

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

Note: This SPC, labelling and packages leaflet is the version valid at the time of Commission decision.

After the Commission decision the Member State competent authorities, in liaison with the reference Member State, will update the product information as required. Therefore, this SPC, labelling and package leaflet may not necessarily represent the current text.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Diflucan and associated names (see Annex I) 150 mg hard capsules

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains fluconazole 150 mg.

Excipients: each hard capsule also contains 149.12 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

The 150 mg hard gelatin capsule has a turquoise blue body and turquoise blue cap overprinted with "Pfizer" and the code "FLU-150" with black ink. The capsule size is no. 1.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diflucan is indicated in the following fungal infections in adults (see section 5.1):

- Acute vaginal candidiasis when local therapy is not appropriate.
- *Candidal balanitis* when local therapy is not appropriate.

Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.

Consideration should be given to official guidance on the appropriate use of antifungals.

4.2 Posology and method of administration

Posology

Adults

Single dose 150 mg.

Special populations

Elderly

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

Renal impairment

Fluconazole is predominantly excreted in the urine as unchanged active substance. No adjustments in single dose therapy are necessary.

Hepatic impairment

Limited data are available in patients with hepatic impairment, therefore fluconazole should be administered with caution to patients with liver dysfunction (see sections 4.4 and 4.8).

Paediatric population

Safety and efficacy for genital candidiasis indication in paediatric population has not been established. Current available data for other paediatric indications are described in section 4.8. If treatment is imperative in adolescents (from 12 to 17 years old), the posology should be the same as adults posology.

Method of administration

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

4.3 Contraindications

Hypersensitivity to the active substance, to related azole substances, or to any of the excipients (see section 6.1).

Coadministration 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. Coadministration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 such as cisapride, astemizole, pimozide, quinidine and erythromycin are contraindicated in patients receiving fluconazole (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Renal system

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

Hepatobiliary system

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. Fluconazole hepatotoxicity has usually been reversible on discontinuation of therapy.

Patients who develop abnormal liver function tests during fluconazole therapy must be monitored closely for the development of more serious hepatic injury.

The patient should be informed of suggestive symptoms of serious hepatic effect (important asthenia, anorexia, persistent nausea, vomiting and jaundice). Treatment of fluconazole should be immediately discontinued and the patient should consult a physician.

Cardiovascular system

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and *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 treatment that may have been contributory.

Diflucan should be administered with caution to patients with these potentially proarrhythmic conditions. Coadministration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 are contraindicated (see sections 4.3 and 4.5).

Halofantrine

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

Dermatological reactions

Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, during treatment with fluconazole. AIDS patients are more prone to the development of severe cutaneous reactions to many medicinal products. If a rash, which is considered attributable to fluconazole, develops in a patient treated for a superficial fungal infection, further therapy with this medicinal product should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and fluconazole discontinued if *bullous* lesions or *erythema multiforme* develop.

Hypersensitivity

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

Cytochrome P450

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

Terfenadine

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

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of the following other medicinal products is contraindicated

Cisapride: There have been reports of cardiac events including *torsades de pointes* in patients to whom fluconazole and cisapride were coadministered. A controlled study found that concomitant fluconazole 200 mg once daily and cisapride 20 mg four times a day yielded a significant increase in cisapride plasma levels and prolongation of QTc interval. Concomitant treatment with fluconazole and cisapride is contraindicated (see section 4.3).

Terfenadine: Because of the occurrence of serious cardiac dysrhythmias secondary to prolongation of the QTc interval in patients receiving azole antifungals in conjunction with terfenadine, interaction studies have been performed. One study at a 200 mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. Another study at a 400 mg and 800 mg daily dose of fluconazole demonstrated that fluconazole taken in doses of 400 mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. The combined use of fluconazole at doses of 400 mg or greater with terfenadine is contraindicated (see section 4.3). The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored.

Astemizole: Concomitant administration of fluconazole with astemizole may decrease the clearance of astemizole. Resulting increased plasma concentrations of astemizole can lead to QT prolongation and rare occurrences of *torsades de pointes*. Coadministration of fluconazole and astemizole is contraindicated (see section 4.3).

Pimozide: Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with pimozide may result in inhibition of pimozide metabolism. Increased pimozide plasma concentrations can lead to QT prolongation and rare occurrences of *torsades de pointes*. Coadministration of fluconazole and pimozide is contraindicated (see section 4.3).

Quinidine: Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with quinidine may result in inhibition of quinidine metabolism. Use of quinidine has been associated with QT prolongation and rare occurrences of *torsades de pointes*. Coadministration of fluconazole and quinidine is contraindicated (see section 4.3).

Erythromycin: Concomitant use of fluconazole and erythromycin has the potential to increase the risk of cardiotoxicity (prolonged QT interval, *torsades de pointes*) and consequently sudden heart death. Coadministration of fluconazole and erythromycin is contraindicated (see section 4.3).

Concomitant use of the following other medicinal products cannot be recommended:

Halofantrine: Fluconazole can increase halofantrine plasma concentration due to an inhibitory effect on CYP3A4. Concomitant use of fluconazole and halofantrine has the potential to increase the risk of cardiotoxicity (prolonged QT interval, *torsades de pointes*) and consequently sudden heart death. This combination should be avoided (see section 4.4).

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

The effect of other medicinal products on fluconazole

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

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

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. Fluconazole is also an inhibitor of the isozyme CYP2C19. In addition to the observed/documented interactions mentioned below, there is a risk of increased plasma concentration of other compounds metabolized by CYP2C9 and CYP3A4 coadministered with fluconazole. Therefore caution should be exercised when using these combinations and the patients should be carefully monitored. The enzyme inhibiting effect of fluconazole persists 4-5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole (see section 4.3).

Alfentanil: During concomitant treatment with fluconazole (400 mg) and intravenous alfentanil (20 µg/kg) in healthy volunteers the alfentanil AUC₁₀ increased 2-fold, probably through inhibition of CYP3A4. Dose adjustment of alfentanil may be necessary.

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

Amphotericin B: Concurrent administration of fluconazole and amphotericin B in infected normal and immunosuppressed mice showed the following results: a small additive antifungal effect in systemic infection with *C. albicans*, no interaction in intracranial infection with *Cryptococcus neoformans*, and antagonism of the two medicinal products in systemic infection with *A. fumigatus*. The clinical significance of results obtained in these studies is unknown.

Anticoagulants: In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria, and melena) have been reported, in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. During concomitant treatment with fluconazole and warfarin the prothrombin time was prolonged up to 2-fold, probably due to an inhibition of the warfarin metabolism through CYP2C9. In patients receiving

coumarin-type anticoagulants concurrently with fluconazole the prothrombin time should be carefully monitored. Dose adjustment of warfarin may be necessary.

Benzodiazepines (short acting), i.e. midazolam, triazolam: Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. Concomitant intake of fluconazole 200 mg and midazolam 7.5 mg orally increased the midazolam AUC and half-life 3.7-fold and 2.2-fold, respectively. Fluconazole 200 mg daily given concurrently with triazolam 0.25 mg orally increased the triazolam AUC and half-life 4.4-fold and 2.3-fold, respectively. Potentiated and prolonged effects of triazolam have been observed at concomitant treatment with fluconazole. If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dose, and the patients should be appropriately monitored.

Carbamazepine: Fluconazole inhibits the metabolism of carbamazepine and an increase in serum carbamazepine of 30% has been observed. There is a risk of developing carbamazepine toxicity. Dose 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. Fluconazole has the potential to increase the systemic exposure of the calcium channel antagonists. Frequent monitoring for adverse events is recommended.

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

Cyclophosphamide: Combination therapy with cyclophosphamide and fluconazole results in an increase in serum bilirubin and serum creatinine. The combination may be used while taking increased consideration to the risk of increased serum bilirubin and serum creatinine.

Fentanyl: One fatal case of fentanyl intoxication due to possible fentanyl fluconazole interaction was reported. Furthermore, it was shown in healthy volunteers that fluconazole delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to respiratory depression. Patients should be monitored closely for the potential risk of respiratory depression. Dosage adjustment of fentanyl may be necessary.

HMG CoA reductase inhibitors: The risk of myopathy and rhabdomyolysis increases when fluconazole is coadministered 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.

Immunosuppressors (i.e. ciclosporin, everolimus, sirolimus and tacrolimus):

Ciclosporin: Fluconazole significantly increases the concentration and AUC of ciclosporin. During concomitant treatment with fluconazole 200 mg daily and ciclosporin (2.7 mg/kg/day) there was a 1.8 fold increase in ciclosporin AUC. This combination may be used by reducing the dose of ciclosporin depending on ciclosporin concentration.

Everolimus: Although not studied *in vivo* or *in vitro*, fluconazole may increase serum concentrations of everolimus through inhibition of CYP3A4.

Sirolimus: Fluconazole increases plasma concentrations of sirolimus presumably by inhibiting the metabolism of sirolimus via CYP3A4 and P-glycoprotein. This combination may be used with a dose adjustment of sirolimus depending on the effect/concentration measurements.

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

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

Methadone: Fluconazole may enhance the serum concentration of methadone. Dose adjustment of methadone may be necessary.

Non-steroidal anti-inflammatory drugs: The C_{max} and AUC of flurbiprofen was increased by 23% and 81%, respectively, when coadministered with fluconazole compared to administration of flurbiprofen alone. Similarly, the C_{max} and AUC of the pharmacologically active isomer [S-(+)-ibuprofen] was increased by 15% and 82%, respectively, when fluconazole was coadministered with racemic ibuprofen (400 mg) compared to administration of racemic ibuprofen alone.

Although not specifically studied, fluconazole has the potential to increase the systemic exposure of other NSAIDs that are metabolized by CYP2C9 (e.g. naproxen, lornoxicam, meloxicam, diclofenac). Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Adjustment of dose of NSAIDs may be needed.

Phenytoin: Fluconazole inhibits the hepatic metabolism of phenytoin. Concomitant repeated administration of 200 mg fluconazole and 250 mg phenytoin intravenously, caused an increase of the phenytoin AUC_{24} by 75% and C_{min} by 128%. With coadministration, serum phenytoin concentration levels should be monitored in order to avoid phenytoin toxicity.

Prednisone: There was a case report that a liver-transplanted patient treated with prednisone developed acute adrenal cortex insufficiency when a three month therapy with fluconazole was discontinued. The discontinuation of fluconazole presumably caused an enhanced CYP3A4 activity which led to increased metabolism of prednisone. Patients on long-term treatment with fluconazole and prednisone should be carefully monitored for adrenal cortex insufficiency when fluconazole is discontinued.

Rifabutin: Fluconazole increases serum concentrations of rifabutin, leading to increase in the AUC of rifabutin up to 80%. There have been reports of uveitis in patients to whom fluconazole and rifabutin were coadministered. In combination therapy, symptoms of rifabutin toxicity should be taken into consideration.

Saquinavir: Fluconazole increases the AUC and C_{max} of saquinavir with approximately 50% and 55% respectively, due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein. Interaction with saquinavir/ritonavir has not been studied and might be more marked. Dose adjustment of saquinavir may be necessary.

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

Theophylline: In a placebo controlled interaction study, the administration of fluconazole 200 mg for 14 days resulted in an 18% decrease in the mean plasma clearance rate of theophylline. Patients who are receiving high dose theophylline or who are otherwise at increased risk for theophylline toxicity should be observed for signs of theophylline toxicity while receiving fluconazole. Therapy should be modified if signs of toxicity develop.

Vinca alkaloids: Although not studied, fluconazole may increase the plasma levels of the vinca alkaloids (e.g. vincristine and vinblastine) and lead to neurotoxicity, which is possibly due to an inhibitory effect on CYP3A4.

Vitamin A: Based on a case-report in one patient receiving combination therapy with all-trans-retinoid acid (an acid form of vitamin A) and fluconazole, CNS related undesirable effects have developed in the form of pseudotumour *cerebri*, which disappeared after discontinuation of fluconazole treatment. This combination may be used but the incidence of CNS related undesirable effects should be borne in mind.

Voriconazole: (CYP2C9 and CYP3A4 inhibitor): Coadministration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 2.5 days) and oral fluconazole (400 mg on day 1, then 200 mg Q24h for 4 days) to 8 healthy male subjects resulted in an increase in C_{max} and AUC_{τ} of voriconazole by an average of 57% (90% CI: 20%, 107%) and 79% (90% CI: 40%, 128%), respectively. The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole associated adverse events is recommended if voriconazole is used sequentially after fluconazole.

Zidovudine: Fluconazole increases C_{max} and AUC of zidovudine by 84% and 74%, respectively, due to an approx. 45% decrease in oral zidovudine clearance. The half-life of zidovudine was likewise prolonged by approximately 128% following combination therapy with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions. Dose reduction of zidovudine may be considered.

Azithromycin: An open-label, randomized, three-way crossover study in 18 healthy subjects assessed the effect of a single 1200 mg oral dose of azithromycin on the pharmacokinetics of a single 800 mg oral dose of fluconazole as well as the effects of fluconazole on the pharmacokinetics of azithromycin. There was no significant pharmacokinetic interaction between fluconazole and azithromycin.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Data from several hundred pregnant women treated with standard doses (<200 mg/day) of fluconazole, administered as a single or repeated dose in the first trimester, show no undesirable effects in the foetus. There have been reports of multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in infants whose mothers were treated for at least three or more months with high doses (400-800 mg daily) of fluconazole for coccidioidomycosis. The relationship between fluconazole use and these events is unclear.

Studies in animals have shown reproductive toxicity (see section 5.3).

Fluconazole in standard doses and short-term treatments should not be used in pregnancy unless clearly necessary.

Fluconazole in high dose and/or in prolonged regimens should not be used during pregnancy except for potentially life-threatening infections.

Breast-feeding

Fluconazole passes into breast milk to reach concentrations lower than those in plasma. Breast-feeding may be maintained after a single use of a standard dose 200 mg fluconazole or less. Breast-feeding is not recommended after repeated use or after high dose fluconazole.

Fertility

Fluconazole did not affect the fertility of male or female rats (see section 5.3)

4.7 Effects on ability to drive and use machines

No studies have been performed on the effects of Diflucan on the ability to drive or use machines. Patients should be warned about the potential for dizziness or seizures (see section 4.8) while taking Diflucan and should be advised not to drive or operate machines if any of these symptoms occur.

4.8 Undesirable effects

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

The following adverse reactions have been observed and reported during treatment with Diflucan with the following frequencies: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

System Organ Class	Common	Uncommon	Rare
Blood and the lymphatic system disorders		Anaemia	Agranulocytosis, leukopenia, thrombocytopenia, neutropenia
Immune system disorders			Anaphylaxis
Metabolism and nutrition disorders		Decreased appetite	Hypercholesterolaemia, hypertriglyceridaemia, hypokalemia
Psychiatric disorders		Somnolence, insomnia	
Nervous system disorders	Headache	Seizures, paraesthesia, dizziness, taste perversion	Tremor
Ear and labyrinth disorders		Vertigo	
Cardiac disorders			<i>Torsade de pointes</i> (see section 4.4), QT prolongation (see section 4.4)
Gastrointestinal disorders	Abdominal pain, vomiting, diarrhoea, nausea	Constipation, dyspepsia, flatulence, dry mouth	
Hepatobiliary disorders	Alanine aminotransferase increased (see section 4.4), aspartate aminotransferase increased (see section 4.4), blood alkaline	Cholestasis (see section 4.4), jaundice (see section 4.4), bilirubin increased (see section 4.4)	Hepatic failure (see section 4.4), hepatocellular necrosis (see section 4.4), hepatitis (see section 4.4), hepatocellular damage (see section 4.4)

	phosphatase increased (see section 4.4)		
Skin and subcutaneous tissue disorders	Rash (see section 4.4)	Drug eruption (see section 4.4), urticaria (see section 4.4), pruritus, increased sweating	Toxic epidermal necrolysis, (see section 4.4), Stevens-Johnson syndrome (see section 4.4), acute generalised exanthematous-pustulosis (see section 4.4), dermatitis exfoliative, angioedema, face oedema, alopecia
Musculoskeletal and connective tissue disorders		Myalgia	
General disorders and administration site conditions		Fatigue, malaise, asthenia, fever	

Paediatric population

The pattern and incidence of adverse reactions and laboratory abnormalities recorded during paediatric clinical trials, excluding the genital candidiasis indication, are comparable to those seen in adults.

4.9 Overdose

There have been reports of overdose with Diflucan and hallucination and paranoid behaviour have been concomitantly reported.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC classification

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02AC01.

Mode of action

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

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

Susceptibility in vitro

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

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

PK/PD relationship

In animal studies, there is a correlation between MIC values and efficacy against experimental mycoses due to *Candida* spp. In clinical studies, there is an almost 1:1 linear relationship between the AUC and the dose of fluconazole. There is also a direct though imperfect relationship between the AUC or dose and a successful clinical response of oral candidosis and to a lesser extent candidaemia to treatment. Similarly cure is less likely for infections caused by strains with a higher fluconazole MIC.

Mechanism(s) of resistance

Candida spp have developed a number of resistance mechanisms to azole antifungal agents. Fungal strains which have developed one or more of these resistance mechanisms are known to exhibit high minimum inhibitory concentrations (MICs) to fluconazole which impacts adversely efficacy *in vivo* and clinically.

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

Breakpoints (according to EUCAST)

Based on analyses of pharmacokinetic/pharmacodynamic (PK/PD) data, susceptibility *in vitro* and clinical response EUCAST-AFST (European Committee on Antimicrobial susceptibility Testing-subcommittee on Antifungal Susceptibility Testing) has determined breakpoints for fluconazole for *Candida* species (EUCAST Fluconazole rational document (2007)-version 2). These have been divided into non-species related breakpoints; which have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species, and species related breakpoints for those species most frequently associated with human infection. These breakpoints are given in the table below:

Antifungal	Species-related breakpoints (S</R>)					Non-species related breakpoints ^A S</R>
	<i>Candida albicans</i>	<i>Candida glabrata</i>	<i>Candida krusei</i>	<i>Candida parapsilosis</i>	<i>Candida tropicalis</i>	
Fluconazole	2/4	IE	--	2/4	2/4	2/4

S = Susceptible, R = Resistant

A. = Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the medicinal product.

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

5.2 Pharmacokinetic properties

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

Absorption

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

Distribution

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

Fluconazole achieves good penetration in all body fluids studied. The levels of fluconazole in saliva and sputum are similar to plasma levels. In patients with fungal meningitis, fluconazole levels in the CSF are approximately 80% the corresponding plasma levels.

High skin concentration of fluconazole, above serum concentrations, are achieved in the stratum corneum, epidermis-dermis and eccrine sweat. Fluconazole accumulates in the stratum corneum. At a dose of 50 mg once daily, the concentration of fluconazole after 12 days was 73 µg/g and 7 days after cessation of treatment the concentration was still 5.8 µg/g. At the 150 mg once-a-week dose, the concentration of fluconazole in stratum corneum on day 7 was 23.4 µg/g and 7 days after the second dose was still 7.1 µg/g.

Concentration of fluconazole in nails after 4 months of 150 mg once-a-week dosing was 4.05 µg/g in healthy and 1.8 µg/g in diseased nails; and, fluconazole was still measurable in nail samples 6 months after the end of therapy.

Biotransformation

Fluconazole is metabolised only to a minor extent. Of a radioactive dose, only 11% is excreted in a changed form in the urine. Fluconazole is a selective inhibitor of the isozymes CYP2C9 and CYP3A4 (see section 4.5). Fluconazole is also an inhibitor of the isozyme CYP2C19.

Excretion

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

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

Pharmacokinetics in renal impairment

In patients with severe renal insufficiency, (GFR < 20 ml/min) half life increased from 30 to 98 hours. Consequently, reduction of the dose is needed. Fluconazole is removed by haemodialysis and to a lesser extent by peritoneal dialysis. After three hours of haemodialysis session, around 50% of fluconazole is eliminated from blood.

Pharmacokinetics in children

Pharmacokinetic data were assessed for 113 paediatric patients from 5 studies; 2 single-dose studies, 2 multiple-dose studies, and a study in premature neonates. Data from one study were not interpretable due to changes in formulation pathway through the study. Additional data were available from a compassionate use study.

After administration of 2-8 mg/kg fluconazole to children between the ages of 9 months to 15 years, an AUC of about 38 µg·h/ml was found per 1 mg/kg dose units. The average fluconazole plasma elimination half-life varied between 15 and 18 hours and the distribution volume was approximately 880 ml/kg after multiple doses. A higher fluconazole plasma elimination half-life of approximately 24 hours was found

after a single dose. This is comparable with the fluconazole plasma elimination half-life after a single administration of 3 mg/kg i.v. to children of 11 days-11 months old. The distribution volume in this age group was about 950 ml/kg.

Experience with fluconazole in neonates is limited to pharmacokinetic studies in premature newborns. The mean age at first dose was 24 hours (range 9-36 hours) and mean birth weight was 0.9 kg (range 0.75-1.10 kg) for 12 pre-term neonates of average gestation around 28 weeks. Seven patients completed the protocol; a maximum of five 6 mg/kg intravenous infusions of fluconazole were administered every 72 hours. The mean half-life (hours) was 74 (range 44-185) on day 1 which decreased, with time to a mean of 53 (range 30-131) on day 7 and 47 (range 27-68) on day 13. The area under the curve (microgram.h/ml) was 271 (range 173-385) on day 1 and increased with a mean of 490 (range 292-734) on day 7 and decreased with a mean of 360 (range 167-566) on day 13. The volume of distribution (ml/kg) was 1183 (range 1070-1470) on day 1 and increased, with time, to a mean of 1184 (range 510-2130) on day 7 and 1328 (range 1040-1680) on day 13.

Pharmacokinetics in elderly

A pharmacokinetic study was conducted in 22 subjects, 65 years of age or older receiving a single 50 mg oral dose of fluconazole. Ten of these patients were concomitantly receiving diuretics. The C_{max} was 1.54 µg/ml and occurred at 1.3 hours post-dose. The mean AUC was 76.4 ± 20.3 µg·h/ml, and the mean terminal half-life was 46.2 hours. These pharmacokinetic parameter values are higher than analogous values reported for normal young male volunteers. Coadministration of diuretics did not significantly alter AUC or C_{max} . In addition, creatinine clearance (74 ml/min), the percent of medicinal product recovered unchanged in urine (0-24 h, 22%) and the fluconazole renal clearance estimates (0.124 ml/min/kg) for the elderly were generally lower than those of younger volunteers. Thus, the alteration of fluconazole disposition in the elderly appears to be related to reduced renal function characteristics of this group.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the human exposure indicating little relevance to clinical use.

Carcinogenesis

Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5, or 10 mg/kg/day (approximately 2-7 times the recommended human dose). Male rats treated with 5 and 10 mg/kg/day had an increased incidence of hepatocellular adenomas.

Reproductive toxicity

Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10, or 20 mg/kg or with parenteral doses of 5, 25, or 75 mg/kg.

There were no foetal effects at 5 or 10 mg/kg; increases in foetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg to 320 mg/kg embryoletality in rats was increased and foetal abnormalities included wavy ribs, cleft palate, and abnormal cranio-facial ossification.

The onset of parturition was slightly delayed at 20 mg/kg orally and dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg and 40 mg/kg intravenously. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal survival at these dose levels. These effects on parturition are consistent with the species specific oestrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole (see section 5.1).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Lactose monohydrate

Maize starch
Colloidal silica anhydrous
Magnesium stearate
Sodium laurilsulfate

Capsule shell composition:

Gelatin
Titanium dioxide (E171)
Patent blue V (E131)

Printing ink:

Shellac (glaze), black iron oxide, N-Butyl alcohol, dehydrated alcohol, purified water, propylene glycol, industrial methylated spirit, isopropyl alcohol, strong ammonia solution, potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

150 mg capsules: clear PVC blister packs or white opaque PVC/PVDC blister packs with aluminium foil backing.

