**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

Flusum 200 mg Tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each uncoated tablet contains:
Fluconazole USP…….200 mg

For excipients, see 6.1

## 3. PHARMACEUTICAL FORM

Tablets 200 mg
White, round, flat bevelled tablet with breakline on one side.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

- Cryptococcosis, including cryptococcal meningitis and infections of other locations (e.g. lungs, skin), including patients with normal immune response and patients with AIDS, organ transplant recipients and patients with other immunodeficiency forms; supporting therapy to prevent cryptococcosis relapse in AIDS patients.
- Generalized candidiasis, including candidemia, disseminated candidiasis and other forms of invasive candidiasis such as peritoneal, eye, urinary and respiratory tract infections, endocarditis, including patients with malignant tumours in ICU and administered cytotoxic or immunosuppressive agents, also patients with other candidiasis risk factors.
- Mucosal candidiasis including oropharyngeal, oesophageal candidiasis, non-invasive bronchopulmonary infections, candiduria and mucocutaneous and chronic oral atrophic candidiasis (denture sore mouth) including patients with normal and weakened immune fuction; preventative measures against oropharyngeal candidiasis relapse in AIDS patients.
- Genital candidiasis; acute or recurrent vaginal candidiasis; preventative measures to reduce the incidence of recurrent vaginal candidiasis (3 and more episodes a year), candidal balanitis
- Prophylaxis of candidal infections in patients with malignant tumours predisposed to such infections due to received cytotoxic therapy or chemotherapy
- Dermatomycosis including tinea pedis, tinea corporis, tinea cruris, tinea versicolor, tinea unguim and dermal candida infections.
- Deep endemic mycoses in patients with normal immune system, coccidioidomycosis, paracoccidioidomycosis, sporotrichosis and histoplasmosis.

### 4.2 Posology and method of administration

*Adults*
*For cryptococcal meningitis and cryptococcal infections at other sites*, the usual dose is 400 mg on the first day followed by 200 – 400 mg once daily. Duration of treatment for cryptococcal infections will depend on the clinical and mycological response but is usually at least 6 – 8 weeks for cryptococcal meningitis.

For the prevention of relapse of cryptococcal meningitis in patients with AIDS, Flusum daily dose of 200 mg is recommended.
*For candidaemia, disseminated candidiasis and other invasive candidal infections* the usual dose is 400 mg on the first day followed by 200 mg daily. Depending on the clinical response the dose may be increased to 400 mg daily. Duration of treatment is based upon the clinical and mycological response.
*For oropharyngeal candidiasis* the usual dose is 200 mg on the first day, then continue with 100 mg once daily. Treatment lasts for 2 weeks to reduce the probability of relapse.
*For atrophic oral candidiasis associated with dentures* the usual dose is 50 mg once daily for 14 days administered concurrently with local antiseptic measures to the denture.
*For other candidal infections of mucosa* (except genital candidiasis, see below), e.g. oesophagitis, non-invasive bronchopulmonary infections, candiduria, cutaneous candidiasis the usual effective dose is 50-100 mg daily, given for 14 – 30 days.
For the prevention of relapses of oropharyngeal candidiasis in AIDS patients after the patient receives a full course of primary therapy, Flusum can be administered in the dose of 150 mg once weekly.
*For vaginal candidiasis*, oral dose of 150 mg once. For the prevention of vaginal candidiasis the medicine may be taken in the dose of 150 mg once a month. Duration of treatment is determined individually; it varies from 4 to 12 months.
*For candidal balanitis* the usual oral dose of Flusum is 150 mg.
*For the prevention of fungal infections in patients with malignant tumours* the dose of Flusum should be 50 to 400 mg once daily, based on the patient's risk for developing fungal infection. For patients at high risk of systemic infection e.g. profound or long-lasting neutropenia, the recommended dose is 400 mg once daily.
*For cutaneous infections, including tinea pedis, corporis, cruris*, the recommended dosage is 150 mg once weekly or 50 mg once daily. Duration of treatment is normally 2 to 4 weeks but tinea pedis may require longer treatment (up to 6 weeks).
*For tinea versicolour* the recommended dosage is 300 mg once weekly for 2 weeks. Some patients need third dose of 300 mg a week, whereas 300-400 mg dose once may be sufficient for some patients. Alternative scheme of treatment is the dose of 50 mg once daily for 2-4 weeks.
*For tinea unguim* the recommended dose is 150 mg once weekly. Treatment should be continued until a healthy nail plate grows completely. For new nails and toenails to grow it usually takes 3-6 months and 6-12 months respectively.
Though the speed can vary over a wide range in different people, also it depends on the age. After successful treatment of long lasting chronic infections nail deformation may sometimes be observed.
*For deep endemic micosis* dose of 200-400 mg daily may be required. Duration of treatment should be decided individually.
*Children*
As with similar infections in adults, the duration of treatment is based on the clinical and mycological response.
*For mucosal candidiasis*: The recommended dose of Flusum for the age 7 years and over is 3 mg/kg daily. A loading dose of 6 mg/kg may be used on the first day to achieve steady state levels more rapidly.
*For generalised candidiasis and cryptococcal infection*: The recommended dosage is 6 – 12 mg/kg daily, depending on the severity of the disease.
For prevention of fungal infections in patients with malignant tumours considered at risk in association with neutropenia following cytotoxic chemotherapy or radiotherapy: The dose should be 3 – 12 mg/kg daily, depending on the extent and duration of the induced neutropenia.
*Elderly*

