1. NAME OF THE MEDICINAL PRODUCT:

KINZOCAP (Fluconazole Capsules BP 200 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITIONS:

NAME AND QUANTITY OF EACH INGREDIENT:

UNIT DOSE

Ingredients	Qty./ mg	Batch Formula (kg) for 1,00,000 capsule	Use/Function
Active Ingredient			
Fluconazole BP	200 mg	20.4*	Active
In Active Ingredients			
Micro Crystalline Cellulose BP	6.00	0.60 Kg.	Disintegrant
Starch BP	6.00	0.60 Kg.	Diluent
Magnesium stearate BP	5.00	0.50 Kg.	Lubricant
Talc BP	5.00	0.50 Kg.	Glidant / Diluent
Aerosil BP	4.00	0.40 Kg.	Disintegrant
Red colored size '2' hard gelatin capsules	--	1.03 Lacs	Protective shell

* Including 2 % Overages

Reference:
BP = British Pharmacopoeia
IHS = In-house specification

3. PHARMACEUTICAL FORMS:

Oral capsule
Description: Red colored, hard gelatin capsule containing white color powder

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Systemic mycoses:
1. Cryptococcal infections including cryptococcal meningitis and infections of other areas (e.g. lungs, skin). AIDS patients, as well as patients who have undergone an organ transplant or present other causes of immunosuppression may be treated. Fluconazole may be used for the prevention of recurrent cryptococcal diseases in AIDS patients.
2. Generalized candidiasis including candidaemia in clinically stable and nonneutropenic patients, diffused and metastatic candidiasis (infections of the peritoneum, endocardium, as well as lung and urinary tract infections). Patients with malignant neoplasms or in intensive care units, as well as

patients receiving cytostatic or immunosuppressive drugs or patients presenting other factors in favor of candidiasis may also be treated with the drug. It is self-evident that for indications 1 and 2, cultures and proper laboratory examinations should be conducted before the initiation of the treatment (immediate microscopic examination, biopsies, serum examinations), in order to isolate and identify the causative factor.
3. Deep endemic mycoses, such as coccidioidomycosis, paracoccidioidomycosis, sporotrichosis and histoplasmosis in immunocompetent patients.
4. Mucosal candidiasis. This includes oropharyngeal and oesophageal candidiasis (as an alternative to topical treatment), non-invasive bronchopulmonary candidiasis. Candiduria, chronic mucocutaneous candidiasis. Chronic atrophic oral candidiasis (stomatitis due to dentures), as alternative to local treatment. Patients mostly with immune system disorders can undergo a treatment with the drug.
5. Genital candidiasis:Vaginal candidiasis as an alternative to topical treatment (only as one single dose of 150mg)
a) acute
b) relapsing as long as the infection has been confirmed by culture (usually of non-inflammatory cause but due to allergy or hypersensitivity). Candidal balanitis.
6. Dermatophytoses including infections of the foot, of the thin skin layer and of the bikini line, as well as tinea versicolor, onychomycosis and infections caused by CANDIDA. Note: Systemic treatment in the case of the indications mentioned above is preferable when the infection extends to a large skin area or the scalp, or in patients with disorders of defense mechanisms, unresponsive to local treatment and persistence of the mycotic infection despite treatment.
7. Prevention of candidiasis in patients with neutropenia and malignant diseases that predispose to the development of such infections as a result of chemotherapy with cytostatic drugs or radiotherapy in cases of marrow transplant. Caution: chronic administration of azoles increases the possibility of development of C. KRUSEI, ASPERGILLUS, MUCORALES, FUSARIUM, T. GLABRATA that usually present a natural resistance to azoles.
Therapy may be initiated before the results of the cultures and other laboratory studies are known. However when the results are known, therapy should be adjusted accordingly.

4.2 Posology and Method of Administration

As absorption of orally administered Fluconazole is rapid and complete, the Fluconazole daily dose is the same for both oral and intravenous administration.
The Fluconazole daily dose should be based on the type and severity of the mycotic infection. Most cases of vaginal candidiasis respond therapeutically to single dose administration.
For infections requiring multiple dose administration, treatment should be continued until the clinical parameters and laboratory examinations show resolution of the active mycotic infection. Insufficient duration of Fluconazole treatment may result in a relapse of the active infection. Patients with AIDS and cryptococcal meningitis or recurrent oropharyngeal candidiasis usually require preventative treatment to reduce the occurrence of relapses.

