SUMMARY OF PRODUCT CHARACTERISTIC

1. Name of the medicinal product

Flutrox 200mg Capsules

2. Qualitative and quantitative composition

Each capsule contains 200mg of Fluconazole. For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Capsule
White powder in cream/cream hard gelatin capsule

4. Clinical particulars

4.1 Therapeutic indications

Flutrox 200mg capsule is indicated for:

1. Vaginal candidiasis
2. Mucosal candidiasis e.g. oropharyngeal, mucocutaneous and chronic oral atrophic candidiasis.
3. Systemic candidiasis: candidemia, disseminated candidiasis, infection of peritoneum, respiratory and urinary tract
4. Cryptococcus: cryptococcal meningitis, primary as well as maintenance therapy
5. Prevention of fungal infection in patients with malignancy, AIDS, in intensive care units and patients on immunosuppressive drugs
6. Fungal infections of the skin and nails

4.2 Posology and method of administration

Flutrox is administered orally.

Adults (16 to 60 years):
One capsule should be swallowed whole.

Children (under 16 years):
Paediatric use is not recommended.

Elderly:
Not recommended in patients over 60 years.

Renal Impairment:
There is no separate dosage schedule in patients with renal impairment for single dose therapy.

4.3 Contraindications

Fluconazole should not be used in patients with known sensitivity to the drug, any of the inert ingredients or to related azole compounds.

Coadministration of terfenadine is contraindicated in patients receiving fluconazole at multiple doses of 400mg 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 (see section 4.4 and 4.5).
Fluconazole should not be used in patients with porphyria.

4.4 Special warnings and precautions for use

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 is described in section 4.5 The effect of fluconazole on other medicinal products.

Fluconazole should be administered with caution to patients with liver dysfunction (see also 4.2). Fluconazole has been associated with rare cases of serious hepatic toxicity including fatalities, primarily in patients with serious underlying medical conditions. In cases of fluconazole-associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of patient has been observed. Fluconazole hepatotoxicity has usually been reversible on discontinuation of therapy.

Patients who develop abnormal liver function tests during fluconazole therapy should be monitored for the development of more serious hepatic injury. Fluconazole should be discontinued if clinical signs or symptoms consistent with liver disease develop that may be attributable to fluconazole.

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

The coadministration of fluconazole at doses lower than 400mg per day

with terfenadine should be carefully monitored (see section 4.3 Contraindications and 4.5 Interaction with Other Medicaments and Other Forms of Interaction).

In rare cases, as with other azoles, anaphylaxis has been reported.
Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and torsade de pointes in patients taking fluconazole. These reports included seriously ill patients with multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities and concomitant medicines that may have been contributory.

Fluconazole should be administered with caution to patients with these potentially proarrythmic conditions.
Fluconazole should be administered with caution to patients with renal dysfunction (see also 4.2)

Fluconazole is a potent CYP2C9 inhibitor and a moderate CYP3A4 inhibitor. Fluconazole treated patients who are concomitantly treated with drugs with a narrow therapeutic window metabolised through CYP2C9 and CYP3A4, should be monitored (see section 4.5 Interaction with Other Medicaments and Other Forms of Interaction)

Fluconazole tablets contain lactose and should not be given to patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

The product intended for pharmacy availability without prescription will carry a leaflet which will advise the patient:

Do not use Fluconazole 200mg tablets without first consulting your doctor:
•If you are under 16 or over 60 years of age.
•If you are allergic to any of the ingredients in Fluconazole 150mgcapsule or other antifungals and other thrush treatments.
•If you are taking any medicine other than the contraceptive pill.
•If you are taking the antihistamine terfenadine or the prescriptionmedicine cisapride.
•If you have had thrush more than twice in the last six months.
•If you have any disease or illness affecting your liver or kidneys orhave had unexplained jaundice.
•If you suffer from any other chronic disease or illness.
•If you or your partner have had exposure to a sexually transmitteddisease.
•If you are unsure about the cause of your symptoms.