The normal dose should be used if there are no signs of renal impairment. In patients with renal impairment (creatinine clearance less than 50 ml/min) the dosage schedule should be adjusted as described below.

*Use in renal impairment*

No adjustments in single dose therapy are required. In patients with impaired renal function who will receive multiple doses of fluconazole, the loading dose of 50-400 mg is recommended, followed by a daily dose (according to indication) based on the following table:

| Creatinine clearance (ml/min) | Percent of recommended doses |
|---|---|
| >50 | 100% |
| ≤50 (no dialysis) | 50% |
| Patients receiving regular dialysis | 100% after each dialysis |

**4.3 Contraindications**

- Hypersensitivity to fluconazole or to any other ingredient within the formulation or to azole compounds with similar to fluconazole structure
- Co-administration with terfenadine at multiple fluconazole doses of 400mg per day or higher
- Co-administrationwith cisapride
- Pregnancy and lacation
- Children below 7 years

*With caution*

Worsening of liver function due to administration of fluconazole; rash due to fluconazole administered to patients with superficial fungal infections and invasive/systemic fungal infections; co-administration of terfenadine with fluconazole in doses less 400mg per day; potential proarrhythmia conditions with multiple risk factors (organic heart disease, electrolyte disturbance and therapy leading to such disorders).

**4.4 Special warnings and precautions for use**

Fluconazole has been associated with rare cases of hepatic toxicity including fatalities, primarily in patients with serious underlying medical conditions. Fluconazole hepatotoxicity has usually been reversible on discontinuation of therapy. Patients who develop abnormal liver function tests during fluconazole therapy must be monitored closely for the development of more serious hepatic injury. Upon identification of clinical signs of hepatic injury which may be associated with fluconazole administration, Flusum should be discontinued.

In rare cases Flusum can inflict anaphylaxis.

Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, during treatment with Flusum. AIDS patients are more prone to the development of severe cutaneous reactions to many medicinal products. If a rash, which is considered attributable to fluconazole, develops in a patient treated for a superficial fungal infection, further therapy 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.

Flusum may be associated with prolongation of the QT interval on the electrocardiogram. There have been very rare cases of QT prolongation and *torsades de pointes* in patients taking Flusum. These

reports included seriously ill patients with multiple confounding risk factors, such as organic heart diseases, electrolyte disbalance and concomitant treatment that may have been contributory. Flusum should be administered with caution to patients with these potentially proarrhythmic conditions.
Patients with liver, heart, and kidney conditions prior to use of Flusum should consult a physician.
Prior to initiation of vaginal candidiasis treatment with 150 mg Flusum, patients should be warned, that symptoms usually improve within 24 h, but for their complete elimination several days are sometimes required. If symptoms persist for several days, consult a physician.

