SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fluconazole 150mg Capsule.
Sainsbury’s Pharmacy Fluconazole 150mg Capsule

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 150 mg of fluconazole.

Excipients: Lactose 141 mg per capsule

For a full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Hard capsules.

Gelatine capsules filled with white to yellowish white homogeneous powder, with a light blue opaque cap and light blue opaque body.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fluconazole is indicated for the treatment of vaginal candidiasis, acute or recurrent. It may also be used for the treatment of partners with associated candidal balanitis.
4.2  **Posology and method of administration**

*Adults (aged 16 to 60 years of age)*

Candidal vaginitis or balanitis: 150 mg single oral dose.

*Children (under 16 years of age)*

Not recommended.

*Elderly*

Not recommended in patients over 60 years of age.

*Renal Impairment*

No adjustments in single dose therapy are necessary.

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4.3  **Contraindications**

Fluconazole should not be used in patients with known hypersensitivity to fluconazole, related azole compounds or any other ingredient in the formulation.

Co-administration of terfenadine, cisapride or ergot-derivatives is contra-indicated in patients receiving fluconazole (See section 4.5 Interactions with other medicinal products and other forms of Interaction).

4.4  **Special warnings and precautions for use**

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

Do not use the capsule 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 the capsule or other antifungals and other thrush treatments (see section “After taking Fluconazole 150 mg Capsule”).
If you have been told by your doctor that you have an intolerance to some sugars.
If you are taking any medicine other than the Pill.
If you are taking the antihistamine terfenadine or the prescription medicine 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 or have had unexplained jaundice.
If you suffer from any other chronic disease or illness.
If you or your partner have had exposure to a sexually transmitted disease.
If you are unsure about the cause of your symptoms.

**Women only:**

If you are pregnant, suspect you might be pregnant or are breast-feeding.
If you have any abnormal or irregular vaginal bleeding or blood stained discharge.
If you have vulval or vaginal sores, ulcers or blisters.
If you are experiencing lower abdominal pain or burning on passing urine.

**Men only:**

If your sexual partner does not have 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.

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

**Recurrent use (men and women):**

Patients should be advised to consult their doctor if the symptoms have not been relieved within one week of taking the capsule. The medicine can be used again if the candidal infection returns after seven days. However, if the candidal infection recurs more than twice in six months, patients should be advised to consult their doctor.

Fluconazole has been associated with rare cases of serious hepatic toxicity, including fatalities primarily in patients with serious underlying medical conditions.

Fluconazole must be taken with particular care in patients with congenital or acquired QT prolongation and torsades de pointes or a history thereof, known cardiomyopathy, sinus bradycardia, cardiac arrhythmia, or are treated with a co-medication potentially leading to QT prolongation (see 4.5).

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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

Fluconazole, like other azoles, may interfere with the metabolism of some drugs if given concomitantly, mainly through inhibition of the cytochrome P450 isoenzymes CYP3A4 and CYP2C9. The vast majority of formal interaction studies and case reports are related
to multiple dose fluconazole use, therefore, the magnitude of the effect of this inhibition on an individual patient after a single dose of fluconazole is hard to predict, particularly in light of the individual variability in the activity of the isoenzymes. Nonetheless, single dose pharmacokinetic studies have demonstrated that the inhibitory action of fluconazole is immediate and leads, dose-dependently, to increased plasma concentrations of the interacting agents. Given fluconazole’s long plasma elimination half-life of approximately 30 hours and substantially longer tissue bioavailability (see section 5.2 Pharmacokinetic Properties), these interactions may be clinically relevant following coadministration with drugs that have both a narrow therapeutic window and also act on vital organ systems like the heart and brain or are involved with glucose metabolism.

Anticoagulants: In an interaction study, fluconazole increased the prothrombin time (12%) after warfarin administration in healthy males. In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, haematuria and melaena) have been reported in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. Prothrombin time in patients receiving coumarin-type anticoagulants should be carefully monitored.