Each pack contains 1 hard capsule.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Detailed information on this medicinal product is available on the website of {name of MS/Agency}

[To be completed nationally]

1. NAME OF THE MEDICINAL PRODUCT

Diflucan and associated names (see Annex I) 50 mg hard capsules
Diflucan and associated names (see Annex I) 100 mg hard capsules
Diflucan and associated names (see Annex I) 150 mg hard capsules
Diflucan and associated names (see Annex I) 200 mg hard capsules
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains fluconazole 50 mg
Excipients: each hard capsule also contains 49.70 mg lactose monohydrate

Each hard capsule contains fluconazole 100 mg
Excipients: each hard capsule also contains 99.41 mg lactose monohydrate

Each hard capsule contains fluconazole 150 mg
Excipients: each hard capsule also contains 149.12 mg lactose monohydrate

Each hard capsule contains fluconazole 200 mg
Excipients: each hard capsule also contains 198.82 mg lactose monohydrate

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule.

The 50 mg hard gelatin capsule has a white body and a turquoise blue cap overprinted with “Pfizer” and the code “FLU-50” with black ink. The capsule size is no. 4.

The 100 mg hard gelatin capsule has a white body and blue cap overprinted with “Pfizer” and the code “FLU-100” with black ink. The capsule size is no. 2.

The 150 mg hard gelatin capsule has a turquoise blue body and turquoise blue cap overprinted with “Pfizer” and the code “FLU-150” with black ink. The capsule size is no. 1.

The 200 mg hard gelatin capsule has a white body and a purple cap overprinted with “Pfizer” and the code “FLU-200” with black ink. The capsule size is no. 0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diflucan is indicated in the following fungal infections (see section 5.1).

Diflucan is indicated in adults for the treatment of:

- Cryptococcal meningitis (see section 4.4).
- Coccidioidomycosis (see section 4.4).
- Invasive candidiasis.
- Mucosal candidiasis including oropharyngeal, oesophageal candidiasis, candiduria and chronic mucocutaneous candidiasis.

- Chronic oral atrophic candidiasis (denture sore mouth) if dental hygiene or topical treatment are insufficient.
- Vaginal candidiasis, acute or recurrent; when local therapy is not appropriate.
- *Candidal balanitis* when local therapy is not appropriate.
- Dermatomycosis including *tinea pedis*, *tinea corporis*, *tinea cruris*, *tinea versicolor* and dermal *candida* infections when systemic therapy is indicated.
- *Tinea unguium* (*onychomycosis*) when other agents are not considered appropriate.

Diflucan is indicated in adults for the prophylaxis of:

- Relapse of cryptococcal meningitis in patients with high risk of recurrence.
- Relapse of oropharyngeal or oesophageal candidiasis in patients infected with HIV who are at high risk of experiencing relapse.
- To reduce the incidence of recurrent vaginal candidiasis (4 or more episodes a year).
- Prophylaxis of candidal infections in patients with prolonged neutropenia (such as patients with haematological malignancies receiving chemotherapy or patients receiving Hematopoietic Stem Cell Transplantation (see section 5.1)).

Diflucan is indicated in term newborn infants, infants, toddlers, children, and adolescents aged from 0 to 17 years old:

Diflucan is used for the treatment of mucosal candidiasis (oropharyngeal, oesophageal), invasive candidiasis, cryptococcal meningitis and the prophylaxis of candidal infections in immunocompromised patients. Diflucan can be used as maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of reoccurrence (see section 4.4). Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.

Consideration should be given to official guidance on the appropriate use of antifungals.

4.2 Posology and method of administration

Posology

The dose should be based on the nature and severity of the fungal infection. Treatment of infections requiring multiple dosing 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.

Adults

Indications		Posology	Duration of treatment
Cryptococcosis	- Treatment of cryptococcal meningitis.	Loading dose: 400 mg on Day 1 Subsequent dose: 200 mg to 400 mg daily	Usually at least 6 to 8 weeks. In life threatening infections the daily dose can be increased to 800 mg
	- Maintenance therapy to prevent relapse of cryptococcal meningitis in patients with high risk of recurrence.	200 mg daily	Indefinitely at a daily dose of 200 mg

Coccidioidomycosis		200 mg to 400 mg	11 months up to 24 months or longer depending on the patient. 800 mg daily may be considered for some infections and especially for meningeal disease
Invasive candidiasis		Loading dose: 800 mg on Day 1 Subsequent dose: 400 mg daily	In general, the recommended duration of therapy for candidemia is for 2 weeks after first negative blood culture result and resolution of signs and symptoms attributable to candidemia.
Treatment of mucosal candidiasis	- Oropharyngeal candidiasis	Loading dose: 200 mg to 400 mg on Day 1 Subsequent dose: 100 mg to 200 mg daily	7 to 21 days (until oropharyngeal candidiasis is in remission). Longer periods may be used in patients with severely compromised immune function
	- Oesophageal candidiasis	Loading dose: 200 mg to 400 mg on Day 1 Subsequent dose: 100 mg to 200 mg daily	14 to 30 days (until oesophageal candidiasis is in remission). Longer periods may be used in patients with severely compromised immune function
	- Candiduria	200 mg to 400 mg daily	7 to 21 days. Longer periods may be used in patients with severely compromised immune function.
	- Chronic atrophic candidiasis	50 mg daily	14 days
	- Chronic mucocutaneous candidiasis	50 mg to 100 mg daily	Up to 28 days. Longer periods depending on both the severity of infection or underlying immune compromise and infection
Prevention of relapse of mucosal candidiasis in patients infected with HIV who are at high risk of experiencing relapse	- Oropharyngeal candidiasis	100 mg to 200 mg daily or 200 mg 3 times per week	An indefinite period for patients with chronic immune suppression
	- Oesophageal candidiasis	100 mg to 200 mg daily or 200 mg 3 times per week	An indefinite period for patients with chronic immune suppression
Genital candidiasis	- Acute vaginal candidiasis - Candidal balanitis	150 mg	Single dose

	- Treatment and prophylaxis of recurrent vaginal candidiasis (4 or more episodes a year).	150 mg every third day for a total of 3 doses (day 1, 4, and 7) followed by 150 mg once weekly maintenance dose	Maintenance dose: 6 months.
Dermatomycosis	- <i>tinea pedis</i> , - <i>tinea corporis</i> , - <i>tinea cruris</i> , - <i>candida</i> infections	150 mg once weekly or 50 mg once daily	2 to 4 weeks, <i>tinea pedis</i> may require treatment for up to 6 weeks
	- <i>tinea versicolor</i>	300 mg to 400 mg once weekly	1 to 3 weeks
		50 mg once daily	2 to 4 weeks
	- <i>tinea unguium</i> (<i>onychomycosis</i>)	150 mg once weekly	Treatment should be continued until infected nail is replaced (uninfected nail grows in). Regrowth of fingernails and toenails normally requires 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.
Prophylaxis of candidal infections in patients with prolonged neutropenia		200 mg to 400 mg	Treatment should start several days before the anticipated onset of neutropenia and continue for 7 days after recovery from neutropenia after the neutrophil count rises above 1000 cells per mm ³ .

Special populations

Elderly

Dosage should be adjusted based on the renal function (see “*Renal impairment*”).

Renal impairment

No adjustments in single dose therapy are necessary. In patients (including paediatric population) with impaired renal function who will receive multiple doses of fluconazole, an initial dose of 50 mg to 400 mg should be given, based on the recommended daily dose for the indication. After this initial loading dose, the daily dose (according to indication) should be based on the following table:

Creatinine clearance (ml/min)	Percent of recommended dose
>50	100%
≤50 (no dialysis)	50%
Regular dialysis	100% after each dialysis

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.

Hepatic impairment

Limited data are available in patients with hepatic impairment, therefore fluconazole should be administered with caution to patients with liver dysfunction (see sections 4.4 and 4.8).

Paediatric population

A maximum dose of 400 mg daily should not be exceeded in paediatric population.

As with similar infections in adults, the duration of treatment is based on the clinical and mycological response. Diflucan is administered as a single daily dose.

For paediatric patients with impaired renal function, see dosing in “*Renal impairment*”. The pharmacokinetics of fluconazole has not been studied in paediatric population with renal insufficiency (for “Term newborn infants” who often exhibit primarily renal immaturity please see below).

Infants, toddlers and children (from 28 days to 11 years old):

Indication	Posology	Recommendations
- Mucosal candidiasis	Initial dose: 6 mg/kg Subsequent dose: 3 mg/kg daily	Initial dose may be used on the first day to achieve steady state levels more rapidly
- Invasive candidiasis - Cryptococcal meningitis	Dose: 6 to 12 mg/kg daily	Depending on the severity of the disease
- Maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of recurrence	Dose: 6 mg/kg daily	Depending on the severity of the disease
- Prophylaxis of <i>Candida</i> in immunocompromised patients	Dose: 3 to 12 mg/kg daily	Depending on the extent and duration of the induced neutropenia (see Adults posology)

Adolescents (from 12 to 17 years old):

Depending on the weight and pubertal development, the prescriber would need to assess which posology (adults or children) is the most appropriate. Clinical data indicate that children have a higher fluconazole clearance than observed for adults. A dose of 100, 200 and 400 mg in adults corresponds to a 3, 6 and 12 mg/kg dose in children to obtain a comparable systemic exposure.

Safety and efficacy for genital candidiasis indication in paediatric population has not been established. Current available safety data for other paediatric indications are described in section 4.8. If treatment for genital candidiasis is imperative in adolescents (from 12 to 17 years old), the posology should be the same as adults posology.

Term newborn infants (0 to 27 days):

Neonates excrete fluconazole slowly. There are few pharmacokinetic data to support this posology in term newborn infants (see section 5.2).

Age group	Posology	Recommendations
Term newborn infants (0 to 14 days)	The same mg/kg dose as for infants, toddlers and children should be given every 72 hours	A maximum dose of 12 mg/kg every 72 hours should not be exceeded
Term newborn infants (from 15 to 27 days)	The same mg/kg dose as for infants, toddlers and children should be given every 48 hours	A maximum dose of 12 mg/kg every 48 hours should not be exceeded

Method of administration

Diflucan may be administered either orally or by intravenous infusion, the route being dependent on the clinical state of the patient. On transferring from the intravenous to the oral route, or *vice versa*, there is no need to change the daily dose.

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

4.3 Contraindications

Hypersensitivity to the active substance, to related azole substances, or to any of the excipients (see section 6.1).

Coadministration 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. Coadministration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 such as cisapride, astemizole, pimozone, quinidine and erythromycin are contraindicated in patients receiving fluconazole (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Tinea capitis

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

Cryptococcosis

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

Deep endemic mycoses

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

Renal system

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

Hepatobiliary system

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. Fluconazole hepatotoxicity has usually been reversible on discontinuation of therapy.

Patients who develop abnormal liver function tests during fluconazole therapy must be monitored closely for the development of more serious hepatic injury.

The patient should be informed of suggestive symptoms of serious hepatic effect (important asthenia, anorexia, persistent nausea, vomiting and jaundice). Treatment of fluconazole should be immediately discontinued and the patient should consult a physician.

Cardiovascular system

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and *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 treatment that may have been contributory.

Diflucan should be administered with caution to patients with these potentially proarrhythmic conditions. Coadministration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 are contraindicated (see sections 4.3 and 4.5).

Halofantrine

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

Dermatological reactions

Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, during treatment with fluconazole. AIDS patients are more prone to the development of severe cutaneous reactions to many medicinal products. If a rash, which is considered attributable to fluconazole, develops in a patient treated for a superficial fungal infection, further therapy with this medicinal product should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and fluconazole discontinued if *bullous* lesions or *erythema multiforme* develop.

Hypersensitivity

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

Cytochrome P450

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

Terfenadine

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

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of the following other medicinal products is contraindicated:

Cisapride: There have been reports of cardiac events including *torsades de pointes* in patients to whom fluconazole and cisapride were coadministered. A controlled study found that concomitant fluconazole 200 mg once daily and cisapride 20 mg four times a day yielded a significant increase in cisapride plasma levels and prolongation of QTc interval. Concomitant treatment with fluconazole and cisapride is contraindicated (see section 4.3).

Terfenadine: Because of the occurrence of serious cardiac dysrhythmias secondary to prolongation of the QTc interval in patients receiving azole antifungals in conjunction with terfenadine, interaction studies have been performed. One study at a 200 mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. Another study at a 400 mg and 800 mg daily dose of fluconazole demonstrated that fluconazole taken in doses of 400 mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. The combined use of fluconazole at doses of 400 mg or greater with terfenadine is contraindicated (see section 4.3). The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored.

Astemizole: Concomitant administration of fluconazole with astemizole may decrease the clearance of astemizole. Resulting increased plasma concentrations of astemizole can lead to QT prolongation and rare occurrences of *torsades de pointes*. Coadministration of fluconazole and astemizole is contraindicated (see section 4.3).

Pimozide: Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with pimozide may result in inhibition of pimozide metabolism. Increased pimozide plasma concentrations can lead to QT prolongation and rare occurrences of *torsades de pointes*. Coadministration of fluconazole and pimozide is contraindicated (see section 4.3).

Quinidine: Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with quinidine may result in inhibition of quinidine metabolism. Use of quinidine has been associated with QT prolongation and rare occurrences of *torsades de pointes*. Coadministration of fluconazole and quinidine is contraindicated (see section 4.3).

Erythromycin: Concomitant use of fluconazole and erythromycin has the potential to increase the risk of cardiotoxicity (prolonged QT interval, *torsades de pointes*) and consequently sudden heart death. Coadministration of fluconazole and erythromycin is contraindicated (see section 4.3).

Concomitant use of the following other medicinal products cannot be recommended:

Halofantrine: Fluconazole can increase halofantrine plasma concentration due to an inhibitory effect on CYP3A4. Concomitant use of fluconazole and halofantrine has the potential to increase the risk of cardiotoxicity (prolonged QT interval, *torsades de pointes*) and consequently sudden heart death. This combination should be avoided (see section 4.4).

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

The effect of other medicinal products on fluconazole

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

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

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. Fluconazole is also an inhibitor of the isozyme CYP2C19. In addition to the observed/documented interactions mentioned below, there is a risk of increased plasma concentration of other compounds metabolized by CYP2C9 and CYP3A4 coadministered with fluconazole. Therefore caution should be exercised when using these combinations and the patients should be carefully monitored. The enzyme inhibiting effect of fluconazole persists 4-5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole (see section 4.3).

Alfentanil: During concomitant treatment with fluconazole (400 mg) and intravenous alfentanil (20 µg/kg) in healthy volunteers the alfentanil AUC₁₀ increased 2-fold, probably through inhibition of CYP3A4. Dose adjustment of alfentanil may be necessary.

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

Amphotericin B: Concurrent administration of fluconazole and amphotericin B in infected normal and immunosuppressed mice showed the following results: a small additive antifungal effect in systemic infection with *C. albicans*, no interaction in intracranial infection with *Cryptococcus neoformans*, and antagonism of the two medicinal products in systemic infection with *A. fumigatus*. The clinical significance of results obtained in these studies is unknown.

Anticoagulants: In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria, and melena) have been reported, in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. During concomitant treatment with fluconazole and warfarin the prothrombin time was prolonged up to 2-fold, probably due to an inhibition of the warfarin metabolism through CYP2C9. In patients receiving coumarin-type anticoagulants concurrently with fluconazole the prothrombin time should be carefully monitored. Dose adjustment of warfarin may be necessary.

Benzodiazepines (short acting), i.e. midazolam, triazolam: Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. Concomitant intake of fluconazole 200 mg and midazolam 7.5 mg orally increased the midazolam AUC and half-life 3.7-fold and 2.2-fold, respectively. Fluconazole 200 mg daily given concurrently with triazolam 0.25 mg orally increased the triazolam AUC and half-life 4.4-fold and 2.3-fold, respectively. Potentiated and prolonged effects of triazolam have been observed at concomitant treatment with fluconazole. If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dose, and the patients should be appropriately monitored.

Carbamazepine: Fluconazole inhibits the metabolism of carbamazepine and an increase in serum carbamazepine of 30% has been observed. There is a risk of developing carbamazepine toxicity. Dose 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. Fluconazole has the potential to increase the systemic exposure of the calcium channel antagonists. Frequent monitoring for adverse events is recommended.

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

Cyclophosphamide: Combination therapy with cyclophosphamide and fluconazole results in an increase in serum bilirubin and serum creatinine. The combination may be used while taking increased consideration to the risk of increased serum bilirubin and serum creatinine.

Fentanyl: One fatal case of fentanyl intoxication due to possible fentanyl fluconazole interaction was reported. Furthermore, it was shown in healthy volunteers that fluconazole delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to respiratory depression. Patients should be monitored closely for the potential risk of respiratory depression. Dosage adjustment of fentanyl may be necessary.

HMG CoA reductase inhibitors: The risk of myopathy and rhabdomyolysis increases when fluconazole is coadministered 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.

Immunosuppressors (i.e. ciclosporin, everolimus, sirolimus and tacrolimus):

Ciclosporin: Fluconazole significantly increases the concentration and AUC of ciclosporin. During concomitant treatment with fluconazole 200 mg daily and ciclosporin (2.7 mg/kg/day) there was a 1.8-fold increase in ciclosporin AUC. This combination may be used by reducing the dose of ciclosporin depending on ciclosporin concentration.

Everolimus: Although not studied *in vivo* or *in vitro*, fluconazole may increase serum concentrations of everolimus through inhibition of CYP3A4.

Sirolimus: Fluconazole increases plasma concentrations of sirolimus presumably by inhibiting the metabolism of sirolimus via CYP3A4 and P-glycoprotein. This combination may be used with a dose adjustment of sirolimus depending on the effect/concentration measurements.

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

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

Methadone: Fluconazole may enhance the serum concentration of methadone. Dose adjustment of methadone may be necessary.

Non-steroidal anti-inflammatory drugs: The C_{max} and AUC of flurbiprofen was increased by 23% and 81%, respectively, when coadministered with fluconazole compared to administration of flurbiprofen alone. Similarly, the C_{max} and AUC of the pharmacologically active isomer [S-(+)-ibuprofen] was increased by 15% and 82%, respectively, when fluconazole was coadministered with racemic ibuprofen (400 mg) compared to administration of racemic ibuprofen alone.

Although not specifically studied, fluconazole has the potential to increase the systemic exposure of other NSAIDs that are metabolized by CYP2C9 (e.g. naproxen, lornoxicam, meloxicam, diclofenac). Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Adjustment of dose of NSAIDs may be needed.

Phenytoin: Fluconazole inhibits the hepatic metabolism of phenytoin. Concomitant repeated administration of 200 mg fluconazole and 250 mg phenytoin intravenously, caused an increase of the phenytoin AUC₂₄ by 75% and C_{min} by 128%. With coadministration, serum phenytoin concentration levels should be monitored in order to avoid phenytoin toxicity.

Prednisone: There was a case report that a liver-transplanted patient treated with prednisone developed acute adrenal cortex insufficiency when a three month therapy with fluconazole was discontinued. The discontinuation of fluconazole presumably caused an enhanced CYP3A4 activity which led to increased metabolism of prednisone. Patients on long-term treatment with fluconazole and prednisone should be carefully monitored for adrenal cortex insufficiency when fluconazole is discontinued.

Rifabutin: Fluconazole increases serum concentrations of rifabutin, leading to increase in the AUC of rifabutin up to 80%. There have been reports of uveitis in patients to whom fluconazole and rifabutin were coadministered. In combination therapy, symptoms of rifabutin toxicity should be taken into consideration.

Saquinavir: Fluconazole increases the AUC and C_{max} of saquinavir with approximately 50% and 55% respectively, due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P-

glycoprotein. Interaction with saquinavir/ritonavir has not been studied and might be more marked. Dose adjustment of saquinavir may be necessary.

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

Theophylline: In a placebo controlled interaction study, the administration of fluconazole 200 mg for 14 days resulted in an 18% decrease in the mean plasma clearance rate of theophylline. Patients who are receiving high dose theophylline or who are otherwise at increased risk for theophylline toxicity should be observed for signs of theophylline toxicity while receiving fluconazole. Therapy should be modified if signs of toxicity develop.

Vinca alkaloids: Although not studied, fluconazole may increase the plasma levels of the vinca alkaloids (e.g. vincristine and vinblastine) and lead to neurotoxicity, which is possibly due to an inhibitory effect on CYP3A4.

Vitamin A: Based on a case-report in one patient receiving combination therapy with all-trans-retinoid acid (an acid form of vitamin A) and fluconazole, CNS related undesirable effects have developed in the form of pseudotumour *cerebri*, which disappeared after discontinuation of fluconazole treatment. This combination may be used but the incidence of CNS related undesirable effects should be borne in mind.

Voriconazole: (CYP2C9 and CYP3A4 inhibitor): Coadministration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 2.5 days) and oral fluconazole (400 mg on day 1, then 200 mg Q24h for 4 days) to 8 healthy male subjects resulted in an increase in C_{max} and AUC_{τ} of voriconazole by an average of 57% (90% CI: 20%, 107%) and 79% (90% CI: 40%, 128%), respectively. The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole associated adverse events is recommended if voriconazole is used sequentially after fluconazole.

Zidovudine: Fluconazole increases C_{max} and AUC of zidovudine by 84% and 74%, respectively, due to an approx. 45% decrease in oral zidovudine clearance. The half-life of zidovudine was likewise prolonged by approximately 128% following combination therapy with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions. Dose reduction of zidovudine may be considered.

Azithromycin: An open-label, randomized, three-way crossover study in 18 healthy subjects assessed the effect of a single 1200 mg oral dose of azithromycin on the pharmacokinetics of a single 800 mg oral dose of fluconazole as well as the effects of fluconazole on the pharmacokinetics of azithromycin. There was no significant pharmacokinetic interaction between fluconazole and azithromycin.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Data from several hundred pregnant women treated with standard doses (<200 mg/day) of fluconazole, administered as a single or repeated dose in the first trimester, show no undesirable effects in the foetus. There have been reports of multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in infants whose mothers were

treated for at least three or more months with high doses (400-800 mg daily) of fluconazole for coccidioidomycosis. The relationship between fluconazole use and these events is unclear.

Studies in animals have shown reproductive toxicity (see section 5.3).

Fluconazole in standard doses and short-term treatments should not be used in pregnancy unless clearly necessary.

Fluconazole in high dose and/or in prolonged regimens should not be used during pregnancy except for potentially life-threatening infections.

Breast-feeding

Fluconazole passes into breast milk to reach concentrations lower than those in plasma. Breast-feeding may be maintained after a single use of a standard dose 200 mg fluconazole or less. Breast-feeding is not recommended after repeated use or after high dose fluconazole.

Fertility

Fluconazole did not affect the fertility of male or female rats (see section 5.3)

4.7 Effects on ability to drive and use machines

No studies have been performed on the effects of Diflucan on the ability to drive or use machines. Patients should be warned about the potential for dizziness or seizures (see section 4.8) while taking Diflucan and should be advised not to drive or operate machines if any of these symptoms occur.

4.8 Undesirable effects

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

The following adverse reactions have been observed and reported during treatment with Diflucan with the following frequencies: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

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

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

Paediatric population

The pattern and incidence of adverse reactions and laboratory abnormalities recorded during paediatric clinical trials, excluding the genital candidiasis indication, are comparable to those seen in adults.

4.9 Overdose

There have been reports of overdose with Diflucan and hallucination and paranoid behaviour have been concomitantly reported.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC classification

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02AC01.

