SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

DIFLUCAN® TABLETS 200 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each DIFLUCAN tablet 200 mg contains 200 mg fluconazole.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

Pink trapezoidal tablets engraved with 'DIFLUCAN' and '200' on the front and 'ROERIG' on the back.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

DIFLUCAN is indicated for the treatment of the following conditions in adults:

- Cryptococcal meningitis in mentally alert patients without localising neurological signs and as a follow up therapy after Amphotericin B therapy
- Maintenance therapy to prevent relapse of cryptococcal disease in patients with acquired immunodeficiency syndrome (AIDs)
- Systemic candidiasis
- Oropharyngeal and oesophageal candidiasis
- Prevention of fungal infections in patients with malignancy who are predisposed to such infections as a result

of cytotoxic chemotherapy and radiotherapy

4.2 Posology and method of administration

Posology

The daily dose of DIFLUCAN should be based on the nature and severity of the fungal infection.

Therapy for those types of infections requiring multiple dose treatment should be continued until clinical parameters or laboratory tests indicate that active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection.

Patients with AIDS and cryptococcal meningitis or recurrent oropharyngeal candidiasis usually require maintenance therapy to prevent relapse.

Use in adults

1. For cryptococcal meningitis the usual dose is 400 mg on the first day followed by 200 mg once daily. Depending on the clinical response of the patient this dose may be increased to 400 mg daily. Usually, duration of treatment for cryptococcal meningitis is 6 to 8 weeks.

For the prevention of relapse of cryptococcal meningitis in patients with AIDS, after the patient receives a full course of primary therapy, DIFLUCAN may be administered at a daily dose of 100 mg to 200 mg until the CD4 count has stabilised at more than 250 cells/mm^3.

2. For systemic candidiasis the usual dose is 400 mg on the first day followed by 200 mg daily. Depending on the clinical response, the dose may be increased to 400 mg daily. Duration of treatment is based upon the clinical response.

3. For oropharyngeal candidiasis, the usual dose is 50 mg to 100 mg once daily for 7 to 14 days. If necessary, treatment can be continued for longer periods in patients with severely compromised immune function.

For the prevention of relapse of oropharyngeal candidiasis in patients with AIDS, after the patient receives a full course of primary therapy, DIFLUCAN may be administered at a 150 mg once weekly dose.

For oesophageal candidiasis, the recommended dose is 200 mg on the first day, followed by 100 mg to 200 mg once daily. Doses up to 400 mg/day may be used, based on medical judgment of the patient's response to therapy. Patients with oesophageal candidiasis should be treated for a minimum of 3 weeks and for at least 2 weeks following resolution of symptoms.

4. The recommended DIFLUCAN dosage for the prevention of candidiasis is 50 mg to 400 mg once daily, based on the patients risk for developing fungal infection. For patients at high risk of systemic infection e.g. patients who are anticipated to have profound or prolonged neutropenia, a dose of 400 mg once daily has been used. DIFLUCAN administration should start several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 1000 cells per mm^3.

Special populations

Use in elderly patients

Where there is no evidence of renal impairment, normal dosage recommendations should be adopted. For patients with renal impairment (creatinine clearance < 50 mL/min) the dosage schedule should be adjusted as described below.

Use in patients with impaired renal function

DIFLUCAN is cleared primarily by renal excretion as unchanged medicine. No adjustments in single dose therapy are necessary. Multiple-dose therapy should be carefully monitored in patients with renal impairment.

In patients with impaired renal function, an initial dose of 50 mg to 400 mg should be given. After the loading dose, the daily dose (according to indication) should be based on the following table:

Creatinine clearance (mL/min)	**DIFLUCAN**

	Percent of recommended dose
> 50	100 %
≤ 50 (no dialysis)	50 %
Haemodialysis	100 % after each haemodialysis

Patients on haemodialysis should receive 100 % of the recommended dose after each haemodialysis; on non-dialysis days, patients should receive a reduced dose according to their creatinine clearance.

These are suggested dose adjustments based on pharmacokinetics following administration of multiple doses. Further adjustment may be needed depending upon clinical condition. When serum creatinine is the only measure of renal function available, the following formula (based on sex, weight, and age of the patient) should be used to estimate the creatinine clearance:

Males:

$$\frac{[140 - \text{age}] \times \text{Wt (kg)} \times \text{constant}}{S_{cr}\ (\text{mmol/L})}$$

Constant = 1,23 for males

Females:

$$\frac{[140 - \text{age}] \times \text{Wt (kg)} \times \text{constant}}{S_{cr}\ (\text{mmol/L})}$$

Constant = 1,04 for females (0,85 x 1,23 = 1,04)

S_{cr} = serum creatinine

Method of administration

For oral use.

