SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) FOR DRUG PRODUCTS IN NIGERIA

FUNTOL 150

(Fluconazole Capsules)

1. **NAME OF THE DRUG PRODUCT**
   Brand Name: FUNTOL 150
   Generic Name: Fluconazole Capsules

   Strength:

   Fluconazole USP…….. 150 Mg

   Dosage form: Solid Oral Dosage Form (Hard Gelatin Capsule)

   Rout of administration: Oral

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

   Label claim:

   Each Hard Gelatin Capsule Contains:

   Fluconazole USP……..150 Mg

   Excipients……..Q.S

   Approved colours are added in capsule shells

3. **PHARMACEUTICAL FORM**
   Solid Oral Dosage Form

4. **CLINICAL PARTICULARS**

4.1 Therapeutic indications:

For treatment and prophylaxis of fungal infections where other antifungals have failed or are not tolerated (e.g due to adverse reactions). FUNTOL 150 is effective in treatment of coccidioidomycosis , mucosal candidiasis, systemic candidiasis, cryptococcosis, Prophylaxis of fungal infections following cytotoxic, chemotherapy or radiotherapy and Prophylaxis of candidiasis in immunocompromised people. Maintenance to prevent relapse of cryptococcal meningitis in patients with AIDS. Sporotrichosis, histoplasmosis and vaginal candidiasis.

4.2 Posology/Dosage and method of administration:

<u>Posology</u>

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.

Adults

Mucosal: 50-100 mg daily for 14-30 days

Vaginal : 150 mg as a single oral dose

Systemic : 400 mg on first day as loading dose, then 200-400 mg once daily for minimum 28 days.

Cryptococcal meningitis : 400mg on first day, followed by 200 mg once daily for 10-12 weeks after CSF is sterile.

Prophylaxis of fungal infections (in immunocompromised / at risk patients): 50-100 mg once daily. Doses may be given orally or by IV infusion at rate of 5-10 ml/min

Children : severe life threatening infections in over 1 year 3-6 mg/kg body weight daily.

Method of administration

Fluconazole may be administered either orally (Capsules and powder for oral suspension) or by intravenous infusion (Solution for infusion), the route being dependent on the clinical state of the patient. On transferring from the intravenous to the oral route, or *vice versa*, there is no need to change the daily dose.

The physician should prescribe the most appropriate pharmaceutical form and strength according to age, weight and dose. The capsule formulation is not adapted for use in infants and small children. Oral liquid formulations of fluconazole are available that are more suitable in this population

4.3 Contraindication:

Hypersensitivity to the active substance, to related azole substances, or to any of the excipients listed in section 6.1.

Co-administration of terfenadine is contra-indicated in patients receiving fluconazole at multiple doses of 400 mg per day or higher based upon results of a multiple dose interaction study.

Co-administration 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 contra-indicated in patients receiving fluconazole (see sections 4.4 and 4.5).

4.4 Special warnings and precautions 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, Fluconazole Tablets 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

Fluconazole Tablets 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.The effect of fluconazole on other medicinal products.

4.5 Interaction with other drug products and other forms of interaction

Concomitant use of the following other medicinal products is contraindicated:
Cisapride: There have been reports of cardiac events including torsades de pointes in patients to whom fluconazole and cisapride were co-administered. 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 contra-indicated .
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.
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
Concomitant use of the following other medicinal products cannot be recommended:
Halofantrine: Fluconazole can increase halofantrine plasma concentration due to an inhibitory effect on CYP3A4. Concomitant use of fluconazole and halofantrine has the potential to increase

the risk of cardiotoxicity (prolonged QT interval, torsades de pointes) and consequently sudden heart death. This combination should be avoided .
Concomitant use that should be used with caution:

4.6 Fertility, pregnancy and lactation

Pregnancy

Observational studies suggest an increased risk of spontaneous abortion in women treated with fluconazole during the first and/or second trimester compared to women not treated with fluconazole or treated with topical azoles during the same period.
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 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

