

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1 NAME OF THE MEDICINAL PRODUCT

Blicanz Thrush Relief 150 mg capsule  
Fluconazole 150mg capsule  
Boots Thrush 150mg Capsule (Fluconazole)  
Numark Fluconazole 150mg capsule

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains Fluconazole 150mg  
Also contains 150mg of Anhydrous lactose

For the full list of excipients, see section 6.1

### 3. PHARMACEUTICAL FORM

Capsule for oral administration

White to off white powder filled in Blue/Blue coloured hard gelatin capsules of size '1'.

### 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

##### Route of administration

Oral.

Fluconazole 150mg capsules should be swallowed whole

*In adults* aged 16 - 60 years

One capsule should be swallowed whole.

**In children** - Not recommended in children aged under 16 years.

**Use in elderly** - Not recommended in patients aged over 60 years.

**Use in renal impairment**-No adjustments in single dose therapy are required.

#### 4.3. Contraindications

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

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, pimozone, quinidine, amiodarone and erythromycin are contraindicated in patients receiving fluconazole (see sections 4.4 and 4.5).

#### 4.4. Special warnings and special 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 patients 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.

##### Tinea capitis

Fluconazole has been studied for treatment of *tinea capitis* in children. It was shown not to be superior to griseofulvin and the overall success rate was less than 20%. Therefore, Fluconazole should not be used for *tinea capitis*.

##### Cryptococcosis

The evidence for efficacy of fluconazole in the treatment of cryptococcosis of other sites (e.g. pulmonary and cutaneous cryptococcosis) is limited, which prevents dosing recommendations.

#### Deep endemic mycoses

The evidence for efficacy of fluconazole in the treatment of other forms of endemic mycoses such as *paracoccidioidomycosis*, *lymphocutaneous sporotrichosis* and *histoplasmosis* is limited, which prevents specific dosing recommendations.

#### Renal system

Fluconazole should be administered with caution to patients with renal dysfunction (see section 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

#### 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).

#### Dermatological reactions:

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 medicinal products. 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 400 mg per day with terfenadine should be carefully monitored (see sections 4.3 and 4.5).

#### 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. 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 medications that may have been contributory. Fluconazole should be administered with caution to patients with these potentially proarrhythmic 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).

### Cytochrome P450

Fluconazole is a potent CYP2C9 inhibitor and a moderate CYP3A4 inhibitor. Fluconazole is also an inhibitor of CYP2C19. Fluconazole treated patients who are concomitantly treated with drugs with a narrow therapeutic window metabolized through CYP2C9, CYP2C19 and CYP3A4, should be monitored (see section 4.5).

Fluconazole capsules contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

The product available from pharmacies without prescription will carry a leaflet that advises the patient:

#### **Do not use Fluconazole 150mg 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 capsules or other antifungals and other thrush treatments. 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 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 a blood-stained discharge.

If you have vulval or vaginal sores, ulcers or blisters.

If you are experiencing lower abdominal pain or burning sensation 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.

The 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 physician if the symptoms have not been relieved within one week of taking Fluconazole 150mg Capsules. Fluconazole 150mg Capsules 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 product is contraindicated:***

**Terfenadine:** Because of the occurrence of serious cardiac dysrhythmias secondary to prolongation of the QTc interval in patients receiving other azole antifungals in conjunction with terfenadine, interactions 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. 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. The combined use of fluconazole at doses of 400mg or greater with terfenadine is contraindicated (see section 4.3). The co-administration of fluconazole at doses lower than 400mg per day with terfenadine should be carefully monitored.

**Cisapride:** There have been reports of cardiac events including Torsades de Pointes in patients to whom fluconazole and cisapride were coadministered. In most of these cases, the patients appear to have been predisposed to arrhythmias or had serious underlying medical conditions, and the relationship of the reported events to a possible drug interaction is unclear. A controlled study found that concomitant fluconazole 200mg once daily and cisapride 20mg four times a day yielded a significant increase in cisapride levels and prolongation of QT interval. Because of the potential seriousness of such an interaction, co-administration of cisapride is contra-indicated in patients receiving fluconazole. (See section 4.3.)

**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*. Co-administration of fluconazole and astemizole is contraindicated (see section 4.3). Fluconazole should be co-administered with caution in these circumstances and careful monitoring of patients should be undertaken.

**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*. Co-administration of fluconazole and pimozide is contraindicated (see section 4.3).

**Erythromycin:** Concomitant use of fluconazole and erythromycin has the potential to increase the risk of cardio toxicity (prolonged QT interval, Torsades de Pointes) and consequently sudden heart death. This combination should be avoided (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*. Co-administration of fluconazole and quinidine is contraindicated (see section 4.3).

