SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fluconazole 150 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 150 mg fluconazole.

Excipient with known effect: Each tablet contains 146.25 mg of lactose (as lactose monohydrate)

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Hard gelatine capsule

White cap, white body with the imprint FC150, containing a white odourless powder,

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fluconazole 150mg Capsules are recommended for the treatment of candidal vaginitis, acute or recurrent. It should also be used for the treatment of partners with associated candidal balanitis.

4.2 Posology and method of administration

Posology

Adults (16 to 60 years):
Vaginal candidiasis or candidal balanitis – 150mg single oral dose.

Paediatric population

Not recommended in children aged under 16 years

Elderly:
Not recommended in patients aged over 60 years.

Renal impairment
Fluconazole is excreted predominantly in the urine as unchanged drug. No adjustments in single dose therapy are required.

Method of administration
For oral use.

4.3 Contraindications

Fluconazole should not be used in patients with known hypersensitivity to fluconazole, to related other azole derivatives or to any of the excipients listed in section 6.1.

Co-administration of terfenadine is contraindicated 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 contraindicated in patients receiving fluconazole (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Hepatobiliary system
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.
The patient should be informed of suggestive symptoms of serious hepatic effect (important asthenia, anorexia, persistent nausea, vomiting and jaundice). Treatment of fluconazole should be immediately discontinued and the patient should consult a physician.

Dermatological reactions
Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, during treatment with fluconazole. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported 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.

Terfenadine
The coadministration of fluconazole at doses lower than 400mg per day with terfenadine should be carefully monitored (see section 4.3).

Hypersensitivity
In rare cases, anaphylaxis has been reported (see section 4.3).

Cardiovascular system
Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. Fluconazole causes QT prolongation via the inhibition of Rectifier Potassium Channel current (Ikr). The QT prolongation caused by other medicinal products (such as amiodarone) may be amplified via the inhibition of cytochrome P450 (CYP) 3A4. 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.

Patients with hypokalaemia and advanced cardiac failure are at an increased risk for the occurrence of life threatening ventricular arrhythmias and torsades de pointes.

Fluconazole should be administered with caution to patients with these potentially proarrythmic conditions.
Coadministration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 are contraindicated (see sections 4.3 and 4.5).

Renal System
Fluconazole should be administered with caution to patients with renal dysfunction (see also 4.2)

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.

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, Diflucan 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.

Halofantrine
Halofantrine has been shown to prolong QTc interval at the recommended therapeutic dose and is a substrate of CYP3A4. The concomitant use of fluconazole and halofantrine is therefore not recommended (see section 4.5).

Cytochrome P450
Fluconazole is a moderate CYP2C9 and CYP3A4 inhibitor. Fluconazole is also a strong inhibitor of CYP2C19. Fluconazole treated patients who are concomitantly treated with medicinal products with a narrow therapeutic window metabolised through CYP2C9 and CYP3A4, should be monitored (see section 4.5).

Terfenadine
The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored (see sections 4.3 and 4.5).

Candidiasis
Studies have shown an increasing prevalence of infections with Candida species other than C. albicans. These are often inherently resistant (e.g. C. krusei and C. auris) or show reduced susceptibility to fluconazole (C. glabrata). Such infections may require alternative antifungal therapy secondary to treatment failure. Therefore, prescribers are advised to take into account the prevalence of resistance in various Candida species to fluconazole.

Excipients
Fluconazole Capsules contain lactose and should not be given to patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.
Fluconazole capsules contain less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

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

Do not use Fluconazole 150mg 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 Fluconazole 150mg capsule 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 prescription medicine cisapride, pimozide, quinidine and erythromycin.
- 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 heart disease including heart rhythm problems.
- If you have abnormal levels of potassium, calcium or magnesium in your blood.
- If you develop severe skin reactions (itching, reddening of the skin or difficulty in breathing).
- If you develop signs of 'adrenal insufficiency' where the adrenal glands do not produce adequate amounts of certain steroid hormones such as cortisol (chronic, or long lasting fatigue, muscle weakness, loss of appetite, weight loss, abdominal pain).
- 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 a 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 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

The following drug interactions relate to the use of multiple-dose fluconazole, and the relevance to single-dose fluconazole 150mg has not yet been established:

Concomitant use of the following other medicinal products is contraindicated:

Cisapride: There have been reports about cardiac cases including torsades de pointes in patients receiving fluconazole concomitantly with cisapride. Concomitant treatment with fluconazole and cisapride is contra-indicated (see section 4.3). 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 (see section 4.3).

