SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Flucazol Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Qualitative declaration

Each capsule contains Fluconazole 150 mg

2.2 Quantitative declaration

Excipients with known effect

Each Hard Gelatin Capsule Contains Lactose monohydrate

Composition of the shell

Gelatin, Propyl Paraben, Methyl Paraben, Colour Brilliant blue colour, Quinoline yellow.

For full list of Excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral Capsule

Hard gelatin capsules, size-I with blue clear body printed with radial print “Flucazol 150” and blue clear cap with radial print “NPI” logo thrice contains white to off-white powder

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

It is indicated in adults and child for the treatment of follow fungal infections: Invasive candidal infections (including candidaemia and disseminated candidiasis) and cryptococcal infections (including meningitis), treatment continued according to response cryptococcal meningitis). Prevention of relapse of cryptococcal meningitis in HIV infected patients after completion of primary therapy. Mucosal candidiasis (except genital): oropharyngeal candidiasis oesophagitis, candiduria, non-invasive bronchopulmonary infections atrophic oral candidiasis associated with dentures.Vaginal candidiasis and candidal balanitis: tinea pedis, corporis, cruris, pityriasis versicolor. Dermal candidiasis. Prevention of fungal infections in immunocompromised patients (for patients with high risk of systemic infections e.g. following bone-marrow transplantation). It is indicated in term newborn infants, infants, toddlers, children, and adolescents aged from 0 to 17 years old: Candidal balanitis, mucosal candidiasis: oropharyngeal candidiasis other mucosal infections (e.g. oesophagitis, candiduria, non-invasive bronchopulmonary infections), unusually difficult infections. Treatment for cryptococcal meningitis and prevention of fungal infections in immunocompromised patients. 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

Route of administration: Oral, The capsules should be swallowed whole and independent of food intake. The dose should be based on the nature and severity of the fungal infection.

Invasive candidal infections (including candidaemia and disseminated candidiasis)

and cryptococcal infections (including meningitis), treatment continued according to response cryptococcal meningitis); adult: 400 mg, dose to be given on first day, then 200–400 mg daily (max. per dose 800 mg once daily), treatment continued according to response (at least 8 weeks for cryptococcal meningitis), maximum dose for use in severe infections.

Prevention of relapse of cryptococcal meningitis in HIV infected patients after completion of primary therapy; adult: 200 mg daily.

Mucosal candidiasis (except genital): oropharyngeal candidiasis oesophagitis, candiduria, non-invasive bronchopulmonary infections, atrophic oral candidiasis associated with dentures; adult: 50 mg daily given for 7–14 days in oropharyngeal candidiasis (max. 14 days except in severely immunocompromised patients); for 14 days in atrophic oral candidiasis associated with dentures; for 14–30 days in other mucosal infections (e.g. oesophagitis, candiduria, non-invasive bronchopulmonary infections; increased to 100 mg daily, increased dose only for unusually difficult infections.

Vaginal candidiasis and candidal balanitis; adult: 150 mg for single dose.
Tinea pedis, corporis, cruris, pityriasis versicolor. Dermal candidiasis: Adult: 50 mg daily for 2–4 weeks (for up to 6 weeks in tinea pedis); max. duration of treatment 6 weeks.

Prevention of fungal infections in immunocompromised patients (for patients with high risk of systemic infections e.g. following bone-marrow transplantation); adult: 50-400 mg daily, commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range.

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

Candidal balanitis: Child 16–17 years: 150 mg for single dose.
Mucosal candidiasis:
Child 1 month–11 years: 3–6 mg/kg, dose to be given on first day, then 3 mg/kg daily (max. per dose 100 mg) for 7–14 days in oropharyngeal candidiasis (max. 14 days except in severely immunocompromised patients); for 14–30 days in other mucosal infections (e.g. oesophagitis, candiduria, non-invasive bronchopulmonary infections).