**Amiodarone:** Concomitant administration of fluconazole with amiodarone may result in inhibition of amiodarone metabolism. Use of amiodarone has been associated with QT prolongation. Co-administration of fluconazole and amiodarone 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 of 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 of the following other medicinal products lead to precautions and dose adjustments:***

**The effect of other medicinal products on fluconazole**

**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.

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.

**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.<sup>1</sup>

<sup>1</sup> Mesure R. Protocol 245. An open placebo-controlled crossover study to determine any effect of concomitant diuretic treatment on fluconazole pharmacokinetics in healthy volunteers.

**The effect of fluconazole on other medicinal products**

Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and 2C19 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 metabolized by CYP2C9, CYP2C19 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 long half-life of fluconazole (See section 4.3).

**Alfentanil:** During concomitant treatment with fluconazole (400 mg) and intravenous alfentanil (20 µg/kg) in healthy volunteers the alfentanil AUC 10 increased 2-fold, probably through 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 1 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:** Fluconazole increased the prothrombin time after warfarin administration in healthy males during an interaction study. In post-marketing experience, as with other azole antifungals, the change was small (12%) but bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria and melaena) have been reported in association with increases in prothrombin time in patients receiving fluconazole and warfarin concomitantly. 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, 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.

**Benzodiazepines (Short Acting), i.e, midazolam, triazolam:** Following oral administration of midazolam, fluconazole resulted in substantial increases 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. Fluconazole 200 mg

daily given concurrently with triazolam 0.25 mg orally increased the triazolam AUC and half-life 4.4-fold and 2.3-fold, respectively. Potentiated and prolonged effects of triazolam have been observed at concomitant treatment with fluconazole. The effect on midazolam appears to be more pronounced following oral administration of fluconazole than with fluconazole administered 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.

**Carbamazepine, Phenobarbital, Rifapentine:** Fluconazole inhibits the metabolism of carbamazepine, Phenobarbital, Rifapentine and an increase in the fluconazole dose should be considered in patients receiving concomitant carbamazepine, Phenobarbital or rifapentin. There is a risk of developing toxicity. Dose adjustment of carbamazepine, Phenobarbital or rifapentine may be necessary depending on concentration measurements/effect.

**Calcium Channel Blockers:** Certain calcium channel antagonists (nifedipine, verapamil, isradipine, amlodipine and felodipine) are metabolized 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 (200 mg daily) and celecoxib (200 mg) the celecoxib C<sub>max</sub> and AUC increased by 68% and 134%, respectively. Half of the celecoxib dose may be necessary when combined with fluconazole.

**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 dosage of ciclosporin depending on the 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 dose 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. Dose of orally administered tacrolimus should be decreased depending on tacrolimus 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.

**Fentanyl:** One fatal case of possible fentanyl fluconazole interaction was reported. Furthermore, it was shown in healthy volunteers that fluconazole delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to CNS depression or respiration depression. Patients 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 increases when fluconazole is co-administered with HMG-CoA reductase inhibitors metabolized 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 the 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 C<sub>max</sub> and AUC of flurbiprofen were increased by 23% and 81%, respectively, when co-administered with fluconazole compared to administration of flurbiprofen alone. Similarly, the C<sub>max</sub> and AUC of the pharmacologically active isomer [S-(+)-ibuprofen] was increased by 15% and 82%, respectively, when fluconazole was co-administered 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 dose of NSAIDs may be needed.

**Oral contraceptives:** Two pharmacokinetic studies with combined oral contraceptives have been performed using multiple doses of fluconazole. There were no relevant effects on 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.

**Phenytoin:** Fluconazole inhibits the hepatic metabolism of phenytoin. Concomitant repeated administration of 200 mg fluconazole and 250 mg phenytoin intravenously, caused an increase of the phenytoin AUC<sub>24</sub> by 75% and C<sub>min</sub> by 128%. With co-administration, serum phenytoin concentration levels should be monitored to avoid phenytoin toxicity.

**Prednisone:** There was a case report that a liver-transplanted patient treated with prednisone developed acute adrenal cortex insufficiency when a three month therapy with fluconazole was discontinued. This discontinuation of fluconazole presumably caused an enhanced CYP3A4 activity which led to increase 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 co-administered. In combination therapy, symptoms of rifabutin toxicity should be taken into consideration

**Saquinavir:** Fluconazole increases the AUC and C<sub>max</sub> of saquinavir with approximately 50%, and 55% respectively, due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein. Dosage adjustment of saquinavir may be necessary.