Terfenadine: Due to the occurrence of serious cardiac dysrhythmias secondarily to prolongation of the QTc-interval in patients on treatment with azole antifungals products concomitantly with terfenadine, interaction studies have been performed. One study with 200 mg fluconazole daily did not show any prolongation of the QTc-interval. Another study with 400 mg and 800 mg fluconazole daily showed that fluconazole in doses of 400 mg or more daily significantly increases the plasma level of terfenadine, if the two medicinal products are taken concomitantly. Concomitant treatment with terfenadine and fluconazole doses of 400 mg or more is contraindicated (see section 4.3). At fluconazole doses below 400 mg, the patient should be closely monitored.

Astemizole: Concomitant administration of fluconazole with astemizole may decrease the clearance of astemizole. Astemizole overdoses have led to prolonged QT interval and severe ventricular arrhythmia, rare occurrences of torsades de pointes. Concomitant treatment with fluconazole and astemizole is contraindicated (see section 4.3).

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 (see section 4.3).

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 (see section 4.3).

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 (see section 4.3)

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 (see section 4.4).

Concomitant use that should be used with caution:

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).

Concomitant use of the following other medicinal products lead to precautions and dose adjustments:

Medicinal products affecting the metabolism of fluconazole:

Hydrochlorothiazide: In a pharmacokinetic interaction study, co-administration of multiple-dose hydrochlorothiazide to healthy volunteers receiving fluconazole increased plasma concentration 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 intake of fluconazole and rifampicin resulted in a 25 % reduction of AUC and 20 % shorter half-life of fluconazole.
In patients receiving concomitant rifampicin, an increase in the fluconazole dose should 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.

Effect of fluconazole on the metabolism of other medicinal products:
Fluconazole is a moderate inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and 3A4. Fluconzole is also a strong inhibitor of the isozyme CYP2C19. Besides the observed/documented interactions listed below there is a risk of increased plasma concentrations of other medicinal products metabolised by CYP2C9 or CYP3A4 (e.g. ergot-alkaloids, quinidine) when co-administered with fluconazole. Therefore, care should always be taken when using these combinations and the patients should be carefully monitored. The enzyme-inhibiting effect of fluconazole may persist for 4–5 days after end of fluconazole treatment due to the long half-life of fluconazole (see section 4.3).

Abrocitinib: Fluconazole (inhibitor of CYP2C19, 2C9, 3A4) increased exposure of abrocitinib active moiety by 155%. If co-administered with fluconazole, adjust the dose of abrocitinib in the abrocitinib prescribing information.

Alfentanil: Concomitant intake of fluconazole 400 mg and alfentanil 20 µg/kg intravenously in healthy volunteers increased the alfentanil AUC10 by approximately 2-fold, probably through inhibition of CYP3A4. When using these combinations a dose adjustment may be required.

Amitriptyline, nortriptyline: Fluconazole increases the effect of amitriptyline and nortriptyline. 5- nortriptyline and/or S -amitnptyline may be measured at initiation of the combination therapy and after one week. Dosage of amitriptyline/nortriptyline should be adjusted, if necessary.

Anticoagulants: In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria and melena) have been reported in association with increase 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 warfarin metabolism via CYP2C9. The prothrombin time must be closely monitored in patients on treatment with coumarin derivatives or indanedione. Dose adjustment of the anticoagulant may be necessary.

Benzodiazepines (Short Acting) i.e. midazolam, triazolam: Following oral administration of midazolam, fluconazole resulted in substantial increase in midazolam concentrations and psychomotor effects. Concomitant intake of fluconazole 200 mg and midazolam 7.5 mg orally increased the midazolam AUC and half-life 3.7- fold and 2.2-fold, respectively. Potentiated and

prolonged effects of triazolam have been observed at concomitant treatment with fluconazole. If it is necessary to treat patients with a benzodiazepine concomitantly with fluconazole, a reduction of the benzodiazepine dose should be considered, and the patients should be closely monitored.

