FINAL APPROVED PACKAGE INSERT

SCHEDULING STATUS S4

PROPRIETARY NAME (AND DOSAGE FORM)

DIFLUCAN® CAPSULES 150 mg

COMPOSITION

DIFLUCAN (fluconazole) is a bis-triazole: 2-(2,4-Difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)-2-propanol. Fluconazole is a white to off-white crystalline powder which is sparingly soluble in water and saline. It has a molecular weight of 306,3.

Each DIFLUCAN Capsule 150 mg contains 150 mg fluconazole.

DIFLUCAN Capsules 150 mg contain the following inactive ingredients: lactose, maize starch, colloidal silicone dioxide, magnesium stearate and sodium lauryl sulphate in a hard gelatin capsule with titanium dioxide and patent blue as colourants.

PHARMACOLOGICAL CLASSIFICATION

A.20.2.2 Fungicides

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Fluconazole, a member of the triazole antifungal agents, is an inhibitor of fungal sterol synthesis.

Pharmacokinetic properties

After oral administration fluconazole is well absorbed with systemic bioavailability being over 90 %. Peak plasma concentrations in the fasting state occur between 0,5 and 1,5 hours post dose with a plasma elimination half-life of approximately 30 hours. Plasma protein binding is low (12 %).

The major route of excretion is renal with approximately 80 % of the administered dose appearing in the urine as unchanged drug. Fluconazole clearance is proportional to creatinine clearance. There is no evidence of circulating metabolites, but accumulation is significant over 15 days and concentrations may rise 2 - 3 fold.

The long plasma elimination half-life (approximately 30 hours) provides the basis for once daily dosing in the treatment of systemic conditions, single dose therapy for vaginal candidiasis and once weekly dosing for other indications.

There have been reports of cases of superinfection with *Candida* species other than *C. albicans,* which are often inherently not susceptible to fluconazole (e.g., *Candida krusei*). Such cases may require alternative antifungal therapy.

Fluconazole is highly specific for fungal cytochrome P-450 dependant enzymes. Fluconazole has been shown not to affect testosterone plasma concentrations in males or steroid concentrations in females of child-bearing age.

INDICATIONS

Once the results of the cultures and other laboratory studies become available, anti-infective therapy should be adjusted accordingly.

When systemic treatment is indicated and appropriate, DIFLUCAN is used in the following conditions:

1. Vaginal candidiasis, acute or recurrent and prophylaxis to reduce the incidence of recurrent vaginal candidiasis.

2. Candidial balanitis

3. Dermatomycosis including tinea pedis, tinea corporis, tinea cruris, tinea unguium (onychomycosis), and dermal candida infections.

CONTRA-INDICATIONS

DIFLUCAN should not be used in patients with known hypersensitivity to fluconazole or to related azole compounds or any of the excipients.

Co-administration of other medicines known to prolong the QT interval and which are metabolised via the enzyme CYP3A4 such as cisapride, astemizole, erythromycin, pimozide and quinidine are contra-indicated in patients receiving DIFLUCAN (see INTERACTIONS section).

Pregnancy and lactation.

WARNINGS AND SPECIAL PRECAUTIONS

DIFLUCAN should be administered with caution to patients with liver dysfunction.

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

Patients have less frequently developed pruritus, rashes, urticaria, angio-oedema, dry skin, abnormal odour, exfoliative cutaneous reactions, such as Stevens-Johnson Syndrome and toxic epidermal necrolysis during treatment with DIFLUCAN. AIDS patients are more prone to the development of severe cutaneous reactions to many medicines. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and fluconazole discontinued if bullous lesions or erythema multiforme develop.

Anaphylaxis has been reported with the use of DIFLUCAN.

DIFLUCAN has been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been cases of QT prolongation and *torsade de pointes* in patients taking DIFLUCAN. 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.

DIFLUCAN should be administered with caution to patients with these potentially prodysrhythmic conditions.

DIFLUCAN should be administered with caution to patients with renal dysfunction.

DIFLUCAN is a potent CYP2C9 inhibitor and a moderate CYP3A4 inhibitor. DIFLUCAN treated patients who are concomitantly treated with medicines with a narrow therapeutic window metabolised through CYP2C9 and CYP3A4 should be monitored (see INTERACTIONS section).

