PROFESSIONAL INFORMATION FOR DIFLUZOLE 150 CAPSULES

SCHEDULING STATUS:

S2

1. NAME OF THE MEDICINE

DIFLUZOLE 150 (Capsule)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DIFLUZOLE 150: Each capsule contains 150 mg fluconazole.

Contains sugar: lactose monohydrate 111,96 mg

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Capsules

DIFLUZOLE 150: White powder filled in hard gelatin capsule of size '1' with sky blue opaque body and sky blue opaque cap having 'FCZ 150' printed on body and cap in black linear pattern.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DIFLUZOLE 150 as a single dose is indicated for the treatment of the following fungal infections in adults:

- Vaginal candidiasis, recurrent
- Candidial balanitis associated with vaginal candidiasis.

4.2 Posology and method of administration

Posology:

Vaginal candidiasis, recurrent:

Adults: 150 mg administered as a single dose.

Should the infection persist, the patient should consult a medical practitioner.

Candida balanitis:

Adults: 150 mg administered as a single dose.

Should the infection persist, the patient should consult a medical practitioner.

Special populations:

Normal dosage recommendations are used in the elderly unless the patient has decreased renal function (see "Renal failure" below).

Pediatric population:

Not recommended in children.

Renal failure:

DIFLUZOLE 150 should be used with caution in patients with renal function impairment. DIFLUZOLE 150 is excreted through the kidneys.

Method of administration:

For oral use.

The capsules should be swallowed whole and independent of food intake.

4.3 Contraindications

- Hypersensitivity to fluconazole, other azole antifungal medicines, or to any of the excipients listed in **(see section 6.1).**
- Co-administration of other medicines 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).**

- Pregnancy and lactation **(see section 4.6)**.

4.4 Special warnings and precautions for use

Recurrent vaginal candidiasis and candidial balanitis associated with vaginal candidiasis:

Should the infection persist, the patient should consult a medical practitioner.

Renal system:

DIFLUZOLE 150 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 **(see section 4.5 'The effect of fluconazole on other medicine')**

Hepatobiliary system:

DIFLUZOLE 150 should be administered with caution to patients with liver dysfunction.

DIFLUZOLE 150 has been associated with rare cases of serious hepatic toxicity, including fatalities related to dose and duration of use, primarily in patients with serious underlying medical conditions. Fluconazole hepatotoxicity has usually been reversible on discontinuation of therapy. Liver functions should be monitored periodically in all patients receiving continuous treatment with DIFLUZOLE 150 for more than one month. Patients who develop abnormal liver function test during DIFLUZOLE 150 therapy must be monitored closely 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). DIFLUZOLE 150 should be immediately discontinued, and the patient should consult a doctor if these symptoms are experienced.

Underlying diseases:

DIFLUZOLE 150 should be used with caution in patients with underlying disease, such as AIDS or malignancy. Abnormalities in haematological, hepatic and renal function have been observed.

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 medicines (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 *torsades 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 treatment 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*. DIFLUZOLE 150 should be administered with caution to patients with potentially prodysrrhythmic conditions. Co-administration of other medicines 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)**.

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 less frequently developed pruritus, rashes, urticaria, angioedema, dry skin, abnormal odour, exfoliative cutaneous reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis during treatment with DIFLUZOLE 150. Drug Reaction with Eosinophilia and Systemic

Symptoms (DRESS) has been reported. AIDS patients attributable to fluconazole, develops in a patient treated for o superficial fungal infection, further therapy with DIFLUZOLE 150 should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and DIFLUZOLE 150 discontinued if bullous lesions or erythema multiforme develop.

Hypersensitivity:

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

Cytochrome P450:

Fluconazole is a moderate CYP2C9 and CYP3A4 inhibitor. Fluconazole is also a strong inhibitor of CYP2C19. DIFLUZOLE 150 treated patients who are concomitantly treated with medicines of a narrow therapeutic window metabolised through CYP2C9, CYP2C19 and CYP3A4, should be monitored **(see section 4.5).**

Terfenadine:

The co-administration of DIFLUZOLE 150 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 in account the prevalence of resistance in various Candida species to fluconazole.