Calcium channel antagonists: Some dihydropyridine calcium channel antagonists, including nifedipine, isradipine, nicardipine, amlodipine, verapamil and felodipine, are metabolised via CYP3A4. Fluconazole has the potential to increase the systemic exposure of the calcium channel antagonists. Literature reports have documented substantial peripheral oedema and/or elevated calcium antagonist serum concentrations during concurrent use of itraconazole and felodipine, isradipine, or nifedipine. An interaction might also occur with fluconazole. Frequent monitoring for adverse events is recommended.

Carbamazepine: Due to the CYP3A4-inhibiting effect of fluconazole concomitant treatment with carbamazepine may lead to increased plasma levels of carbamazepine by 30%. There is a risk of developing carbamazepine toxicity. Dosage adjustment of carbamazepine may be necessary depending on concentration measurements/effect.

Celecoxib: In a clinical study, concomitant treatment with Fluconazole 200 mg daily and celecoxib 200 mg resulted in 68 % and 134 % increase in celecoxib Cmax and AUC, respectively. Half of the celecoxib dose may be necessary when combined with fluconazole.

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.

Fentanyl: One fatal case of fentanyl intoxication due to possible fentanyl fluconazole interaction was reported. The author judged that the patient died from fentanyl intoxication. Furthermore, in a randomized 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. Patient should be monitored closely for the potential risk of respiratory depression. Dosage adjustment of fentanyl may be necessary.

HMG-CoA reductase inhibitors: The risk of myopathy and rhabdomyolysis is increased when fluconazole is administered concurrently with HMG-CoA reductase inhibitors that are metabolised via CYP3A4, such as atorvastatin and simvastatin, or via CYP2C9, such as fluvastatin. If concomitant therapy is necessary, patients should be monitored for signs and symptoms of myopathy or rhabdomyolysis and creatine kinase (CK) levels. HMG-CoA therapy should be discontinued if CK levels show a marked increase, or if myopathy or rhabdomyolysis is diagnosed or suspected. Lower doses of HMG-CoA reductase inhibitors may be necessary as instructed in the statins prescribing information.

Ibrutinib: Moderate inhibitors of CYP3A4 such as fluconazole increase plasma ibrutinib concentrations and may increase risk of toxicity. If the combination cannot be avoided, reduce the dose of ibrutinib to 280 mg once daily (two capsules) for the duration of the inhibitor use and provide close clinical monitoring.

Olaparib: Moderate inhibitors of CYP3A4 such as fluconazole increase olaparib plasma concentrations; concomitant use is not recommended. If the combination cannot be avoided, limit the dose of olaparib to 200 mg twice daily.

Ivacaftor (alone or combined with drugs in the same therapeutic class): Co-administration with ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, increased ivacaftor exposure by 3-fold and hydroxymethyl-ivacaftor (M1) exposure by 1.9-fold. A reduction of the ivacaftor (alone or combined) dose is necessary as instructed in the ivacaftor (alone or combined) prescribing information.

Immunosuppressors (i.e. ciclosporin, everolimus, sirolimus and tacrolimus):

Ciclosporin: Fluconazole significantly increases the concentration and AUC of ciclosporin. During concomitant treatment with fluconazole 200 mg daily and ciclosporin (2.7 mg/kg/day) there was a 1.8-fold increase in ciclosporin AUC. This combination may be used by reducing the dose of ciclosporin depending on ciclosporin concentration.

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

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.

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.

Losartan: Fluconazole inhibits the metabolism of losartan to its active metabolite (E-3174), which is responsible for a large part of the angiotensin II receptor antagonism that occurs with losartan therapy. It is recommended that patients receiving the combination be monitored for continued control of their blood pressure.