**Sulphonylureas:** Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulphonylureas (e.g., chlorpropamide, glibenclamide, glipizide and tolbutamide) in healthy volunteers. Frequent monitoring of blood glucose and appropriate reduction of sulphonylurea dosage

is recommended during coadministration. Fluconazole and oral sulphonylureas may be concomitantly administered to diabetics but the possibility of an hypoglycaemic episode should be considered.

**Endogenous steroid:** No effect on endogenous steroid levels was observed in females when treated with fluconazole 50mg daily. No significant effect on endogenous steroid levels or on ACTH stimulated response was observed in healthy male volunteers when treated with fluconazole 200 to 400mg daily.

**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). 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.

**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.

**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<sub>max</sub> and AUC<sub>τ</sub> 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 C<sub>max</sub> and AUC of zidovudine by 84% and 74%, 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.

**Ivacaftor:** 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 dose to 150 mg once daily is recommended for patients taking concomitant moderate CYP3A inhibitors, such as fluconazole and erythromycin.

#### 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 being treated for at least 3 or more months with high doses (400-800 mg/day) of fluconazole therapy 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 passes into breast milk to reach concentrations lower than those in plasma. Breast-feeding may be maintained after a single use of a standard dose 200 mg fluconazole or less. Breast-feeding is not recommended after repeated use or after high dose fluconazole.

##### 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

The most frequently (>1/10) reported adverse reactions are headache, abdominal pain, diarrhoea, nausea, vomiting, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased and rash.

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

System Organ Class	Common	Uncommon	Rare
<b>Blood and the lymphatic system disorders</b>		Anaemia	Agranulocytosis, leukopenia, thrombocytopenia, neutropenia
<b>Immune system disorders</b>			Anaphylaxis, Hypersensitivity (rash, urticarial, oedema, pruritus, cardiorespiratory distress)
<b>Metabolism and nutrition disorders</b>		Decreased appetite	Hypercholesterolaemia, hypertriglyceridaemia, hypokalemia
<b>Psychiatric disorders</b>		Somnolence, insomnia	
<b>Nervous system disorders</b>	Headache	Seizures, paraesthesia, dizziness, taste perversion	Tremor
<b>Ear and labyrinth disorders</b>		Vertigo	
<b>Cardiac disorders</b>			Torsade de pointes (see section 4.4), QT prolongation (see section 4.4)

<b>Gastrointestinal disorders</b>	Gastrointestinal and Abdominal pain, vomiting, diarrhoea, nausea	Constipation dyspepsia, flatulence, dry mouth	
<b>Hepatobiliary disorders</b>	Alanine aminotransferase increased (see section 4.4), aspartate aminotransferase increased (see section 4.4), blood alkaline phosphatase increased (see section 4.4)	Cholestasis (see section 4.4), jaundice (see section 4.4), bilirubin increased (see section 4.4)	Hepatic failure (see section 4.4), hepatocellular necrosis (see section 4.4), hepatitis (see section 4.4), hepatocellular damage (see section 4.4)
<b>Skin and subcutaneous tissue disorders</b>	Rash (see section 4.4)	Drug eruption * (see section 4.4), urticaria (see section 4.4), pruritus, increased sweating	Toxic epidermal necrolysis, (see section 4.4), Stevens-Johnson syndrome (see section 4.4), acute generalised exanthematouspustulosis (see section 4.4), dermatitis exfoliative, angioedema, face oedema, alopecia
<b>Musculoskeletal and connective tissue disorders</b>		Myalgia	
<b>General disorders and administration site conditions</b>		Fatigue, malaise, asthenia, fever	

\*Fixed Drug Eruption

### Paediatric Population

The pattern and incidence of adverse reactions 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](http://www.mhra.gov.uk/yellowcard).

#### 4.9. Overdose

There have been reports of overdosage with fluconazole and hallucinations and paranoid behaviour concomitantly reported.

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

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Triazole derivatives,  
ATC code-J02AC01

##### **Mode of action**

Fluconazole is a triazole antifungal agent, Its primary mode of action is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of fluconazole. Fluconazole has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.

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

##### Susceptibility *in vitro*

*In vitro*, fluconazole displays antifungal activity against most clinically common *Candida* species (including *C. albicans*, *C. parapsilosis*, *C. tropicalis*). *C. glabrata* shows a wide range of susceptibility while *C. krusei* is resistant to fluconazole.

Fluconazole also exhibits activity *in vitro* against *Cryptococcus neoformans* and *Cryptococcus gattii* as well as the endemic moulds *Blastomyces dermatitidis*, *Coccidioides immitis*, *Histoplasma capsulatum* and *Paracoccidioides brasiliensis*.