Mode of action

Fluconazole is a triazole antifungal agent. Its primary mode of action is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of

ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of fluconazole. Fluconazole has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.

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

Susceptibility *in vitro*

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

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

PK/PD relationship

In animal studies, there is a correlation between MIC values and efficacy against experimental mycoses due to *Candida* spp. In clinical studies, there is an almost 1:1 linear relationship between the AUC and the dose of fluconazole. There is also a direct though imperfect relationship between the AUC or dose and a successful clinical response of oral candidosis and to a lesser extent candidaemia to treatment. Similarly cure is less likely for infections caused by strains with a higher fluconazole MIC.

Mechanism(s) of resistance

Candida spp have developed a number of resistance mechanisms to azole antifungal agents. Fungal strains which have developed one or more of these resistance mechanisms are known to exhibit high minimum inhibitory concentrations (MICs) to fluconazole which impacts adversely efficacy *in vivo* and clinically.

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

Breakpoints (according to EUCAST)

Based on analyses of pharmacokinetic/pharmacodynamic (PK/PD) data, susceptibility *in vitro* and clinical response EUCAST-AFST (European Committee on Antimicrobial susceptibility Testing-subcommittee on Antifungal Susceptibility Testing) has determined breakpoints for fluconazole for *Candida* species (EUCAST Fluconazole rational document (2007)-version 2). These have been divided into non-species related breakpoints; which have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species, and species related breakpoints for those species most frequently associated with human infection. These breakpoints are given in the table below:

Antifungal	Species-related breakpoints (S\leq/R>)					Non-species related breakpoints ^A S\leq/R>
	<i>Candida albicans</i>	<i>Candida glabrata</i>	<i>Candida krusei</i>	<i>Candida parapsilosis</i>	<i>Candida tropicalis</i>	
Fluconazole	2/4	IE	--	2/4	2/4	2/4

S = Susceptible, R = Resistant

A = Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the medicinal product.

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

5.2 Pharmacokinetic properties

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

Absorption

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

Distribution

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

Fluconazole achieves good penetration in all body fluids studied. The levels of fluconazole in saliva and sputum are similar to plasma levels. In patients with fungal meningitis, fluconazole levels in the CSF are approximately 80% the corresponding plasma levels.

High skin concentration of fluconazole, above serum concentrations, are achieved in the stratum corneum, epidermis-dermis and eccrine sweat. Fluconazole accumulates in the stratum corneum. At a dose of 50 mg once daily, the concentration of fluconazole after 12 days was 73 µg/g and 7 days after cessation of treatment the concentration was still 5.8 µg/g. At the 150 mg once-a-week dose, the concentration of fluconazole in stratum corneum on day 7 was 23.4 µg/g and 7 days after the second dose was still 7.1 µg/g.

Concentration of fluconazole in nails after 4 months of 150 mg once-a-week dosing was 4.05 µg/g in healthy and 1.8 µg/g in diseased nails; and, fluconazole was still measurable in nail samples 6 months after the end of therapy.

Biotransformation

Fluconazole is metabolised only to a minor extent. Of a radioactive dose, only 11% is excreted in a changed form in the urine. Fluconazole is a selective inhibitor of the isozymes CYP2C9 and CYP3A4 (see section 4.5). Fluconazole is also an inhibitor of the isozyme CYP2C19.

Excretion

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

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

Pharmacokinetics in renal impairment

In patients with severe renal insufficiency, (GFR < 20 ml/min) half life increased from 30 to 98 hours. Consequently, reduction of the dose is needed. Fluconazole is removed by haemodialysis and to a lesser

extent by peritoneal dialysis. After three hours of haemodialysis session, around 50% of fluconazole is eliminated from blood.

Pharmacokinetics in children

Pharmacokinetic data were assessed for 113 paediatric patients from 5 studies; 2 single-dose studies, 2 multiple-dose studies, and a study in premature neonates. Data from one study were not interpretable due to changes in formulation pathway through the study. Additional data were available from a compassionate use study.

After administration of 2-8 mg/kg fluconazole to children between the ages of 9 months to 15 years, an AUC of about 38 µg·h/ml was found per 1 mg/kg dose units. The average fluconazole plasma elimination half-life varied between 15 and 18 hours and the distribution volume was approximately 880 ml/kg after multiple doses. A higher fluconazole plasma elimination half-life of approximately 24 hours was found after a single dose. This is comparable with the fluconazole plasma elimination half-life after a single administration of 3 mg/kg i.v. to children of 11 days-11 months old. The distribution volume in this age group was about 950 ml/kg.

Experience with fluconazole in neonates is limited to pharmacokinetic studies in premature newborns. The mean age at first dose was 24 hours (range 9-36 hours) and mean birth weight was 0.9 kg (range 0.75-1.10 kg) for 12 pre-term neonates of average gestation around 28 weeks. Seven patients completed the protocol; a maximum of five 6 mg/kg intravenous infusions of fluconazole were administered every 72 hours. The mean half-life (hours) was 74 (range 44-185) on day 1 which decreased, with time to a mean of 53 (range 30-131) on day 7 and 47 (range 27-68) on day 13. The area under the curve (microgram.h/ml) was 271 (range 173-385) on day 1 and increased with a mean of 490 (range 292-734) on day 7 and decreased with a mean of 360 (range 167-566) on day 13. The volume of distribution (ml/kg) was 1183 (range 1070-1470) on day 1 and increased, with time, to a mean of 1184 (range 510-2130) on day 7 and 1328 (range 1040-1680) on day 13.

Pharmacokinetics in elderly

A pharmacokinetic study was conducted in 22 subjects, 65 years of age or older receiving a single 50 mg oral dose of fluconazole. Ten of these patients were concomitantly receiving diuretics. The C_{max} was 1.54 µg/ml and occurred at 1.3 hours post-dose. The mean AUC was 76.4 ± 20.3 µg·h/ml, and the mean terminal half-life was 46.2 hours. These pharmacokinetic parameter values are higher than analogous values reported for normal young male volunteers. Coadministration of diuretics did not significantly alter AUC or C_{max} . In addition, creatinine clearance (74 ml/min), the percent of medicinal product recovered unchanged in urine (0-24 h, 22%) and the fluconazole renal clearance estimates (0.124 ml/min/kg) for the elderly were generally lower than those of younger volunteers. Thus, the alteration of fluconazole disposition in the elderly appears to be related to reduced renal function characteristics of this group.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the human exposure indicating little relevance to clinical use.

Carcinogenesis

Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5, or 10 mg/kg/day (approximately 27 times the recommended human dose). Male rats treated with 5 and 10 mg/kg/day had an increased incidence of hepatocellular adenomas.

Reproductive toxicity

Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10, or 20 mg/kg or with parenteral doses of 5, 25, or 75 mg/kg.

There were no foetal effects at 5 or 10 mg/kg; increases in foetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg to 320 mg/kg embryoletality in rats was increased and foetal abnormalities included wavy ribs, cleft palate, and abnormal cranio-facial ossification.

The onset of parturition was slightly delayed at 20 mg/kg orally and dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg and 40 mg/kg intravenously. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal survival at these dose levels. These effects on parturition are consistent with the species specific oestrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole (see section 5.1).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:

Lactose monohydrate
Maize starch
Colloidal silica anhydrous
Magnesium stearate
Sodium laurilsulfate

Capsule shell composition:

50 mg capsules
Gelatin
Titanium dioxide (E171)
Patent blue V (E131)

100 mg capsules
Gelatin
Titanium dioxide (E171)
Erythrosin (E127)
Patent blue V (E131)

150 mg capsules
Gelatin
Titanium dioxide (E171)
Patent blue V (E131)

200 mg capsules
Gelatin
Titanium dioxide (E171)
Erythrosin (E127)
Indigo carmine (E132)

Printing ink:

Shellac (glaze), black iron oxide, N-Butyl alcohol, dehydrated alcohol, purified water, propylene glycol, industrial methylated spirit, isopropyl alcohol, strong ammonia solution, potassium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

50 mg and 150 mg capsules: clear PVC blister packs or white opaque PVC/PVDC blister packs with aluminium foil backing.

100 mg and 200 mg capsules: clear PVC blister packs or white opaque PVC blister packs with aluminium foil backing.

Each pack contains 1, 2, 3, 4, 6, 7, 10, 12, 14, 20, 28, 30, 42, 50, 60, 100 or 500 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Detailed information on this medicinal product is available on the website of {name of MS/Agency}
[To be completed nationally].

1. NAME OF THE MEDICINAL PRODUCT

Diflucan and associated names (see Annex I) 5 mg/ml oral solution
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of oral solution contains 5 mg of fluconazole.

Excipient: each 1 ml also contains 0.1334 g of sucrose and 0.9635 g of glycerol.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution

A clear, colourless to slightly yellow solution with a viscosity greater than water.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diflucan is indicated in the following fungal infections (see section 5.1).

Diflucan is indicated in adults for the treatment of:

- Cryptococcal meningitis (see section 4.4).
- Coccidioidomycosis (see section 4.4).
- Invasive candidiasis.
- Mucosal candidiasis including oropharyngeal, oesophageal candidiasis, candiduria and chronic mucocutaneous candidiasis.
- Chronic oral atrophic candidiasis (denture sore mouth) if dental hygiene or topical treatment are insufficient.
- Vaginal candidiasis, acute or recurrent; when local therapy is not appropriate.
- *Candidal balanitis* when local therapy is not appropriate.
- Dermatomycosis including tinea pedis, *tinea corporis*, *tinea cruris*, *tinea versicolor* and dermal *candida* infections when systemic therapy is indicated.
- *Tinea unguinum (onychomycosis)* when other agents are not considered appropriate.

Diflucan is indicated in adults for the prophylaxis of:

- Relapse of cryptococcal meningitis in patients with high risk of recurrence.
- Relapse of oropharyngeal or oesophageal candidiasis in patients infected with HIV who are at high risk of experiencing relapse.
- To reduce the incidence of recurrent vaginal candidiasis (4 or more episodes a year).
- Prophylaxis of candidal infections in patients with prolonged neutropenia (such as patients with haematological malignancies receiving chemotherapy or patients receiving Hematopoietic Stem Cell Transplantation (see section 5.1)).

Diflucan is indicated in term newborn infants, infants, toddlers, children, and adolescents aged from 0 to 17 years old:

Diflucan is used for the treatment of mucosal candidiasis (oropharyngeal, oesophageal), invasive candidiasis, cryptococcal meningitis and the prophylaxis of candidal infections in immunocompromised patients. Diflucan can be used as maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of reoccurrence (see section 4.4).

Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.

Consideration should be given to official guidance on the appropriate use of antifungals.

4.2 Posology and method of administration

Posology

The dose should be based on the nature and severity of the fungal infection. Treatment of infections requiring multiple dosing 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.

Adults:

<u>Indications</u>		<u>Posology</u>	<u>Duration of treatment</u>
Cryptococcosis	- Treatment of cryptococcal meningitis	Loading dose: 400 mg on Day 1 Subsequent dose: 200 mg to 400 mg daily	Usually at least 68 weeks. In life threatening infections the daily dose can be increased to 800 mg
	- Maintenance therapy to prevent relapse of cryptococcal meningitis in patients with high risk of recurrence.	200 mg daily	Indefinitely at a daily dose of 200 mg
Coccidioidomycosis		200 mg to 400 mg	11 months up to 24 months or longer depending on the patient. 800 mg daily may be considered for some infections and especially for meningeal disease.
Invasive candidiasis		Loading dose: 800 mg on Day 1 Subsequent dose: 400 mg daily	In general, the recommended duration of therapy for candidemia is for 2 weeks after first negative blood culture result and resolution of signs and symptoms attributable to candidemia.
Treatment of mucosal candidiasis	- Oropharyngeal candidiasis	Loading dose: 200 mg to 400 mg on Day 1 Subsequent dose: 100 mg to 200 mg daily	7 to 21 days (until oropharyngeal candidiasis is in remission). Longer periods may be used in patients with severely compromised immune function

	- Oesophageal candidiasis	Loading dose: 200 mg to 400 mg on Day 1 Subsequent dose: 100 mg to 200 mg daily	14 to 30 days (until oesophageal candidiasis is in remission). Longer periods may be used in patients with severely compromised immune function
	- Candiduria	200 mg to 400 mg daily	7 to 21 days Longer periods may be used in patients with severely compromised immune function.
	- Chronic atrophic candidiasis	50 mg daily	14 days
	- Chronic mucocutaneous candidiasis	50 to 100 mg daily	Up to 28 days. Longer periods depending on both the severity of infection or underlying immune compromise and infection
Prevention of relapse of mucosal candidiasis in patients infected with HIV who are at high risk of experiencing relapse	- Oropharyngeal candidiasis	100 to 200 mg daily or 200 mg 3 times per week.	An indefinite period for patients with chronic immune suppression
	- Oesophageal candidiasis	100 mg to 200 mg daily or 200 mg 3 times per week.	An indefinite period for patients with chronic immune suppression
Genital candidiasis	- Acute vaginal candidiasis - <i>Candidal balanitis</i>	150 mg	Single dose
	- Treatment and prophylaxis of recurrent vaginal candidiasis (4 or more episodes a year)	150 mg every third day for a total of 3 doses (day 1, 4, and 7) followed by 150 mg once weekly maintenance dose	Maintenance dose: 6 months.
Dermatomycosis	- <i>tinea pedis</i> , - <i>tinea corporis</i> , - <i>tinea cruris</i> , - <i>candida</i> infections	150 mg once weekly or 50 mg once daily	2 to 4 weeks, <i>tinea pedis</i> may require treatment for up to 6 weeks
	- <i>tinea versicolor</i>	300 mg to 400 mg once weekly	1 to 3 weeks
		50 mg once daily	2 to 4 weeks

	- <i>tinea unguium</i> (<i>onychomycosis</i>)	150 mg once weekly	Treatment should be continued until infected nail is replaced (uninfected nail grows in). Regrowth of fingernails and toenails normally requires 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.
Prophylaxis of candidal infections in patients with prolonged neutropenia		200 mg to 400 mg	Treatment should start several days before the anticipated onset of neutropenia and continue for 7 days after recovery from neutropenia after the neutrophil count rises above 1000 cells per mm ³ .

Special populations

Elderly

Dosage should be adjusted based on the renal function (see “*Renal Impairment*”).

Renal impairment

No adjustments in single dose therapy are necessary. In patients (including paediatric population) with impaired renal function who will receive multiple doses of fluconazole, an initial dose of 50 mg to 400 mg should be given, based on the recommended daily dose for the indication. After this initial loading dose, the daily dose (according to indication) should be based on the following table:

Creatinine clearance (ml/min)	Percent of recommended dose
>50	100%
≤50 (no dialysis)	50%
Regular dialysis	100% after each dialysis

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

Hepatic impairment

Limited data are available in patients with hepatic impairment, therefore fluconazole should be administered with caution to patients with liver dysfunction (see sections 4.4 and 4.8).

Paediatric population

A maximum dose of 400 mg daily should not be exceeded in paediatric population.

As with similar infections in adults, the duration of treatment is based on the clinical and mycological response. Diflucan is administered as a single daily dose.

For paediatric patients with impaired renal function, see dosing in “Renal impairment”. The pharmacokinetics of fluconazole has not been studied in paediatric population with renal insufficiency (for “Term newborn infants” who often exhibit primarily renal immaturity please see below).

Infants, toddlers and children (from 28 days to 11 years old):

Indication	Posology	Recommendations
- Mucosal candidiasis	Initial dose: 6 mg/kg Subsequent dose: 3 mg/kg daily	Initial dose may be used on the first day to achieve steady state levels more rapidly
- Invasive candidiasis - Cryptococcal meningitis	Dose: 6 to 12 mg/kg daily	Depending on the severity of the disease
- Maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of recurrence	Dose: 6 mg/kg daily	Depending on the severity of the disease
- Prophylaxis of <i>Candida</i> in immunocompromised patients	Dose: 3 to 12 mg/kg daily	Depending on the extent and duration of the induced neutropenia (see Adults posology)

Adolescents (from 12 to 17 years old):

Depending on the weight and pubertal development, the prescriber would need to assess which posology (adults or children) is the most appropriate. Clinical data indicate that children have a higher fluconazole clearance than observed for adults. A dose of 100, 200 and 400 mg in adults corresponds to a 3, 6 and 12 mg/kg dose in children to obtain a comparable systemic exposure.

Safety and efficacy for genital candidiasis indication in paediatric population has not been established. Current available safety data for other paediatric indications are described in section 4.8. If treatment for genital candidiasis is imperative in adolescents (from 12 to 17 years old), the posology should be the same as adults posology.

Term newborn infants (0 to 27 days):

Neonates excrete fluconazole slowly.

There are few pharmacokinetic data to support this posology in term newborn infants (see section 5.2).

Age group	Posology	Recommendations
Term newborn infants (0 to 14 days)	The same mg/kg dose as for infants, toddlers and children should be given every 72 hours	A maximum dose of 12 mg/kg every 72 hours should not be exceeded
Term newborn infants (from 15 to 27 days)	The same mg/kg dose as for infants, toddlers and children should be given every 48 hours	A maximum dose of 12 mg/kg every 48 hours should not be exceeded

Method of administration

Diflucan may be administered either orally or by intravenous infusion, the route being dependent on the clinical state of the patient. On transferring from the intravenous to the oral route, or *vice versa*, there is no need to change the daily dose.

Diflucan can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance, to related azole substances, or to any of excipients (see section 6.1).

Coadministration 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. Coadministration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 such as ascisapride, astemizole, pimozide, quinidine and erythromycin are contraindicated in patients receiving fluconazole (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Tinea capitis

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

Cryptococcosis

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

Deep endemic mycoses

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

Renal system

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

Hepatobiliary system

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. Fluconazole hepatotoxicity has usually been reversible on discontinuation of therapy.

Patients who develop abnormal liver function tests during fluconazole therapy must be monitored closely for the development of more serious hepatic injury.

The patient should be informed of suggestive symptoms of serious hepatic effect (important asthenia, anorexia, persistent nausea, vomiting and jaundice). Treatment of fluconazole should be immediately discontinued and the patient should consult a physician.

Cardiovascular system

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and *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 treatment that may have been contributory.

Diflucan should be administered with caution to patients with these potentially proarrhythmic conditions. Coadministration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 are contraindicated (see sections 4.3 and 4.5).

Halofantrine

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

Dermatological reactions

Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, during treatment with fluconazole. AIDS patients are more prone to the development of severe cutaneous reactions to many medicinal products. If a rash, which is considered attributable to fluconazole, develops in a patient treated for a superficial fungal infection, further therapy with this medicinal product should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and fluconazole discontinued if *bullous* lesions or *erythema multiforme* develop.

Hypersensitivity

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

Cytochrome P450

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

Terfenadine

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

Excipients

Diflucan oral solution contains glycerol. Glycerol may cause headache, stomach upset, and diarrhoea (see section 4.8).

Diflucan oral solution contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of the following other medicinal products is contraindicated:

Cisapride: There have been reports of cardiac events including *torsades de pointes* in patients to whom fluconazole and cisapride were coadministered. A controlled study found that concomitant fluconazole 200 mg once daily and cisapride 20 mg four times a day yielded a significant increase in cisapride plasma levels and prolongation of QTc interval. Concomitant treatment with fluconazole and cisapride is contraindicated (see section 4.3).

Terfenadine: Because of the occurrence of serious cardiac dysrhythmias secondary to prolongation of the QTc interval in patients receiving azole antifungals in conjunction with terfenadine, interaction studies have been performed. One study at a 200 mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. Another study at a 400 mg and 800 mg daily dose of fluconazole demonstrated that fluconazole taken in doses of 400 mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. The combined use of fluconazole at doses of 400 mg or greater with terfenadine is contraindicated (see section 4.3). The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored.

Astemizole: Concomitant administration of fluconazole with astemizole may decrease the clearance of astemizole. Resulting increased plasma concentrations of astemizole can lead to QT prolongation and rare occurrences of *torsades de pointes*. Coadministration of fluconazole and astemizole is contraindicated (see section 4.3).

Pimozide: Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with pimozide may result in inhibition of pimozide metabolism. Increased pimozide plasma concentrations can lead to QT prolongation and rare occurrences of *torsades de pointes*. Coadministration of fluconazole and pimozide is contraindicated (see section 4.3).

Quinidine: Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with quinidine may result in inhibition of quinidine metabolism. Use of quinidine has been associated with QT prolongation and rare occurrences of *torsades de pointes*. Coadministration of fluconazole and quinidine is contraindicated (see section 4.3).

Erythromycin: Concomitant use of fluconazole and erythromycin has the potential to increase the risk of cardiotoxicity (prolonged QT interval, *torsades de pointes*) and consequently sudden heart death. Coadministration of fluconazole and erythromycin is contraindicated (see section 4.3).

Concomitant use of the following other medicinal products cannot be recommended:

Halofantrine: Fluconazole can increase halofantrine plasma concentration due to an inhibitory effect on CYP3A4. Concomitant use of fluconazole and halofantrine has the potential to increase the risk of cardiotoxicity (prolonged QT interval, *torsades de pointes*) and consequently sudden heart death. This combination should be avoided (see section 4.4).

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

The effect of other medicinal products on fluconazole

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

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

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. Fluconazole is also an inhibitor of the isozyme CYP2C19. In addition to the observed/documentated interactions mentioned below, there is a risk of increased plasma concentration of other compounds metabolized by CYP2C9 and CYP3A4 coadministered with fluconazole. Therefore caution should be exercised when using these combinations and the patients should be carefully monitored. The enzyme inhibiting effect of fluconazole persists 4-5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole (see section 4.3).

Alfentanil: During concomitant treatment with fluconazole (400 mg) and intravenous alfentanil (20 µg/kg) in healthy volunteers the alfentanil AUC₁₀ increased 2-fold, probably through inhibition of CYP3A4.

Dose adjustment of alfentanil may be necessary.

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

Amphotericin B: Concurrent administration of fluconazole and amphotericin B in infected normal and immunosuppressed mice showed the following results: a small additive antifungal effect in systemic infection with *C. albicans*, no interaction in intracranial infection with *Cryptococcus neoformans*, and antagonism of the two medicinal products in systemic infection with *A. fumigatus*. The clinical significance of results obtained in these studies is unknown.

Anticoagulants: In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria, and melena) have been reported, in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. During

concomitant treatment with fluconazole and warfarin the prothrombin time was prolonged up to 2-fold, probably due to an inhibition of the warfarin metabolism through CYP2C9. In patients receiving coumarin-type anticoagulants concurrently with fluconazole the prothrombin time should be carefully monitored. Dose adjustment of warfarin may be necessary.

Benzodiazepines (short acting), i.e. midazolam, triazolam: Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. Concomitant intake of fluconazole 200 mg and midazolam 7.5 mg orally increased the midazolam AUC and half life 3.7 fold and 2.2 fold, respectively. Fluconazole 200 mg daily given concurrently with triazolam 0.25 mg orally increased the triazolam AUC and half-life 4.4-fold and 2.3-fold, respectively. Potentiated and prolonged effects of triazolam have been observed at concomitant treatment with fluconazole. If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dose, and the patients should be appropriately monitored.

Carbamazepine: Fluconazole inhibits the metabolism of carbamazepine and an increase in serum carbamazepine of 30% has been observed. There is a risk of developing carbamazepine toxicity. Dose 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. Fluconazole has the potential to increase the systemic exposure of the calcium channel antagonists. Frequent monitoring for adverse events is recommended.

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

Cyclophosphamide: Combination therapy with cyclophosphamide and fluconazole results in an increase in serum bilirubin and serum creatinine. The combination may be used while taking increased consideration to the risk of increased serum bilirubin and serum creatinine.