Lurasidone: Moderate inhibitors of CYP3A4 such as fluconazole may increase lurasidone plasma concentrations. If concomitant use cannot be avoided, reduce the dose of lurasidone as instructed in the lurasidone prescribing information.

Methadone: Fluconazole may enhance the serum concentration of methadone. Dosage adjustment of methadone may be necessary.

Non-steroidal anti-inflammatory drugs: The C_{max} and AUC of flurbiprofen were 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 (400 mg) compared to administration of racemic ibuprofen alone. Although not specifically studied, fluconazole has the potential to increase the systemic exposure of other NSAIDs that are metabolized 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 have been performed with a combined oral contraceptive and multiple dosing of fluconazole. There were no relevant effects on hormone level in a 50 mg fluconazole study, while at 200 mg daily increased AUC of ethinyloestradiol and levonorgestrel with 40 % and 24 %, respectively. Thus, it is hardly likely that multiple dosing of fluconazole at these doses has an influence on the effect of the combined oral contraceptive.

Phenytoin: Fluconazole inhibits the hepatic metabolism of phenytoin. Intake of fluconazole 200 mg concomitantly with phenytoin 250 mg intravenously increased the phenytoin AUC by 75 % and Cmin by 128 %. If it is necessary to administer both substances concomitantly, the phenytoin concentration must be controlled, and the phenytoin dose adjusted, in order to avoid toxic concentrations.

Prednisone: There was a case report that a liver transplant patient receiving prednisone experienced an acute adrenal cortex insufficiency when a three-month course of fluconazole was discontinued. The withdrawal of fluconazole likely caused an increase in CYP3A4 activity, leading to an increase in the degradation of prednisone. Patients receiving long-term therapy with fluconazole and prednisone should be closely monitored for signs of adrenal cortex insufficiency when fluconazole is withdrawn.

Rifabutine: Fluconazole leading to increased serum levels of rifabutine and increase in the AUC of rifabutin up to 80%. There have been reports of uveitis in patients treated concomitantly with fluconazole and rifabutine has been reported. Patients who receive rifabutine and fluconazole concomitantly must be closely followed and symptoms of rifabutin toxicity should be taken into consideration.

Saquinavir: Fluconazole increases the AUC of saquinavir with approximately 50%, Cmax with approximately 55% due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein. Interaction with saquinavir/ritonavir has not been studied and might be more marked. Dosage adjustment of saquinavir may be necessary.

Sulphonyl urea: It has been demonstrated that fluconazole prolongs the plasma half-life of concomitantly administered sulphonyl urea (chlorpropamide, glibenclamide, glipizide and tolbutamide) in healthy volunteers. Frequent monitoring of blood glucose and appropriate reduction of sulfonylurea dosage is recommended during co-administration.

Theophylline: In a placebo controlled interaction study, intake of fluconazole 200 mg for 14 days resulted in 18 % decrease in the mean plasma clearance of theophylline. Patients on treatment with high doses of theophylline or with other reason to be at increased risk of theophylline toxicity should be carefully observed for signs of theophylline toxicity during fluconazole therapy, and the theophylline dose should be adjusted as necessary if signs of toxicity develop.

Tofacitinib: Exposure of tofacitinib is increased when tofacitinib is co-administered with medications that result in both moderate inhibition of CYP3A4 and strong inhibition of CYP2C19 (e.g., fluconazole). Therefore, it is recommended to reduce tofacitinib dose to 5 mg once daily when it is combined with these drugs.

Tolvaptan: Exposure to tolvaptan is significantly increased (200% in AUC; 80% in Cmax) when tolvaptan, a CYP3A4substrate, is co-administered with fluconazole, a moderate CYP3A4 inhibitor, with risk of significant increase in adversereactions particularly significant diuresis, dehydration and acute renal failure. In case of concomitant use, the tolvaptandose should be reduced as instructed in the tolvaptan prescribing information and the patient should be frequently monitored for any adverse reactions associated with tolvaptan.

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.

Vitamin A: Based on a case-report in one patient receiving combination therapy with all-trans-retinoid acid (an acid form of vitamin A) and fluconazole, CNS related undesirable effects have developed in the form of pseudotumour 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.