Women only:
•If you are pregnant, suspect you might be pregnant or are breastfeeding.
•If you have any abnormal or irregular vaginal bleeding or a bloodstained

discharge.
•If you have vulval or vaginal sores, ulcers or blisters.
•If you are experiencing lower abdominal pain or burning onpassing urine.

Men only:
•If your sexual partner does not have vaginal thrush.
•If you have penile sores, ulcers or blisters.
•If you have an abnormal penile discharge (leakage).
•If your penis has started to smell.
•If you have pain on passing urine.

The product should never be used again if the patient experiences a rash or anaphylaxis follows the use of the drug.

Recurrent use (men and women): Patients should be advised to consult their physician if the symptoms have not been relieved within one week of taking Fluconazole. A further capsule can be used if the candidal infection returns after 7 days. However, if the candidal infection recurs more than twice within six months, patients should be advised to consult their physician.

4.5 Interaction with other medicinal 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 torsade de pointes in patients to whom fluconazole and cisapride were coadministered. A controlled study found that concomitant fluconazole 200mg once daily and cisapride 20mg 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 (see section 4.3 Contraindications).

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 200mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. Another study at a 400mg and 800mg daily dose of fluconazole demonstrated that fluconazole taken in doses of 400mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. The combined use of fluconazole at doses of 400mg or greater with terfenadine is contraindicated (see section 4.3 Contraindications). The coadministration of fluconazole at doses lower than 400mg 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.

Concomitant use of the following other medicinal products cannot be recommended: *Amiodarone: concomitant administration of fluconazole with amiodarone may increase QT prolongation. Therefore, caution should be taken when both drugs are combined, notably with high dose fluconazole (800mg).*
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. This combination should be avoided.

Concomitant use of the following other medicinal products lead to precautions and dose adjustments:
The effect of other medicinal products on fluconazole
Hydrochlorothiazide: In a pharmacokinetic interaction study, co-administration of multiple- dose hydrochlorothiazide to healthy volunteers receiving fluconazole increased 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.
Rifampicin: Concomitant administration of fluconazole and rifampicin resulting in a 25% decrease in the AUC and 20% shorter half-life of fluconazole. In patients receiving concomitant rifampicin, an increase of the fluconazole dose should be considered.

The effect of fluconazole on other medicinal products
Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4. In addition to the observed/documented interactions mentioned below there is a risk of increased plasma concentration of other compounds metabolised by CYP2C9 and CYP3A4 co- administered with fluconazole. Therefore caution should be exercised when using these combinations and the patients should be carefully monitored. The enzyme inhibiting effect of fluconazole persists 4-5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole (See section 4.3)
Alfentanil: A study observed a reduction in clearance and distribution volume as well as prolongation of T½ of alfentanil following concomitant treatment with fluconazole. A possible mechanism of action is fluconazole's inhibition of CYP3A4. Dosage adjustment of alfentanil may be necessary.
Amitriptyline, nortriptyline: Fluconazole increases the effect of amitriptyline and nortriptyline. 5- nortriptyline and/or S-amitriptyline may be measured

at initiation of the combination therapy and after one week. Dosage of amitriptyline/nortriptyline should be adjusted, if necessary.
Amphotericin B: Concurrent administration of fluconazole and amphotericin B in infected normal and immunosuppressed mice showed the following results: a small additive antifungal effect in systemic infection with C. albicans, no interaction in intracranial infection with Cryptococcus neoformans, and antagonism of the two drugs in systemic infection with *A. fumigatus*. The clinical significance of results obtained in these studies is unknown.
Anticoagulants: In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, haematuria and melena) have been reported, in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. During concomitant treatment with fluconazole and warfarin the prothrombin time was prolonged up to 2-fold, probably due to an inhibition of the warfarin metabolism through CYP2C9. In patients receiving coumarin-type or indanedione anticoagulants concurrently with fluconazole the prothrombin time should be carefully monitored. Dose adjustment of the anticoagulant may be necessary.