Fentanyl: One fatal case of fentanyl intoxication due to possible fentanyl fluconazole interaction was reported. Furthermore, it was shown in healthy volunteers that fluconazole delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to respiratory depression. Patients should be monitored closely for the potential risk of respiratory depression. Dosage adjustment of fentanyl may be necessary.

HMG CoA reductase inhibitors: The risk of myopathy and rhabdomyolysis increases when fluconazole is coadministered 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.

Immunosuppressors (i.e. ciclosporin, everolimus, sirolimus and tacrolimus):

Ciclosporin: Fluconazole significantly increases the concentration and AUC of ciclosporin. During concomitant treatment with fluconazole 200 mg daily and ciclosporin (2.7 mg/kg/day) there was a 1.8-fold increase in ciclosporin AUC. This combination may be used by reducing the dose of ciclosporin depending on ciclosporin concentration.

Everolimus: Although not studied *in vivo* or *in vitro*, fluconazole may increase serum concentrations of everolimus through inhibition of CYP3A4.

Sirolimus: Fluconazole increases plasma concentrations of sirolimus presumably by inhibiting the metabolism of sirolimus via CYP3A4 and P-glycoprotein. This combination may be used with a dose adjustment of sirolimus depending on the effect/concentration measurements.

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

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

Methadone: Fluconazole may enhance the serum concentration of methadone. Dose adjustment of methadone may be necessary.

Non-steroidal anti-inflammatory drugs: The C_{max} and AUC of flurbiprofen was increased by 23% and 81%, respectively, when coadministered with fluconazole compared to administration of flurbiprofen alone. Similarly, the C_{max} and AUC of the pharmacologically active isomer [S-(+)-ibuprofen] was increased by 15% and 82%, respectively, when fluconazole was coadministered with racemic ibuprofen (400 mg) compared to administration of racemic ibuprofen alone.

Although not specifically studied, fluconazole has the potential to increase the systemic exposure of other NSAIDs that are metabolized by CYP2C9 (e.g. naproxen, lornoxicam, meloxicam, diclofenac). Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Adjustment of dose of NSAIDs may be needed.

Phenytoin: Fluconazole inhibits the hepatic metabolism of phenytoin. Concomitant repeated administration of 200 mg fluconazole and 250 mg phenytoin intravenously, caused an increase of the phenytoin AUC_{24} by 75% and C_{min} by 128%. With coadministration, serum phenytoin concentration levels should be monitored in order to avoid phenytoin toxicity.

Prednisone: There was a case report that a liver-transplanted patient treated with prednisone developed acute adrenal cortex insufficiency when a three month therapy with fluconazole was discontinued. The discontinuation of fluconazole presumably caused an enhanced CYP3A4 activity which led to increased metabolism of prednisone. Patients on long-term treatment with fluconazole and prednisone should be carefully monitored for adrenal cortex insufficiency when fluconazole is discontinued.

Rifabutin: Fluconazole increases serum concentrations of rifabutin, leading to increase in the AUC of rifabutin up to 80%. There have been reports of uveitis in patients to whom fluconazole and rifabutin were coadministered. In combination therapy, symptoms of rifabutin toxicity should be taken into consideration.

Saquinavir: Fluconazole increases the AUC and C_{max} of saquinavir with approximately 50% and 55% respectively, due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein. Interaction with saquinavir/ritonavir has not been studied and might be more marked. Dose adjustment of saquinavir may be necessary.

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

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

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

Vinca alkaloids: Although not studied, fluconazole may increase the plasma levels of the vinca alkaloids (e.g. vincristine and vinblastine) and lead to neurotoxicity, which is possibly due to an inhibitory effect on CYP3A4.

Vitamin A: Based on a case-report in one patient receiving combination therapy with all-trans-retinoid acid (an acid form of vitamin A) and fluconazole, CNS related undesirable effects have developed in the form of pseudotumour *cerebri*, which disappeared after discontinuation of fluconazole treatment. This combination may be used but the incidence of CNS related undesirable effects should be borne in mind.

Voriconazole: (CYP2C9 and CYP3A4 inhibitor): Coadministration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 2.5 days) and oral fluconazole (400 mg on day 1, then 200 mg Q24h for 4 days) to 8 healthy male subjects resulted in an increase in C_{max} and AUC_{τ} of voriconazole by an average of 57% (90% CI: 20%, 107%) and 79% (90% CI: 40%, 128%), respectively. The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole associated adverse events is recommended if voriconazole is used sequentially after fluconazole.

Zidovudine: Fluconazole increases C_{max} and AUC of zidovudine by 84% and 74%, respectively, due to an approx. 45% decrease in oral zidovudine clearance. The half-life of zidovudine was likewise prolonged by approximately 128% following combination therapy with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions. Dose reduction of zidovudine may be considered.

Azithromycin: An open-label, randomized, three-way crossover study in 18 healthy subjects assessed the effect of a single 1200 mg oral dose of azithromycin on the pharmacokinetics of a single 800 mg oral dose of fluconazole as well as the effects of fluconazole on the pharmacokinetics of azithromycin. There was no significant pharmacokinetic interaction between fluconazole and azithromycin.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Data from several hundred pregnant women treated with standard doses (<200 mg/day) of fluconazole, administered as a single or repeated dose in the first trimester, show no undesirable effects in the foetus.

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

Studies in animals have shown reproductive toxicity (see section 5.3).

Fluconazole in standard doses and short-term treatments should not be used in pregnancy unless clearly necessary.

Fluconazole in high dose and/or in prolonged regimens should not be used during pregnancy except for potentially life-threatening infections.

Breast-feeding

Fluconazole passes into breast milk to reach concentrations lower than those in plasma. Breast-feeding may be maintained after a single use of a standard dose 200 mg fluconazole or less. Breast-feeding is not recommended after repeated use or after high dose fluconazole.

Fertility

Fluconazole did not affect the fertility of male or female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies have been performed on the effects of Diflucan on the ability to drive or use machines. Patients should be warned about the potential for dizziness or seizures (see section 4.8) while taking Diflucan and should be advised not to drive or operate machines if any of these symptoms occur.

4.8 Undesirable effects

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

The following adverse reactions have been observed and reported during treatment with Diflucan with the following frequencies: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

System Organ Class	Common	Uncommon	Rare
Blood and the lymphatic system disorders		Anaemia	Agranulocytosis, leukopenia, thrombocytopenia, neutropenia
Immune system disorders			Anaphylaxis
Metabolism and nutrition disorders		Decreased appetite	Hypercholesterolaemia, hypertriglyceridaemia, hypokalemia
Psychiatric disorders		Somnolence, insomnia	
Nervous system disorders	Headache	Seizures, paraesthesia, dizziness, taste perversion	Tremor
Ear and labyrinth disorders		Vertigo	
Cardiac disorders			<i>Torsade de pointes</i> (see section 4.4), QT prolongation (see section 4.4)
Gastrointestinal disorders	Abdominal pain, vomiting, diarrhoea, nausea	Constipation, dyspepsia, flatulence, dry mouth	

Hepatobiliary disorders	Alanine aminotransferase increased (see section 4.4), aspartate aminotransferase increased (see section 4.4), blood alkaline phosphatase increased (see section 4.4)	Cholestasis (see section 4.4), jaundice (see section 4.4), bilirubin increased (see section 4.4)	Hepatic failure (see section 4.4), hepatocellular necrosis (see section 4.4), hepatitis (see section 4.4), hepatocellular damage (see section 4.4)
Skin and subcutaneous tissue disorders	Rash (see section 4.4)	Drug eruption (see section 4.4), urticaria (see section 4.4), pruritus, increased sweating	Toxic epidermal necrolysis, (see section 4.4), Stevens-Johnson syndrome (see section 4.4), acute generalised exanthematous-pustulosis (see section 4.4), dermatitis exfoliative, angioedema, face oedema, alopecia
Musculoskeletal and connective tissue disorders		Myalgia	
General disorders and administration site conditions		Fatigue, malaise, asthenia, fever	

Paediatric population

The pattern and incidence of adverse reactions and laboratory abnormalities recorded during paediatric clinical trials, excluding the genital candidiasis indication, are comparable to those seen in adults.

4.9 Overdose

There have been reports of overdose with Diflucan and hallucination and paranoid behaviour have been concomitantly reported.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC classification

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02AC01.

Mode of action

Fluconazole is a triazole antifungal agent. Its primary mode of action is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of

fluconazole. Fluconazole has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.

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

Susceptibility *in vitro*

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

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

PK/PD relationship

In animal studies, there is a correlation between MIC values and efficacy against experimental mycoses due to *Candida* spp. In clinical studies, there is an almost 1:1 linear relationship between the AUC and the dose of fluconazole. There is also a direct though imperfect relationship between the AUC or dose and a successful clinical response of oral candidosis and to a lesser extent candidaemia to treatment. Similarly cure is less likely for infections caused by strains with a higher fluconazole MIC.

Mechanism(s) of resistance

Candida spp have developed a number of resistance mechanisms to azole antifungal agents. Fungal strains which have developed one or more of these resistance mechanisms are known to exhibit high minimum inhibitory concentrations (MICs) to fluconazole which impacts adversely efficacy *in vivo* and clinically.

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

Breakpoints (according to EUCAST)

Based on analyses of pharmacokinetic/pharmacodynamic (PK/PD) data, susceptibility *in vitro* and clinical response EUCAST-AFST (European Committee on Antimicrobial susceptibility Testing-subcommittee on Antifungal Susceptibility Testing) has determined breakpoints for fluconazole for *Candida* species (EUCAST Fluconazole rational document (2007)-version 2). These have been divided into non-species related breakpoints; which have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species, and species related breakpoints for those species most frequently associated with human infection. These breakpoints are given in the table below:

Antifungal	Species-related breakpoints (S</R>)					Non-species related breakpoints ^A S</R>
	<i>Candida albicans</i>	<i>Candida glabrata</i>	<i>Candida krusei</i>	<i>Candida parapsilosis</i>	<i>Candida tropicalis</i>	
Fluconazole	2/4	IE	--	2/4	2/4	2/4

S = Susceptible, R = Resistant

A. = Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the medicinal product.

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

5.2 Pharmacokinetic properties

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

Absorption

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

Distribution

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

Fluconazole achieves good penetration in all body fluids studied. The levels of fluconazole in saliva and sputum are similar to plasma levels. In patients with fungal meningitis, fluconazole levels in the CSF are approximately 80% the corresponding plasma levels.

High skin concentration of fluconazole, above serum concentrations, are achieved in the stratum corneum, epidermis-dermis and eccrine sweat. Fluconazole accumulates in the stratum corneum. At a dose of 50 mg once daily, the concentration of fluconazole after 12 days was 73 µg/g and 7 days after cessation of treatment the concentration was still 5.8 µg/g. At the 150 mg once-a-week dose, the concentration of fluconazole in stratum corneum on day 7 was 23.4 µg/g and 7 days after the second dose was still 7.1 µg/g.

Concentration of fluconazole in nails after 4 months of 150 mg once-a-week dosing was 4.05 µg/g in healthy and 1.8 µg/g in diseased nails; and, fluconazole was still measurable in nail samples 6 months after the end of therapy.

Biotransformation

Fluconazole is metabolised only to a minor extent. Of a radioactive dose, only 11% is excreted in a changed form in the urine. Fluconazole is a selective inhibitor of the isozymes CYP2C9 and CYP3A4 (see section 4.5). Fluconazole is also an inhibitor of the isozyme CYP2C19.

Excretion

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

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

Pharmacokinetics in renal impairment

In patients with severe renal insufficiency, (GFR < 20 ml/min) half life increased from 30 to 98 hours. Consequently, reduction of the dose is needed. Fluconazole is removed by haemodialysis and to a lesser extent by peritoneal dialysis. After three hours of haemodialysis session, around 50% of fluconazole is eliminated from blood.

Pharmacokinetics in children

Pharmacokinetic data were assessed for 113 paediatric patients from 5 studies; 2 single-dose studies, 2 multiple-dose studies, and a study in premature neonates. Data from one study were not interpretable due to changes in formulation pathway through the study. Additional data were available from a compassionate use study.

After administration of 2-8 mg/kg fluconazole to children between the ages of 9 months to 15 years, an AUC of about 38 µg·h/ml was found per 1 mg/kg dose units. The average fluconazole plasma elimination half-life varied between 15 and 18 hours and the distribution volume was approximately 880 ml/kg after multiple doses. A higher fluconazole plasma elimination half-life of approximately 24 hours was found after a single dose. This is comparable with the fluconazole plasma elimination half-life after a single administration of 3 mg/kg i.v. to children of 11 days-11 months old. The distribution volume in this age group was about 950 ml/kg.

Experience with fluconazole in neonates is limited to pharmacokinetic studies in premature newborns. The mean age at first dose was 24 hours (range 9-36 hours) and mean birth weight was 0.9 kg (range 0.75-1.10 kg) for 12 pre-term neonates of average gestation around 28 weeks. Seven patients completed the protocol; a maximum of five 6 mg/kg intravenous infusions of fluconazole were administered every 72 hours. The mean half-life (hours) was 74 (range 44-185) on day 1 which decreased, with time to a mean of 53 (range 30-131) on day 7 and 47 (range 27-68) on day 13. The area under the curve (microgram.h/ml) was 271 (range 173-385) on day 1 and increased with a mean of 490 (range 292-734) on day 7 and decreased with a mean of 360 (range 167-566) on day 13. The volume of distribution (ml/kg) was 1183 (range 1070-1470) on day 1 and increased, with time, to a mean of 1184 (range 510-2130) on day 7 and 1328 (range 1040-1680) on day 13.

Pharmacokinetics in elderly

A pharmacokinetic study was conducted in 22 subjects, 65 years of age or older receiving a single 50 mg oral dose of fluconazole. Ten of these patients were concomitantly receiving diuretics. The C_{max} was 1.54 µg/ml and occurred at 1.3 hours post-dose. The mean AUC was 76.4 ± 20.3 µg·h/ml, and the mean terminal half-life was 46.2 hours. These pharmacokinetic parameter values are higher than analogous values reported for normal young male volunteers. Coadministration of diuretics did not significantly alter AUC or C_{max} . In addition, creatinine clearance (74 ml/min), the percent of medicinal product recovered unchanged in urine (0-24 hr, 22%) and the fluconazole renal clearance estimates (0.124 ml/min/kg) for the elderly were generally lower than those of younger volunteers. Thus, the alteration of fluconazole disposition in the elderly appears to be related to reduced renal function characteristics of this group.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the human exposure indicating little relevance to clinical use.

Carcinogenesis

Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5, or 10 mg/kg/day (approximately 2-7 times the recommended human dose). Male rats treated with 5 and 10 mg/kg/day had an increased incidence of hepatocellular adenomas.

Reproductive toxicity

Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10, or 20 mg/kg or with parenteral doses of 5, 25, or 75 mg/kg.

There were no foetal effects at 5 or 10 mg/kg; increases in foetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg to 320 mg/kg embryoletality in rats was increased and foetal abnormalities included wavy ribs, cleft palate, and abnormal cranio-facial ossification.

The onset of parturition was slightly delayed at 20 mg/kg orally and dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg and 40 mg/kg intravenously. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal

survival at these dose levels. These effects on parturation are consistent with the species specific oestrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole (see section 5.1).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Glycerol 85%
Purified water
Citric acid monohydrate
Sodium citrate
Cherry liquid flavor

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

Once opened, Diflucan may be used for a maximum of 30 days.

6.4 Special precautions for storage

The medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

One 180 ml amber Type III glass bottle with threaded aluminum caps.

A 20 ml measuring cup is also provided.

6.6 Special precautions for disposal and other handling

Do not use the medicinal product if you notice signs of deterioration such as unusual odour, product discoloration, visible particles or crystallization.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Detailed information on this medicinal product is available on the website of {name of MS/Agency}
[To be completed nationally].

1. NAME OF THE MEDICINAL PRODUCT

Diflucan and associated names (see Annex I) 10 mg/ml powder for oral suspension
Diflucan and associated names (see Annex I) 40 mg/ml powder for oral suspension
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of reconstituted suspension contains 10 mg fluconazole.
Excipient: 0.58 g sucrose per ml of reconstituted suspension.

1 ml of reconstituted suspension contains 40 mg fluconazole.
Excipient: 0.55 g sucrose per ml of reconstituted suspension

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for oral suspension

White to off-white powder for oral suspension providing a white to off-white orange-flavoured suspension after reconstitution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diflucan is indicated in the following fungal infections (see section 5.1).

Diflucan is indicated in adults for the treatment of:

- Cryptococcal meningitis (see section 4.4).
- Coccidioidomycosis (see section 4.4).
- Invasive candidiasis.
- Mucosal candidiasis including oropharyngeal, oesophageal candidiasis, candiduria and chronic mucocutaneous candidiasis.
- Chronic oral atrophic candidiasis (denture sore mouth) if dental hygiene or topical treatment are insufficient.
- Vaginal candidiasis, acute or recurrent; when local therapy is not appropriate.
- *Candidal balanitis* when local therapy is not appropriate.
- Dermatomycosis including *tinea pedis*, *tinea corporis*, *tinea cruris*, *tinea versicolor* and dermal *candida* infections when systemic therapy is indicated.
- *Tinea unguium* (*onychomycosis*) when other agents are not considered appropriate

Diflucan is indicated in adults for the prophylaxis of:

- Relapse of cryptococcal meningitis in patients with high risk of recurrence.
- Relapse of oropharyngeal or oesophageal candidiasis in patients infected with HIV who are at high risk of experiencing relapse.
- To reduce the incidence of recurrent vaginal candidiasis (4 or more episodes a year).
- Prophylaxis of candidal infections in patients with prolonged neutropenia (such as patients with haematological malignancies receiving chemotherapy or patients receiving Hematopoietic Stem Cell Transplantation (see section 5.1)).

Diflucan is indicated in term newborn infants, infants, toddlers, children, and adolescents aged from 0 to 17 years old:

Diflucan is used for the treatment of mucosal candidiasis (oropharyngeal, oesophageal), invasive candidiasis and cryptococcal meningitis and the prophylaxis of candidal infections in immunocompromised patients. Diflucan can be used as maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of reoccurrence (see section 4.4).

Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.

Consideration should be given to official guidance on the appropriate use of antifungals.

4.2 Posology and method of administration

Posology

The dose should be based on the nature and severity of the fungal infection. Treatment of infections requiring multiple dosing 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.

Adults:

<u>Indications</u>		<u>Posology</u>	<u>Duration of treatment</u>
Cryptococcosis	- Treatment of cryptococcal meningitis	Loading dose: 400 mg on Day 1 Subsequent dose: 200 mg to 400 mg daily	Usually at least 6 to 8 weeks. In life threatening infections the daily dose can be increased to 800 mg
	- Maintenance therapy to prevent relapse of cryptococcal meningitis in patients with high risk of recurrence.	200 mg daily	Indefinitely at a daily dose of 200 mg
Coccidioidomycosis		200 mg to 400 mg	11 months up to 24 months or longer depending on the patient. 800 mg daily may be considered for some infections and especially for meningeal disease
Invasive candidiasis		Loading dose: 800 mg on Day 1 Subsequent dose: 400 mg daily	In general, the recommended duration of therapy for candidemia is for 2 weeks after first negative blood culture result and resolution of signs and symptoms attributable to candidemia.
Treatment of mucosal candidiasis	- Oropharyngeal candidiasis	Loading dose: 200 mg to 400 mg on Day 1 Subsequent dose: 100 mg to 200 mg daily	7 to 21 days (until oropharyngeal candidiasis is in remission). Longer periods may be used in patients with severely compromised immune function

	- Oesophageal candidiasis	Loading dose: 200 mg to 400 mg on Day 1 Subsequent dose: 100 mg to 200 mg daily	14 to 30 days (until oesophageal candidiasis is in remission). Longer periods may be used in patients with severely compromised immune function
	- Candiduria	200 mg to 400 mg daily	7 to 21 days. Longer periods may be used in patients with severely compromised immune function.
	- Chronic atrophic candidiasis	50 mg daily	14 days
	- Chronic mucocutaneous candidiasis	50 mg to 100 mg daily	Up to 28 days. Longer periods depending on both the severity of infection or underlying immune compromise and infection
Prevention of relapse of mucosal candidiasis in patients infected with HIV who are at high risk of experiencing relapse	- Oropharyngeal candidiasis	100 mg to 200 mg daily or 200 mg 3 times per week.	An indefinite period for patients with chronic immune suppression
	- Oesophageal candidiasis	100 mg to 200 mg daily or 200 mg 3 times per week	An indefinite period for patients with chronic immune suppression
Genital candidiasis	- Acute vaginal candidiasis - Candidal balanitis	150 mg	Single dose
	- Treatment and prophylaxis of recurrent vaginal candidiasis (4 or more episodes a year)	150 mg every third day for a total of 3 doses (day 1, 4, and 7) followed by 150 mg once weekly maintenance dose	Maintenance dose: 6 months.
Dermatomycosis	- <i>tinea pedis</i> , - <i>tinea corporis</i> , - <i>tinea cruris</i> , - <i>candida</i> infections	150 mg once weekly or 50 mg once daily	2 to 4 weeks, <i>tinea pedis</i> may require treatment for up to 6 weeks
	- <i>tinea versicolor</i>	300 mg to 400 mg once weekly	1 to 3 weeks
		50 mg once daily	2 to 4 weeks

	- <i>tinea unguium</i> (<i>onychomycosis</i>)	150 mg once weekly	Treatment should be continued until infected nail is replaced (uninfected nail grows in). Regrowth of fingernails and toenails normally requires 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.
Prophylaxis of candidal infections in patients with prolonged neutropenia		200 mg to 400 mg	Treatment should start several days before the anticipated onset of neutropenia and continue for 7 days after recovery from neutropenia after the neutrophil count rises above 1000 cells per mm ³ .

Special populations

Elderly

Dosage should be adjusted based on the renal function (see “*Renal impairment*”).

Renal impairment

No adjustments in single dose therapy are necessary. In patients (including paediatric population) with impaired renal function who will receive multiple doses of fluconazole, an initial dose of 50 mg to 400 mg should be given, based on the recommended daily dose for the indication. After this initial loading dose, the daily dose (according to indication) should be based on the following table:

Creatinine clearance (ml/min)	Percent of recommended dose
>50	100%
≤50 (no dialysis)	50%
Regular dialysis	100% after each dialysis

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

Hepatic impairment

Limited data are available in patients with hepatic impairment, therefore fluconazole should be administered with caution to patients with liver dysfunction (see sections 4.4 and 4.8).

Paediatric population

A maximum dose of 400 mg daily should not be exceeded in paediatric population.

As with similar infections in adults, the duration of treatment is based on the clinical and mycological response. Diflucan is administered as a single daily dose.

For paediatric patients with impaired renal function, see dosing in “*Renal impairment*”. The pharmacokinetics of fluconazole has not been studied in paediatric population with renal insufficiency (for “Term newborn infants” who often exhibit primarily renal immaturity please see below).

Infants, toddlers and children (from 28 days to 11 years old):

Indication	Posology	Recommendations
- Mucosal candidiasis	Initial dose: 6 mg/kg Subsequent dose: 3 mg/kg daily	Initial dose may be used on the first day to achieve steady state levels more rapidly
- Invasive candidiasis - Cryptococcal meningitis	Dose: 6 to 12 mg/kg daily	Depending on the severity of the disease
- Maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of recurrence	Dose: 6 mg/kg daily	Depending on the severity of the disease
- Prophylaxis of <i>Candida</i> in immunocompromised patients	Dose: 3 to 12 mg/kg daily	Depending on the extent and duration of the induced neutropenia (see Adults posology)

Adolescents (from 12 to 17 years old):

Depending on the weight and pubertal development, the prescriber would need to assess which posology (adults or children) is the most appropriate. Clinical data indicate that children have a higher fluconazole clearance than observed for adults. A dose of 100, 200 and 400 mg in adults corresponds to a 3, 6 and 12 mg/kg dose in children to obtain a comparable systemic exposure.