Voriconazole: (CYP2C9, CYP2C19 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 AUCτ 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.

Zidovudine: Fluconazole increases Cmax and AUC of zidovudine by 85% and 75%, respectively, due to an approx. 45% decrease in oral zidovudine clearance.

The increase in AUC is, probably due to inhibition of the glucuronidation. The half life of zidovudine was likewise prolonged by approximately 128% following combination therapy with fluconazole. Dosage reduction of zidovudine may be considered. Patients receiving this combination must be controlled for zidovudine related side-effects.

Azithromycin: An open-label, randomized, three-way crossover study in 18 healthy subjects assessed the effect of a single 1200 mg oral dose of azithromycin on the pharmacokinetics of a single 800 mg 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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Before initiating treatment, the patient should be informed of the potential risk to the fetus.

After single dose treatment, a washout period of 1 week (corresponding to 5-6 half-lives) is recommended before becoming pregnant (see section 5.2).

For longer courses of treatment, contraception may be considered, as appropriate, in women of childbearing potential throughout the treatment period and for 1 week after the final dose.

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**.

Data from several thousand pregnant women treated with a cumulative dose of ≤ 150 mg of fluconazole, administered in the first trimester, show no increase in the overall risk of malformations in the foetus. In one large observational cohort study, first trimester exposure to oral fluconazole was associated with a small increased risk of musculoskeletal malformations, corresponding to approximately 1 additional case per 1000 women treated with cumulative doses ≤ 450mg compared with women treated with topical azoles and to approximately 4 additional cases per 1000 women treated with cumulative doses over 450 mg. The adjusted relative risk was 1.29 (95% CI 1.05 to 1.58) for 150 mg oral fluconazole and 1.98 (95% CI 1.23 to 3.17) for doses over 450 mg fluconazole.

Available epidemiological studies on cardiac malformations with use of fluconazole during pregnancy provide inconsistent results. However, a

meta-analysis of 5 observational studies including several thousand pregnant women exposed to fluconazole during the first trimester finds a 1.8-2 fold increased risk of cardiac malformations when compared to no fluconazole use and/or topical azoles use.

Case reports describe a pattern of birth defects among infants whose mothers received high-dose (400 to 800 mg/day) fluconazole during pregnancy for 3 months or more, in the treatment of coccidioidomycosis. The birth defects seen in these infants include brachycephaly, ears dysplasia, giant anterior fontanelles, femoral bowing and radio-humeral synostosis. A causal relationship between fluconazole use and these birth defects is uncertain.

Fluconazole in standard doses and short-term treatment should not be used during pregnancy unless clearly necessary.

Fluconazole in high doses or in prolonged regimens should not be used during pregnancy except for life threatening infections.

Breast-feeding
Fluconazole passes into breast milk to reach concentrations lower than those in plasma (see section 5.2). Breast-feeding may be maintained after a single use of a standard dose 150 mg fluconazole or less. 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.

Fertility
Fluconazole did not affect the fertility of male or female rats (see section 5.3).

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 (see section 4.8) 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 (see section 4.4).

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
Blood and the lymphatic system disorders	Uncommon	Anaemia
	Rare	Agranulocytosis, leukopenia, neutropenia, thrombocytopenia
Immune system disorders	Rare	Anaphylaxis
Metabolism and nutrition disorders	Uncommon	Decreased appetite
	Rare	Hypertriglyceredaemia, Hypercholesterolaemia, Hypokalaemia
Psychiatric disorders	Uncommon	Insomnia, somnolence
Nervous system disorders	Common	Headache
	Uncommon	Seizures, dizziness, paraesthesia, taste perversion
	Rare	Tremor
Ear and labyrinth disorders	Uncommon	Vertigo
Cardiac disorders	Rare	Torsade de pointes (See section 4.4), QT Prolongation (See section 4.4)
Gastrointestinal disorders	Common	Abdominal pain, diarrhoea, nausea, vomiting
	Uncommon	Dyspepsia, flatulence, dry mouth, constipation
Hepato-biliary disorders	Common	Alanine aminotransferase increased (see section 4.4), aspartate aminotransferase increased (see section 4.4), blood alkaline phosphatase increased (see section 4.4)
	Uncommon	Cholestasis (see section 4.4), jaundice clinically significant (see section 4.4), bilirubin increased (see section 4.4).
	Rare	Hepatic failure (see section 4.4), hepatocellular Necrosis (see section 4.4), hepatitis, hepatocellular Damage (see section 4.4)
Skin and subcutaneous tissue	Common	Rash (see section 4.4)