Use in Children

Insufficient evidence is available to establish safety and efficacy of DIFLUCAN in the above indications for use in children.

Special precautions

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

Effects on Ability to Drive and Use Machines

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

INTERACTIONS

Concomitant use of the following other medicinal products is contra-indicated:

Cisapride: There have been reports of cardiac events including *torsade de pointes* in patients to whom

DIFLUCAN and cisapride were co-administered. A controlled study found that concomitant DIFLUCAN 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 DIFLUCAN and cisapride is contra-indicated in patients receiving DIFLUCAN (see CONTRA-INDICATIONS section).

Astemizole: Concomitant administration of DIFLUCAN with astemizole may decrease the clearance of astemizole. Resulting increased plasma concentrations of astemizole can lead to QT prolongation and *torsade de pointes*. Co-administration of DIFLUCAN and astemizole is contra- indicated (see CONTRA-INDICATIONS section).

Pimozide: Although not studied *in vitro* or *in vivo*, concomitant administration of DIFLUCAN with pimozide may result in inhibition of pimozide metabolism. Increased pimozide plasma concentrations can lead to QT prolongation and *torsade de pointes*. Co-administration of DIFLUCAN and pimozide is contra-indicated (see CONTRA-INDICATIONS section).

Quinidine: Although not studied *in vitro* or *in vivo*, concomitant administration of DIFLUCAN with quinidine may result in inhibition of quinidine metabolism. Use of quinidine has been associated with QT prolongation and *torsades de pointes*. Co-administration of DIFLUCAN and quinidine is contra-indicated (see CONTRA-INDICATIONS section).

Erythromycin: Concomitant use of DIFLUCAN and erythromycin has the potential to increase the risk of cardiotoxicity (prolonged QT interval, *torsades de pointes*) and consequently sudden death. Co-administration of DIFLUCAN and erythromycin is contra-indicated (see CONTRA-INDICATIONS section).

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

The effect of other medicinal products on fluconazole

Hydrochlorothiazide: In a pharmacokinetic interaction study, co-administration of multiple-dose hydrochlorothiazide to healthy volunteers receiving DIFLUCAN increased plasma concentrations of DIFLUCAN

by 40 %. An effect of this magnitude may necessitate a change in the DIFLUCAN dose regimen in subjects receiving concomitant diuretics.

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

The effect of fluconazole on other medicinal products

Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4. In addition to the observed /documented interactions mentioned below, there is a risk of increased plasma concentration of other compounds metabolised by CYP2C9 and CYP3A4 co-administered with DIFLUCAN. 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 DIFLUCAN treatment due to the long half-life of fluconazole (see CONTRA-INDICATIONS section).

Alfentanil: A study observed a reduction in clearance and distribution volume as well as prolongation of $t_{½}$ of alfentanil following concomitant treatment with DIFLUCAN. A possible mechanism of action is fluconazole's inhibition of CYP3A4. Dosage adjustment of alfentanil may be necessary.

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

Anticoagulants: In an interaction study, DIFLUCAN increased the prothrombin time/ international normalised ratio (INR) (12 %) after warfarin administration in healthy males. In post-marketing experience, bleeding events (bruising, epistaxis, gastrointestinal bleeding, haematuria, and melena) have been reported, in association with increases in prothrombin time/INR in patients receiving DIFLUCAN concurrently with warfarin. Prothrombin time in patients receiving warfarin should be carefully monitored. Dose adjustment of warfarin may be necessary.

Azithromycin: There was no significant pharmacokinetic interaction between DIFLUCAN and azithromycin.

Benzodiazepines (Short Acting): Following oral administration of midazolam, DIFLUCAN resulted in substantial increases in midazolam concentrations and psychomotor effects. This effect on midazolam appears to be more pronounced following oral administration of DIFLUCAN than with DIFLUCAN administered intravenously. If concomitant benzodiazepine therapy is necessary in patients being treated with DIFLUCAN, consideration should be given to decreasing the benzodiazepine dosage, and the patients should be appropriately monitored.

DIFLUCAN increases the AUC of triazolam (single dose) by approximately 50 %, C_{max} with 20 – 32 % and increases $t_{½}$ by 25 - 50 % due to the inhibition of metabolism of triazolam. Dosage adjustments of triazolam may be necessary.