Precautions relating to excipients:

DIFLUZOLE 150 capsules contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactose deficiency or glucose galactose malabsorption should not take

DIFLUZOLE 150.

DIFLUZOLE 150 contains lactose monohydrate which may have on effect on the glycaemic control of patients with diabetes mellitus.

Difluzole 150 contains Sodium

This medicine contains less than 1 mmoL sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

Interaction studies have shown that when oral fluconazole is co-administered with food, cimetidine, antacids or following total body irradiation for bone marrow transplantation, no clinically significant impairment of fluconazole absorption occurs.

Concomitant use of the following other medicine is contraindicated:

Cisapride:

There have been reports of cardiac events including torsades de pointes in patients to whom fluconazole and cisapride were co-administered. 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 QTc interval. Concomitant treatment with DIFLUZOLE 150 and cisapride is contraindicated because of the possible increase in serum cisapride concentrations which can increase the risk of serious and life-threatening cardiac arrhythmias including torsades de pointes (**see section 4.3**).

Terfenadine:

Because of the occurrence of serious cardiac dysrhythmias secondary to prolongation of the QTc interval in patients receiving azole antifungals in conjunction with terfenadine, interaction studies have been performed. One study at a 200 mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. Another study at a 400 mg and 800 mg daily dose of fluconazole

demonstrated that fluconazole taken in doses of 400 mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. If co-administration of terfenadine and DIFLUZOLE 150 at doses less than 400 mg is considered essential, terfenadine concentrations should be closely monitored.

Astemizole:

Concomitant administration of DIFLUZOLE 150 with astemizole may decrease the clearance of astemizole. The resulting increased plasma concentrations of astemizole can lead to QT prolongation and rare occurrences of *torsades de pointes*. Co-administration of DIFLUZOLE 150 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 torsades de pointes. Co-administration of DIFLUZOLE 150 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. Co-administration of DIFLUZOLE 150 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. Co-administration of DIFLUZOLE 150 and erythromycin is contraindicated (**see section 4.3**)

Concomitant use of the following other medicines cannot be recommended:

Halofantrine:

Fluconazole can increase halofantrine plasma concentration due to on 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. Caution must be exercised if the concomitant use of DIFLUZOLE 150 and amiodarone is necessary.

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

The effect of other medicines on fluconazole:

Rifampicin:

Concomitant administration of fluconazole and rifampicin resulted in a 25 % decrease in the AUC and a 20 % shorter half-life of fluconazole. In patients receiving concomitant rifampicin, an increase of the DIFLUZOLE 150 dose should be considered.

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 DIFLUZOLE 150 dose regimen in subjects receiving concomitant diuretics.

The effect of fluconazole on other medicines:

DIFLUZOLE 150 is a moderate inhibitor of cytochrome P450 (CYP) isoenzymes 3A4 and 2C9. DIFLUZOLE 150 is also a strong inhibitor of the isozyme CYP2C19. In addition to the

observed/documented interactions mentioned below, there is a risk of increased plasma concentrations of the other medicines metabolised by CYP2C9, CYP2C19 and CYP3A4 co-administered with DIFLUZOLE 150. Therefore, caution should be exercised when using these combinations and the patients should be carefully monitored. The enzymes inhibiting effect of fluconazole persists 4 – 5 days after discontinuation of DIFLUZOLE 150 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 as instructed in the abrocitinib prescribing information.

Alfentanil:

During concomitant treatment with fluconazole and intravenous alfentanil in healthy volunteers the alfentanil AUC increased, probably through inhibition of CYP3A4. Dose adjustment of alfentanil may be necessary.

Amitriptyline, nortriptyline:

Fluconazole increases the effect of amitriptyline and nortriptyline. 5-nortriptyline and/or S-amitriptyline may be measured at initiation of the combination therapy and after one week. Dose 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 medicines in systemic infection with *Aspergillus fumigatus*. The clinical significance of results obtained in these studies is unknown.