Azithromycin: An open-label, randomised, three-way crossover study in 18 healthy subjects assessed the effect of a single 1200mg oral dose of azithromycin on the pharmacokinetics of a single 800mg oral dose of fluconazole as well as the effects of fluconazole on the pharmacokinetics of azithromycin. There was no significant pharmacokinetic interaction between fluconazole and azithromycin.
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 administration intravenously. If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dosage, and the patients should be appropriately monitored.

Fluconazole increases the AUC of triazolam (single dose) by approximately 50%, Cmax with 20-32% and increases t1/2 by 25-50% due to the inhibition of metabolism of triazolam.
Dosage adjustments of triazolam may be necessary.
Carbamazepine: Fluconazole inhibits the metabolism of carbamazepine and an increase in serum carbamazepine of 30% has been observed. There is a risk of developing carbamazepine toxicity. Dosage adjustment of carbamazepine may be necessary depending on concentrating measurements/effect.

Calcium Channel Blockers: Certain dihydropyridine calcium channel antagonists (nifedipine, isradipine, amlodipine and felodipine) are

metabolised by CYP3A4. Fluconazole has the potential to increase the systemic exposure of the calcium channel antagonists. Frequent monitoring for adverse events is recommended.
Celecoxib: During concomitant treatment with fluconazole (200mg daily) and celecoxib (200mg) the celecoxib Cmax and AUC increased by 68% and 134%, respectively. Half of the celecoxib dose may be necessary when combined with fluconazole.

Ciclosporin: Fluconazole significantly increases the concentration and AUC of ciclosporin. This combination may be used by reducing the dosage of ciclosporin depending on ciclosporin concentration.

Cyclophosphamide: combination therapy with cyclophosphamide and fluconazole results in an increase in serum bilirubin and serum creatinine. The combination may be used while taking increased consideration to the risk of increased serum bilirubin and serum creatinine.

Everolimus*:* Although not studied *in vivo* or *in vitro*, fluconazole may increase serum concentrations of everolimus through inhibition of CYP3A4.

Fentanyl: One fatal case of possible fentanyl fluconazole interaction was reported. The author judged that the patient died from fentanyl intoxication. Furthermore, in a randomised crossover study with twelve healthy volunteers it was shown that fluconazole delayed the elimination of fentanyl significantly.
Elevated fentanyl concentration may lead to respiratory depression.

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.
HMG-CoA reductase inhibitors: The risk of myopathy and rhabdomyolysis increases when fluconazole is coadministered with HMG-CoA reductase inhibitors metabolised through CYP3A4, such as atorvastatin and simvastatin or through CYP2C9, such as fluvastatin. If concomitant therapy is necessary, the patient should be observed for symptoms of myopathy and rhabdomyolysis and creatinine kinase should be monitored. HMG-CoA reductase inhibitors should be discontinued if a marked increase in creatinine kinase is observed or myopathy/rhabdomyolysis is diagnosed or suspected.

Losartan: Fluconazole inhibits the metabolism of losartan to its active metabolite (E-31 74) which is responsible for most of the angiotensin II-receptor antagonism which occurs during treatment with losartan. Patients should have their blood pressure monitored continuously.

Methadone: Fluconazole may enhance the serum concentration of methadone. Dosage adjustment of methadone may be necessary.
Non-steroidal anti-inflammatory drugs: The Cmax and AUC of flurbiprofen was increased by 23% and 81%, respectively, when coadministered with fluconazole compared to administration of flurbiprofen alone. Similarly, the Cmax and AUC of the pharmacologically active isomer (S-(+)-ibuprofen) was increased by 15% and 82%, respectively, when fluconazole was coadministered with racemic ibuprofen (400mg) compared to administration of racemic ibuprofen alone.

Although not specifically studied, fluconazole has the potential to increase the systemic exposure or other NSAIDs that are metabolised by CYP2C9 (e.g. naproxen, lornoxicam, meloxicam, diclofenac). Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Adjustment of dosage of NSAIDs may be needed.