Child 12–17 years: 50 mg daily for 7–14 days in oropharyngeal candidiasis (max. 14 days except in severely immunocompromised patients); for 14–30 days in other mucosal infections (e.g. oesophagitis, candiduria, non-invasive bronchopulmonary infections); increased to 100 mg daily, increased dose only for unusually difficult infections.

Treatment for cryptococcal meningitis; child: 6–12 mg/kg daily (max. per dose 800 mg), treatment continued according to response (at least 8 weeks).
Prevention of fungal infections in immunocompromised patients; child: 3–12 mg/kg daily (max. per dose 400 mg), commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range, dose given according to extent and duration of neutropenia.

Special populations: Renal Impairment: Dose adjustments: In adult’s Usual initial dose then halve subsequent doses if eGFR less than 50 mL/minute/1.73 m2. In children usual initial dose then halve subsequent doses if estimated glomerular filtration rate less than 50 mL/minute/1.73 m2. Hepatic impairment: Limited data are

available in patients with hepatic impairment, therefore fluconazole should be administered with caution to patients with liver dysfunction. Paediatric population: A maximum dose of 400 mg daily should not be exceeded. As with similar infections in adults, the duration of treatment is based on the clinical and mycological response. It is single daily dose. Children: Oropharyngeal candidiasis: 6 mg/kg on the first day, followed by 3 mg/kg once daily. Treatment should be administered for at least 2 weeks.

4.3 Contraindications

It is contraindicated in patients with a history of hypersensitivity to the active substance, to related azole substances, or to any of the excipients. Co-administration of terfenadine with fluconazole multiple doses 400 mg per day or higher and known to prolong the QT interval, (CYP) 3A4 erythromycin, astemizole, pimozide, quinidine or cisapride is contra-indicated in patients receiving fluconazole.

4.4 Special Warnings and Special Precautions for Use

Patients should take following special warnings and precautions for use:

Patients have liver or kidney problems. Patients suffer from heart disease, including heart rhythm problems. 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. The QT prolongation caused by other medicinal products (such as amiodarone) may be amplified via the inhibition of cytochrome P450 (CYP) 3A4. There have been very rare cases of QT prolongation and torsades de pointes. These reports included seriously ill patients with multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities and concomitant treatment that may have been contributory. Patients with hypokalaemia and advanced cardiac failure are at an increased risk for the occurrence of life-threatening ventricular arrhythmias and torsades de pointes. Coadministration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 are contraindicated.

Patients have abnormal levels of potassium, calcium or magnesium in your blood. Patients may have developed a severe skin rash or skin peeling (itching, reddening of the skin or difficulty in breathing), blistering and/or mouth sores after taking fluconazole. Serious skin reactions including drug reaction with eosinophilia and systemic symptoms (DRESS) reported in association with fluconazole treatment. Stop taking fluconazole and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions. In rare cases anaphylaxis reported.

Patients develop signs of ‘adrenal insufficiency’ where the adrenal glands do not produce adequate amounts of certain steroid hormones such as cortisol (chronic, or long lasting fatigue, muscle weakness, loss of appetite, weight loss, abdominal pain).

Excipients: It contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. Fluconazole capsules contain less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of the following other medicinal products is contraindicated: Cisapride, terfenadine, astemizole, pimozide, quinidine, erythromycin, concomitant use of the following other medicinal products cannot be recommended, halofantrine, concomitant use that should be used with caution: amiodarone, rifampicin, hydrochlorothiazide, alfentanil, amitriptyline, nortriptyline,

amphotericin B, anticoagulants, as with other azole antifungals, benzodiazepines (short acting), midazolam, triazolam, carbamazepine, certain calcium channel antagonists nifedipine, isradipine, amlodipine, verapamil and felodipine, celecoxib, cyclophosphamide, fentanyl, HMG CoA reductase inhibitors, ibrutinib, ivacaftor, olaparib, ciclosporin, tacrolimus, ciclosporin, everolimus sirolimus, methadone, non-steroidal anti-inflammatory drugs, naproxen, lornoxicam, meloxicam, diclofenac, phenytoin, prednisone, rifabutin, saquinavir, sulfonylureas, chlorpropamide, glibenclamide, glipizide, tolbutamide, theophylline, tofacitinib, tolvaptan, vinca alkaloids, vincristine and vinblastine, vitamin A, zidovudine, oralcontraceptives.