**4.5 Interaction with other medicinal products and other types of interaction**

Bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria, and melena) can occur with the increase in prothrombin time (for 12%) as the result of receiving fluconazole with warfarin concomitantly. In patients receiving coumarin-type anticoagulants the prothrombin time should be carefully monitored.
Concomitant administration of fluconazole with azithromycin has not shown pronounced pharmacokinetic interaction between two medicinal preparations.
Benzodiazepines (Short Acting): Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. This effect on midazolam appears to be more pronounced following oral administration of fluconazole than with fluconazole administered intravenously. If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, patients should be monitored with consideration to decrease the benzodiazepine dosage.
200 mg daily of fluconazole leads to the increase of cyclosporine concentration in patients with transplanted kidney. Although multiple doses of fluconazole 100 mg daily have not demonstrated changes in cyclosporine concentration in marrow recipients. It is recommended to monitor cyclosporine concentration in blood when it is co-administered with fluconazole.
Coadministration of multiple-dose hydrochlorothiazide with fluconazole increases plasma concentrations of fluconazole by 40%. An effect of this magnitude should not necessitate a change in the fluconazole dose regimen in subjects receiving concomitant diuretics.
There were no relevant effects on hormone level in co-administration of combined oral contraceptives with 50 mg fluconazole.
Concomitant administration of fluconazole and phenytoin can be followed by clinically significant increase in phenytoin concentration. If co-administration of two drugs is necessary, phenytoin concentration levels should be monitored in order to correct its dose and achieve therapeutic consentration in serum.
Concomitant administration of fluconazole and rifabutin increases serum concentrations of the latter. There have been reports of uveitis when fluconazole and rifabutin were co-administered. Patients to whom fluconazole and rifabutin are co-administered should be under thorough control.
In patients receiving concomitant rifampicin, an increase of the fluconazole dose should be considered.
Fluconazole has been shown to prolong the half-life of concomitantly administered oral sulfonylureas (e.g., chlorpropamide, glibenclamide, glipizide, tolbutamide). Diabetic patients may be prescribed concomitant administration of fluconazole and oral sulfonylureas, but the risk of hypoglycaemia development should be considered.
Fluconazole may increase the serum concentrations of orally administered tacrolimus. There have been reported cases of nephrotoxicity. Patients to whom fluconazole and tacrolimus are coadministered should be under thorough control.
Coadministration of azole antifungals and terfenadine may cause serious arrhythmia due to the

increase of QT interval. At a 200 mg daily dose of fluconazole there was no prolongation in QT interval. Another study at a 400 mg daily dose of fluconazole demonstrated significant increases in plasma levels of terfenadine. The combined use of fluconazole at doses of 400 mg or greater daily with terfenadine is contraindicated. The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored.
Concomitant administration of fluconazole and theophylline leads to the increase in serum levels of the latter.
Patients who are receiving high dose theophylline should be observed as for theophylline concentration and if required the therapy should be modified accordingly.
Concomitant administration of fluconazole and zidovudine has demonstrated increase of zidovudine concentration probably due to the decrease of metabolism of the latter. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions.
Concomitant administration of fluconazole with astemizole or any other drugs metabolised via the cytochrome P450 may increase the serum concentration of such drugs.
Patients should be carefully monitored.
Single or multiple doses of fluconazole 50 mg do not affect antipyrine metabolism when co-administered.
Listed interactions have been determined at multiple doses of fluconazole. Any interaction of medicinal preparations with fluconazole administered in single dose are not known.

**4.6 Pregnancy and lactation**

Contraindicated

**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 to drive or operate machines carefully if any of these symptoms occur.