Safety and efficacy for genital candidiasis indication in paediatric population has not been established. Current available safety data for other paediatric indications are described in section 4.8. If treatment for genital candidiasis is imperative in adolescents (from 12 to 17 years old), the posology should be the same as adults posology.

Term newborn infants (0 to 27 days):

Neonates excrete fluconazole slowly.

There are few pharmacokinetic data to support this posology in term newborn infants (see section 5.2).

Age group	Posology	Recommendations
Term newborn infants (0 to 14 days)	The same mg/kg dose as for infants, toddlers and children should be given every 72 hours	A maximum dose of 12 mg/kg every 72 hours should not be exceeded
Term newborn infants (from 15 to 27 days)	The same mg/kg dose as for infants, toddlers and children should be given every 48 hours	A maximum dose of 12 mg/kg every 48 hours should not be exceeded

Method of administration

Diflucan may be administered either orally or by intravenous infusion, the route being dependent on the clinical state of the patient. On transferring from the intravenous to the oral route, or *vice versa*, there is no need to change the daily dose.

Diflucan can be taken with or without food.

For instructions on reconstitution of the powder for oral suspension, (see section 6.6). The reconstituted suspension will provide a white to off-white orange-flavoured suspension after reconstitution.

4.3 Contraindications

Hypersensitivity to the active substance, to related azole substances, or to any of the excipients (see section 6.1).

Coadministration 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. Coadministration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 such as cisapride, astemizole, pimozone, quinidine and erythromycin are contraindicated in patients receiving fluconazole (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Tinea capitis

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

Cryptococcosis

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

Deep endemic mycoses

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

Renal system

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

Hepatobiliary system

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. Fluconazole hepatotoxicity has usually been reversible on discontinuation of therapy.

Patients who develop abnormal liver function tests during fluconazole therapy must be monitored closely for the development of more serious hepatic injury.

The patient should be informed of suggestive symptoms of serious hepatic effect (important asthenia, anorexia, persistent nausea, vomiting and jaundice). Treatment of fluconazole should be immediately discontinued and the patient should consult a physician.

Cardiovascular system

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and *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 treatment that may have been contributory.

Diflucan should be administered with caution to patients with these potentially proarrhythmic conditions. Coadministration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 are contraindicated (see sections 4.3 and 4.5).

Halofantrine

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

Dermatological reactions

Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, during treatment with fluconazole. AIDS patients are more prone to the development of severe cutaneous reactions to many medicinal products. If a rash, which is considered attributable to fluconazole, develops in a patient treated for a superficial fungal infection, further therapy with this medicinal product should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and fluconazole discontinued if *bullous* lesions or *erythema multiforme* develop.

Hypersensitivity

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

Cytochrome P450

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

Terfenadine

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

Excipients

Diflucan powder for oral suspension contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucose/galactose malabsorption and sucrase-isomaltase insufficiency should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of the following other medicinal products is contraindicated:

Cisapride: There have been reports of cardiac events including *torsades de pointes* in patients to whom fluconazole and cisapride were coadministered. A controlled study found that concomitant fluconazole 200 mg once daily and cisapride 20 mg four times a day yielded a significant increase in cisapride plasma levels and prolongation of QTc interval. Concomitant treatment with fluconazole and cisapride is contraindicated (see section 4.3).

Terfenadine: Because of the occurrence of serious cardiac dysrhythmias secondary to prolongation of the QTc interval in patients receiving azole antifungals in conjunction with terfenadine, interaction studies have been performed. One study at a 200 mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. Another study at a 400 mg and 800 mg daily dose of fluconazole demonstrated that fluconazole taken in doses of 400 mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. The combined use of fluconazole at doses of 400 mg or greater with terfenadine is contraindicated (see section 4.3). The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored.

Astemizole: Concomitant administration of fluconazole with astemizole may decrease the clearance of astemizole. Resulting increased plasma concentrations of astemizole can lead to QT prolongation and rare occurrences of *torsades de pointes*. Coadministration of fluconazole and astemizole is contraindicated (see section 4.3).

Pimozide: Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with pimozide may result in inhibition of pimozide metabolism. Increased pimozide plasma concentrations can lead to QT prolongation and rare occurrences of *torsades de pointes*. Coadministration of fluconazole and pimozide is contraindicated (see section 4.3).

Quinidine: Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with quinidine may result in inhibition of quinidine metabolism. Use of quinidine has been associated with QT prolongation and rare occurrences of *torsades de pointes*. Coadministration of fluconazole and quinidine is contraindicated (see section 4.3).

Erythromycin: Concomitant use of fluconazole and erythromycin has the potential to increase the risk of cardiotoxicity (prolonged QT interval, *torsades de pointes*) and consequently sudden heart death. Coadministration of fluconazole and erythromycin is contraindicated (see section 4.3).

Concomitant use of the following other medicinal products cannot be recommended:

Halofantrine: Fluconazole can increase halofantrine plasma concentration due to an inhibitory effect on CYP3A4. Concomitant use of fluconazole and halofantrine has the potential to increase the risk of cardiotoxicity (prolonged QT interval, *torsades de pointes*) and consequently sudden heart death. This combination should be avoided (see section 4.4).

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

The effect of other medicinal products on fluconazole

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

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

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. Fluconazole is also an inhibitor of the isozyme CYP2C19. In addition to the observed/documented interactions mentioned below, there is a risk of increased plasma concentration of other compounds metabolized by CYP2C9 and CYP3A4 coadministered with fluconazole. Therefore caution should be exercised when using these combinations and the patients should be carefully monitored. The enzyme inhibiting effect of fluconazole persists 4-5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole (see section 4.3).

Alfentanil: During concomitant treatment with fluconazole (400 mg) and intravenous alfentanil (20 µg/kg) in healthy volunteers the alfentanil AUC₁₀ increased 2-fold, probably through inhibition of CYP3A4.

Dose adjustment of alfentanil may be necessary.

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

Amphotericin B: Concurrent administration of fluconazole and amphotericin B in infected normal and immunosuppressed mice showed the following results: a small additive antifungal effect in systemic infection with *C. albicans*, no interaction in intracranial infection with *Cryptococcus neoformans*, and antagonism of the two medicinal products in systemic infection with *A. fumigatus*. The clinical significance of results obtained in these studies is unknown.

Anticoagulants: In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria, and melena) have been reported, in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. During concomitant treatment with fluconazole and warfarin the prothrombin time was prolonged up to 2-fold,

probably due to an inhibition of the warfarin metabolism through CYP2C9. In patients receiving coumarin-type anticoagulants concurrently with fluconazole the prothrombin time should be carefully monitored. Dose adjustment of warfarin may be necessary.

Benzodiazepines (short acting), i.e. midazolam, triazolam: Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. Concomitant intake of fluconazole 200 mg and midazolam 7.5 mg orally increased the midazolam AUC and half-life 3.7-fold and 2.2 fold, respectively. Fluconazole 200 mg daily given concurrently with triazolam 0.25 mg orally increased the triazolam AUC and half-life 4.4-fold and 2.3-fold, respectively. Potentiated and prolonged effects of triazolam have been observed at concomitant treatment with fluconazole. If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dose, and the patients should be appropriately monitored.

Carbamazepine: Fluconazole inhibits the metabolism of carbamazepine and an increase in serum carbamazepine of 30% has been observed. There is a risk of developing carbamazepine toxicity. Dose 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. Fluconazole has the potential to increase the systemic exposure of the calcium channel antagonists. Frequent monitoring for adverse events is recommended.

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

Cyclophosphamide: Combination therapy with cyclophosphamide and fluconazole results in an increase in serum bilirubin and serum creatinine. The combination may be used while taking increased consideration to the risk of increased serum bilirubin and serum creatinine.

Fentanyl: One fatal case of fentanyl intoxication due to possible fentanyl fluconazole interaction was reported. Furthermore, it was shown in healthy volunteers that fluconazole delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to respiratory depression. Patients should be monitored closely for the potential risk of respiratory depression. Dosage adjustment of fentanyl may be necessary.

HMG CoA reductase inhibitors: The risk of myopathy and rhabdomyolysis increases when fluconazole is coadministered 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.

Immunosuppressors (i.e. ciclosporin, everolimus, sirolimus and tacrolimus):

Ciclosporin: Fluconazole significantly increases the concentration and AUC of ciclosporin. During concomitant treatment with fluconazole 200 mg daily and ciclosporin (2.7 mg/kg/day) there was a 1.8-fold increase in ciclosporin AUC. This combination may be used by reducing the dose of ciclosporin depending on ciclosporin concentration.

Everolimus: Although not studied *in vivo* or *in vitro*, fluconazole may increase serum concentrations of everolimus through inhibition of CYP3A4.

Sirolimus: Fluconazole increases plasma concentrations of sirolimus presumably by inhibiting the metabolism of sirolimus via CYP3A4 and P-glycoprotein. This combination may be used with a dose adjustment of sirolimus depending on the effect/concentration measurements.

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

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

Methadone: Fluconazole may enhance the serum concentration of methadone. Dose adjustment of methadone may be necessary.

Non-steroidal anti-inflammatory drugs: The C_{max} and AUC of flurbiprofen was increased by 23% and 81%, respectively, when coadministered with fluconazole compared to administration of flurbiprofen alone. Similarly, the C_{max} and AUC of the pharmacologically active isomer [S-(+)-ibuprofen] was increased by 15% and 82%, respectively, when fluconazole was coadministered with racemic ibuprofen (400 mg) compared to administration of racemic ibuprofen alone.

Although not specifically studied, fluconazole has the potential to increase the systemic exposure of other NSAIDs that are metabolized by CYP2C9 (e.g. naproxen, lornoxicam, meloxicam, diclofenac). Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Adjustment of dose of NSAIDs may be needed.

Phenytoin: Fluconazole inhibits the hepatic metabolism of phenytoin. Concomitant repeated administration of 200 mg fluconazole and 250 mg phenytoin intravenously, caused an increase of the phenytoin AUC_{24} by 75% and C_{min} by 128%. With coadministration, serum phenytoin concentration levels should be monitored in order to avoid phenytoin toxicity.

Prednisone: There was a case report that a liver-transplanted patient treated with prednisone developed acute adrenal cortex insufficiency when a three month therapy with fluconazole was discontinued. The discontinuation of fluconazole presumably caused an enhanced CYP3A4 activity which led to increased metabolism of prednisone. Patients on long-term treatment with fluconazole and prednisone should be carefully monitored for adrenal cortex insufficiency when fluconazole is discontinued.

Rifabutin: Fluconazole increases serum concentrations of rifabutin, leading to increase in the AUC of rifabutin up to 80%. There have been reports of uveitis in patients to whom fluconazole and rifabutin were coadministered. In combination therapy, symptoms of rifabutin toxicity should be taken into consideration.

Saquinavir: Fluconazole increases the AUC and C_{max} of saquinavir with approximately 50% and 55% respectively, due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein. Interaction with saquinavir/ritonavir has not been studied and might be more marked. Dose adjustment of saquinavir may be necessary.

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

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

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

Vinca alkaloids: Although not studied, fluconazole may increase the plasma levels of the vinca alkaloids (e.g. vincristine and vinblastine) and lead to neurotoxicity, which is possibly due to an inhibitory effect on CYP3A4.

Vitamin A: Based on a case-report in one patient receiving combination therapy with all-trans-retinoid acid (an acid form of vitamin A) and fluconazole, CNS related undesirable effects have developed in the form of pseudotumour *cerebri*, which disappeared after discontinuation of fluconazole treatment. This combination may be used but the incidence of CNS related undesirable effects should be borne in mind.

Voriconazole: (CYP2C9 and CYP3A4 inhibitor): Coadministration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 2.5 days) and oral fluconazole (400 mg on day 1, then 200 mg Q24h for 4 days) to 8 healthy male subjects resulted in an increase in C_{max} and AUC_{τ} of voriconazole by an average of 57% (90% CI: 20%, 107%) and 79% (90% CI: 40%, 128%), respectively. The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole associated adverse events is recommended if voriconazole is used sequentially after fluconazole.

Zidovudine: Fluconazole increases C_{max} and AUC of zidovudine by 84% and 74%, respectively, due to an approx. 45% decrease in oral zidovudine clearance. The half-life of zidovudine was likewise prolonged by approximately 128% following combination therapy with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions. Dose reduction of zidovudine may be considered.

Azithromycin: An open-label, randomized, three-way crossover study in 18 healthy subjects assessed the effect of a single 1200 mg oral dose of azithromycin on the pharmacokinetics of a single 800 mg oral dose of fluconazole as well as the effects of fluconazole on the pharmacokinetics of azithromycin. There was no significant pharmacokinetic interaction between fluconazole and azithromycin.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Data from several hundred pregnant women treated with standard doses (<200 mg/day) of fluconazole, administered as a single or repeated dose in the first trimester, show no undesirable effects in the foetus. There have been reports of multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in infants whose mothers were treated for at least three or more months with high doses (400-800 mg daily) of fluconazole for coccidioidomycosis. The relationship between fluconazole use and these events is unclear.

Studies in animals have shown reproductive toxicity (see section 5.3).

Fluconazole in standard doses and short-term treatments should not be used in pregnancy unless clearly necessary.

Fluconazole in high dose and/or in prolonged regimens should not be used during pregnancy except for potentially life-threatening infections.

Breast-feeding

Fluconazole passes into breast milk to reach concentrations lower than those in plasma. Breast-feeding may be maintained after a single use of a standard dose 200 mg fluconazole or less. Breast-feeding is not recommended after repeated use or after high dose fluconazole.

Fertility

Fluconazole did not affect the fertility of male or female rats (see section 5.3)

4.7 Effects on ability to drive and use machines

No studies have been performed on the effects of Diflucan on the ability to drive or use machines. Patients should be warned about the potential for dizziness or seizures (see section 4.8) while taking Diflucan and should be advised not to drive or operate machines if any of these symptoms occur.

4.8 Undesirable effects

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

The following adverse reactions have been observed and reported during treatment with Diflucan with the following frequencies: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

System Organ Class	Common	Uncommon	Rare
Blood and the lymphatic system disorders		Anaemia	Agranulocytosis, leukopenia, thrombocytopenia, neutropenia
Immune system disorders			Anaphylaxis
Metabolism and nutrition disorders		Decreased appetite	Hypercholesterolaemia, hypertriglyceridaemia, hypokalemia
Psychiatric disorders		Somnolence, insomnia	
Nervous system disorders	Headache	Seizures, paraesthesia, dizziness, taste perversion	Tremor
Ear and labyrinth disorders		Vertigo	
Cardiac disorders			<i>Torsade de pointes</i> (see section 4.4), QT prolongation (see section 4.4)
Gastrointestinal disorders	Abdominal pain, vomiting, diarrhoea, nausea	Constipation, dyspepsia, flatulence, dry mouth	
Hepatobiliary disorders	Alanine aminotransferase increased (see section 4.4), aspartate aminotransferase increased (see section 4.4), blood	Cholestasis (see section 4.4), jaundice (see section 4.4), bilirubin increased (see section 4.4)	Hepatic failure (see section 4.4), hepatocellular necrosis (see section 4.4), hepatitis (see section 4.4), hepatocellular damage (see section 4.4)

	alkaline phosphatase increased (see section 4.4)		
Skin and subcutaneous tissue disorders	Rash (see section 4.4)	Drug eruption (see section 4.4), urticaria (see section 4.4), pruritus, increased sweating	Toxic epidermal necrolysis, (see section 4.4), Stevens-Johnson syndrome (see section 4.4), acute generalised exanthematous-pustulosis (see section 4.4), dermatitis exfoliative, angioedema, face oedema, alopecia
Musculoskeletal and connective tissue disorders		Myalgia	
General disorders and administration site conditions		Fatigue, malaise, asthenia, fever	

Paediatric population

The pattern and incidence of adverse reactions and laboratory abnormalities recorded during paediatric clinical trials, excluding the genital candidiasis indication, are comparable to those seen in adults.

4.9 Overdose

There have been reports of overdose with Diflucan and hallucination and paranoid behaviour have been concomitantly reported.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC classification

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02AC01.

Mode of action

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

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

Susceptibility *in vitro*

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

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

PK/PD relationship

In animal studies, there is a correlation between MIC values and efficacy against experimental mycoses due to *Candida* spp. In clinical studies, there is an almost 1:1 linear relationship between the AUC and the dose of fluconazole. There is also a direct though imperfect relationship between the AUC or dose and a successful clinical response of oral candidosis and to a lesser extent candidaemia to treatment. Similarly cure is less likely for infections caused by strains with a higher fluconazole MIC.

Mechanism(s) of resistance

Candida spp have developed a number of resistance mechanisms to azole antifungal agents. Fungal strains which have developed one or more of these resistance mechanisms are known to exhibit high minimum inhibitory concentrations (MICs) to fluconazole which impacts adversely efficacy *in vivo* and clinically.

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

Breakpoints (according to EUCAST)

Based on analyses of pharmacokinetic/pharmacodynamic (PK/PD) data, susceptibility *in vitro* and clinical response EUCAST-AFST (European Committee on Antimicrobial susceptibility Testing-subcommittee on Antifungal Susceptibility Testing) has determined breakpoints for fluconazole for *Candida* species (EUCAST Fluconazole rational document (2007)-version 2). These have been divided into non-species related breakpoints; which have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species, and species related breakpoints for those species most frequently associated with human infection. These breakpoints are given in the table below:

Antifungal	Species-related breakpoints (S</R>)					Non-species related breakpoints ^A S</R>
	<i>Candida albicans</i>	<i>Candida glabrata</i>	<i>Candida krusei</i>	<i>Candida parapsilosis</i>	<i>Candida tropicalis</i>	
Fluconazole	2/4	IE	--	2/4	2/4	2/4

S = Susceptible, R = Resistant

A. = Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the medicinal product.

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

5.2 Pharmacokinetic properties

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

Absorption

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

Distribution

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

Fluconazole achieves good penetration in all body fluids studied. The levels of fluconazole in saliva and sputum are similar to plasma levels. In patients with fungal meningitis, fluconazole levels in the CSF are approximately 80% the corresponding plasma levels.

High skin concentration of fluconazole, above serum concentrations, are achieved in the stratum corneum, epidermis-dermis and eccrine sweat. Fluconazole accumulates in the stratum corneum. At a dose of 50 mg once daily, the concentration of fluconazole after 12 days was 73 µg/g and 7 days after cessation of treatment the concentration was still 5.8 µg/g. At the 150 mg once-a-week dose, the concentration of fluconazole in stratum corneum on day 7 was 23.4 µg/g and 7 days after the second dose was still 7.1 µg/g.

Concentration of fluconazole in nails after 4 months of 150 mg once-a-week dosing was 4.05 µg/g in healthy and 1.8 µg/g in diseased nails; and, fluconazole was still measurable in nail samples 6 months after the end of therapy.

Biotransformation

Fluconazole is metabolised only to a minor extent. Of a radioactive dose, only 11% is excreted in a changed form in the urine. Fluconazole is a selective inhibitor of the isozymes CYP2C9 and CYP3A4 (see section 4.5). Fluconazole is also an inhibitor of the isozyme CYP2C19.

Excretion

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

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

Pharmacokinetics in renal impairment

In patients with severe renal insufficiency, (GFR < 20 ml/min) half life increased from 30 to 98 hours. Consequently, reduction of the dose is needed. Fluconazole is removed by haemodialysis and to a lesser extent by peritoneal dialysis. After three hours of haemodialysis session, around 50% of fluconazole is eliminated from blood.

Pharmacokinetics in children

Pharmacokinetic data were assessed for 113 paediatric patients from 5 studies; 2 single-dose studies, 2 multiple-dose studies, and a study in premature neonates. Data from one study were not interpretable due to changes in formulation pathway through the study. Additional data were available from a compassionate use study.

After administration of 2-8 mg/kg fluconazole to children between the ages of 9 months to 15 years, an AUC of about 38 µg·h/ml was found per 1 mg/kg dose units. The average fluconazole plasma elimination half-life varied between 15 and 18 hours and the distribution volume was approximately 880 ml/kg after multiple doses. A higher fluconazole plasma elimination half-life of approximately 24 hours was found

after a single dose. This is comparable with the fluconazole plasma elimination half-life after a single administration of 3 mg/kg i.v. to children of 11 days-11 months old. The distribution volume in this age group was about 950 ml/kg.

Experience with fluconazole in neonates is limited to pharmacokinetic studies in premature newborns. The mean age at first dose was 24 hours (range 9-36 hours) and mean birth weight was 0.9 kg (range 0.75-1.10 kg) for 12 pre-term neonates of average gestation around 28 weeks. Seven patients completed the protocol; a maximum of five 6 mg/kg intravenous infusions of fluconazole were administered every 72 hours. The mean half-life (hours) was 74 (range 44-185) on day 1 which decreased, with time to a mean of 53 (range 30-131) on day 7 and 47 (range 27-68) on day 13. The area under the curve (microgram.h/ml) was 271 (range 173-385) on day 1 and increased with a mean of 490 (range 292-734) on day 7 and decreased with a mean of 360 (range 167-566) on day 13. The volume of distribution (ml/kg) was 1183 (range 1070-1470) on day 1 and increased, with time, to a mean of 1184 (range 510-2130) on day 7 and 1328 (range 1040-1680) on day 13.

Pharmacokinetics in elderly

A pharmacokinetic study was conducted in 22 subjects, 65 years of age or older receiving a single 50 mg oral dose of fluconazole. Ten of these patients were concomitantly receiving diuretics. The C_{max} was 1.54 µg/ml and occurred at 1.3 hours post-dose. The mean AUC was 76.4 ± 20.3 µg·h/ml, and the mean terminal half-life was 46.2 hours. These pharmacokinetic parameter values are higher than analogous values reported for normal young male volunteers. Coadministration of diuretics did not significantly alter AUC or C_{max} . In addition, creatinine clearance (74 ml/min), the percent of medicinal product recovered unchanged in urine (0-24 hr, 22%) and the fluconazole renal clearance estimates (0.124 ml/min/kg) for the elderly were generally lower than those of younger volunteers. Thus, the alteration of fluconazole disposition in the elderly appears to be related to reduced renal function characteristics of this group.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the human exposure indicating little relevance to clinical use.

Carcinogenesis

Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5, or 10 mg/kg/day (approximately 2-7 times the recommended human dose). Male rats treated with 5 and 10 mg/kg/day had an increased incidence of hepatocellular adenomas.

Reproductive toxicity

Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10, or 20 mg/kg or with parenteral doses of 5, 25, or 75 mg/kg.

There were no foetal effects at 5 or 10 mg/kg; increases in foetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg to 320 mg/kg embryoletality in rats was increased and foetal abnormalities included wavy ribs, cleft palate, and abnormal cranio-facial ossification.

The onset of parturition was slightly delayed at 20 mg/kg orally and dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg and 40 mg/kg intravenously. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal survival at these dose levels. These effects on parturition are consistent with the species specific oestrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole (see section 5.1).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose

Silica, colloidal anhydrous
Titanium dioxide (E 171)
Xanthan gum
Sodium citrate
Citric acid anhydrous
Sodium benzoate
Natural orange flavour (containing orange oil and maltodextrin)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The shelf life of the powder for oral suspension is 24 months.

The shelf life of the reconstituted suspension is 28 days.

Reconstituted suspension: Store below 30°C, do not freeze.

6.4 Special precautions for storage

Powder for oral suspension 10 mg/ml and 40 mg/ml (60 ml bottle): Store below 25°C.