disorders	Uncommon	Increased sweating, pruritus, drug eruption and urticaria* (see section 4.4)
	Rare	Toxic epidermal necrolysis (see section 4.4), Stevens-Johnson syndrome (see section 4.4), acute generalised exanthematous pustulosis (see section 4.4), exfoliative skin disorder (dermatitis exfoliative), angiooedema, face oedema, alopecia
	Not Known	Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal, connective tissue bone disorders	Uncommon	Myalgia
General disorders and administration site conditions	Uncommon	Fatigue, malaise, 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 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 or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There have been reports of overdose with Fluconazole and hallucination and paranoid behaviour have been concomitantly reported.

In case of overdosing the treatment is symptomatic with supporting measures and gastric lavage, if necessary.

Fluconazole is mainly excreted in the urine. Forced volume diuresis will probably increase the elimination rate. Haemodialysis for 3 hours decreases the plasma levels with approx. 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 derivative with fungistatic effect, which specifically 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 is highly specific for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.
Doses of fluconazole 50 mg daily for 28 days have not been shown to influence serum levels of testosterone in males or the 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.

Susceptibility in vitro:

The spectrum of application includes a number of pathogens including *Candida albicans* and non-*Candida albicans* species, *Cryptococcus* spp and dermatophytes. *Candida krusei* and *C. auris* are resistant to fluconazole. Forty percent of *Candida glabrata* are primarily resistant to fluconazole. Infections caused by Aspergillus-species should not be treated with fluconazole. The MICs and epidemiological cut-off value (ECOFF) of fluconazole for C. guilliermondii are higher than for C. albicans.

Fluconazole also exhibits activity in vitro against Cryptococcus neoformans and Cryptococcus. gattii as well as the endemic moulds Blastomyces dermatiditis, Coccidioidesimmitis, Histoplasma capsulatum and Paracoccidioides brasiliensis.

Pharmacokinetic/pharmacodynamic relationship

In animal studies, there is a correlation between MIC values and efficacy against experimental mycoses due to Candida spp. In clinical studies, there is an almost 1:1 linear relationship between the AUC and the dose of fluconazole. There is also a direct though imperfect relationship between the AUC or dose and a successful clinical response of oral candidosis and to a lesser extent candidaemia to treatment. Similarly cure is less likely for infections caused by strains with a higher fluconazole MIC.

Mechanisms of resistance

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

In usually susceptible species of Candida, the most commonly encountered mechanism of resistance development involves the target enzymes of the azoles, which are responsible for the biosynthesis of ergosterol. Resistance may be caused by mutation, increased production of an enzyme, drug efflux mechanisms, or the development of compensatory pathways.

There have been reports of superinfection with Candida species other than C. albicans, which often have inherently reduced susceptibility (C. glabrata) or resistance to fluconazole (e.g. C krusei, C. auris). Such infections may require alternative antifungal therapy. The resistance mechanisms have not been completely elucidated in some intrinsically resistant (C. krusei) or emerging (C. auris) species of Candida Breakpoints (according to EUCAST).

Based on analyses of pharmacokinetic/pharmacodynamic (PK/PD) data, susceptibility in vitro and clinical response EUCAST-AFST (European Committee on Antimicrobial Susceptibility Testing-Subcommitte on Antifungal Susceptibility Testing) has determined breakpoints for fluconazole for Candida species (EUCAST Fluconazole rationale document (2020)-version 3). European Committee on Antimicrobial Susceptibility Testing, Antifungal Agents, Breakpoint tables for interpretation of MICs, Version 10.0, valid from 2020-02-04). These have been divided into nonspecies related breakpoints; which have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species, and species related breakpoints for those species most frequently associated with human infection. These breakpoints are given in the table below:

Antifungal		Species-related breakpoints (S≤/R>) in mg/L					Non-species related breakpointsA S≤/R> in mg/L
	Candida albicans	Candida dubliniensis	Candida glabrata	Candida krusei	Candida parapsilosis	Candida tropicalis	
Fluconazole	2/4	2/4	0.001*/16	--	2/4	2/4	2/4

S = Susceptible, R = Resistant

A = Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the medicinal product.