Anticoagulants:

In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, haematuria, and melena) have been reported, in association with 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 the warfarin metabolism through CYP2C9. In patients receiving coumarin-type or indanedione anticoagulants concurrently with DIFLUZOLE 150, the prothrombin time should be carefully monitored. Dose adjustments of the anticoagulant may be necessary.

Benzodiazepines *(short* acting), i.e. midazolam, triazolam:

Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychometer 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. This effect appears to be more pronounced following oral administration of DIFLUZOLE 150 than with DIFLUZOLE 150 administered intravenously.

If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dose, and the patients should be appropriately monitored.

Carbamazepine:

Due to the CYP3A4 inhibiting effect of fluconazole, concomitant treatment with carbamazepine may lead to increased plasma levels of carbamazepine and an increase of

30 % has been observed. There is a risk of developing carbamazepine toxicity. The literature includes reports that document increased undesirable effects described for carbamazepine. The

literature includes reports that document increased undesirable effects described for carbamazepine e.g. vertigo, unsteady gait and diplopia. For this reason, the carbamazepine plasma concentrations should be checked if such symptoms occur, and the dose reduced if necessary.

Calcium channel blockers:

Certain calcium channel antagonists (nifedipine, isradipine, amlodipine, verapamil and felodipine) are metabolised by CYP3A4. Fluconazole has the potential to increase the systemic exposure of the calcium channel antagonists. Frequent monitoring for adverse events is recommended.

Celecoxib:

During concomitant treatment with fluconazole (200 mg daily) and celecoxib (200 mg) the celecoxib C_{max} and AUC increased by 68 % and 134 %, respectively. Half of the celecoxib dose may be necessary when combined with DIFLUZOLE 150.

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. Furthermore, it was shown in healthy volunteers that fluconazole delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to respiratory 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 metabolised through CYP3A4, such as atorvastatin and simvastatin, or through CYP2C9, such as fluvastatin. If concomitant therapy is necessary, the patient should be observed for symptoms of myopathy and rhabdomyolysis and creatine kinase should be monitored. HMG-CoA reductase inhibitors should be discontinued if a marked increase in creatine kinase is observed, or myopathy/rhabdomyolysis is diagnosed or suspected.

Ibrutinib:

Moderate inhibitors of CYP3A4 such cs 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 doily for the duration of the inhibitor use and provide close clinical monitoring.

Ivacaftor:

Co-administration with ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, increased ivacaftor exposure by 3-fold and hydroxymethyl-ivacaftor (M 1) exposure by 1,9-fold. A reduction of the ivacaftor dose to 150 mg once doily is recommended for patients taking concomitant moderate CYP3A inhibitors, such as fluconazole and erythromycin.

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.

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.

Ciclosporin plasma concentrations should be monitored in all patients receiving DIFLUZOLE 150.

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. Patients on this combination need to have serum concentrations of tacrolimus monitored. Dose of orally administered tacrolimus should be decreased depending on tacrolimus concentration.

Losartan:

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

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. Dose adjustment of methadone may be necessary.

Nevirapine:

Co-administration of fluconazole and nevirapine resulted in approximately 100 % increase in nevirapine exposure as compared with historical data where nevirapine was administered alone. Because of the risk of increased exposure lo nevirapine, caution should be exercised if nevirapine and DIFLUZOLE 150 are given concomitantly, and patients should be monitored closely.

Non-steroidal anti-inflammatory drugs (NSAIDS):

The C_{max} and AUC of flurbiprofen was increased by 23 % and 81 %, respectively, when co-administered with fluconazole compared to administration of flurbiprofen alone. Similarly, the C_{max} and AUC of the pharmacologically active isomer (S-(+)-ibuprofen) was increased by 15 % and 82 %, respectively, when fluconazole was co-administered with the 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 metabolised by CYP2C9 (e.g. naproxen, lornoxicam, meloxicam, diclofenac). Frequent monitoring of adverse events and toxicity related to NSAIDS is recommended. Adjustment of dose of NSAIDs may be needed.