Oral Contraceptives: Two pharmacokinetic studies with a combined oral contraceptive have been performed using multiple doses of fluconazole. There were no relavent effects on hormone level in the 50mg fluconazole study, while at 200mg daily, the AUCs of ethinyl estradiol and levonorgestrel were increased 40% and 24%, respectively. Thus, multiple dose use of fluconazole at these doses is unlikely to have an effect on the efficacy of the combined oral contraceptive.

Phenytoin: Fluconazole inhibits the hepatic metabolism of phenytoin. With coadministration, serum phenytoin concentration levels should be monitored in order to avoid phenytoin toxicity.

Prednisone: There was a case report that a liver-transplant patient treated with prednisone developed acute adrenal cortex insufficiency when a three month therapy with fluconazole was discontinued. The discontinuation of fluconazole presumably caused an enhanced CYP3A4 activity which led to increased metabolism of prednisone. Patients on long-term treatment with fluconazole and prednisone should be carefully monitored for adrenal cortex insufficiency when fluconazole is discontinued.

Rifabutin: Fluconazole increases serum concentrations of rifabutin, leading to increase in the AUC of rifabutin up to 80%. There have been reports of uveitis in patients to whom fluconazole and rifabutin were coadministered. In combination therapy, symptoms of rifabutin toxicity should be taken into consideration.

Saquinavir: Fluconazole increases the AUC of saquinavir with approximately 50%, Cmax with approximately 55% and decreases clearance of saquinavir with approximately 50% due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein. Dosage adjustment of saquinavir may be necessary.

Sirolimus: Fluconazole increases plasma concentrations of sirolimus presumably by inhibiting the metabolism of sirolimus via CYP3A4 and P-glycoprotein. This combination may be used with a dosage adjustment of sirolimus depending on the effect/concentration measurements.

Sulfonylureas: Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulfonylureas (e.g. chlorpropamide, glibenclamide, glipizide, tolbutamide) in healthy volunteers.
Frequent monitoring of blood glucose and appropriate reduction of sulfonylurea dosage is recommended during coadministration.

Tacrolimus: Fluconazole may increase the serum concentrations of orally administered tacrolimus up to 5 times due to inhibition of tacrolimus metabolism through CYP3A4 in the intestines. No significant pharmacokinetic changes have been observed when tacrolimus is given intravenously. Increased tacrolimus levels have been associated with nephrotoxicity.

Dosage of orally administered tacrolimus should be decreased depending on tacrolimus concentration.

Theophylline: In a placebo-controlled interaction study, the administration of fluconazole 200mg for 14 days resulted in an 18% decrease in the mean plasma clearance rate of theophylline. Patients who are receiving high dose theophylline or who are otherwise at increased risk for theophylline toxicity should be observed for signs of theophylline toxicity while receiving fluconazole. Therapy should be modified if signs of toxicity develop.

Vinca Alkaloids: Although not studied, fluconazole may increase the plasma levels of the vinca alkaloids (e.g. vincristine and vinblastine) and lead to neurotoxicity, which is possibly due to an inhibitory effect on CYP3A4.

Voriconazole*:* (CYP2C9 and CYP3A4 inhibitor): Coadministration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 2.5 days) and oral fluconazole (400 mg on day 1, then 200 mg Q24h for 4 days) to 8 healthy male subjects resulted in an increase in C
max and AUC of voriconazole by an average of 57% (90% CI: 20%, 107%) and 79% (90% CI: 40%, 128%), respectively. The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole associated adverse events is recommended if voriconazole is used sequentially after fluconazole.

Vitamin A: Based on a case-report in one patient receiving combination therapy with all- trans-retinoic acid (an acid form of vitamin A) and fluconazole, CNS related undesirable effects have developed in the form of pseudo tumour cerebri, which disappeared after discontinuation of fluconazole treatment. This combination may be used but the incidence of

CNS related undesirable effects should be borne in mind.

Zidovudine: Fluconazole increases Cmax and AUC of zidovudine by 85% and 75%, respectively, due to an approx. 45% decrease in oral zidovudine clearance. The half-life of zidovudine was likewise prolonged by approximately 128% following combination therapy with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions. Dosage reduction of zidovudine may be considered
Interaction studies have shown that when oral fluconazole is coadministered with food, cimetidine, antacids or following total body irradiation for bone marrow transplantation, no clinically significant impairment of fluconazole absorption occurs.