* = The entire C. glabrata is in the I category. MICs against C. glabrata should be interpreted as resistant when above 16mg/L. Susceptible category (≤0.001 mg/L) is simply to avoid misclassification of "I" strains as "S" strains. I – Susceptible, increased exposure: A microorganism is categorised as Susceptible, increased exposure when there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.

5.2 Pharmacokinetic properties

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

Absorption:

Fluconazole is well absorbed after oral intake and plasma levels (and systemic bioavailability) are over 90 % of the levels achieved after intravenous administration. The oral absorption is not affected by concomitant food intake. The maximum fasting plasma concentration is reached 0.5–1.5 hours after dose intake. 90 % of the steady-state level is reached 4–5 days after dosing once daily. Plasma concentration is proportional to the dose.
Ninety percent steady state levels are reached by day 4-5 with multiple once daily dosing. Intake of a double dose on day 1 results in plasma concentrations of approx. 90 % of steady-state on day 2.

Distribution:

The volume of distribution corresponds to the total body water. The protein binding in plasma is low (11–12 %).

Fluconazole achieves good penetration in all body fluids studied. The concentration in saliva and sputum are similar to plasma concentration. In patients with fungal meningitis the concentration of fluconazole in the cerebrospinal fluid is approx. 80 % of the corresponding plasma concentration.

In stratum corneum, epidermis-dermis and in exocrine sweat higher concentrations of fluconazole are reached compared to those in serum. Fluconazole is accumulated in stratum corneum. Fluconazole accumulates in the stratum corneum. At a dose of 50mg once daily, the concentration of fluconazole after 12 days was 73 µg /g and 7 days after cessation of treatment the concentration was still 5.8 microgram/g. At a dose of 150 mg once weekly the concentration of fluconazole in stratum corneum was after 2 doses 23.4 µg/g and 7 days after the second dosing it was still 7.1 µg/g.

Concentration of fluconazole in nails after 4 months of 150 mg once-a-week dosing was 4.05 μg/g in healthy and 1.8 μg/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:

Fluconazole is mainly renally excreted. Approx. 80 % of the taken dose is excreted in the urine in non-metabolized form. Fluconazole clearance is proportional to the creatinine clearance. Circulating metabolites have not been demonstrated.
The half-life in plasma is approximately 30 hours.

Children eliminate fluconazole more rapidly than adults do. The half-life in children and adolescents of 5–15 years is between 15.2–17.6 hours.

The long plasma elimination half-life provides the basis for single dose therapy for vaginal candidiasis, once daily and once weekly dosing for other indications.

Pharmacokinetics in renal impairment

In patients with severe renal insufficiency, (GFR< 20 ml/min) half life increased from 30 to 98 hours. Consequently, reduction of the dose is needed.
Fluconazole is removed by haemodialysis and to a lesser extent by peritoneal dialysis. After three hours of haemodialysis session, around 50% of fluconazole is eliminated from blood.

Pharmacokinetics during lactation

A pharmacokinetic study in ten lactating women, who had temporarily or permanently stopped breast-feeding their infants, evaluated fluconazole concentrations in plasma and breast milk for 48 hours following a single 150 mg dose of Fluconazole. Fluconazole was detected in breast milk at an average concentration of approximately 98% of those in maternal plasma. The mean peak breast milk concentration was 2.61 mg/L at 5.2 hours postdose. The estimated daily infant dose of fluconazole from breast milk (assuming mean milk consumption of 150 ml/kg/day) based on the mean peak milk concentration is 0.39 mg/kg/day, which is approximately 40% of the recommended neonatal dose (<2 weeks of age) or 13% of the recommended infant dose for mucosal candidiasis.