4.3 Contraindications

- DIFLUCAN should not be used in patients with known hypersensitivity to fluconazole or to related azole

medicines or any of the excipients of DIFLUCAN (listed in section 6.1).

- Co-administration of terfenadine is contraindicated in patients receiving DIFLUCAN at multiple doses of 400 mg per day or higher based upon results of a multiple dose interaction study. 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, erythromycin, pimozide and quinidine are contraindicated in patients receiving DIFLUCAN (see sections 4.4 and 4.5).
- Pregnancy and lactation.

4.4 Special warnings and precautions for use

Hepatobiliary system

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

DIFLUCAN has been associated with cases of serious hepatic toxicity including fatalities, primarily in patients with serious underlying medical conditions. In cases of DIFLUCAN-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 DIFLUCAN.

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 DIFLUCAN. AIDS patients are more prone to the development of severe cutaneous reactions to many medicines. If a rash, which is considered attributable to DIFLUCAN, develops in a patient treated for a superficial fungal infection, further therapy with DIFLUCAN should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and DIFLUCAN discontinued if bullous lesions or erythema multiforme develop.

Hypersensitivity

Anaphylaxis has been reported with the use of DIFLUCAN.

Cardiovascular system

DIFLUCAN has been associated with prolongation of the QT interval on the electrocardiogram. DIFLUCAN causes QT prolongation via the inhibition of Rectifier Potassium Channel current (I_{kr}). 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 cases of QT prolongation and *torsades 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 medicines that may have been contributory. Patients with hypokalaemia and advanced cardiac failure are at an increased risk for the occurrence of life-threatening ventricular dysrhythmias and *torsades de pointes.*

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

Halofantrine

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

Renal system

DIFLUCAN should be administered with caution to patients with renal dysfunction (see section 4.2).

Adrenal insufficiency

DIFLUCAN may cause adrenal insufficiency relating to concomitant treatment with prednisone (see section 4.5, *The effect of DIFLUCAN on other medicines*).

Cytochrome P450

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

Terfenadine

The co-administration of DIFLUCAN at doses lower than 400 mg per day with terfenadine should be carefully monitored (see sections 4.3 and 4.5).

4.5 Interaction with other medicines and other forms of interaction

Concomitant use of the following other medicines is contraindicated:

Cisapride

There have been reports of cardiac events including *torsades 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 contraindicated in patients receiving DIFLUCAN (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 DIFLUCAN failed to demonstrate a prolongation in QTc interval. Another study at a 400 mg and 800 mg daily dose of DIFLUCAN demonstrated that DIFLUCAN taken in doses of 400 mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. The combined use of DIFLUCAN at doses of 400 mg or greater with terfenadine is contraindicated. The coadministration of DIFLUCAN at doses lower than 400 mg per day with terfenadine should be carefully monitored (see section 4.3).

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 *torsades de*

pointes. Co-administration of DIFLUCAN and astemizole is contraindicated (see section 4.3).

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 *torsades de pointes*. Co-administration of DIFLUCAN and pimozide is contraindicated (see section 4.3).

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 contraindicated (see section 4.3).

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 contraindicated (see section 4.3).

Concomitant use of the following other medicines cannot be recommended:

Halofantrine

DIFLUCAN can increase halofantrine plasma concentration due to an inhibitory effect on CYP3A4. Concomitant use of DIFLUCAN 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 DIFLUCAN with amiodarone may increase QT prolongation. Caution must be exercised if the concomitant use of DIFLUCAN and amiodarone is necessary, notably with high dose DIFLUCAN (800 mg) (see section 4.4).

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

The effect of other medicines on DIFLUCAN

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.

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 absorption occurs.

The effect of DIFLUCAN on other medicines

DIFLUCAN is a moderate inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and 3A4. DIFULCAN is also a strong inhibitor of the isoenzyme CYP2C19. In addition to the observed/documented interactions mentioned below, there is a risk of increased plasma concentration of other medicines metabolised by CYP2C9, CYP2C19 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 DIFLUCAN persists for 4 – 5 days after discontinuation of DIFLUCAN treatment due to the long half-life of DIFLUCAN (see section 4.3).

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 DIFLUCAN'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.