##### PK/PD 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.

#### Mechanism(s) 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.

There have been reports 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.

#### 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-subcommittee on Antifungal Susceptibility Testing) has determined breakpoints for fluconazole for *Candida* species (EUCAST Fluconazole rational document (2007)-version 2). These have been divided into non-species 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>)					Non-species related breakpoints <sup>A</sup> S≤/R>
	<i>Candida albicans</i>	<i>Candida glabrata</i>	<i>Candida krusei</i>	<i>Candida parapsilosis</i>	<i>Candida tropicalis</i>	
Fluconazole	2/4	IE	--	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.

IE = There is insufficient evidence that the species in question is a good target for therapy with the medicinal product

## 5.2 Pharmacokinetic properties

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

### Absorption

After oral administration fluconazole is well absorbed and plasma levels (and systemic bioavailability) are over 90% of the levels achieved after intravenous administration. Oral absorption is not affected by concomitant food intake. Peak plasma concentrations in the fasting state occur between 0.5 and 1.5 hours post-dose. Plasma concentrations are proportional to dose. Ninety percent steady-state levels are reached by day 4 -5 with multiple once daily dosing. Administration of a loading dose (on day 1) of twice the usual daily dose enables plasma levels to approximate to 90% steady-state levels by day 2.

### Distribution

The apparent volume of distribution approximates to total body water. Plasma protein binding is low (11-12%).

Fluconazole achieves good penetration in all body fluids studied. The levels of fluconazole in saliva and sputum are similar to plasma levels. In patients with fungal meningitis, fluconazole levels in the CSF are approximately 80% 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 microgram/g and 7 days after cessation of treatment the concentration was still 5.8 microgram/g. At the 150 mg once-a-week dose, the concentration of fluconazole in stratum corneum on day 7 was 23.4 µg/g and 7 days after the second dose 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 selective inhibitor of the isozymes CYP2C9 and CYP3A4 (see section 4.5). Fluconazole is also an inhibitor of the isozyme CYP2C19.

### Elimination

Plasma elimination half-life for fluconazole is approximately 30 hours. The major route of excretion is renal, with approximately 80% of the administered dose appearing in the urine as unchanged medicinal product. Fluconazole clearance is proportional to creatinine clearance. There is no evidence of circulating metabolites.

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

#### Pharmacokinetics in renal impairment

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 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  $C_{max}$  was 1.54  $\mu\text{g/ml}$  and occurred at 1.3 hours post-dose. The mean AUC was  $76.4 \pm 20.3 \mu\text{g}\cdot\text{h/ml}$ , 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. Coadministration of diuretics did not significantly alter AUC or  $C_{max}$ . 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**

### ***Reproductive toxicity***

At 25 and 50mg/kg and higher doses, increases in foetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed. At doses ranging from 80mg/kg (approximately 20-60 times the recommended human dose) to 320mg/kg embryoletality 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. No evidence of chromosomal mutations was observed in cytogenetic studies *in vivo* (murine bone marrow cells, following oral administration of fluconazole). Data derived from *in vitro* studies (human lymphocytes exposed to fluconazole) are not consistent.

## **Impairment of fertility**

The fertility of male or female rats treated orally with daily doses of fluconazole at 5, 10 or 20 mg/kg or with parenteral doses of 5, 25 or 75 mg/kg was not affected, although the onset of parturition was slightly delayed at 20mg/kg orally. 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 dose levels. The effects on parturition in rats are consistent with the species specific estrogen-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**

Colloidal anhydrous silica

Lactose

Magnesium Stearate

Maize Starch

Sodium Lauryl Sulfate

Capsule shell contains

Patent blue ( E 131)

Titanium dioxide (E171)

Methyl parahydroxybenzoate (E218)

Propyl parahydroxybenzoate (E216)

Gelatin

### **6.2. Incompatibilities**

No specific incompatibilities have been noted.

### **6.3. Shelf life**

2 years

### **6.4. Special precautions for storage**

Blisters : Do not store above 25°C. Store in the original package.

**6.5. Nature and contents of container**

PVC/PVdC/Al blister pack size of 1 capsule

**6.6. Instruction for use and handling**

No special requirements

**7. MARKETING AUTHORISATION HOLDER**

Bristol Laboratories Limited  
Unit 3, Canalside  
Northbridge Road  
Berkhamsted  
HP4 1EG  
United Kingdom

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

PL 17907/0055

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24<sup>th</sup> May 2005

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

26/09/2017