Powder for oral suspension 10 mg/ml (175 ml bottle): Store below 25°C.

Keep the bottle tightly closed.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

A 60 ml or a 175 ml high density polyethylene (HDPE) bottle with either a plastic child-resistant closure or continuous thread aluminum closure containing a white to off-white powder for oral suspension providing a white to off-white orange-flavoured suspension after reconstitution.

Diflucan and associated names 10 mg/ml powder for oral suspension:

A 60 ml bottle contains 24.4 g of powder for oral suspension. After reconstitution, the volume of the suspension is 40 ml, providing a usable volume of 35 ml.

A 175 ml bottle contains 67.1 g of powder for oral suspension. After reconstitution, the volume of the suspension is 110 ml, providing a usable volume of 100 ml.

Diflucan and associated names 40 mg/ml powder for oral suspension:

A 60 ml bottle contains 24.4 g powder for oral suspension. After reconstitution, the volume of the suspension is 40 ml, providing a usable volume of 35 ml.

Not all pack sizes may be marketed.

A 5 ml measuring spoon and/or a 5 ml graduated syringe with a press-in bottle adaptor might also be provided with the 60 ml bottle.

A measuring cup is provided with the 175 ml bottle.

6.6 Special precautions for disposal and other handling

Reconstitution instructions:

The reconstituted suspension will provide a white to off-white orange-flavoured suspension after reconstitution.

For the 60 ml bottle:

1. Tap the bottle to release the powder.
2. Add a small quantity of still water and shake it vigorously. Add water up to the level marked on the bottle (this corresponds to adding 24 ml of water)
3. Shake well for 1 to 2 minutes to obtain a homogenous suspension.
4. Write the date of expiration of the reconstituted suspension on the bottle label (the shelf life of the reconstituted suspension is 28 days).

For the 175 ml bottle: (Applicable only if marketed in your country)

1. Tap the bottle to release the powder.
2. Measure 66 ml of still water and add the water to the bottle.
3. Shake well for 1 to 2 minutes to obtain a homogenous suspension.
4. Write the date of expiration of the reconstituted suspension on the bottle label (the shelf life of the reconstituted suspension is 28 days).

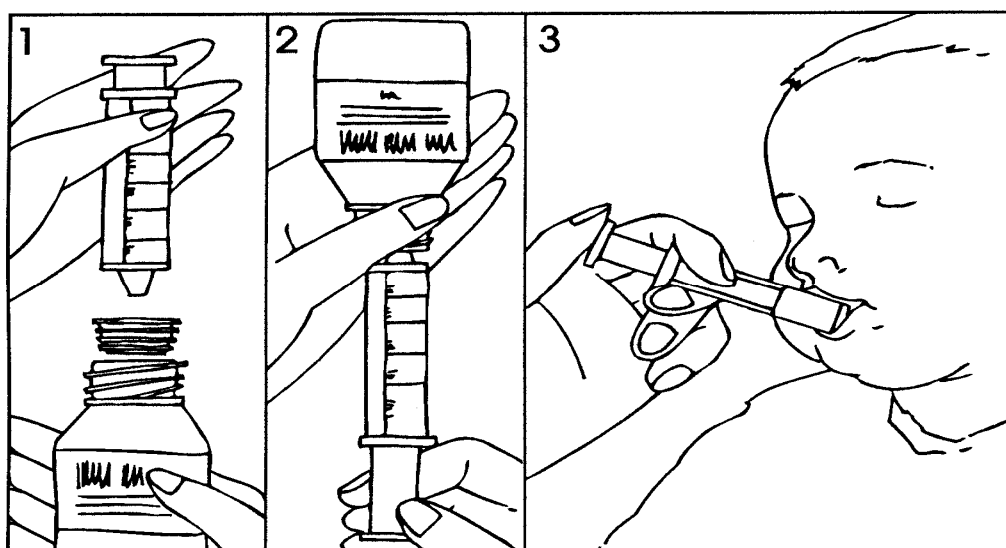
Instructions for use:

Shake the closed bottle of the reconstituted suspension before each use.

Instructions to use the paediatric syringe: (Applicable only if marketed in your country)

Shake the prepared suspension well.

1. Open the bottle (safety cap);
2. Insert the adapter fitted onto the syringe into the bottle neck (1, 2 - see Figure 1);
3. Turn the bottle with the syringe upside down and withdraw the quantity of suspension prescribed by the doctor (Figure 2). The graduations on the syringe are shown in ml. The maximum adult daily dose should not be exceeded in children (see section 4.2)
4. Remove the syringe from the bottle;
5. For younger children, the medicinal product may be given directly into the mouth from the syringe. The child should remain upright during administration. Point the syringe at the inside of the cheek; release the suspension slowly into the child's mouth (Figure 3). For older children, the suspension may be put in a spoon and drunk by the child.
6. Rinse the syringe after use.
7. Close the bottle with the safety cap; the adapter will remain on the bottle neck.



Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Any remaining suspension should be discarded 28 days after reconstitution.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally].

Detailed information on this medicinal product is available on the website of {name of MS/Agency}
[To be completed nationally].

1. NAME OF THE MEDICINAL PRODUCT

Diflucan and associated names (see Annex I) 2 mg/ml solution for infusion
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 25 ml solution for infusion contains 50 mg fluconazole.
Each 50 ml solution for infusion contains 100 mg fluconazole.
Each 100 ml solution for infusion contains 200 mg fluconazole.
Each 200 ml solution for infusion contains 400 mg fluconazole.

Each ml contains 2 mg of fluconazole.

Excipient: each ml also contains 9 mg sodium chloride (equivalent to 0.154 mmol sodium).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion

Clear, colourless solution with no visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diflucan is indicated in the following fungal infections (see section 5.1).

Diflucan is indicated in adults for the treatment of:

- Cryptococcal meningitis (see section 4.4).
- Coccidioidomycosis (see section 4.4).
- Invasive candidiasis.
- Mucosal candidiasis including oropharyngeal, oesophageal candidiasis, candiduria and chronic mucocutaneous candidiasis.
- Chronic oral atrophic candidiasis (denture sore mouth) if dental hygiene topical treatment are insufficient.

Diflucan is indicated in adults for the prophylaxis of:

- Relapse of cryptococcal meningitis in patients with high risk of recurrence.
- Relapse of oropharyngeal or oesophageal candidiasis in patients infected with HIV who are at high risk of experiencing relapse.
- Prophylaxis of candidal infections in patients with prolonged neutropenia (such as patients with haematological malignancies receiving chemotherapy or patients receiving Hematopoietic Stem Cell Transplantation (see section 5.1)).

Diflucan is indicated in term newborn infants, infants, toddlers, children and adolescents aged from 0 to 17 years old:

Diflucan is used for the treatment of mucosal candidiasis (oropharyngeal, oesophageal), invasive candidiasis, cryptococcal meningitis and the prophylaxis of candidal infections in

immunocompromised patients. Diflucan can be used as maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of recurrence (see section 4.4).

Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.

Consideration should be given to official guidance on the appropriate use of antifungals.

4.2 Posology and method of administration

Posology

The dose should be based on the nature and severity of the fungal infection. Treatment of infections requiring multiple dosing 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.

Adults:

Indications		Posology	Duration of treatment
Cryptococcosis	- Treatment of cryptococcal meningitis	Loading dose: 400 mg on Day 1 Subsequent dose: 200 mg to 400 mg daily	Usually at least 6 to 8 weeks. In life threatening infections the daily dose can be increased to 800 mg
	- Maintenance therapy to prevent relapse of cryptococcal meningitis in patients with high risk of recurrence.	200 mg daily	Indefinitely at a daily dose of 200 mg
Coccidioidomycosis		200 mg to 400 mg	11 months up to 24 months or longer depending on the patient. 800 mg daily may be considered for some infections and especially for meningeal disease
Invasive candidiasis		Loading dose: 800 mg on Day 1 Subsequent dose: 400 mg daily	In general, the recommended duration of therapy for candidemia is for 2 weeks after first negative blood culture result and resolution of signs and symptoms attributable to candidemia.
Treatment of mucosal candidiasis	- Oropharyngeal candidiasis	Loading dose: 200 mg to 400 mg on Day 1 Subsequent dose: 100 mg to 200 mg daily	7 to 21 days (until oropharyngeal candidiasis is in remission). Longer periods may be used in patients with severely compromised immune function
	- Oesophageal candidiasis	Loading dose: 200 mg to 400 mg on Day 1 Subsequent dose: 100 mg to 200 mg daily	14 to 30 days (until oesophageal candidiasis is in remission). Longer periods may be used in patients with severely compromised immune function

	- Candiduria	200 mg to 400 mg daily	7 to 21 days. Longer periods may be used in patients with severely compromised immune function.
	- Chronic atrophic candidiasis	50 mg daily	14 days
	- Chronic mucocutaneous candidiasis	50 mg to 100 mg daily	Up to 28 days. Longer periods depending on both the severity of infection or underlying immune compromise and infection
Prevention of relapse of mucosal candidiasis in patients infected with HIV who are at high risk of experiencing relapse	- Oropharyngeal candidiasis	100 mg to 200 mg daily or 200 mg 3 times per week.	An indefinite period for patients with chronic immune suppression
	- Oesophageal candidiasis	100 mg to 200 mg daily or 200 mg 3 times per week	An indefinite period for patients with chronic immune suppression
Prophylaxis of candidal infections in patients with prolonged neutropenia		200 mg to 400 mg	Treatment should start several days before the anticipated onset of neutropenia and continue for 7 days after recovery from neutropenia after the neutrophil count rises above 1000 cells per mm ³ .

Special populations

Elderly

Dosage should be adjusted based on the renal function (see “*Renal impairment*”).

Renal impairment

Diflucan is predominantly excreted in the urine as unchanged active substance. No adjustments in single dose therapy are necessary. In patients (including paediatric population) with impaired renal function who will receive multiple doses of fluconazole, an initial dose of 50 mg to 400 mg should be given, based on the recommended daily dose for the indication. After this initial loading dose, the daily dose (according to indication) should be based on the following table:

Creatinine clearance (ml/min)	Percent of recommended dose
>50	100%
≤50 (no dialysis)	50%
Regular dialysis	100% after each dialysis

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

Hepatic impairment

Limited data are available in patients with hepatic impairment, therefore fluconazole should be administered with caution to patients with liver dysfunction (see sections 4.4 and 4.8).

Paediatric population:

A maximum dose of 400 mg daily should not be exceeded in paediatric population.

As with similar infections in adults, the duration of treatment is based on the clinical and mycological response. Diflucan is administered as a single daily dose.

For paediatric patients with impaired renal function, see dosing in “*Renal impairment*”. The pharmacokinetics of fluconazole has not been studied in paediatric population with renal insufficiency (for “Term newborn infants” who often exhibit primarily renal immaturity please see below).

Infants, toddlers and children (from 28 days to 11 years old):

Indication	Posology	Recommendations
- Mucosal candidiasis	Initial dose: 6 mg/kg Subsequent dose: 3 mg/kg daily	Initial dose may be used on the first day to achieve steady state levels more rapidly
- Invasive candidiasis - Cryptococcal meningitis	Dose: 6 to 12 mg/kg daily	Depending on the severity of the disease
- Maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of recurrence	Dose: 6 mg/kg daily	Depending on the severity of the disease
- Prophylaxis of <i>Candida</i> in immunocompromised patients	Dose: 3 to 12 mg/kg daily	Depending on the extent and duration of the induced neutropenia (see Adults posology)

Adolescents (from 12 to 17 years old):

Depending on the weight and pubertal development, the prescriber would need to assess which posology (adults or children) is the most appropriate. Clinical data indicate that children have a higher fluconazole clearance than observed for adults. A dose of 100, 200 and 400 mg in adults corresponds to a 3, 6 and 12 mg/kg dose in children to obtain a comparable systemic exposure.

Term newborn infants (0 to 27 days):

Neonates excrete fluconazole slowly.

There are few pharmacokinetic data to support this posology in term newborn infants (see section 5.2).

Age group	Posology	Recommendations
Term newborn infants (0 to 14 days)	The same mg/kg dose as for infants, toddlers and children should be given every 72 hours	A maximum dose of 12 mg/kg every 72 hours should not be exceeded
Term newborn infants (from 15 to 27 days)	The same mg/kg dose as for infants, toddlers and children should be given every 48 hours	A maximum dose of 12 mg/kg every 48 hours should not be exceeded

Method of administration

Diflucan may be administered either orally or by intravenous infusion, the route being dependent on the clinical state of the patient. On transferring from the intravenous to the oral route, or *vice versa*, there is no need to change the daily dose.

Intravenous infusion should be administered at a rate not exceeding 10 ml/minute. Diflucan is formulated in sodium chloride 9 mg/ml (0.9%) solution for infusion, each 200 mg (100 ml bottle) containing 15 mmol each of Na⁺ and Cl⁻. Because Diflucan is available as a dilute sodium chloride solution, in patients requiring sodium or fluid restriction, consideration should be given to the rate of fluid administration.

For instruction on handling of the product, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance to related azole substances, or to any of the excipients (see section 6.1).

Coadministration 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. Coadministration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 such as cisapride, astemizole, pimozone, quinidine and erythromycin are contraindicated in patients receiving fluconazole (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Tinea capitis

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

Cryptococcosis

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

Deep endemic mycoses

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

Renal system

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

Hepatobiliary system

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. Fluconazole hepatotoxicity has usually been reversible on discontinuation of therapy.

Patients who develop abnormal liver function tests during fluconazole therapy must be monitored closely for the development of more serious hepatic injury.

The patient should be informed of suggestive symptoms of serious hepatic effect (important asthenia, anorexia, persistent nausea, vomiting and jaundice). Treatment of fluconazole should be immediately discontinued and the patient should consult a physician.

Cardiovascular system

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and *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 treatment that may have been contributory.

Diflucan should be administered with caution to patients with these potentially proarrhythmic conditions. Coadministration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 are contraindicated (see sections 4.3 and 4.5).

Halofantrine

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

Dermatological reactions

Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, during treatment with fluconazole. AIDS patients are more prone to the development of severe cutaneous reactions to many medicinal products. If a rash, which is considered attributable to fluconazole, develops in a patient treated for a superficial fungal infection, further therapy with this medicinal product should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and fluconazole discontinued if *bullous* lesions or *erythema multiforme* develop.

Hypersensitivity

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

Cytochrome P450

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

Terfenadine

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

Excipients

This medicinal product contains 0.154 mmol sodium per ml. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of the following other medicinal products is contraindicated:

Cisapride: There have been reports of cardiac events including *torsades de pointes* in patients to whom fluconazole and cisapride were coadministered. A controlled study found that concomitant fluconazole 200 mg once daily and cisapride 20 mg four times a day yielded a significant increase in cisapride plasma levels and prolongation of QTc interval. Concomitant treatment with fluconazole and cisapride is contraindicated (see section 4.3).

Terfenadine: Because of the occurrence of serious cardiac dysrhythmias secondary to prolongation of the QTc interval in patients receiving azole antifungals in conjunction with terfenadine, interaction studies have been performed. One study at a 200 mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. Another study at a 400 mg and 800 mg daily dose of fluconazole demonstrated that fluconazole taken in doses of 400 mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. The combined use of fluconazole at doses of 400 mg or greater with terfenadine is contraindicated (see section 4.3). The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored.

Astemizole: Concomitant administration of fluconazole with astemizole may decrease the clearance of astemizole. Resulting increased plasma concentrations of astemizole can lead to QT prolongation and rare occurrences of *torsades de pointes*. Coadministration of fluconazole and astemizole is contraindicated (see section 4.3).

Pimozide: Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with pimozide may result in inhibition of pimozide metabolism. Increased pimozide plasma concentrations can

lead to QT prolongation and rare occurrences of *torsades de pointes*. Coadministration of fluconazole and pimozide is contraindicated (see section 4.3).

Quinidine: Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with quinidine may result in inhibition of quinidine metabolism. Use of quinidine has been associated with QT prolongation and rare occurrences of *torsades de pointes*. Coadministration of fluconazole and quinidine is contraindicated (see section 4.3).

Erythromycin: Concomitant use of fluconazole and erythromycin has the potential to increase the risk of cardiotoxicity (prolonged QT interval, *torsades de pointes*) and consequently sudden heart death. Coadministration of fluconazole and erythromycin is contraindicated (see section 4.3).

Concomitant use of the following other medicinal products cannot be recommended:

Halofantrine: Fluconazole can increase halofantrine plasma concentration due to an inhibitory effect on CYP3A4. Concomitant use of fluconazole and halofantrine has the potential to increase the risk of cardiotoxicity (prolonged QT interval, *torsades de pointes*) and consequently sudden heart death. This combination should be avoided (see section 4.4).

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

The effect of other medicinal products on fluconazole

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

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

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. Fluconazole is also an inhibitor of the isozyme CYP2C19. In addition to the observed/documentated interactions mentioned below, there is a risk of increased plasma concentration of other compounds metabolized by CYP2C9 and CYP3A4 coadministered with fluconazole. Therefore caution should be exercised when using these combinations and the patients should be carefully monitored. The enzyme inhibiting effect of fluconazole persists 4-5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole (see section 4.3).

Alfentanil: During concomitant treatment with fluconazole (400 mg) and intravenous alfentanil (20 µg/kg) in healthy volunteers the alfentanil AUC₁₀ increased 2-fold, probably through inhibition of CYP3A4.

Dose adjustment of alfentanil may be necessary.

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

Amphotericin B: Concurrent administration of fluconazole and amphotericin B in infected normal and immunosuppressed mice showed the following results: a small additive antifungal effect in systemic infection with *C. albicans*, no interaction in intracranial infection with *Cryptococcus neoformans*, and antagonism of the two medicinal products in systemic infection with *A. fumigatus*. The clinical significance of results obtained in these studies is unknown.

Anticoagulants: In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria, and melena) have been reported, in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. During concomitant treatment with fluconazole and warfarin the prothrombin time was prolonged up to 2-fold, probably due to an inhibition of the warfarin metabolism through CYP2C9. In patients receiving coumarin-type anticoagulants concurrently with fluconazole the prothrombin time should be carefully monitored. Dose adjustment of warfarin may be necessary.

Benzodiazepines (short acting), i.e. midazolam, triazolam: Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. Concomitant intake of fluconazole 200 mg and midazolam 7.5 mg orally increased the midazolam AUC and half-life 3.7-fold and 2.2-fold, respectively. Fluconazole 200 mg daily given concurrently with triazolam 0.25 mg orally increased the triazolam AUC and half-life 4.4-fold and 2.3-fold, respectively. Potentiated and prolonged effects of triazolam have been observed at concomitant treatment with fluconazole. If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dose, and the patients should be appropriately monitored.

Carbamazepine: Fluconazole inhibits the metabolism of carbamazepine and an increase in serum carbamazepine of 30% has been observed. There is a risk of developing carbamazepine toxicity. Dose 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. Fluconazole has the potential to increase the systemic exposure of the calcium channel antagonists. Frequent monitoring for adverse events is recommended.

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

Cyclophosphamide: Combination therapy with cyclophosphamide and fluconazole results in an increase in serum bilirubin and serum creatinine. The combination may be used while taking increased consideration to the risk of increased serum bilirubin and serum creatinine.

Fentanyl: One fatal case of fentanyl intoxication due to possible fentanyl fluconazole interaction was reported. Furthermore, it was shown in healthy volunteers that fluconazole delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to respiratory depression. Patients should be monitored closely for the potential risk of respiratory depression. Dosage adjustment of fentanyl may be necessary.

HMG CoA reductase inhibitors: The risk of myopathy and rhabdomyolysis increases when fluconazole is coadministered 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.

Immunosuppressors (i.e. ciclosporin, everolimus, sirolimus and tacrolimus):

Ciclosporin: Fluconazole significantly increases the concentration and AUC of ciclosporin. During concomitant treatment with fluconazole 200 mg daily and ciclosporin (2.7 mg/kg/day) there was a 1.8-fold increase in ciclosporin AUC. This combination may be used by reducing the dose of ciclosporin depending on ciclosporin concentration.

Everolimus: Although not studied *in vivo* or *in vitro*, fluconazole may increase serum concentrations of everolimus through inhibition of CYP3A4.

Sirolimus: Fluconazole increases plasma concentrations of sirolimus presumably by inhibiting the metabolism of sirolimus via CYP3A4 and P-glycoprotein. This combination may be used with a dose adjustment of sirolimus depending on the effect/concentration measurements.

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

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

Methadone: Fluconazole may enhance the serum concentration of methadone. Dose adjustment of methadone may be necessary.

Non-steroidal anti-inflammatory drugs: The C_{max} and AUC of flurbiprofen was increased by 23% and 81%, respectively, when coadministered with fluconazole compared to administration of flurbiprofen alone. Similarly, the C_{max} and AUC of the pharmacologically active isomer [S-(+)-ibuprofen] was increased by 15% and 82%, respectively, when fluconazole was coadministered with racemic ibuprofen (400 mg) compared to administration of racemic ibuprofen alone.

Although not specifically studied, fluconazole has the potential to increase the systemic exposure of other NSAIDs that are metabolized by CYP2C9 (e.g. naproxen, lornoxicam, meloxicam, diclofenac). Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Adjustment of dose of NSAIDs may be needed.

Phenytoin: Fluconazole inhibits the hepatic metabolism of phenytoin. Concomitant repeated administration of 200 mg fluconazole and 250 mg phenytoin intravenously, caused an increase of the phenytoin AUC₂₄ by 75% and C_{min} by 128%. With coadministration, serum phenytoin concentration levels should be monitored in order to avoid phenytoin toxicity.

Prednisone: There was a case report that a liver-transplanted patient treated with prednisone developed acute adrenal cortex insufficiency when a three month therapy with fluconazole was discontinued. The discontinuation of fluconazole presumably caused an enhanced CYP3A4 activity which led to increased metabolism of prednisone. Patients on long-term treatment with fluconazole and prednisone should be carefully monitored for adrenal cortex insufficiency when fluconazole is discontinued.

Rifabutin: Fluconazole increases serum concentrations of rifabutin, leading to increase in the AUC of rifabutin up to 80%. There have been reports of uveitis in patients to whom fluconazole and rifabutin were coadministered. In combination therapy, symptoms of rifabutin toxicity should be taken into consideration.

Saquinavir: Fluconazole increases the AUC and C_{max} of saquinavir with approximately 50% and 55% respectively, due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein. Interaction with saquinavir/ritonavir has not been studied and might be more marked. Dose adjustment of saquinavir may be necessary.

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

Theophylline: In a placebo controlled interaction study, the administration of fluconazole 200 mg for 14 days resulted in an 18% decrease in the mean plasma clearance rate of theophylline. Patients who are receiving high dose theophylline or who are otherwise at increased risk for theophylline toxicity should be observed for signs of theophylline toxicity while receiving fluconazole. Therapy should be modified if signs of toxicity develop.

Vinca alkaloids: Although not studied, fluconazole may increase the plasma levels of the vinca alkaloids (e.g. vincristine and vinblastine) and lead to neurotoxicity, which is possibly due to an inhibitory effect on CYP3A4.

Vitamin A: Based on a case-report in one patient receiving combination therapy with all-trans-retinoid acid (an acid form of vitamin A) and fluconazole, CNS related undesirable effects have developed in the form of pseudotumour *cerebri*, which disappeared after discontinuation of fluconazole treatment. This combination may be used but the incidence of CNS related undesirable effects should be borne in mind.

Voriconazole: (CYP2C9 and CYP3A4 inhibitor): Coadministration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 2.5 days) and oral fluconazole (400 mg on day 1, then 200 mg Q24h for 4 days) to 8 healthy male subjects resulted in an increase in C_{max} and AUC_{τ} of voriconazole by an average of 57% (90% CI: 20%, 107%) and 79% (90% CI: 40%, 128%), respectively. The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole associated adverse events is recommended if voriconazole is used sequentially after fluconazole.