**4.8 Undesirable effects**

Fluconazole is usually well tolerated.
Common (≥1/100 to <1/10);
- Headache,
- Nausea, vomiting, abdominal pain, diarrhoea,
- Increase of blood alkaline phosphatase, serum aminotransferase level (ALT and AST),
- Rash,

Uncommon (≥1/1,000 to <1/100);
- Somnolence, insomnia
- Seizures, paraesthesia, dizziness, taste perversion
- Vertigo
- Dyspepsia, flatulence, dry mouth.
- Cholestasis, jaundice, bilirubin increased
- Pruritus, urticaria, increased sweating.
- Myalgia

Rare (≥1/10,000 to <1/1,000);

- Agranulocytosis, leukopenia, thrombocytopenia, neutropenia
- Anaphylaxis, anaphylactic shock.
- Hypercholesterolaemia, hypertriglyceridaemia, hypokalemia
- Tremor
- Tachycardia, Ventricular tachycardia/fibrillation, QT prolongation
- Hepatotoxicity, including rare death cases, hepatic failure, hepatocellular necrosis, hepatitis, hepatocellular damage.
- Toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalised exanthematous-pustulosis, dermatitis exfoliative, face oedema, alopecia.

In AIDS and cancer patients when treated with Flusum or similar drugs, there were observed changes in blood values, liver and kidney function, however no clinical relevance or association of such changes with treatment have been established.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via EFDA yellow Card Scheme, online at https://primaryreporting.who-umc.org/ET or toll free call 8482 to Ethiopian food and drug authority (EFDA).

**4.9 Overdose**

*Symptoms*: - aggravation of side effects.
*Treatment*: - symptomatic (with supportive measures and gastric lavage if necessary).
Flusum is largely excreted in the urine; forced volume diuresis would probably increase the elimination rate.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

**Pharmacotherapeutic group**
Antifungal agents for systemic use. Triazole derivatives.
**ATC code** J02AC01
Fluconazole is a triazole antifungal agent. It is a selective inhibitor of sterol synthesis in fungal cells, and it is active against infections caused by:
- Candida spp., including generalized candidiasis
- Cryptococcus neoformans, including intracranial infections
- Microsporum spp.
- Trychoptyton spp.
- Blastomyces dermatitides
- Coccidioides immitis
- Histoplasma capsulatum

Fluconazole is highly specific for fungal cytochrome P-450 dependent enzymes.

**5.2 Pharmacokinetic properties**

After oral administration fluconazole is well absorbed, and total bioavailability is 90%. 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, and plasma elimination half-life for fluconazole is approximately 30 hours. Plasma concentrations are proportional to dose. 90% steady state levels are reached by day 4-5 after the beginning of treatment (with multiple once daily dosing).
Plasma protein binding is low (11-12%). Fluconazole achieves good penetration in all body fluids.
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.

**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 27 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**

Microcrystalline cellulose, Lactose monohydrate, Povidone K30, Talc, Magnesium stearate, Sodium starch glycolate, Croscarmellose sodium, Isopropyl alcohol

**6.2 Incompatibilities**

Not available.

**6.3 Shelf Life**:

3 years.

**6.3 Special precautions for storage**

Store below 30°C.
Keep all medicines out of reach of children.

**6.4 Nature and content of container**
**6.5**
4 or 10 tablets are packed in Alu/PVC blister, such 1 blister is packed in a carton along with pack insert.
10 tablets are packed in Alu/PVC blister, such 10 blisters are packed in a carton along with pack insert.

**7. MANUFACTURER KUSUM HEALTHCARE PVT. LTD.**

Kusum Healthcare Pvt. Ltd.
SP-289(A), RIICO Industrial Area, Chopanki, Bhiwadi, Dist. Alwar (Rajasthan) India

**8. MARKETING AUTHORIZATION NUMBER**

07727/08415/NMR/2020

**9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF AUTHORIZATION**

22 August 2022

**10. DATE OF REVISION OF THE TEXT**

08/2023

**11. REFERENCES**

SmPC published on electronic medicines compendium
https://www.medicines.org.uk/emc#gref

The MHRA published product information
https://products.mhra.gov.uk/

Human medicine European public assessment report
https://www.ema.europa.eu/en/medicines