Anti-arrhythmic drugs: Cases of QTc prolongation and/or torsades de pointes may occur after concomitant use of fluconazole with Class I, Class Ia, and all Class III anti-arrhythmic agents. Even though no formal drug interaction studies have been done, concomitant use of these anti-arrhythmic agents and drugs known to prolong the QT interval is not recommended.

Pharmacodynamic interactions

Medicinal products that prolong QT interval: Case reports indicate that fluconazole might have the potential to induce QT prolongation leading to serious cardiac arrhythmia. Patients treated concomitantly with fluconazole and other drugs that prolong QT interval should be carefully monitored, since an additive effect cannot be excluded.

Benzodiazepines: Substantial increases in midazolam concentrations and psychomotor effects are observed when oral midazolam and fluconazole (oral or intravenous) are coadministered. The effect on midazolam appears to be greater when fluconazole is administered orally than when fluconazole is administered intravenously. If concomitant administration of benzodiazepines and fluconazole is required then the prescriber should consider reducing the benzodiazepine dose and appropriate monitoring of the patient should be undertaken.

Rifampicin: Concomitant administration of fluconazole and rifampicin resulted in a 25% decrease in the AUC and 20% shorter half-life of fluconazole. In patients receiving concomitant rifampicin, an increase in the fluconazole dose should be considered.

Hydrochlorothiazide: In a kinetic 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, although the prescriber should bear it in mind.

Sulphonylureas: Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulphonylureas (chlorpropamide, glibenclamide,
glipizide and tolbutamide) in healthy volunteers. Fluconazole and oral sulphonylureas may be co-administered to diabetic patients, but the possibility of a hypoglycaemic episode should be borne in mind.

Phenytoin: Concomitant administration of fluconazole and phenytoin may increase the levels of phenytoin to a clinically significant degree. If it is necessary to administer both drugs concomitantly, phenytoin levels should be monitored and the phenytoin dose adjusted to maintain therapeutic levels.

Carbamazepine, Phenobarbital, Phenytoin, Rifapentine: Concurrent administration of fluconazole and carbamazepine, phenobarbital, phenytoin or rifapentine results in enhanced metabolism of fluconazole, potentially reducing fluconazole effective inhibitory serum concentrations. An increase in the fluconazole dose should be considered in patients receiving concomitant carbamazepine, phenobarbital, phenytoin or rifapentine.

Oral contraceptives: Two kinetic studies with combined oral contraceptives have been performed using multiple doses of fluconazole. There were no relevant effects on either hormone level in the 50mg fluconazole study, while at 200mg daily the AUCs of ethinylestradiol 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.

Endogenous steroid: Fluconazole 50mg daily does not affect endogenous steroid levels in females: 200-400mg daily has no clinically significant effect on endogenous steroid levels or on ACTH stimulated response in healthy male volunteers.

Ergot derivatives: Because of the potential for serious toxicity including vasospasm that can occur with increased plasma concentrations of ergot derivatives (dihydroergotamine, ergoloid mesylates, ergonovine, ergotamine, methylergonovine, methysergide) the concurrent use of fluconazole and ergot derivatives is contraindicated (see section 4.3 Contraindications). Fluconazole and ergot derivatives are both metabolized by cytochrome P450 3A4 enzymes, and the competition for metabolism could result in a rapid onset of increased plasma concentration of the ergot derivative.

Losartan: CYP2C9 and CYP3A4 are involved in the metabolism of losartan to its active carboxylic acid metabolite E-3174 that is responsible for most of the angiotensin II receptor antagonism that occurs with losartan therapy. Fluconazole was shown to significantly inhibit the conversion of losartan to this metabolite. Monitoring of patients for continued control of their hypertension is recommended.