Pharmacokinetics in children

Pharmacokinetic data were assessed for 113 paediatric patients from 5 studies; 2 single-dose studies, 2 multiple-dose studies, and a study in premature neonates. Data from one study were not interpretable due to changes in formulation

pathway through the study. Additional data were available from a compassionate use study.
After administration of 2-8 mg/kg fluconazole to children between the ages of 9 months to 15 years, an AUC of about 38 µg•h/ml was found per 1 mg/kg dose units. The average fluconazole plasma elimination half-life varied between 15 and 18 hours and the distribution volume was approximately 880 ml/kg after multiple doses. A higher fluconazole plasma elimination half-life of approximately 24 hours was found after a single dose. This is comparable with the fluconazole plasma elimination half-life after a single administration of 3 mg/kg i.v. to children of 11 days-11 months old. The distribution volume in this age group was about 950 ml/kg.

Experience with fluconazole in neonates is limited to pharmacokinetic

studies in premature newborns. The mean age at first dose was 24 hours (range 9-36 hours) and mean birth weight was 0.9 kg (range 0.75-1.10 kg) for 12 pre-term neonates of average gestation around 28 weeks. Seven patients completed the protocol; a maximum of five 6 mg/kg intravenous infusions of fluconazole were administered every 72 hours. The mean half-life (hours) was 74 (range 44-185) on day 1 which decreased, with time to a mean of 53 (range 30-131) on day 7 and 47 (range 27-68) on day 13. The area under the curve (microgram.h/ml) was 271 (range 173-385) on day 1 and increased with a mean of 490 (range 292-734) on day 7 and decreased with a mean of 360 (range 167-566) on day 13. The volume of distribution (ml/kg) was 1183 (range 1070-1470) on day 1 and increased, with time, to a mean of 1184 (range 510-2130) on day 7 and 1328 (range 1040-1680) on day 13.

Pharmacokinetics in elderly

A pharmacokinetic study was conducted in 22 subjects, 65 years of age or older receiving a single 50 mg oral dose of fluconazole. Ten of these patients were concomitantly receiving diuretics. The Cmax was 1.54 µg/ml and occurred at 1.3 hours post-dose. The mean AUC was 76.4 ± 20.3 µg·h/ml, and the mean terminal half-life was 46.2 hours. These pharmacokinetic parameter values are higher than analogous values reported for normal young male volunteers. Coadministation of diuretics did not significantly alter AUC or Cmax. In addition, creatinine clearance (74 ml/min), the percent of medicinal product recovered unchanged in urine (0-24 h, 22%) and the fluconazole renal clearance estimates (0.124 ml/min/kg) for the elderly were generally lower than those of younger volunteers. Thus, the alteration of fluconazole disposition in the elderly appears to be related to reduced renal function characteristics of this group.

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.

Reproductive toxicity:

Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10, or 20 mg/kg or with parenteral doses of 5, 25, or 75 mg/kg. There were no foetal effects at 5 or 10 mg/kg; Increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg to 320 mg/kg embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate and abnormal cranio-facial ossification.
The onset of parturition was slightly delayed at 20 mg/kg orally and dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg and 40 mg/kg intravenously. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal survival at these dose levels.
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 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 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate,
Maize starch,
Magnesium stearate,
Sodium lauryl sulfate,
Colloidal silicon dioxide

Capsule shell contains:
Titanium dioxide (E171),
Gelatin

Printing ink composition:
Shellac,

Isopropyl alcohol,
Black iron oxide (E 172),
N-Butyl alcohol,
Propylene glycol (E 1520),
Ammonium Hydroxide (E 527)

6.2 Incompatibilities

No incompatibilities are known to date.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25 °C.

6.5 Nature and contents of container

The hard capsules are packed in PVC white, opaque/aluminium blisters and inserted into a carton.

Pack sizes*:* 1 capsule.

6.6 Special precautions for disposal

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Crescent Pharma Limited
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RG21 8SR
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20416/0759

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10 DATE OF REVISION OF THE TEXT

28/03/2024