Amphotericin B

Concurrent administration of DIFLUCAN 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 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 coumarin-type (warfarin) or indanedione anticoagulants should be carefully monitored. Dose adjustment of these anticoagulants may be necessary.

Azithromycin

There was no significant pharmacokinetic interaction between DIFLUCAN and azithromycin.

Benzodiazepines (short-acting), i.e. midazolam, triazolam

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} by 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 metabolised 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. The combination may be used while taking increased consideration to the risk of increased serum bilirubin and serum creatinine.

Endogenous steroid

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

Fentanyl

One fatal case of possible fentanyl DIFLUCAN interaction was reported. The author judged that the patient died from fentanyl intoxication. Furthermore, in a randomised 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.

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 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.

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 (NSAIDS)

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.

Olaparib

Moderate inhibitors of CYP3A4 such as DIFLUCAN 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.

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 DIFLUCAN 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.

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 (see section 4.4).

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} by approximately 55 % and decreases the clearance of saquinavir by 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.

Tofacitinib

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

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. Potential central nervous system (CNS) adverse events should be monitored for when this combination of medicines is used.

Voriconazole (CYP2C9, CYP2C19 and CYP3A4 inhibitor)

Concurrent administration of oral voriconazole (400 mg every 12 hours for 1 day, then 200 mg every 12 hours for 2,5 days) and oral DIFLUCAN (400 mg on day 1, then 200 mg every 24 hours for 4 days) to 8 healthy male subjects resulted in an increase in C_{max}, and AUCτ, of voriconazole by an average of 57 % (90 % CI: 20 %, 107 %) and 79 % (90 % CI: 40 %, 128 %), respectively. 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.

Zidovudine

DIFLUCAN increases C_{max} and AUC of zidovudine by 84 % and 74 %, respectively, due to an approximately 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.

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females

Effective contraceptive measures must be used in women of childbearing potential and should continue throughout the treatment period and for approximately 1 week (5 to 6 half-lives) after the final dose.

Pregnancy

DIFLUCAN is contraindicated for use during pregnancy (see section 4.3).

There have been reports of congenital abnormalities in infants whose mothers were treated with DIFLUCAN.

There have been reports of multiple congenital abnormalities in infants whose mothers were being treated for 3 or more months with high dose (400 to 800 mg/day) DIFLUCAN therapy for coccidioidomycosis.

A few published case reports describe a distinctive and a rare pattern of birth defects among infants whose mother received high-dose (400 to 800 mg/day) DIFLUCAN during most or all of the first trimester of pregnancy. The features seen in these infants include: brachycephaly, abnormal facies, abnormal calvarial

development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital heart disease.

Breastfeeding

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

DIFLUCAN should not be used in mothers breastfeeding their infants.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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.

Tabulated summary of adverse reactions

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 lymphatic system disorders	Rare	Agranulocytosis, leukopenia, neutropenia, thrombocytopenia
Immune system	Rare	Anaphylaxis

disorders		
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	*Torsades de pointes*, QT prolongation
Gastrointestinal disorders	Common	Abdominal pain, diarrhoea, nausea, vomiting
	Uncommon	Dyspepsia, flatulence, dry mouth
Hepato-biliary disorders	Common	Increased alanine aminotransferase, increased aspartate aminotransferase, increased blood alkaline phosphatase
	Uncommon	Cholestasis, jaundice, increased bilirubin
	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 (including fixed drug eruption)
	Rare	Toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalised exanthematous-pustulosis, exfoliative dermatitis, angioedema, face oedema, alopecia
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders	Uncommon	Myalgia
General disorders and administration site conditions	Uncommon	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 asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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 %.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.2.2 Fungicides

Mechanism of action

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

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 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.

5.2 Pharmacokinetic properties

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

Absorption

After oral administration in adults, 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. 90 % 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.

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 medicine. 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 and single dose therapy for vaginal candidiasis and once-weekly dosing for

other indications.

A pharmacokinetic study in 10 lactating women, who had temporarily or permanently stopped breastfeeding 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Dibasic calcium phosphate anhydrous

Povidone

Croscarmellose sodium

FD&C Red No. 40 aluminium lake dye

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months

6.4 Special precautions for storage

Store at or below 30 ^{o}C.

6.5 Nature and contents of container

Blue-white HDPE bottles containing 28 tablets.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

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South Africa

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8. REGISTRATION NUMBER

35/20.2.2/0187

9. DATE OF FIRST AUTHORISATION

19 February 2001

10. DATE OF REVISION OF THE TEXT

09 November 2020

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