Fentanyl, Methadone: Coadministration of fluconazole may cause decreased clearance of fentanyl or methadone and subsequent increased or prolonged opioid effects (CNS depression, respiratory depression) Dosage adjustment of the opioid may be necessary.

Cyclosporin: A kinetic study in renal transplant patients found fluconazole 200mg daily to slowly increase cyclosporin concentrations. However, in another multiple dose study with 100mg daily, fluconazole did not affect cyclosporin levels in patients with bone marrow transplants. Cyclosporin plasma concentration monitoring in patients receiving fluconazole is recommended.
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 of theophylline. Patients who are receiving high doses of theophylline or who are otherwise at increased risk for theophylline toxicity should be observed for signs of theophylline toxicity while receiving fluconazole and the therapy modified appropriately if signs of toxicity develop.

Terfenadine: Fluconazole 200mg daily did not show a prolongation in the QTc interval. Use of fluconazole (taken in multiple doses of 400mg and 800mg per day) and terfenadine concomitantly, significantly increased plasma levels of terfenadine. Spontaneous reports of palpitations, tachycardia, dizziness and chest pains have occurred in patients taking fluconazole and terfenadine concomitantly where the relationship of the reported adverse events to drug therapy or underlying medical condition is uncertain. It is recommended that terfenadine and fluconazole should not be administered concomitantly due to the potential seriousness of such an interaction (See section 4.3 Contraindications).

Cisapride: There have been reports of cardiac events including torsades de pointes in patients to whom fluconazole and cisapride were co-administered. In most of these cases, the patients appear to have been predisposed to arrhythmias or had serious underlying illnesses, and the relationship of the reported events to a possible fluconazole-cisapride drug interaction is unclear. Because of the potential seriousness of such an interaction, co-administration of cisapride is contra-indicated in patients receiving fluconazole. (See section 4.3 ‘Contraindications’).

Zidovudine: Two kinetic studies resulted in increased levels of zidovudine most likely caused by the decreased conversion of zidovudine to its major metabolite. One study determined zidovudine levels in AIDS or ARC patients before and following fluconazole 200mg daily for 15 days. There was a significant increase in zidovudine AUC (20%). A second randomised, two-period, two-treatment cross-over study examined zidovudine levels in HIV infected patients. On two occasions, 21 days apart, patients received zidovudine 200mg every eight hours either with or without fluconazole 400mg daily for seven days. The AUC of zidovudine significantly increased (74%) during co-administration with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions.

Rifabutin: There have been reports that an interaction exists when fluconazole is administered concomitantly with rifabutin, leading to increased serum levels of rifabutin. There have been reports of uveitis in patients to whom fluconazole and rifabutin were co-administered. Patients receiving rifabutin and fluconazole concomitantly should be carefully monitored.

Tacrolimus, Sirolimus: There have been reports that an interaction exists when fluconazole is administered concomitantly with tacrolimus, leading to increased serum levels of tacrolimus. There have been reports of nephrotoxicity in patients to whom fluconazole and tacrolimus were co-administered. Patients receiving tacrolimus or sirolimus and fluconazole concomitantly should be carefully monitored.

The use of fluconazole in patients concurrently taking astemizole or other drugs metabolised by the cytochrome P450 system may be associated with elevations in serum levels of these drugs. In the absence of definitive information, caution should be used when co-administering fluconazole. Patients should be carefully monitored.
Interaction studies have shown that when oral fluconazole is co-administered with food, cimetidine, antacids or following total body irradiation for bone marrow transplantation, no clinically significant impairment of fluconazole absorption occurs.

Physicians should be aware that drug-drug interaction studies with other medications have not been conducted, but that such interactions may occur.

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 (400-800 mg 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.

4.7 Effects on ability to drive and use machines

Experience with fluconazole indicates that therapy is unlikely to impair a patient’s ability to drive or use machinery.

4.8 Undesirable effects

The listed undesirable effects are based on spontaneous reports, thus an organisation according to CIOMS III categories of frequency is not possible.