4.6 Fertility, 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 (400-800mg daily) of fluconazole for coccidioidomycosis. The relationship between fluconazole use and these events is unclear.
Studies in animals have shown reproductive toxicity (see section 5.3)

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 is found in human breast milk at concentrations similar to plasma, hence its use in nursing mothers is not recommended.

4.7 Effects on ability to drive and use machines

When driving vehicles or operating machines it should be taken into account that occasionally dizziness or seizures may occur**.**

4.8 Undesirable effects

In some patients, particularly those with serious underlying diseases such as AIDS and cancer, changes in renal and haematological function test results and hepatic abnormalities (see section 4.4 Special Warnings and Special Precautions for Use) have been observed during treatment with fluconazole and comparative agents, but the clinical significance and relationship to treatment is uncertain.

The following undesirable effects have been observed and reported during treatment with fluconazole with the following frequencies: Very common (≥1/10); common (≥1/100 to
≤1/10); uncommon (≥1/1000, <1/100) rare (≥1/10000, <1/1000) and very rare (>1/10000) not known (cannot be estimated from the available data).

System Organ
Class Frequency
Undesirable
effects

i) Blood and the lymphatic system disorders
Rare: Agranulocytosis, leukopenia, neutropenia, thrombocytopenia
Uncommon: Anaemia

ii) Immune system disorders
Rare: Anaphylaxis

iii) Metabolism and nutrition disorders
Uncommon: Hypokalaemia, decreased appetite
Rare: Hypertriglyceridaemia, Hypercholeosterolaemia

iv) Psychiatric disorders
Uncommon: Insomnia, somnolence

v) Nervous system disorders
Common: Headache
Uncommon: Seizures, dizziness, paraesthesia, taste perversion
Rare: Tremor

vi) Ear and labyrinth disorders
Uncommon: Vertigo

vii) Cardiac disorders
Rare: Torsade de pointes, QT prolongation

viii) Gastrointestinal disorders
Common: Abdominal pain, diarrhoea, nausea, vomiting
Uncommon: Dyspepsia, flatulence, dry mouth

ix) Hepato-biliary disorders
Common: Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased
Uncommon: Cholestasis, jaundice, bilirubin increased
Rare: Hepatic failure,hepatocellular necrosis, hepatitis, hepatocellular damage

x) Skin and subcutaneous tissue disorders
Common: Rash
Uncommon: Pruritus, urticaria, increased sweating, drug eruption*
Rare: Toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalised exanthematous-pustulosis, dermatitis exfoliative, angioedema, face oedema, alopecia

xi) Musculoskeletal, connective tissue and bone disorders
Uncommon: Myalgia

xii) General disorders and administration site conditions
Uncommon: Fatigue, malaisse, asthenia, fever

**Including Fixed Drug Eruption*

Paediatric Population
The pattern and incidence of side effects and laboratory abnormalities recorded during paediatric clinical trials are comparable to those seen in adults.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 the yellow card scheme at www.mhra.gov.uk/yellowcard.

4.9 Overdose
There have been reports of overdose with fluconazole 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 hemodialysis session decreases plasma levels by approximately 50%.

5. Pharmacological properties
5.1 Pharmacodynamic
properties ATC code: J02A
C01
Mechanism of action and pharmacodynamic effects
Fluconazole is a member of the triazole class of antifungal agents. Itis a potent and selective inhibitor of fungal enzymes necessary for the synthesis of ergosterol.
Fluconazole shows little pharmacological activity in a wide range of animal studies. Some prolongation of pentabarbitone sleeping timesin mice (p.o) increased mean arterial and left ventricular blood pressure and increased heart rate in anaesthetised cats (i.v.)occurred.
Inhibition of rat ovarian aromatase was observed at high concentrations.
Fluconazole was active in a variety of animal fungal infection models.
Activity has been demonstrated against opportunistic mycoses, such as infections with *Candida* spp. including systemic candidiasis in immuno-comprised animals; with *Cryptococcus neoformans*, including intracranial infections; with *Microsporum* spp. and with *Trichophyton* spp.
Fluconazole has also been shown to be active in animal models of endemic mycoses, including infections with *Blastomyces dermatitides;* with *Coccidoides immitis*,including intracranial infection and with *Histoplasma capsulatum* in normal and immuno- compromised animals.
There have been reports of cases of superinfection with *Candida* species other than *C. albicans*, which are often inherently not
susceptible to fluconazole (e.g. *Candida krusei*). Such cases may require alternative antifungal therapy.