Zidovudine: Fluconazole increases C_{max} and AUC of zidovudine by 84% and 74%, respectively, due to an approx. 45% decrease in oral zidovudine clearance. The half-life of zidovudine was likewise prolonged by approximately 128% following combination therapy with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions. Dose reduction of zidovudine may be considered.

Azithromycin: An open-label, randomized, three-way crossover study in 18 healthy subjects assessed the effect of a single 1200 mg oral dose of azithromycin on the pharmacokinetics of a single 800 mg oral dose of fluconazole as well as the effects of fluconazole on the pharmacokinetics of azithromycin. There was no significant pharmacokinetic interaction between fluconazole and azithromycin.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

Data from several hundred pregnant women treated with standard doses (<200 mg/day) of fluconazole, administered as a single or repeated dose in the first trimester, show no undesirable effects in the foetus.

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

Studies in animals have shown reproductive toxicity (see section 5.3).

Fluconazole in standard doses and short-term treatments should not be used in pregnancy unless clearly necessary.

Fluconazole in high dose and/or in prolonged regimens should not be used during pregnancy except for potentially life-threatening infections.

Breast-feeding

Fluconazole passes into breast milk to reach concentrations lower than those in plasma. Breast-feeding may be maintained after a single use of a standard dose 200 mg fluconazole or less. Breast-feeding is not recommended after repeated use or after high dose fluconazole.

Fertility

Fluconazole did not affect the fertility of male or female rats (see section 5.3)

4.7 Effects on ability to drive and use machines

No studies have been performed on the effects of Diflucan on the ability to drive or use machines. Patients should be warned about the potential for dizziness or seizures (see section 4.8) while taking Diflucan and should be advised not to drive or operate machines if any of these symptoms occur.

4.8 Undesirable effects

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

The following adverse reactions have been observed and reported during treatment with Diflucan with the following frequencies: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

System Organ Class	Common	Uncommon	Rare
Blood and the lymphatic system disorders		Anaemia	Agranulocytosis, leukopenia, thrombocytopenia, neutropenia
Immune system disorders			Anaphylaxis
Metabolism and nutrition disorders		Decreased appetite	Hypercholesterolaemia, hypertriglyceridaemia, hypokalemia
Psychiatric disorders		Somnolence, insomnia	
Nervous system disorders	Headache	Seizures, paraesthesia, dizziness, taste perversion	Tremor
Ear and labyrinth disorders		Vertigo	
Cardiac disorders			<i>Torsade de pointes</i> (see section 4.4), QT prolongation (see section 4.4)
Gastrointestinal disorders	Abdominal pain, vomiting, diarrhoea, nausea	Constipation, dyspepsia, flatulence, dry mouth	
Hepatobiliary disorders	Alanine aminotransferase increased (see section 4.4), aspartate aminotransferase	Cholestasis (see section 4.4), jaundice (see section 4.4), bilirubin increased (see section 4.4)	Hepatic failure (see section 4.4), hepatocellular necrosis (see section 4.4), hepatitis (see section 4.4), hepatocellular

	increased (see section 4.4), blood alkaline phosphatase increased (see section 4.4)		damage (see section 4.4)
Skin and subcutaneous tissue disorders	Rash (see section 4.4)	Drug eruption (see section 4.4), urticaria (see section 4.4), pruritus, increased sweating	Toxic epidermal necrolysis, (see section 4.4), Stevens-Johnson syndrome (see section 4.4), acute generalised exanthematous-pustulosis (see section 4.4), dermatitis exfoliative, angioedema, face oedema, alopecia
Musculoskeletal and connective tissue disorders		Myalgia	
General disorders and administration site conditions		Fatigue, malaise, asthenia, fever	

Paediatric population

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

4.9 Overdose

There have been reports of overdose with Diflucan and hallucination and paranoid behaviour have been concomitantly reported.

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC classification

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02AC01.

Mode of action

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

Fluconazole 50 mg daily given up to 28 days has been shown not to effect testosterone plasma concentrations in males or steroid concentration in females of child-bearing age. Fluconazole 200 mg to 400 mg daily has no clinically significant effect on endogenous steroid levels or on ACTH

stimulated response in healthy male volunteers. Interaction studies with antipyrine indicate that single or multiple doses of fluconazole 50 mg do not affect its metabolism.

Susceptibility *in vitro*

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

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

PK/PD relationship

In animal studies, there is a correlation between MIC values and efficacy against experimental mycoses due to *Candida* spp. In clinical studies, there is an almost 1:1 linear relationship between the AUC and the dose of fluconazole. There is also a direct though imperfect relationship between the AUC or dose and a successful clinical response of oral candidosis and to a lesser extent candidaemia to treatment. Similarly cure is less likely for infections caused by strains with a higher fluconazole MIC.

Mechanism(s) of resistance

Candida spp have developed a number of resistance mechanisms to azole antifungal agents. Fungal strains which have developed one or more of these resistance mechanisms are known to exhibit high minimum inhibitory concentrations (MICs) to fluconazole which impacts adversely efficacy *in vivo* and clinically.

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

Breakpoints (according to EUCAST)

Based on analyses of pharmacokinetic/pharmacodynamic (PK/PD) data, susceptibility *in vitro* and clinical response EUCAST-AFST (European Committee on Antimicrobial susceptibility Testing-subcommittee on Antifungal Susceptibility Testing) has determined breakpoints for fluconazole for *Candida* species (EUCAST Fluconazole rational document (2007)-version 2). These have been divided into non-species related breakpoints; which have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species, and species related breakpoints for those species most frequently associated with human infection. These breakpoints are given in the table below:

Antifungal	Species-related breakpoints (S</R>)					Non-species related breakpoints ^A S</R>
	<i>Candida albicans</i>	<i>Candida glabrata</i>	<i>Candida krusei</i>	<i>Candida parapsilosis</i>	<i>Candida tropicalis</i>	
Fluconazole	2/4	IE	--	2/4	2/4	2/4

S = Susceptible, R = Resistant

A. = Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints.

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the medicinal product.

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

5.2 Pharmacokinetic properties

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

Absorption

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

Distribution

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

Fluconazole achieves good penetration in all body fluids studied. The levels of fluconazole in saliva and sputum are similar to plasma levels. In patients with fungal meningitis, fluconazole levels in the CSF are approximately 80% the corresponding plasma levels.

High skin concentration of fluconazole, above serum concentrations, are achieved in the stratum corneum, epidermis-dermis and eccrine sweat. Fluconazole accumulates in the stratum corneum. At a dose of 50 mg once daily, the concentration of fluconazole after 12 days was 73 µg/g and 7 days after cessation of treatment the concentration was still 5.8 µg/g. At the 150 mg once-a-week dose, the concentration of fluconazole in stratum corneum on day 7 was 23.4 µg/g and 7 days after the second dose was still 7.1 µg/g.

Concentration of fluconazole in nails after 4 months of 150 mg once-a-week dosing was 4.05 µg/g in healthy and 1.8 µg/g in diseased nails; and, fluconazole was still measurable in nail samples 6 months after the end of therapy.

Biotransformation

Fluconazole is metabolised only to a minor extent. Of a radioactive dose, only 11% is excreted in a changed form in the urine. Fluconazole is a selective inhibitor of the isozymes CYP2C9 and CYP3A4 (see section 4.5). Fluconazole is also an inhibitor of the isozyme CYP2C19.

Excretion

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

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

Pharmacokinetics in renal impairment

In patients with severe renal insufficiency, (GFR < 20 ml/min) half life increased from 30 to 98 hours. Consequently, reduction of the dose is needed. Fluconazole is removed by haemodialysis and to a lesser extent by peritoneal dialysis. After three hours of haemodialysis session, around 50% of fluconazole is eliminated from blood.

Pharmacokinetics in children

Pharmacokinetic data were assessed for 113 paediatric patients from 5 studies; 2 single-dose studies, 2 multiple-dose studies, and a study in premature neonates. Data from one study were not interpretable due to changes in formulation pathway through the study. Additional data were available from a compassionate use study.

After administration of 2-8 mg/kg fluconazole to children between the ages of 9 months to 15 years, an AUC of about 38 µg·h/ml was found per 1 mg/kg dose units. The average fluconazole plasma elimination half-life varied between 15 and 18 hours and the distribution volume was approximately 880 ml/kg after multiple doses. A higher fluconazole plasma elimination half-life of approximately 24 hours was found after a single dose. This is comparable with the fluconazole plasma elimination half-life after a single administration of 3 mg/kg i.v. to children of 11 days-11 months old. The distribution volume in this age group was about 950 ml/kg.

Experience with fluconazole in neonates is limited to pharmacokinetic studies in premature newborns. The mean age at first dose was 24 hours (range 9-36 hours) and mean birth weight was 0.9 kg (range 0.75-1.10 kg) for 12 pre-term neonates of average gestation around 28 weeks. Seven patients completed the protocol; a maximum of five 6 mg/kg intravenous infusions of fluconazole were administered every 72 hours. The mean half-life (hours) was 74 (range 44-185) on day 1 which decreased, with time to a mean of 53 (range 30-131) on day 7 and 47 (range 27-68) on day 13. The area under the curve (microgram.h/ml) was 271 (range 173-385) on day 1 and increased with a mean of 490 (range 292-734) on day 7 and decreased with a mean of 360 (range 167-566) on day 13. The volume of distribution (ml/kg) was 1183 (range 1070-1470) on day 1 and increased, with time, to a mean of 1184 (range 510-2130) on day 7 and 1328 (range 1040-1680) on day 13.

Pharmacokinetics in elderly

A pharmacokinetic study was conducted in 22 subjects, 65 years of age or older receiving a single 50 mg oral dose of fluconazole. Ten of these patients were concomitantly receiving diuretics. The C_{max} was 1.54 µg/ml and occurred at 1.3 hours post-dose. The mean AUC was 76.4 ± 20.3 µg·h/ml, and the mean terminal half-life was 46.2 hours. These pharmacokinetic parameter values are higher than analogous values reported for normal young male volunteers. Coadministration of diuretics did not significantly alter AUC or C_{max} . In addition, creatinine clearance (74 ml/min), the percent of medicinal product recovered unchanged in urine (0-24 hr, 22%) and the fluconazole renal clearance estimates (0.124 ml/min/kg) for the elderly were generally lower than those of younger volunteers. Thus, the alteration of fluconazole disposition in the elderly appears to be related to reduced renal function characteristics of this group.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the human exposure indicating little relevance to clinical use.

Carcinogenesis

Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5, or 10 mg/kg/day (approximately 2-7 times the recommended human dose). Male rats treated with 5 and 10 mg/kg/day had an increased incidence of hepatocellular adenomas.

Reproductive toxicity

Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10, or 20 mg/kg or with parenteral doses of 5, 25, or 75 mg/kg.

There were no foetal effects at 5 or 10 mg/kg; increases in foetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg to 320 mg/kg embryoletality in rats was increased and foetal abnormalities included wavy ribs, cleft palate, and abnormal cranio-facial ossification.

The onset of parturition was slightly delayed at 20 mg/kg orally and dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg and 40 mg/kg intravenously. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal survival at these dose levels. These effects on parturition are consistent with the species specific oestrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole (see section 5.1).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Glass vials: 5 years.
Plasticised PVC bags: 18 months.

This medicinal product is for single use. Once opened, any unused infusion should be discarded.

6.4 Special precautions for storage

Glass vials: Do not freeze.
Plasticised PVC bags: Store below 30°C. Do not freeze.

From a microbiological point of view, the dilutions should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 ° C, unless dilution has taken place in controlled and validated aseptic conditions.

6.5 Nature and contents of container

Clear Type I glass infusion vial sealed closed with rubber stoppers and aluminium caps.
Plasticised PVC bag.

Pack sizes: 30, 50, 100 or 250 ml glass vials.
1, 5, 10 or 20 plasticised PVC bags (100 or 200 ml).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Fluconazole intravenous infusion is compatible with the following administration fluids:

- a) Dextrose 5% and 20%
- b) Ringer's solution
- c) Hartmann's solution
- d) Potassium chloride in dextrose
- e) Sodium bicarbonate 4.2% and 5%
- f) Aminosyn 3.5%
- g) Sodium chloride 9 mg/ml (0.9%)
- h) Dialaflex (interperitoneal dialysis Soln 6.36%)

Fluconazole may be infused through an existing line with one of the above listed fluids. Although no specific incompatibilities have been noted, mixing with any other medicinal products prior to infusion is not recommended.

The solution for infusion is for single use only.

The dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Detailed information on this medicinal product is available on the website of {name of MS/Agency}
[To be completed nationally].

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON(capsules)

1. NAME OF THE MEDICINAL PRODUCT

Diflucan and associated names (see Annex I) 150 mg hard capsules
[See Annex I - To be completed nationally]

Fluconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains fluconazole 150 mg.

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

1 hard capsule.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Diflucan and associated names (see Annex I) 150 mg

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (capsules)

1. NAME OF THE MEDICINAL PRODUCT

Diflucan and associated names (see Annex 1) 150 mg hard capsule
[See Annex I - To be completed nationally]

Fluconazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (capsules)

1. NAME OF THE MEDICINAL PRODUCT

Diflucan and associated names (see Annex I) 50 mg hard capsules
Diflucan and associated names (see Annex I) 100 mg hard capsules
Diflucan and associated names (see Annex I) 150 mg hard capsules
Diflucan and associated names (see Annex I) 200 mg hard capsules
[See Annex I - To be completed nationally]

Fluconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains fluconazole 50 mg
Each hard capsule contains fluconazole 100 mg
Each hard capsule contains fluconazole 150 mg
Each hard capsule contains fluconazole 200 mg

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule.
1, 2, 3, 4, 6, 7, 10, 12, 14, 20, 28, 30, 42, 50, 60, 100 or 500 hard capsules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

{Name and Address}

<{tel}>

<{fax}>

<{e-mail}>

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

[To be completed nationally]

16. INFORMATION IN BRAILLE

Diflucan and associated names (see Annex I) 50 mg Diflucan and associated names (see Annex I)
100 mg Diflucan and associated names (see Annex I) 150 mg Diflucan and associated names (see
Annex I) 200 mg

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS (capsules)

1. NAME OF THE MEDICINAL PRODUCT

Diflucan and associated names (see Annex 1) 50 mg hard capsules
Diflucan and associated names (see Annex 1) 100 mg hard capsules
Diflucan and associated names (see Annex 1) 150 mg hard capsules
Diflucan and associated names (see Annex 1) 200 mg hard capsules
[See Annex I – To be completed nationally]

Fluconazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING PACKAGING

CARTON (5 mg/ml oral solution)

1. NAME OF THE MEDICINAL PRODUCT

Diflucan and associated names (see Annex I) 5 mg/ml oral solution
[See Annex I – To be completed nationally]

Fluconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of oral solution contains 5 mg of fluconazole.

3. LIST OF EXCIPIENTS

Also contains sucrose, glycerol.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution.
1 bottle - 150 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Once opened, Diflucan may be used for a maximum of 30 days.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Diflucan and associated names (see Annex I) 5 mg/ml
[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL(5 mg/ml oral solution)

1. NAME OF THE MEDICINAL PRODUCT

Diflucan and associated names (see Annex I) 5 mg/ml oral solution
[See Annex I - To be completed nationally]

Fluconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of oral solution contains 5 mg of fluconazole.

3. LIST OF EXCIPIENTS

Contains sucrose, and glycerol.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution
1 bottle - 150 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Once opened, Diflucan may be used for a maximum of 30 days.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (10 mg/ml powder for oral suspension – 60 ml and 175 ml bottles)

1. NAME OF THE MEDICINAL PRODUCT

Diflucan and associated names (see Annex I) 10 mg/ml powder for oral suspension
[See Annex I – To be completed nationally]
Fluconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of reconstituted suspension contains 10 mg fluconazole.

3. LIST OF EXCIPIENTS

Also contains sucrose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral suspension.
1 bottle – 35 ml suspension after reconstitution
1 bottle – 100 ml suspension after reconstitution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use after reconstitution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Any remaining suspension should be discarded 28 days after reconstitution.

9. SPECIAL STORAGE CONDITIONS

Powder for oral suspension (60 ml bottle): Store below 25°C
Powder for oral suspension (175 ml bottle): Store below 25°C.
Keep the bottle tightly closed.

Reconstituted suspension: Store below 30°C, do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Diflucan and associated names (see Annex I) 10 mg/ml

[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL (10 mg/ml powder for oral suspension – 60 ml and 175 ml bottles)

1. NAME OF THE MEDICINAL PRODUCT

Diflucan and associated names (see Annex I) 10 mg/ml powder for oral suspension
[See Annex I – To be completed nationally]

Fluconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of reconstituted suspension contains 10 mg fluconazole.

3. LIST OF EXCIPIENTS

Also contains sucrose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral suspension.
1 bottle - 35 ml suspension after reconstitution
1 bottle - 100 ml suspension after reconstitution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use after reconstitution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Any remaining suspension should be discarded 28 days after reconstitution.

9. SPECIAL STORAGE CONDITIONS

(Powder for oral suspension (60 ml bottle): Store below 25°C no special storage conditions.

(Powder for oral suspension (175 ml bottle): Store below 25°C.

Keep the bottle tightly closed.

Reconstituted suspension: Store below 30°C, do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (40 mg/ml powder for oral suspension – 60 ml bottle)

1. NAME OF THE MEDICINAL PRODUCT

Diflucan and associated names (see Annex I) 40 mg/ml powder for oral suspension
[See Annex I – To be completed nationally]

Fluconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of reconstituted suspension contains 40 mg fluconazole.

3. LIST OF EXCIPIENTS

Contains sucrose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral suspension.
1 bottle – 35 ml suspension after reconstitution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use after reconstitution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Any remaining suspension should be discarded 28 days after reconstitution.

9. SPECIAL STORAGE CONDITIONS

Powder for oral suspension: Store below 25°C.
Keep the bottle tightly closed.

Reconstituted suspension: Store below 30°C, do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Diflucan and associated names (see Annex I) 40 mg/ml
[To be completed nationally]

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL(40 mg/ml powder for oral suspension – 60 ml bottle)

1. NAME OF THE MEDICINAL PRODUCT

Diflucan and associated names (see Annex I) 40 mg/ml powder for oral suspension
[See Annex I – To be completed nationally]

Fluconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of reconstituted suspension contains 40 mg fluconazole.

3. LIST OF EXCIPIENTS

Also contains sucrose.
See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral suspension.
1 bottle – 35 ml suspension after reconstitution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use after reconstitution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Any remaining suspension should be discarded 28 days after reconstitution.

9. SPECIAL STORAGE CONDITIONS

(Powder for oral suspension) Store below 25°C

Keep the bottle tightly closed.

Reconstituted suspension: Store below 30°C, do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (IV 30, 50, 100 or 250 ml glass vials, 100 and 200 ml PVC bags)

1. NAME OF THE MEDICINAL PRODUCT

Diflucan and associated names (see Annex I) 2 mg/ml solution for infusion
[See Annex I – To be completed nationally]

Fluconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 2 mg of fluconazole.

Each 25 ml solution for infusion contains 50 mg fluconazole
Each 50 ml solution for infusion contains 100 mg fluconazole
Each 100 ml solution for infusion contains 200 mg fluconazole
Each 200 ml solution for infusion contains 400 mg fluconazole

3. LIST OF EXCIPIENTS

Excipients: sodium chloride, water for injections and sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial – 25 ml solution
1 vial – 50 ml solution
1 vial – 100 ml solution
1 vial – 200 ml solution
5, 10, 20 PVC bags – 100 ml solution
5, 10, 20 PVC bags – 200 ml solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

(Glass vials) Do not freeze.

(PVC bags) Store below 30°C. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

LABEL (IV- 50, 100 or 250 ml glass vials, 100 and 200 ml PVC bags)

1. NAME OF THE MEDICINAL PRODUCT

Diflucan and associated names (see Annex I) 2 mg/ ml solution for infusion
[See Annex I – To be completed nationally]

Fluconazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 2 mg of fluconazole.

Each 50 ml solution for infusion contains 100 mg fluconazole

Each 100 ml solution for infusion contains 200 mg fluconazole

Each 200 ml solution for infusion contains 400 mg fluconazole

3. LIST OF EXCIPIENTS

Excipients: sodium chloride, water for injections and sodium hydroxide.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial – 50 ml solution

1 vial – 100 ml solution

1 vial – 200 ml solution

1 PVC bag – 100 ml solution

1 PVC bag – 200 ml solution

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Single use only.

Read the package leaflet before use.

Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

(Glass vials) Do not freeze.

(PVC bags) Store below 30°C. Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL (IV - 30 ml glass vial)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Diflucan and associated names (see Annex I) 2 mg/ ml solution for infusion
[See Annex I – To be completed nationally]

Fluconazole

Intravenous use.

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBERS

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

25 ml solution

6. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Diflucan and associated names (see Annex I) 150 mg capsule

[See Annex I - To be completed nationally]

fluconazole

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Diflucan is and what it is used for
2. Before you take Diflucan
3. How to take Diflucan
4. Possible side effects
5. How to store Diflucan
6. Further information

1. WHAT DIFLUCAN IS AND WHAT IT IS USED FOR

Diflucan is one of a group of medicines called “antifungals”. The active substance is fluconazole.

Diflucan is used in adults to treat infections caused by fungi. The most common cause of fungal infections is a yeast called *Candida*.

You might be given this medicine by your doctor to treat genital thrush, infection of the vagina or penis.

2. BEFORE YOU TAKE DIFLUCAN

Do not take Diflucan if you

- are allergic (hypersensitive) to fluconazole, to other medicines you have taken to treat fungal infections or to any of the other ingredients of Diflucan. The symptoms may include itching, reddening of the skin or difficulty in breathing
- are taking astemizole, terfenadine (antihistamine medicines for allergies)
- are taking cisapride (used for stomach upsets)
- are taking pimozone (used for treating mental illness)
- are taking quinidine (used for treating heart arrhythmia)
- are taking erythromycin, (an antibiotic for treating infections)

Take special care with Diflucan

Tell your doctor if you

- have liver or kidney problems
- suffer from heart disease, including heart rhythm problems
- have abnormal levels of potassium, calcium or magnesium in your blood
- develop severe skin reactions (itching, reddening of the skin or difficulty in breathing).

Children

Although this medicine is for adults it can be used in adolescents (from 12 to 17 years old) if treatment is essential and no suitable alternative exists, and should be taken in the same way as for adults.

Taking other medicines

Tell your doctor **immediately** if you are taking astemizole, terfenadine (an antihistamine for treating allergies) or cisapride (used for stomach upsets) or pimozide (used for treating mental illness) or quinidine (used for treating heart arrhythmia) or erythromycin (an antibiotic for treating infections) as these should not be taken with Diflucan (see section: “Do not take Diflucan if you”).

There are some medicines that may interact with Diflucan.