Blood and lymphatic system disorders
Leukopenia, neutropenia, agranulocytosis, thrombocytopenia.

Cardiac disorders
Torsades de pointes/QT prolongation.

Gastrointestinal disorders

Nausea, diarrhea, vomiting, gastrointestinal and abdominal pains, abdominal distension, flatulence.

**Hepatobiliary disorders**

Most events were observed when a multiple treatment was used: mild transient elevations in transaminases, hepatitis (non infective), jaundice, cholestasis and acute hepatic failure, including fatalities.

**Immune System Disorders**

Allergic reaction, anaphylactic reaction, anaphylactic shock.

Hypersensitivity reactions including symptoms such as rash, urticaria, oedema, pruritus, cardio-respiratory distress.

**Investigations**

Electrocardiogram QT prolonged, electrocardiogram QT corrected interval prolonged, hypercholesterolemia, hypertriglyceridemia, hypokalemia.

**Nervous system disorders**

Seizures, dizziness, headache, dysgeusia.

**Skin and subcutaneous tissue disorders**

Rash, pruritus, alopecia, exfoliative skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis.

**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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

**4.9 Overdose**

There have been reports of overdosage with fluconazole. A 42 year-old patient infected with human immunodeficiency virus developed hallucinations and exhibited paranoid behaviour after reportedly ingesting 8200 mg of fluconazole, unverified by his physician. The patient was admitted to the hospital and his condition resolved within 48 hours.

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

As 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%.
PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
ATC Code: J02A C01
Pharmacotherapeutic Group: Antimycotics for systemic use – Triazole derivatives

Fluconazole, a member of the triazole class of antifungal agents, is 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 pentobarbitone sleeping times in 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.

Both orally and intravenously administered 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 immunocompromised 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 immunocompromised 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 50mg daily given up to 28 days has been shown not to affect testosterone plasma concentrations in males or steroid concentrations in females of childbearing age. 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 50mg 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 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 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.

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. 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 73 mg/g and 7 days after cessation of treatment the concentration was still 5.8 mg/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 creatine clearance. There is no evidence of circulating metabolites.

The long plasma elimination half-life provides the basis for single dose therapy for 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 5 minutes after ingestion and was 182 times higher than maximum saliva concentration after the capsule, which occurred 4 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 the 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 50mg/kg and higher doses. At doses ranging from 80mg/kg (approximately 20-60x the recommended human dose) to 320mg/kg embryolethality in rats was increased and foetal abnormalities included wavy ribs, cleft palate and abnormal cranio-facial ossification. These effects are consistent with the inhibition of oestrogen synthesis in rats and may be a result of known effects of lowered oestrogen on pregnancy, organogenesis and parturition.

Carcinogenesis

Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5 or 10mg/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 1000μg/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 20mg/kg or with parenteral doses of 5, 25 or 75mg/kg, although the onset of parturition was slightly delayed at 20mg/kg p.o. In an intravenous perinatal study in rats at 5, 20 and 40mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20mg/kg and 40mg/kg, but not at 5mg/kg. The disturbances in parturition were reflected by a slight increase in the number of stillborn pups and decrease of neonatal survival at these dose levels. The effects 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

Capsule contents
Lactose monohydrate
Maize starch
Silica, colloidal anhydrous
Sodium laurilsulfate
Magnesium stearate

Capsule shell
Titanium dioxide (E171)
Brilliant blue FCF (E133)
Gelatin

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
Transparent or white opaque PVC/PVdC – aluminium blister packs containing 1 capsule.

6.6 Special precautions for disposal
Not applicable.
7. **MARKETING AUTHORISATION HOLDER**

Galpharm Healthcare Limited  
Wrafton  
Braunton  
Devon  
EX33 2DL  
United Kingdom

8. **MARKETING AUTHORISATION NUMBER(S)**

PL 16028/0108

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

03/06/2008

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

27/11/2017