Carbamazepine: DIFLUCAN inhibits the metabolism of carbamazepine and an increase in serum carbamazepine of 30 % has been observed. There is a risk of developing carbamazepine toxicity. Dosage adjustment of carbamazepine may be necessary depending on concentration measurements/effect.

Calcium Channel Blockers: Certain calcium channel antagonists (nifedipine, isradipine, amlodipine, verapamil and felodipine) are metabolized by CYP3A4. DIFLUCAN 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 DIFLUCAN (200 mg daily) and celecoxib (200 mg) the celecoxib C_{max} and AUC increased by 68 % and 134 %, respectively. A 50 % reduction of the celecoxib dose may be necessary when combined with DIFLUCAN.

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

Cyclophosphamide: Combination therapy with cyclophosphamide and DIFLUCAN results in an increase in serum bilirubin and serum creatinine.

Fentanyl: One fatal case of possible fentanyl DIFLUCAN 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 DIFLUCAN delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to respiratory depression.

Halofantrine: DIFLUCAN can increase halofantrine plasma concentration due to an inhibitory effect on CYP3A4.

HMG-CoA reductase inhibitors: The risk of myopathy and rhabdomyolysis increases when DIFLUCAN 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 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: DIFLUCAN 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 regularly.

Methadone: DIFLUCAN 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 co-administered with DIFLUCAN compared to administration of flurbiprofen alone. Similarly, the C_{max} and AUC of the pharmacologically active isomer [S-(+)-ibuprofen] were increased by 15 % and 82 %, respectively, when DIFLUCAN was co-administered with racemic ibuprofen (400 mg) compared to administration of racemic ibuprofen alone.

Although not specifically studied, DIFLUCAN has the potential to increase the systemic exposure of other NSAIDs that are metabolised by CYP2C9 (e.g. naproxen, lornoxicam, meloxicam, diclofenac). Frequent

monitoring for adverse events and toxicity related to NSAIDs is recommended. Adjustment of dosage of NSAIDs may be needed.

Oral Contraceptives: Two pharmacokinetic studies with a combined oral contraceptive have been performed using multiple doses of DIFLUCAN. 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 DIFLUCAN at these doses is unlikely to have an effect on the efficacy of the combined oral contraceptive.

Endogenous steroid: No adverse effect has been seen on endogenous steroid levels or on ACTH stimulated cortisol response.

Phenytoin: DIFLUCAN inhibits the hepatic metabolism of phenytoin. 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 insufficiency when a three month therapy with DIFLUCAN was discontinued. The discontinuation of DIFLUCAN presumably caused an enhanced CYP3A4 activity which led to increased metabolism of prednisone. Patients on long-term treatment with DIFLUCAN and prednisone should be carefully monitored for adrenal insufficiency when DIFLUCAN is discontinued.

Rifabutin: There have been reports that an interaction exists when DIFLUCAN is administered concomitantly with rifabutin, leading to increased serum levels of rifabutin up to 80 %. There have been reports of uveitis in patients to whom DIFLUCAN and rifabutin were co-administered. Patients receiving rifabutin and DIFLUCAN concomitantly should be carefully monitored.

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

Sirolimus: DIFLUCAN increases plasma concentrations of sirolimus presumably by inhibiting the metabolism

of sirolimus via CYP3A4 and P-glycoprotein. This combination may be used with a dosage adjustment of sirolimus depending on the effect/concentration measurements.

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

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

Theophylline: In a placebo controlled interaction study, the administration of DIFLUCAN 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 DIFLUCAN, and therapy modified appropriately if signs of toxicity develop.

Vinca Alkaloids: Although not studied, DIFLUCAN 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 DIFLUCAN, pseudotumour cerebri, which disappeared after discontinuation of DIFLUCAN treatment, occurred. This combination may be used but the incidence of CNS related undesirable effects should be borne in mind.

Zidovudine: DIFLUCAN 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 DIFLUCAN. Patients receiving this combination should be monitored for the development of zidovudine-

related adverse reactions. Dosage reduction of zidovudine may be considered.

Vorizonazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor): Concurrent administration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 2.5 days) and oral DIFLUCAN (400 mg on day 1, then 200 mg Q24h for 4 days) to 6 healthy male subjects resulted in an increase in C, and AUC, of voriconazole by an average of 57 % (90 % C1: 20 %, 107 %) and 79 % (90 % CI: 40 %, 128 %), respectively. In a follow-on clinical study involving 8 healthy male subjects, reduced dosing and/or frequency of voriconazole and DIFLUCAN did not eliminate or diminish this effect. Concomitant administration of voriconazole and DIFLUCAN at any dose is not recommended.

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

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

PREGNANCY AND LACTATION

Pregnancy

Safety in pregnancy and lactation has not been established.

Use in pregnancy should be avoided except in patients with severe or potentially life-threatening fungal infections in whom DIFLUCAN may be used if the anticipated benefit outweighs the possible risk to the foetus.

Lactation

DIFLUCAN is found in breast milk at concentrations similar to plasma.

DIFLUCAN should not be used in mothers breastfeeding their infants.

DOSAGE AND DIRECTIONS FOR USE

For vaginal candidiasis DIFLUCAN 150 mg should be administered as a single oral dose.

To reduce the incidence of recurrent vaginal candidiasis, a 150 mg once monthly dose may be used. The duration of therapy should be individualised, but ranges from 4 - 12 months. Some patients may require more frequent dosing.

For Candida balanitis, DIFLUCAN 150 mg should be administered as a single oral dose.

For dermal infections including tinea pedis, corporis, cruris and candida infections the recommended dosage is 150 mg once weekly. Duration of treatment is normally 2 to 4 weeks but tinea pedis may require treatment for up to 6 weeks.

For tinea unguium, the recommended dosage is 150 mg once weekly. Treatment should be continued until infected nail is replaced (uninfected nail grows in). Regrowth of fingernails and toenails normally require 3 to 6 months and 6 to 12 months, respectively. However, growth rates may vary widely in individuals and by age. After successful treatment of long term chronic infections, nails occasionally remain disfigured.

Use in Elderly

Where there is no evidence of renal impairment, normal dosage recommendations should be adopted.

Use in Renal Impairment

DIFLUCAN is cleared primarily by renal excretion as unchanged drug. No adjustments in single dose therapy are necessary.

SIDE EFFECTS

In some patients, particularly those with serious underlying diseases such as AIDS and cancer, changes in renal and haematological function test results and hepatic abnormalities have been observed during treatment with DIFLUCAN, but the clinical significance and relationship to treatment is uncertain.

The following undesirable effects have been observed and reported during treatment with DIFLUCAN with the following frequencies: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to ≤ 1/100); rare (≥ 1/10,000 to ≤ 1/1,000); very rare (≤ 1/10,000), not known (cannot be estimated form the

available data).

System Organ Class	Frequency	Undesirable effects
Blood and the lymphatic system disorders	Rare	Agranulocytosis, leucopenia, neutropenia, thrombocytopenia
Immune system disorders	Rare	Anaphylaxis, angioedema
Metabolism and nutrition disorders	Rare	Hypertriglyceridaemia, 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*, QT prolongation
Gastrointestinal disorders	Common	Abdominal pain, diarrhoea, nausea, vomiting
	Uncommon	Dyspepsia, flatulence, dry mouth
Hepato-biliary disorders	Common	Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased
	Uncommon	Cholestasis, jaundice, bilirubin increased
	Rare	Hepatic toxicity, including fatal cases, hepatic failure, hepatocellular necrosis, hepatitis, hepatocellular damage

Skin and subcutaneous tissue disorders	Common	Rash
	Uncommon	Pruritus, urticaria, increased sweating, drug eruption
	Rare	Toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalised exanthematous-pustulosis, dermatitis exfoliative, face oedema, alopecia
Musculoskeletal, connective tissue and bone disorders	Uncommon	Myalgia
General disorders and administration site conditions	Uncommon	Fatigue, malaise, asthenia, fever

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

There have been reports of overdose with DIFLUCAN accompanied by hallucinations and paranoid behaviour.

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

DIFLUCAN 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 %.

IDENTIFICATION

Hard gelatin capsules with a turquoise blue body and cap, imprinted with the Pfizer logo and an identity code FLU-150.

PRESENTATION

Blister packs containing 1 or 4 capsules.

STORAGE INSTRUCTIONS

Store at or below 30 ^{o}C in a dry place. Keep out of reach of children.

REGISTRATION NUMBER

V/20.2.2/340

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

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Sandton

2196

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