Adults
1a. For the treatment of cryptococcal meningitis and cryptococcal infections of other body areas, the usual dose is 400mg on the first day of the treatment followed by a dose of 200-400mg once daily. The duration of treatment in cryptococcal infections depends on the clinical mycological response but usually lasts from 6 to 8 weeks in cryptococcal meningitis and 10 to 12 weeks after a negative result of the CSF culture.
1b. For the prevention of cryptococcal meningitis relapse in patients with AIDS, after the completion of the initial treatment it is possible to administer Fluconazole indefinitely at a daily dose of 100-200mg
2. For the treatment of candidaemia, generalized candidiasis and other severe candidiases, the usual dose is 400mg on the first day of the treatment, followed by a daily dose of 200mg.

Depending on the clinical response of the patients, the dose may be increased to 400mg daily. The treatment's duration depends on the clinical response of the patients.
3. With regard to deep endemic mycosis, doses of 200-400mg daily for a duration of treatment which may last 2 years may prove to be necessary. Duration of treatment should be adapted in every case.
4. For the treatment of oropharyngeal candidiasis, the usual dose is 50-100mg once daily for 7-14 days. If necessary, the treatment may be continued for a longer time span in patients with a severe disorder of the immune system. For the treatment of atrophic oral candidiasis associated with artificial dentures, the usual Fluconazole dose is 50mg once daily for 14 days, concurrently administered with the application of local antiseptic measures to the dentures. For the treatment of other candidiasis infections of the mucosa (except vaginal candidiasis, see below), e.g. oesophagitis, non-invasive bronchopulmonary infections, candidurea, chronic muco-cutaneous candidiasis etc., the usual Fluconazole dose is 50-100mg daily for 14-30 days.
5. For the treatment of vaginal candidiasis and candidal balanitis, 150mg of Fluconazole should be administered orally as a single dose.
6. For the treatment of skin infections including infections of the feet, of the thin skin layer and of the bikini line, as well as tinea versicolor and infections caused by Candida, the recommended dose is 150mg once weekly or 50mg once daily. The duration of treatment usually extends from 2 to 4 weeks but in particular infection of the feet may require treatment for up to 6 weeks. For tinea versicolor, the recommended dose is 50mg once daily for 2 to 4 weeks.
7. For onychomycosis, the recommended dose is 150mg once weekly. Treatment should be continued until the infected nail is replaced due to normal nail growth. Normally it takes about 3 to 6 months and 6 to 12 months respectively for fingernails and toenails to grow. Of course the growth rate may vary considerably from person to person and according to patient's age. After a successful long-term treatment of chronic infections, the nails may still show traces of infection.
8. For the prevention of fungal infections in patients with an increased risk of generalized infection e.g. patients who are expected to have severe or prolonged neutropenia, like pre-marrow transplant patients, the daily recommended dose of the drug should be 400mg and for the prevention of fungal infections in patients with neutropenia and malignant diseases who are predisposed to the development of such infections as a result of chemotherapy with cytostatic drugs of radiotherapy, the daily dose of the drug is 50-400mg once daily. Fluconazole administration should start several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count is above 1000 cells per mm^3.

Patients with renal impairment
Fluconazole is largely eliminated in the urine in an unaltered form. In case of administration of a single, dose of the drug its adjustment is not necessary. When multiple doses are administered to patients with renal impairment, a loading dose of 50 to 400 mg is administered. After the loading dose, the daily dose (according to the indications) should be adjusted according the following table:

Creatinine clearance (ml/min)	**Percent of recommended dose**
>50	100%
11 - 50	50%

Patients receiving regular dialysis 100% after each dialysis When serum creatinine is the only measurement of renal failure, the following equation for creatinine is applied:

Men: $\frac{\text{Body weight (kg) x (140 - age)}}{\text{72 x serum creatinine (mg / 100ml)}}$

Women: 0.85 of the male value

4.3 Contraindications

KINZOCAP should not be administered in patients with known sensitivity to Fluconazole or to the excipients or to related azole preparations. Coadministration of cisapride is contra-indicated in patients receiving fluconazole. Based on the results of a multiple dose interaction study, co-administration of terfenadine in patients receiving fluconazole at doses of 400 mg or more per day is contraindicated.

4.4 Special Warnings And Precautions For use

General:

Hepatic failure: the administration of fluconazole has been correlated in rare cases to severe hepatotoxicity which in exceptional cases has led to fatality, especially in patients with severe illness. In patients taking fluconazole and with the appearance of hepatotoxicity, no correlation with the total daily dose, the duration of the therapy, gender or age was observed. Hepatotoxicity from fluconazole is usually, but not always, reversible, after treatment discontinuation. Patients with biochemical disturbances of hepatic function throughout the duration of treatment with fluconazole, must be closely monitored for the possibility of developing severe hepatic failure. Fluconazole should be discontinued if clinical signs and symptoms of hepatic disease are observed. Rarely, patients have developed exfoliative cutaneous reactions such as Stevens-Johnson syndrome or a bullous epidermal necrolysis erythema during treatment with fluconazole. Patients with AIDS are more prone to the development of severe cutaneous reactions with many drugs. If a rash develops in patients treated for superficial fungal infections which is considered attributable to fluconazole, therapy should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and treatment with fluconazole should be discontinued if bullous lesions or erythema multiforme develop. In rare cases, anaphylaxis has been reported.