Fluconazole is highly specific for fungal cytochrome P-450 dependent enzymes. Fluconazole 200mg daily given for up to 28 days has been shown not to affect testosterone plasma concentrations in males or steroid concentrations in females of child-bearing age, when given 50 mg daily for up to 28 days.
Fluconazole 200-400mg 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 200mg do not affect its metabolism.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral route. After oral administration fluconazole is well absorbed and plasma levels (and systemic bioavailability) are over 90% of the levels achieved after intravenous administration. Oral administration is not affected by concomitant food intake. Peak plasma concentrations in the fasting state occur between 0.5 – 1.5 hours post-dose with a plasma elimination half-life of approximately 30 hours. Plasma concentrations are proportional to dose. Ninety percent steady-state levels are reached by day 4 – 5 with multiple once daily dosing.
The administration of a loading dose on the first day, double that of the normal daily dose, raises plasma levels to approximate to 90% steady-state levels by the second day.
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% of the corresponding plasma levels.
High skin concentrations 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 50mg once daily, the concentration of fluconazole after 12 days was 73mg/g and 7 days after cessation of treatment the concentration was still 5.8mg/g. The major route of excretion is renal, with approximately 80% of the administered dose appearing in the urine as unchanged drug.
Fluconazole clearance is proportional to creatinine clearance. There is no evidence of circulating metabolites.
Its long plasma elimination half-life makes it possible to administer a single dose in the treatment of genital candidiasis.
A study compared the saliva and plasma concentrations of a single fluconazole 100mg dose administration in a capsule or in an oral suspension by rinsing and retaining in the mouth for 2 minutes and swallowing.
The maximum concentration of fluconazole in saliva after the suspension was observed five minutes after ingestion and was 182 times higher than maximum saliva concentrations after the capsule, which occurred four

hours after ingestion.
After about 4 hours, the saliva concentrations of fluconazole were similar. The mean AUC (0-96) in saliva was significantly greater after the suspension compared to the capsule. There was no significant difference in the elimination rate from saliva or the plasma pharmacokinetic parameters for the two formulations.

5.3 Preclinical safety data

Reproductive toxicity: 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 from 80 mg/kg to 320 mg/kg embryo lethality in rats was increased and foetal abnormalities included wavy ribs, cleft palate and abnormal cranio-facial ossification. This may be a result of known effects of lowered oestrogen on pregnancy, organogenesis and parturition as it is consistent with the inhibition of oestrogen synthesis in rats.
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. Male rats treated with 5 and 10mg/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 *S. 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.
Impairment of fertility: 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, although the onset of parturition was slightly delayed at 20 mg/kg p.o. In an intravenous perinatal study in rats at 5, 20 and 40 mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg and 40 mg/kg, but not at 5 mg/kg. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal survival at these doses. The affects on parturition in rats 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

Tablet core:
Lactose monohydrate
Sodium starch glycolate
Sodium lauryl sulphate
Talcum

6.2 Incompatibilities

Not applicable.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container ALU/ALU blister packs in unit boxes. Pack sizes:
10's

6.6 Special precautions for disposal and other handling
No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorization holder

Universal Corporation
Limited, Club road, Plot
number 13777,
P.O BOX 1748-00902,
Kikuyu-Kenya.

8. Authorization number (s)
14262

9.Date of first authorization/ Renewal of the authorization
02/2026

10. Date of revision
02/2026