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 AUC24 by 75% and C_{max} by 128 %. With co-administration, serum phenytoin concentration levels should be monitored in order 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. The discontinuation of fluconazole presumably caused on enhanced CYP3A4 activity which led to increased metabolism of prednisone. Patients on long-term treatment with DILFUZOLE and prednisone-should be carefully monitored for adrenal cortex insufficiency when DIFLUZOLE 150 is discontinued.

Rifabutin:

Fluconazole increases serum concentrations of rifabutin leading to increase in the AUC of rifabutin of 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. Patients on this combination need to be carefully monitored.

Saquinavir:

Fluconazole increases the AUC and C_{max} of saquinavir with approximately 50 % and 55 % respectively, 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.

Sulfonylureas:

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

Theophylline:

In a placebo-controlled interaction study, the administration of fluconazole 200 mg for 14 days resulted in an 18% decrease in the mean plasma clearance rate of theophylline. Patients who are receiving high dose theophylline or who are otherwise at increased risk for theophylline toxicity

should be observed for signs of theophylline toxicity while receiving fluconazole. Therapy should be modified if signs of toxicity develop.

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 medicinal products.

Tolvaptan:

Exposure to tolvaptan is significantly increased (200% in AUC, 80% in C_{max}) when tolvaptan, a CYP3A4 substrate, is co-administered with fluconazole, a moderate CYP3A4 inhibitor, with risk of significant increase in adverse reactions particularly significant diuresis, dehydration and acute renal failure. In case of concomitant use, the tolvaptan dose should be reduced as instructed in the tolvaptan prescribing information and the patients 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): Co-administration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 2.5 days) and oral fluconazole (400 mg on day 1, then 200 mg Q24h for 4 days) to 8 healthy male subjects resulted in an increase in C_{max} and AUC_{τ} 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_{max} 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. Dose reduction of zidovudine may be considered.

Azithromycin:

An open label, randomised, 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.

Oral contraceptives:

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

unlikely to have an effect on the efficacy of the combined oral contraceptive.

4.6 Fertility, pregnancy and lactation

Pregnancy:

An observational study has suggested on increased risk of spontaneous abortion in women treated with fluconazole during the first trimester.

There have been reports of multiple congenital abnormalities {including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in infants whose mothers were treated for at least three or more months with high doses (400 – 800 mg daily) of fluconazole for coccidioidomycosis. The relationship between fluconazole uses and these events is unclear.

Before becoming pregnant a washout period of approximately 1 week (corresponding to 5-6 half-lives) is recommended after a single-dose or discontinuation of a course of treatment (**see section 5.2***).*

Breastfeeding:

DIFLUZOLE 150 should not be given to breastfeeding women (see section 4.3). DIFLUZOLE 150 passes into breast milk to reach concentrations similar to those in plasma (**see section 5.2**).

Fertility:

Fluconazole did not affect the fertility of male or female rats in preclinical studies.

4.7 Effects on ability to drive and use machines

No studies have been performed on the effects of DIFLUZOLE 150 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 DIFLUZOLE 150 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 most frequently reported adverse reactions are headache, abdominal pain, diarrhoea, nausea, vomiting, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased and rash.

Tabulated list of adverse reactions

MedDRA system organ class	**Frequency**	**Side effects**
Blood and lymphatic system disorders	Less frequent	Anaemia, leucopenia, neutropenia, agranulocytosis and thrombocytopenia.
Immune system disorders	Less frequent	Anaphylaxis, (including angio-oedema, facial oedema, pruritus), flushing.
Metabolism and nutrition disorders	Less frequent	Decreased appetite, hypokalaemia, hypercholesterolaemia, hypotriglyceridaemia.
Psychiatric disorders	Less frequent	Somnolence, insomnia.
Nervous system disorders	Frequent	Headache.
	Less frequent	Dizziness, seizures, paraesthesia, taste perversion, nervousness, rigors, tremor and hyperkinesia.
Eye disorders:	Less frequent	Abnormal vision.
Ear and labyrinth disorders:	Less frequent	Vertigo.
Cardiac disorders:	Less frequent	Ventricular arrhythmia (QT-prolongation, torsade de pointes (**see section 4.4)**)