Administration in the elderly:

If there are no indication of renal function impairment, the usual dose of the drug should be administered. In patients with renal dysfunction (creatinine clearance <50 ml/min) the dosage regimen should be adjusted as described in "Posology and method of administration".

4.5 Drug Interactions

Cisapride: 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 QT 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. 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 *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, Torsades de Pointes) and consequently sudden heart death. Coadministration of fluconazole and erythromycin is contraindicated.

4.6 Pregnancy and Lactation

Pregnancy

Fluconazole administration in pregnancy should be avoided, except in the case of patients with severe and life threatening fungal infections, in which the drug can be administered if the expected benefits from the treatment outweigh potential risks of toxic effects on the foetus.

Breast-feeding:

Fluconazole passes into breast milk to reach concentrations similar to those in plasma. Fluconazole administration in breast feeding mothers is not recommended.

4.7 Effects on ability to drive and use machines

Fluconazole does not impair a patient's ability to drive or use machinery.

4.8 Undesirable effects

Fluconazole is generally well tolerated. The most common undesirable effects associated with the use of Fluconazole relate to the gastrointestinal system. They include nausea, abdominal discomfort, diarrhoea and flatulence. Other common undesirable effects are headache and skin rashes. Exfoliating dermatitis, such as the Stevens-Johnson syndrome and toxic epidermic necrolysis, especially in patients with AIDS receiving other drugs are rarely reported.

Disorders of renal function, the hematopoietic system function, and hepatic function have been reported (see warning) during treatment with Fluconazole and associated drugs in some patients particularly those with severe underlying diseases such as AIDS and cancer. As with other azoles, cases of anaphylaxis have been reported on rare occasions. Seizures, leucopenia, thrombocytopenia, hypercholesteraemia, hypertriglyceridaemia and hypokalaemia have also been reported.

In case of hepatic dysfunction or rash, consult your doctor.

4.9 Overdose

In the event of overdosage, supportive measures and symptomatic treatment, with gastric lavage if necessary, may be adequate.

As fluconazole is largely excreted in the urine, forced volume diuresis increases the elimination rate. A three hour haemodialysis session decreases plasma levels by approximately 50%.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Fluconazole is a triazole antifungal agent. Fluconazole exerts its antifungal effect by inhibition of sterol 14-alpha-demethylase impairing the biosynthesis of ergosterol, the principal sterol in the fungal cell membrane. This damages the cell membrane, producing alterations in membrane function and permeability.

5.2 Pharmacokinetic properties

Fluconazole is well absorbed after oral administration. Oral bioavailability is more than 90 %. Oral bioavailability is not altered by foods or gastric acidity. The time to peak plasma concentrations is 1 to 2 hours. Protein binding is low (12 %.) The elimination half-life in adults is approximately 30 hours and is increased in patients with impaired renal function. Fluconazole is primarily excreted by the kidneys. Approximately 80 % of the dose is excreted unchanged in the urine. Fluconazole clearance is proportional to creatinine clearance. However, accumulation is significant over 15 days and concentrations may rise 2 to 3 fold. A small amount of fluconazole undergoes hepatic metabolism. Fluconazole is cleared from the body faster in children than in adults. The half-life in

children is 23 hours. During the first 2 weeks of life the half-life is approximately 74 hours on day one and 47 hours on day 13.

5.3 Pre-clinical safety data
Not applicable.

6. Pharmaceutical Particulars

6.1. List of excipients

Raw Materials	**Pharmacopoeia Reference**
Micro Crystalline Cellulose	BP
Starch	BP
Magnesium stearate	BP
Talc	BP
Aerosil	BP
Red colored size '2' hard gelatin capsules	-----

6.2. Incompatibilities

None

6.3. Shelf life
36 Months

6.4 Special precautions for storage

Store in cool & dry place, below 25°C. Protect from light.
Keep out of reach of children.

6.5 Nature and contents of container
1 X 10 Capsules in a monopack with insert

6.6 Special precautions for disposal
No special requirement

7. APPLICANT/MANUFACTURER

APPLICANT
KINGZY PHARMACEUTICALS LTD.,
#142, Okporo Road,
Port Harcourt,
RIVERS STATE, NIGERIA