4.6 Pregnancy and Lactation

Pregnancy: It should not be used during pregnancy.
Lactation: It should not be used during breastfeeding.

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

Drug reaction with eosinophilia and systemic symptoms may reported. The most frequently 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 with the following frequencies: Very common; Common; Uncommon; Rare; Very Rare, Not Known.
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, hypokalaemia, tremor, torsade de pointes, QT prolongation. Hepatic failure, hepatocellular necrosis, hepatitis, hepatocellular damage syndrome, acute generalized exanthematouspustulosis, dermatitis exfoliative, angioedema, face oedema, alopecia. Not Known: Drug reaction with eosinophilia and systemic symptoms.

4.9 Overdose

There have been reports of overdose with fluconazole. 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 Pharmacodynamics Properties

Pharmacotherapeutic Group: Antimycotics for systemic use, triazole derivatives
ATC Code: J02AC01
It is a triazole antifungal agent. Its primary mode of action is the inhibition of

fungal cytochrome P-450 mediated (lanosterol 14-α-demethylase), an essential step in fungal ergosterol biosynthesis and its accumulation correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity. It is more selective for fungal CYP-450 enzymes than for various mammalian enzymes systems. A dose 50 mg daily given up to 28 days shown not to effect testosterone plasma levels in males or steroid levels in females of child-bearing age. Susceptibility invitro, displays antifungal activity against most 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. It 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. In pre-clinical, there is a correlation between MIC values and efficacy against experimental mycoses due to Candida spp.

Mechanism(s) of resistance: Candida spp have developed a number of resistance mechanisms to azole antifungal agents. Fungal strains which have developed one or more of these resistance mechanisms are known to exhibit high minimum inhibitory concentrations to fluconazole which impacts adversely efficacy in vivo and clinically.

5.2 Pharmacokinetic Properties

Absorption: After taking orally it is well absorbed, plasma levels over 90% of the levels achieved after i.v admin. 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. A loading dose (on day one) of twice the usual daily dose enables plasma levels to approx. to 90% steady-state levels by day two.

Distribution: The apparent volume of distribution approx to total body water. Plasma protein binding is low (11-12%). It achieves good penetration in all body fluids. The levels of fluconazole in saliva and sputum are similar to plasma levels. In fungal meningitis, it levels in the CSF approx. 80% the corresponding plasma levels. High skin concentration of fluconazole, above serum concentrations, are achieved in the stratum corneum, epidermis-dermis and eccrine sweat. It accumulates in the stratum corneum.

Biotransformation: It is metabolised only to a minor extent of a radioactive dose, only 11% is excreted in a changed form in the urine. It is a moderate inhibitor of the isozymes CYP2C9 and CYP3A4. It is also a strong inhibitor of the isozyme CYP2C19.

Elimination: Plasma elimination half-life is approx 30 hours. The major route of excretion is renal, with approx 80% of the administered dose appearing in the urine as unchanged, it 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.

Pharmacokinetics in renal impairment: In patients with severe renal insufficiency, (GFR< 20 ml/min) half-life increased from 30 to 98 hours. Consequently, reduction of the dose is needed. It after three hours of haemodialysis session around 50% iseliminated from blood and to a lesser extent by peritoneal dialysis.

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/dayhad 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 as light 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

Lactose monohydrate, sodium starch glycolate, sodium lauryl sulphate, colloidal anhydrous silica, magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

36 months

6.4 Special Precautions for Storage

Do not store above 30°C. Store in a dry place. Protect from light and moisture.

6.5 Nature and Contents of Container

PVC/PE/PVDC clear/ALU blister pack

6.6 Special precaution for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

TAN 22 HM 0194

9. DATE OF FIRST AUTHORIZATION

25th July, 2020

10. DATE OF REVISION OF THE TEXT