Gastrointestinal disorders:	Frequent	Nausea, vomiting, abdominal pain, diarrhoea, flatulence
	Less frequent	Constipation, dyspepsia, dry mouth, thirst.
Hepatobiliary disorders:	Frequent	Hepatotoxicity, (including elevated serum concentrations of alkaline phosphatase, bilirubin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST)).
	Less frequent	Hepatic failure, hepatitis, hepatocellular necrosis, hepatocellular damage, jaundice, cholestasis (**see section 4.4**).
Skin and subcutaneous tissue disorders:	Frequent	Rash.
	Less frequent	Drug eruption*, alopecia, urticaria, increased sweating, dry skin, abnormal odour, dermatitis, exfoliative cutaneous reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis, acute generalised exanthematous pustulosis.
	Frequency unknown	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). * Including Fixed drug eruptions
Musculoskeletal and connective tissue disorders:	Less frequent	Hypertonia, myalgia.
Renal and urinary disorders:	Less frequent	Polyuria
Reproductive system and breast disorder:	Less frequent	Female sexual dysfunction, intermenstrual bleeding, menorrhagia and leucorrhea
General disorders and administration site conditions:	Less frequent	Fatigue, malaise, asthenia, fever.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website, or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

The following have been reported with an overdose of DIFLUZOLE 150:

Insomnia, irritability, vomiting, diarrhea, abdominal pains/cramps, anorexia, bulging fontanel, elevation of alkaline phosphates and gamma glutamyl transpeptidases, increase in serum calcium, renal failure, fatigue, facial rash, skin erythema, generalised urticaria, arthralgia, itching, numbness of the tongue and depressed mood. Hallucinations and paranoid behaviour have been concomitantly reported.

DIFLUZOLE 150 is largely excreted in the urine; forced volume diuresis would probably increase the elimination rate. A three-hour haemodialysis session decreases plasma levels of fluconazole by approximately 50%.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 20.2.2 Antimicrobial (chemotherapeutic) agents. Fungicides.

ATC code: J02AC01

5.1 Pharmacodynamic properties

Mechanism 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.

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 candidiasis and too lesser extent candidaemia to treatment. Similarly, cure is less likely for infections caused by strains with higher fluconazole MIC.

Mechanisms of resistance:

Candida spp. has 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.

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 or gastric activity. Peak plasma concentrations in the fasting state occur between 1 to 2 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% the corresponding plasma levels.

High skin concentration 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 50 mg 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 µg/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 moderate inhibitor of the isozymes CYP2C9 and CYP3A4 (see section 4.5). Fluconazole is also a strong inhibitor of the isozyme CYP2C19.

Elimination

Plasma elimination half-life for fluconazole is approximately 30 hours and is increased in patients with impaired renal function. 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. However, accumulation is significant over 15 days and concentrations may rise 2 to 3 fold. A small amount of fluconazole undergoes hepatic metabolism. The long plasma elimination half-life provides the basis for single dose therapy for vaginal candidiasis, once daily and once weekly do5ing 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 post-dose. 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 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 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. Co-administration 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 - 4 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate

Maize starch

Colloidal anhydrous silica

Purified talc

Sodium lauryl sulphate

Hard gelatin capsule shell: Patent blue V (E131), Titanium dioxide (E171), Gelatin, water, sodium lauryl sulphate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

DIFLUZOLE 150: Carton containing transparent PVC and aluminum foil blister pack of 1 capsule.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9

Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER(S)

DIFLUZOLE 150: 38/20.2.2/0102

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

August 2004

Latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

08 June 2026