediatric clinical trials, excluding the genital candidiasis indication, are comparable to those seen in adults.

Method of administration

For oral use only.

4.3 Contraindications:

Hypersensitivity to the active substance, to related azole substances, or to any of the excipients. Coadministration of terfenadine is contraindicated in patients receiving Fluconazole capsule at multiple doses of 400 mg per day or higher based upon results of a multiple dose interaction study. Coadministration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4

such as cisapride, astemizole, pimozide, quinidine, and erythromycin are contraindicated in patients receiving fluconazole.

4.4 Special warning and precaution for use:

Tinea capitis

Fluconazole has been studied for treatment of tinea capitis in children. It was shown not to be superior to griseofulvin and the overall success rate was less than 20%. Therefore, Diflucan should not be used for tinea capitis.

Cryptococcosis

The evidence for efficacy of fluconazole in the treatment of cryptococcosis of other sites (e.g. pulmonary and cutaneous cryptococcosis) is limited, which prevents dosing recommendations.

Deep endemic mycoses

The evidence for efficacy of fluconazole in the treatment of other forms of endemic mycoses such as paracoccidioidomycosis, lymphocutaneous sporotrichosis and histoplasmosis is limited, which prevents specific dosing recommendations.

Renal system

Diflucan should be administered with caution to patients with renal dysfunction.

Adrenal insufficiency

Ketoconazole is known to cause adrenal insufficiency, and this could also although rarely seen be applicable to fluconazole. Adrenal insufficiency relating to concomitant treatment with prednisone.

4.5 Interaction with other medicinal products and other forms of interaction:

Cisapride: There have been reports of cardiac events including torsades de pointes in patients to whom fluconazole and cisapride were coadministered. A controlled study found that concomitant 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.

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 200 mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. Another study at

a 400 mg and 800 mg daily dose of fluconazole demonstrated that fluconazole taken in doses of 400 mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. 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 per 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 torsades 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 torsades 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, torsades de pointes) and consequently sudden heart death. Coadministration of fluconazole and erythromycin is contraindicated.

4.6 Pregnancy and Lactation:

Pregnancy

An observational study has suggested an increased risk of spontaneous abortion in women treated with fluconazole during the first trimester.

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.

Studies in animals have shown reproductive toxicity.

Fluconazole in standard doses and short-term treatments should not be used in pregnancy unless clearly necessary.

Fluconazole in high dose and/or in prolonged regimens should not be used during pregnancy except for potentially life-threatening infections.

Breast-feeding

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.

Fertility

Fluconazole did not affect the fertility of male or female rats.

4.7 Effects on the ability to drive and use machines:

No studies have been performed on the effects of Fluconazole capsule on the ability to drive or use machines.

Patients should be warned about the potential for dizziness or seizures. while taking Fluconazole capsule and should be advised not to drive or operate machines if any of these symptoms occur.

4.8 Undesirable effects:

The most frequently (>1/10) reported adverse reactions are headache, abdominal pain, diarrhoea, nausea, vomiting, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased and rash.

The following adverse reactions have been observed and reported during treatment with Fluconazole capsule with the following frequencies:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Common: Headache, Abdominal pain, vomiting, diarrhoea, nausea, Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, Rash.

Uncommon: Anaemia, Decreased appetite, Somnolence, insomnia, Seizures, paraesthesia, dizziness, taste perversion, Vertigo, Constipation dyspepsia, flatulence, dry mouth,

Cholestasis, jaundice, bilirubin increased, Drug eruption, urticaria, pruritus, increased sweating, Myalgia, Fatigue, malaise, asthenia, fever

Rare : Agranulocytosis, leukopenia, thrombocytopenia, neutropenia, Anaphylaxis, Hypercholesterolaemia, hypertriglyceridaemia, hypokalemia, Tremor, Torsade de pointes, Hepatic failure, hepatocellular necrosis, Toxic epidermal necrolysis, dermatitis exfoliative, angioedema, face oedema, alopecia.

4.9 Overdose:

There have been reports of overdose with Fluconazole capsule and hallucination and paranoid behaviour have been concomitantly reported.

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 Pharmacodynamic properties

Pharmacotherapeutic group:

Mechanism of action

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:

In vitro, fluconazole displays antifungal activity against most clinically common Candida species (including C. albicans, C. parapsilosis, C. tropicalis). C. glabrata shows a wide range of susceptibility while C. krusei is resistant to fluconazole.

Fluconazole also exhibits activity in vitro against Cryptococcus neoformans and Cryptococcus. gattii as well as the endemic moulds Blastomyces dermatiditis, Coccidioides immitis, 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.

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.

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 Pre-clinical Safety:

Not Applicable

6. Pharmaceutical Particulars:

6.1 List of Excipients:

- Starch Pregelatinised BP
- Lactose BP
- Magnesium stearate BP
- Colloidal Anhydrous Silica BP
- Sodium starch glycolate BP

6.2 Incompatibilities: None

6.3 Shelf Life: 36 months.

6.4 Special Precautions for storage:

Store at below 30° C. Protect from light from moisture.

6.5 Nature and contents of container:

10 Capsules in a ALU-ALU blister. Such one blister along with insert packed in a carton.

6.6 Special precautions for disposal and other handling

None

7. Marketing Authorization Holder:

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8. Marketing Authorization Number:

C4-0744

9. Date of first Authorization /renewal of the authorization:

26 June 2020

10. Date of revision of text:

NA