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

Summary of safety profile

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in association with fluconazole treatment

The most frequently (≥ 1/100 to <1/10) reported adverse reactions are headache, abdominal pain, diarrhoea, nausea, vomiting, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased and rash. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in association with fluconazole treatment

The following adverse reactions have been observed and reported during treatment with Fluconazole 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)

System Organ Class	Common	Uncommon	Rare	Not known

Blood and the lymphatic system disorders		Anaemia	Agranulocytosis, leukopenia,	
			thrombocytopenia, neutropenia	
Immune system disorders			Anaphylaxis	
Metabolism and nutrition disorders		Decreased appetite	Hypercholesterolaemia, hypertriglyceridaemia, hypokalemia	
Psychiatric disorders		Somnolence, insomnia		
Nervous system disorders	Headache	Seizures, paraesthesia, dizziness, taste perversion	Tremor	
Ear and labyrinth disorders		Vertigo		
Cardiac disorders			Torsade de pointes, QT prolongation	
Gastrointestinal disorders	Abdominal pain, vomiting, diarrhoea, nausea	Constipation, dyspepsia, flatulence, dry mouth		
Hepatobiliary disorders	Alanine aminotransferase increased , aspartate aminotransferase increased , blood alkaline phosphatase increased	Cholestasis, jaundice, bilirubin increased	Hepatic failure **, hepatocellular necrosis ,**hepatitis hepatocellular damage	
Skin and subcutaneous tissue disorders	Rash	**Drug eruption*** , urticaria, pruritus, increased sweating	**Toxic epidermal necrolysis, Stevens-Johnson syndrome**, acute generalised exanthematous-pustulosis, dermatitis exfoliative, angioedema, face oedema, alopecia	Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders		Myalgia		
General disorders and administration site conditions		Fatigue, malaise, asthenia, fever		

* including Fixed Drug Eruption.

Pediatric 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.

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 hemodialysis session decreases plasma levels by approximately 50%.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02AC01.

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.

Fluconazole 50 mg daily given up to 28 days has been shown not to effect testosterone plasma concentrations in males or steroid concentration in females of child-bearing age. Fluconazole 200 mg to 400 mg daily has no clinically significant effect on endogenous steroid levels or on ACTH stimulated response in healthy male volunteers. Interaction studies with antipyrine indicate that single or multiple doses of fluconazole 50 mg do not affect its metabolism.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral route.

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 μ g/g and 7 days after cessation of treatment the concentration was still 5.8 μ g/g. At the 150 mg once-a-week dose, the concentration of fluconazole in stratum corneum on day 7 was 23.4 μ g/g and 7 days after the second dose was still 7.1 μ g/g.
Concentration of fluconazole in nails after 4 months of 150 mg once-a-week dosing was 4.05 μ g/g in healthy and 1.8 μ g/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 moderate inhibitor of the isozymes CYP2C9 and CYP3A4 (see section 4.5). 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.
Pharmacokinetics in renal impairment

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.

.6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients:

Ingredients

Microcrystalline Cellulose Powder (102) BP
Purified Talc BP
Magnesium Stearate BP
Empty Hard Gelatin Capsules Blue/White Colour Size - "2" and Printed with FLUCONAZOLE

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store below 30°C. Protects from light.

6.5 Nature and contents of container

FUNTOL 150 is available as blister pack of 10 Capsules, such 1 blister is packed in a carton along with pack insert..

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

None

7.0 Marketed by:

M/S. AQUATIX PHARMACEUTICALS LIMITED

No.7, Sapara Williams Street,

Industrial Estate, Ikeja,

Lagos, Nigeria.

8.0 Manufactured by:

M/S. MCW HEALTHCARE PVT. LTD.

286, 287A, 287B, Sector-E, Industrial Area,

Sanwer Road, Indore (M.P.) India

9. NAFDAC REGISTRATION NUMBER(S): A4-0137