FINAL APPROVED PACKAGE INSERT

SCHEDULING STATUS: S4

PROPRIETARY NAMES (AND DOSAGE FORMS):

DIFLUCAN® CAPSULES 50 mg

DIFLUCAN® CAPSULES 200 mg

DIFLUCAN® IV INFUSION 100 ml

DIFLUCAN® 50 mg/5 ml Powder for Oral Suspension

DIFLUCAN® 200 mg/5 ml Powder for Oral Suspension

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 50 mg contains 50 mg fluconazole.

Each DIFLUCAN Capsule 200 mg contains 200 mg fluconazole.

DIFLUCAN Capsules contain the following inactive ingredients: lactose, maize starch, colloidal silicone dioxide, magnesium stearate and sodium lauryl sulphate in a hard gelatin capsule containing titanium dioxide with or without patent blue as colourants.

Each DIFLUCAN IV Infusion 100 ml contains 200 mg fluconazole (2 mg/ml).

DIFLUCAN Intravenous Infusion is a sterile aqueous solution which is made iso-osmotic with sodium chloride.

DIFLUCAN 50 mg/5 ml Powder for Oral Suspension yields on reconstitution with 24 ml water a suspension containing the equivalent of 50 mg fluconazole per 5 ml with 0,24 % m/v sodium benzoate as preservative.

DIFLUCAN 200 mg/5 ml Powder for Oral Suspension yields on reconstitution with 24 ml water a suspension containing the equivalent of 200 mg fluconazole per 5 ml with 0,24 % m/v sodium benzoate as preservative.

DIFLUCAN Powder for Oral Suspension contains the following inactive ingredients: Sucrose (2,88 g per 50 mg dose in 50 mg/5 ml or 2,73 g per 200 mg dose in 200 mg/5 ml), colloidal anhydrous silica, titanium dioxide, xanthan gum, sodium citrate dihydrate, citric acid anhydrous, sodium benzoate and natural orange flavour as flavourant.

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 in adults, 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 %).

Pharmacokinetic studies performed in children have shown that fluconazole is cleared faster than in adults, with a half-life of 23 hours. The volume of distribution of fluconazole in children under 1 year of age (950 ml/kg) is higher than in adults (700 ml/kg). Accumulation on multiple daily dosing is therefore less and steady state plasma levels are achieved faster than in adults.

In neonates, the half-lives determined over the first 2 weeks of life are considerably longer than adult values with a mean of 74 hours at Day 1 and 47 hours at Day 13 of life. The volume of distribution is about 1 200 ml/kg in neonates.

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 and single dose therapy for vaginal candidiasis.

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.

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 and children:

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

CONTRAINDICATIONS:

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 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 enzyme CYP3A4 such as cisapride, astemizole, erythromycin, pimozide and quinidine are contraindicated 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 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, 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 patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and DIFLUCAN 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 (see DOSAGE AND DIRECTIONS FOR USE section).

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).

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.

DIFLUCAN powder for oral suspension contains sucrose and should not be used in patients with hereditary fructose, glucose/galactose malabsorption and sucrase-isomaltase deficiency.

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 contraindicated:

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 contraindicated in patients receiving DIFLUCAN (see CONTRAINDICATIONS 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 contraindicated (see CONTRAINDICATIONS 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 contraindicated (see CONTRAINDICATIONS 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 contraindicated (see CONTRAINDICATIONS 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 contraindicated (see CONTRAINDICATIONS 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 CONTRAINDICATIONS 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 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.

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.

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 ethinyloestradiol 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.

Voriconazole (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 % 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.

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.

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:

There are no adequate and well-controlled studies which assessed the safety of DIFLUCAN treatment in pregnant women. There have been reports of congenital abnormalities in infants whose mothers were treated with DIFLUCAN. The relationship between DIFLUCAN use and these events is unclear.

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. The relationship between DIFLUCAN use and these events is unclear.

A few published case reports describe a distinctive and a rare pattern of birth defects among infants whose mother received high-dose (400 – 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.

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:

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.

To reconstitute the powder for oral suspension: Tap the bottle to loosen powder. Add 24 ml of water. Shake well. Shake immediately prior to use.

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 – 8 weeks.

   For the prevention of relapse of cryptococcal meningitis in patients with AIDS, after the patient received a full course of primary therapy, DIFLUCAN may be administered at a daily dose of 100 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 to 100 mg once daily for 7 – 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 three weeks and for at least two 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 1 000 cells per mm^3.

Use in elderly:

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.

Dosage in patients with impaired renal function:

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

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

DOSAGE AND ADMINISTRATION

	DIFLUCAN
Creatinine clearance (ml/min)	Percent of recommended dose
> 50	100 %
≤ 50	50 %
Regular haemodialysis	100 % after each dialysis

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

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

Use in children:

As with similar infections in adults, the duration of treatment is based on the clinical and mycological response. The maximum adult daily dosage should not be exceeded in children. DIFLUCAN is administered as a single daily dose.

1. The recommended dosage of DIFLUCAN for oropharyngeal candidiasis in children is 6 mg/kg on the first day, followed by 3 mg/kg once daily.

   Treatment should be administered for at least 2 weeks to decrease the likelihood of relapse.
2. For the treatment of oesophageal candidiasis, the recommended dosage of DIFLUCAN in children is 6 mg/kg on the first day, followed by 3 mg/kg once daily. Doses up to 12 mg/kg/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 three weeks and for at least 2 weeks following the resolution of symptoms.
3. For the treatment of systemic candidiasis and cryptococcal infection, the recommended dosage is 6 – 12 mg/kg/day, depending on the severity of the disease.
4. For the prevention of fungal infections in immunocompromised patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, the dose should be 3 – 12 mg/kg daily, depending on the extent and duration of the induced neutropenia. (For children with impaired renal function, see Dosage in patients with impaired renal function).

For children with impaired renal function the daily dose should be reduced in accordance with the guidelines given for adults, dependent on the degree of renal impairment.

Use in children 4 weeks of age and younger:

Neonates excrete DIFLUCAN slowly. In the first two weeks of life the same mg/kg dosing as in older children should be used but administered every 72 hours. During weeks 3 and 4 of life the same dose should be given every 48 hours.

Intravenous infusion:

DIFLUCAN is formulated in 0,9 % sodium chloride solution, each 200 mg (100 ml bottle) containing 15 mmol each of Na+ and Cl-. Because DIFLUCAN is available as a dilute saline solution, in patients requiring sodium or fluid restriction, consideration should be given to the rate of fluid administration.

DIFLUCAN intravenous infusion is compatible with the following administration fluids:

a) Dextrose 20 %

b) Ringer's solution

c) Normal saline

d) Potassium chloride in dextrose

e) Sodium bicarbonate 4,2 %

DIFLUCAN may be infused at a maximum rate of approximately 200 mg/hour through an existing line with one of the above listed fluids. Although no specific incompatibilities have been noted, mixing with any other drug prior to infusion is not recommended.

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 from 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
Hepatobiliary 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

Paediatric population:

The pattern and incidence of adverse events and laboratory abnormalities recorded during paediatric clinical trials are comparable to those seen in adults.

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:

DIFLUCAN Capsules 50 mg: Hard gelatin capsules with a white opaque body and a turquoise blue cap imprinted with the Pfizer logo and an identity code FLU-50.

DIFLUCAN Capsules 200 mg: Hard gelatin capsules with a white opaque body and a purple opaque cap imprinted with the Pfizer logo and the code FLU-200.

DIFLUCAN IV Infusion 100 ml: Clear glass vials containing a clear, colourless solution.

DIFLUCAN 50 mg/5 ml and 200 mg/5 ml is a dry powder which yields on reconstitution with water an off-white, orange flavoured suspension. The colour of the powder is white to off-white.

PRESENTATION:

DIFLUCAN Capsules 50 mg: Blister packs containing 14 capsules.

DIFLUCAN Capsules 200 mg: Blister packs containing 28 and 30 capsules.

DIFLUCAN IV Infusion 100 ml: Glass vials each containing 100 ml.

DIFLUCAN 50 mg/5 ml and 200 mg/5 ml: Translucent HDPE bottles with child-resistant closures containing 35 ml of reconstituted suspension with a 5 ml overage.

STORAGE INSTRUCTIONS:

DIFLUCAN Capsules 50 mg and 200 mg: Store at or below 30 °C.

DIFLUCAN IV Infusion: Store at or below 30 °C. Do not freeze. Discard remaining contents after use.

DIFLUCAN 50 mg/5 ml and 200 mg/5 ml:

Before reconstitution: Store at or below 30 °C in a dry place.

After reconstitution: Store suspension between 30 °C and 5 °C. Protect from freezing. Discard unused portion after 2 weeks.

Keep out of reach of children.

REGISTRATION NUMBERS:

DIFLUCAN Capsules 50 mg: V/20.2.2/339

DIFLUCAN Capsules 200 mg: 28/20.2.2/151

DIFLUCAN IV Infusion 100 ml: Z/20.2.2/272

DIFLUCAN 50 mg/5 ml: 30/20.2.2/0150

DIFLUCAN 200 mg/5 ml: 30/20.2.2/0151

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

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton, 2196

South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT:

23 March 2015

BOTSWANA: S2

DIFLUCAN Capsules 50 mg: Reg. No.: B9316300

DIFLUCAN Capsules 200 mg: Reg. No.: BOT9800296

DIFLUCAN IV Infusion 100 ml: Reg. No.:BOT0200476

DIFLUCAN 50 mg/5 ml Powder for Oral Suspension: Reg. No.: BOT0200477

NAMIBIA: S2

DIFLUCAN Capsules 50 mg: Reg. No.: 04/20.2.2/1244

DIFLUCAN Capsules 200 mg: Reg. No.: 01/A20.2.2/003

DIFLUCAN IV Infusion 100 ml: Reg. No.: 04/20.2.2/1247

DIFLUCAN 50 mg/5 ml Powder for Oral Suspension: Reg. No.: 04/20.2.2/1248

DIFLUCAN 200 mg/5 ml Powder for Oral Suspension: Reg. No.: 04/20.2.2/1249