Make sure your doctor knows if you are taking any of the following medicines:

- rifampicin or rifabutin (antibiotics for infections)
- alfentanil, fentanyl (used as anaesthetic)
- amitriptyline, nortriptyline (used as anti-depressant)
- amphotericin B, voriconazole (anti-fungal)
- medicines that thin the blood to prevent blood clots (warfarin or similar medicines)
- benzodiazepines (midazolam, triazolam or similar medicines) used to help you sleep or for anxiety
- carbamazepine, phenytoin (used for treating fits)
- nifedipine, isradipine, amlodipine felodipine and losartan (for hypertension- high blood pressure)
- ciclosporin, everolimus, sirolimus or tacrolimus (to prevent transplant rejection)
- cyclophosphamide, vinca alkaloids (vincristine, vinblastine or similar medicines) used for treating cancer
- halofantrine (used for treating malaria)
- statins (atorvastatin, simvastatin and fluvastatin or similar medicines) used for reducing high cholesterol levels
- methadone (used for pain)
- celecoxib, flurbiprofen, naproxen, ibuprofen, lornoxicam, meloxicam, diclofenac (Non-Steroidal Anti-Inflammatory Drugs (NSAID))
- oral contraceptives
- prednisone (steroid)
- zidovudine, also known as AZT; saquinavir (used in HIV-infected patients)
- medicines for diabetes such as chlorpropamide, glibenclamide, glipizide or tolbutamide
- theophylline (used to control asthma)
- vitamin A (nutritional supplement)

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Diflucan with food and drink

You can take your medicine with or without a meal.

Pregnancy and breast-feeding

Tell your doctor if you are pregnant, trying to become pregnant or breast-feeding. You should not take Diflucan while you are pregnant or breast-feeding unless your doctor has told you to.

Ask your doctor or pharmacist for advice before taking any medicines.

Driving and using machines

When driving vehicles or using machines, it should be taken into account that occasionally dizziness or fits may occur.

Important information about some of the ingredients of Diflucan

This medicine contains a small amount of lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, please contact your doctor before taking this medicine.

3. HOW TO TAKE DIFLUCAN

Always take your medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Swallow the capsule whole with a glass of water.

Adults

150 mg as a single dose.

Doctors sometimes prescribe different doses to these. Always take your medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Elderly

The usual adult dose should be given.

Patients with kidney problems

The usual adult dose should be given.

How quickly will the treatment start to work?

Vaginal thrush

Your condition should start to clear up within a few days - some women notice an improvement in one day.

If your condition does not clear up within a few days you should go back to your doctor.

Penis thrush infection

Your condition should start to clear up within a few days but it may take up to a week.

If your condition has not cleared up after one week, you should go back to your doctor.

If you take more Diflucan than you should

Taking too many capsules at once may make you unwell. Contact your doctor or your nearest hospital casualty department at once. The symptoms of a possible overdose may include hearing, seeing, feeling and thinking things that are not real (hallucination and paranoid behaviour). Symptomatic treatment (with supportive measures and gastric lavage if necessary) may be adequate.

If you forget to take Diflucan

Do not take a double dose to make up for a forgotten dose. If you forget to take a dose, take it as soon as you remember. If it is almost time for your next dose, do not take the dose that you missed.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Diflucan can cause side effects, although not everybody gets them

A few people develop **allergic reactions** although serious allergic reactions are rare. If you get any of the following symptoms, **tell your doctor immediately**.

- sudden wheezing, difficulty in breathing or tightness in the chest
- swelling of eyelids, face or lips
- itching all over the body reddening of the skin or itchy red spots
- skin rash
- severe skin reactions such as a rash that causes blistering (this can affect the mouth and tongue).

Diflucan may affect your liver. The signs of liver problems include:

- tiredness
- loss of appetite
- vomiting
- yellowing of your skin or the whites of your eyes (jaundice)

If any of these happen, stop taking Diflucan and **tell your doctor immediately**.

Other side effects:

Additionally, if any of the following side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Common side effects which affect 1 to 10 users in 100 are listed below:

- headache
- stomach discomfort, diarrhoea, feeling sick, vomiting
- increases in blood tests of liver function
- rash

Uncommon side effects which affect 1 to 10 users in 1,000 are listed below:

- reduction in red blood cells which can make skin pale and cause weakness or breathlessness
- decreased appetite
- inability to sleep, feeling drowsy
- fit, dizziness, sensation of spinning, tingling, pricking or numbness, changes in sense of taste
- constipation, difficult digestion, wind, dry mouth
- muscle pain
- liver damage and yellowing of the skin and eyes (jaundice)
- wheals, blistering (hives), itching, increased sweating
- tiredness, general feeling of being unwell, fever

Rare side effects which affect 1 to 10 users in 10,000 are listed below:

- lower than normal white blood cells that help defend against infections and blood cells that help to stop bleeding
- red or purple discoloration of the skin which may be caused by low platelet count, other blood cell changes
- low blood potassium
- blood chemistry changes (high blood levels of cholesterol, fats)
- shaking
- abnormal electrocardiogram (ECG), change in heart rate or rhythm
- liver failure
- allergic reactions (sometimes severe), including widespread blistering rash and skin peeling, severe skin reactions, swelling of the lips or face
- hair loss

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE DIFLUCAN

- Keep out of the reach and sight of children.
- Do not use Diflucan after the expiry date which is stated on the pack after EXP. The expiry date refers to the last day of the month.
- Store below 30°C.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Diflucan contains

- The active substance is fluconazole.
- Each hard capsule contains fluconazole 150 mg.
- The other ingredients are:

Capsule content: lactose monohydrate, maize starch, colloidal silica anhydrous, magnesium stearate and sodium laurilsulfate.

Capsule shell composition: Gelatin, titanium dioxide (E171) and patent blue V (E131)

Printing ink: shellac (glaze), black iron oxide, N-Butyl alcohol, dehydrated alcohol, purified water, propylene glycol, industrial methylated spirit, isopropyl alcohol, strong ammonia solution, potassium hydroxide

What Diflucan looks like and contents of the pack

- Diflucan 150 mg hard capsules have a turquoise blue body and a turquoise blue cap. They have “FLU-150” and “Pfizer” with black ink printed on them.
- Diflucan comes in a blister pack containing one capsule.

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:

[See Annex I - To be completed nationally]

This leaflet was last approved in

[To be completed nationally]

Detailed information on this medicine is available on the web site of {MA/Agency}: [To be completed nationally]

PACKAGE LEAFLET: INFORMATION FOR THE USER

Diflucan and associated names (see Annex I) 50 mg capsules
Diflucan and associated names (see Annex I) 100 mg capsules
Diflucan and associated names (see Annex I) 150 mg capsules
Diflucan and associated names (see Annex I) 200 mg capsules

[See Annex I – To be completed nationally]
fluconazole

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Diflucan is and what it is used for
2. Before you take Diflucan
3. How to take Diflucan
4. Possible side effects
5. How to store Diflucan
6. Further information

1. WHAT DIFLUCAN IS AND WHAT IT IS USED FOR

Diflucan is one of a group of medicines called “antifungals”. The active substance is fluconazole.

Diflucan is used to treat infections caused by fungi and may also be used to stop you from getting a candidal infection. The most common cause of fungal infections is a yeast called *Candida*.

Adults

You might be given this medicine by your doctor to treat the following types of fungal infections:

- Cryptococcal meningitis – a fungal infection in the brain
- Coccidioidomycosis – a disease of the bronchopulmonary system
- Infections caused by *Candida* and found in the blood stream, body organs (e.g. heart, lungs) or urinary tract
- Mucosal thrush - infection affecting the lining of the mouth, throat and denture sore mouth
- Genital thrush – infection of the vagina or penis
- Skin infections - e.g. athlete's foot, ringworm, jock itch, nail infection

You might also be given Diflucan to:

- stop cryptococcal meningitis from coming back
- stop mucosal thrush from coming back
- reduce recurrence of vaginal thrush
- stop you from getting an infection caused by *Candida* (if your immune system is weak and not working properly)

Children and adolescents (0 to 17 years old)

You might be given this medicine by your doctor to treat the following types of fungal infections:

- Mucosal thrush - infection affecting the lining of the mouth, throat
- Infections caused by *Candida* and found in the blood stream, body organs (e.g. heart, lungs) or urinary tract
- Cryptococcal meningitis – a fungal infection in the brain

You might also be given Diflucan to:

- stop you from getting an infection caused by *Candida* (if your immune system is weak and not working properly).
- stop cryptococcal meningitis from coming back

2. BEFORE YOU TAKE DIFLUCAN

Do not take Diflucan if you

- are allergic (hypersensitive) to fluconazole, to other medicines you have taken to treat fungal infections or to any of the other ingredients of Diflucan. The symptoms may include itching, reddening of the skin or difficulty in breathing
- are taking astemizole, terfenadine (antihistamine medicines for allergies)
- are taking cisapride (used for stomach upsets)
- are taking pimozone (used for treating mental illness)
- are taking quinidine (used for treating heart arrhythmia)
- are taking erythromycin (an antibiotic for treating infections)

Take special care with Diflucan

Tell your doctor if you

- have liver or kidney problems
- suffer from heart disease, including heart rhythm problems
- have abnormal levels of potassium, calcium or magnesium in your blood.
- develop severe skin reactions (itching, reddening of the skin or difficulty in breathing).

Taking other medicines

Tell your doctor **immediately** if you are taking astemizole, terfenadine (an antihistamine for treating allergies) or cisapride (used for stomach upsets) or pimozone (used for treating mental illness) or quinidine (used for treating heart arrhythmia) or erythromycin (an antibiotic for treating infections) as these should not be taken with Diflucan (see section: “Do not take Diflucan if you”).

There are some medicines that may interact with Diflucan. Make sure your doctor knows if you are taking any of the following medicines:

- rifampicin or rifabutin (antibiotics for infections)
- alfentanil, fentanyl (used as anaesthetic)
- amitriptyline, nortriptyline (used as anti-depressant)
- amphotericin B, voriconazole (anti-fungal)
- medicines that thin the blood to prevent blood clots (warfarin or similar medicines)
- benzodiazepines (midazolam, triazolam or similar medicines) used to help you sleep or for anxiety
- carbamazepine, phenytoin (used for treating fits)
- nifedipine, isradipine, amlodipine felodipine and losartan (for hypertension- high blood pressure)
- ciclosporin, everolimus, sirolimus or tacrolimus (to prevent transplant rejection)
- cyclophosphamide, vinca alkaloids (vincristine, vinblastine or similar medicines) used for treating cancer
- halofantrine (used for treating malaria)
- statins (atorvastatin, simvastatin and fluvastatin or similar medicines) used for reducing high cholesterol levels
- methadone (used for pain)
- celecoxib, flurbiprofen, naproxen, ibuprofen, lornoxicam, meloxicam, diclofenac (Non-Steroidal Anti-Inflammatory Drugs (NSAID))
- oral contraceptives

- prednisone (steroid)
- zidovudine, also known as AZT; saquinavir (used in HIV-infected patients)
- medicines for diabetes such as chlorpropamide, glibenclamide, glipizide or tolbutamide
- theophylline (used to control asthma)
- vitamin A (nutritional supplement)

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Diflucan with food and drink

You can take your medicine with or without a meal.

Pregnancy and breast-feeding

Tell your doctor if you are pregnant, trying to become pregnant or breast-feeding. You should not take Diflucan while you are pregnant or breast-feeding unless your doctor has told you to.

Ask your doctor or pharmacist for advice before taking any medicines.

Driving and using machines

When driving vehicles or using machines, it should be taken into account that occasionally dizziness or fits may occur.

Important information about some of the ingredients of Diflucan

This medicine contains a small amount of lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, please contact your doctor before taking this medicine.

3. HOW TO TAKE DIFLUCAN

Always take your medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Swallow the capsule whole with a glass of water. It is best to take your capsules at the same time each day.

The usual doses of this medicine for different infections are below:

Adults

Condition	Dose
To treat cryptococcal meningitis	400 mg on the first day then 200 mg to 400 mg once daily for 6 to 8 weeks or longer if needed. Sometimes doses are increased up to 800 mg
To stop cryptococcal meningitis from coming back	200 mg once daily until you are told to stop
To treat coccidioidomycosis	200 mg to 400 mg once daily from 11 months for up to 24 months or longer if needed. Sometimes doses are increased up to 800 mg

To treat internal fungal infections caused by <i>Candida</i>	800 mg on the first day then 400 mg once daily until you are told to stop
To treat mucosal infections affecting the lining of mouth, throat and denture sore mouth	200 mg to 400 mg on the first day then 100 mg to 200 mg until you are told to stop
To treat mucosal thrush – dose depends on where the infection is located	50 mg to 400 mg once daily for 7 to 30 days until you are told to stop
To stop mucosal infections affecting the lining of mouth, throat	100 mg to 200 mg once daily, or 200 mg 3 times a week, while you are at risk of getting an infection
To treat genital thrush	150 mg as a single dose
To reduce recurrence of vaginal trush	150 mg every third day for a total of 3 doses (day 1, 4 and 7) and then once a week for 6 months while you are at risk of getting an infection
To treat fungal skin and nail infections	Depending on the site of the infection 50 mg once daily, 150 mg once weekly, 300 to 400 mg once weekly for 1 to 4 weeks (Athlete's foot may be up to 6 weeks, for nail infection treatment until infected nail is replaced)
To stop you from getting an infection caused by <i>Candida</i> (if your immune system is weak and not working properly)	200 mg to 400 mg once daily while you are at risk of getting an infection

Adolescents from 12 to 17 years old

Follow the dose prescribed by your doctor (either adults or children posology).

Children to 11 years old

The maximum dose for children is 400 mg daily.

The dose will be based on the child's weight in kilograms.

Condition	Daily dose
Mucosal thrush and throat infections caused by <i>Candida</i> – dose and duration depends on the severity of the infection and on where the infection is located	3 mg per kg of body weight (6 mg per kg of body weight might be given on the first day)
Cryptococcal meningitis or internal fungal infections caused by <i>Candida</i>	6 mg to 12 mg per kg of body weight
To stop children from getting an infection caused by <i>Candida</i> (if their immune system is not working properly)	3 mg to 12 mg per kg of body weight

Use in children 0 to 4 weeks of age

Use in children of 3 to 4 weeks of age:

The same dose as above but given once every 2 days. The maximum dose is 12 mg per kg of body weight every 48 hours.

Use in children less than 2 weeks old:

The same dose as above but given once every 3 days. The maximum dose is 12 mg per kg of body weight every 72 hours.

Doctors sometimes prescribe different doses to these. Always take your medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Elderly

The usual adult dose should be given unless you have kidney problems.

Patients with kidney problems

Your doctor may change your dose, depending on your kidney function.

If you take more Diflucan than you should

Taking too many capsules at once may make you unwell. Contact your doctor or your nearest hospital casualty department at once. The symptoms of a possible overdose may include hearing, seeing, feeling and thinking things that are not real (hallucination and paranoid behaviour). Symptomatic treatment (with supportive measures and gastric lavage if necessary) may be adequate.

If you forget to take Diflucan

Do not take a double dose to make up for a forgotten dose. If you forget to take a dose, take it as soon as you remember. If it is almost time for your next dose, do not take the dose that you missed.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Diflucan can cause side effects, although not everybody gets them

A few people develop **allergic reactions** although serious allergic reactions are rare. If you get any of the following symptoms, **tell your doctor immediately**.

- sudden wheezing, difficulty in breathing or tightness in the chest
- swelling of eyelids, face or lips
- itching all over the body reddening of the skin or itchy red spots
- skin rash
- severe skin reactions such as a rash that causes blistering (this can affect the mouth and tongue).

Diflucan may affect your liver. The signs of liver problems include:

- tiredness
- loss of appetite
- vomiting
- yellowing of your skin or the whites of your eyes (jaundice)

If any of these happen, stop taking Diflucan and **tell your doctor immediately**.

Other side effects:

Additionally, if any of the following side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Common side effects which affect 1 to 10 users in 100 are listed below:

- headache
- stomach discomfort, diarrhoea, feeling sick, vomiting
- increases in blood tests of liver function
- rash

Uncommon side effects which affect 1 to 10 users in 1,000 are listed below:

- reduction in red blood cells which can make skin pale and cause weakness or breathlessness

- decreased appetite
- inability to sleep, feeling drowsy
- fit, dizziness, sensation of spinning, tingling, pricking or numbness, changes in sense of taste
- constipation, difficult digestion, wind, dry mouth
- muscle pain
- liver damage and yellowing of the skin and eyes (jaundice)
- wheals, blistering (hives), itching, increased sweating
- tiredness, general feeling of being unwell, fever

Rare side effects which affect 1 to 10 users in 10,000 are listed below:

- lower than normal white blood cells that help defend against infections and blood cells that help to stop bleeding
- red or purple discoloration of the skin which may be caused by low platelet count, other blood cell changes
- blood chemistry changes (high blood levels of cholesterol, fats)
- low blood potassium
- shaking
- abnormal electrocardiogram (ECG), change in heart rate or rhythm
- liver failure
- allergic reactions (sometimes severe), including widespread blistering rash and skin peeling, severe skin reactions, swelling of the lips or face
- hair loss

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE DIFLUCAN

- Keep out of the reach and sight of children.
- Do not use Diflucan after the expiry date which is stated on the pack after EXP. The expiry date refers to the last day of the month.
- Store below 30°C

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Diflucan contains

- The active substance is fluconazole.
- Each hard capsule contains 50 mg, 100 mg, 150 mg or 200 mg of fluconazole.
- The other ingredients are:

Capsule content: lactose monohydrate, maize starch, colloidal silica anhydrous, magnesium stearate and sodium laurilsulfate.

Capsule shell composition:

50 mg hard capsules: gelatin, titanium dioxide (E171) and patent blue V (E131)

100 mg hard capsules: gelatin, titanium dioxide (E171), erythrosin (E127) and patent blue V (E131)

150 mg hard capsules: gelatin, titanium dioxide (E171) and patent blue V (E131)

200 mg hard capsules: gelatin, titanium dioxide (E171), erythrosine (E127) and indigo carmine (E 132)

Printing ink: shellac (glaze), black iron oxide, N-Butyl alcohol, dehydrated alcohol, purified water, propylene glycol, industrial methylated spirit, isopropyl alcohol, strong ammonia solution, potassium hydroxide

What Diflucan 50 mg, 100 mg, 150 mg and 200 mg hard capsules look like and contents of the pack

- Diflucan 50 mg hard capsules have a white body and a turquoise blue cap. They have “FLU-50” and “Pfizer” with black ink printed on them.
- Diflucan 100 mg hard capsules have a white body and a blue cap. They have “FLU-100” and “Pfizer” with black ink printed on them.
- Diflucan 150 mg hard capsules have a turquoise blue body and a turquoise blue cap. They have “FLU-150” and “Pfizer” with black ink printed on them.
- Diflucan 200 mg hard capsules have a white body and a purple cap. They have “FLU-200” and “Pfizer” with black ink printed on them.

Diflucan 50 mg, 100 mg, 150 mg and 200 mg come in packs of 1, 2, 3, 4, 6, 7, 10, 12, 14, 20, 28, 30, 42, 50, 60, 100 or 500 hard capsules. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:

[See Annex I - To be completed nationally]

This leaflet was last approved in.

[To be completed nationally]

Detailed information on this medicine is available on the web site of {MA/Agency}: [To be completed nationally]

PACKAGE LEAFLET: INFORMATION FOR THE USER

Diflucan and associated names (see Annex I) 5 mg/ml oral solution

[See Annex I – To be completed nationally]

fluconazole

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Diflucan is and what it is used for
2. Before you take Diflucan
3. How to take Diflucan
4. Possible side effects
5. How to store Diflucan
6. Further information

1. WHAT DIFLUCAN IS AND WHAT IT IS USED FOR

Diflucan is one of a group of medicines called “antifungals”. The active substance is fluconazole.

Diflucan is used to treat infections caused by fungi and may also be used to stop you from getting a candidal infection. The most common cause of fungal infections is a yeast called *Candida*.

Adults

You might be given this medicine by your doctor to treat the following types of fungal infections:

- Cryptococcal meningitis – a fungal infection in the brain
- Coccidioidomycosis – a disease of the bronchopulmonary system
- Infections caused by *Candida* and found in the blood stream, body organs (e.g. heart, lungs) or urinary tract
- Mucosal thrush - infection affecting the lining of the mouth, throat and denture sore mouth
- Genital thrush - infection of the vagina or penis
- Skin infections - e.g. athlete's foot, ringworm, jock itch, nail infection

You might also be given Diflucan to:

- stop cryptococcal meningitis from coming back
- stop mucosal thrush from coming back
- reduce recurrence of vaginal thrush
- stop you from getting an infection caused by *Candida* (if your immune system is weak and not working properly)

Children and adolescents (0 to 17 years old)

You might be given this medicine by your doctor to treat the following types of fungal infections:

- Mucosal thrush - infection affecting the lining of the mouth, throat
- Infections caused by *Candida* and found in the blood stream, body organs (e.g. heart, lungs) or urinary tract
- Cryptococcal meningitis – a fungal infection in the brain

You might also be given Diflucan to:

- stop you from getting an infection caused by *Candida* (if your immune system is weak and not working properly)
- stop cryptococcal meningitis from coming back

2. BEFORE YOU TAKE DIFLUCAN

Do not take Diflucan if you

- are allergic (hypersensitive) to fluconazole, to other medicines you have taken to treat fungal infections or to any of the other ingredients of Diflucan. The symptoms may include itching, reddening of the skin or difficulty in breathing
- are taking astemizole, terfenadine (antihistamine medicines for allergies)
- are taking cisapride (used for stomach upsets)
- are taking pimozide (used for treating mental illness)
- are taking quinidine (used for treating heart arrhythmia)
- are taking erythromycin (an antibiotic for treating infections)

Take special care with Diflucan

Tell your doctor if you

- have liver or kidney problems
- suffer from heart disease, including heart rhythm problems
- have abnormal levels of potassium, calcium or magnesium in your blood.
- develop severe skin reactions (itching, reddening of the skin or difficulty in breathing).

Taking other medicines

Tell your doctor **immediately** if you are taking astemizole, terfenadine (an antihistamine for treating allergies) or cisapride (used for stomach upsets) or pimozide (used for treating mental illness) or quinidine (used for treating heart arrhythmia) or erythromycin (an antibiotic for treating infections) as these should not be taken with Diflucan (see section: "Do not take Diflucan if you").

There are some medicines that may interact with Diflucan. Make sure your doctor knows if you are taking any of the following medicines:

- rifampicin or rifabutin (antibiotics for infections)
- alfentanil, fentanyl (used as anaesthetic)
- amitriptyline, nortriptyline (used as anti-depressant)
- amphotericin B, voriconazole (anti-fungal)
- medicines that thin the blood to prevent blood clots (warfarin or similar medicines)
- benzodiazepines (midazolam, triazolam or similar medicines) used to help you sleep or for anxiety
- carbamazepine, phenytoin (used for treating fits)
- nifedipine, isradipine, amlodipine felodipine and losartan (for hypertension- high blood pressure)
- ciclosporin, everolimus, sirolimus or tacrolimus (to prevent transplant rejection)
- cyclophosphamide, vinca alkaloids (vincristine, vinblastine or similar medicines) used for treating cancer
- halofantrine (used for treating malaria)
- statins (atorvastatin, simvastatin and fluvastatin or similar medicines) used for reducing high cholesterol levels
- methadone (used for pain)
- celecoxib, flurbiprofen, naproxen, ibuprofen, lornoxicam, meloxicam, diclofenac (Non-Steroidal Anti-Inflammatory Drugs (NSAID))
- oral contraceptives
- prednisone (steroid)
- zidovudine, also known as AZT; saquinavir (used in HIV-infected patients)
- medicines for diabetes such as chlorpropamide, glibenclamide, glipizide or tolbutamide

- theophylline (used to control asthma)
- vitamin A (nutritional supplement)

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Diflucan with food and drink

Diflucan can be taken with or without food.

Pregnancy and breast-feeding

Tell your doctor if you are pregnant, trying to become pregnant or breast-feeding. You should not take Diflucan while you are pregnant or breast-feeding unless your doctor has told you to.

Ask your doctor or pharmacist for advice before taking any medicines.

Driving and using machines

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

Important information about some of the ingredients of Diflucan

Diflucan contains sucrose (sugar).

- If you have an intolerance to some sugars, please contact your doctor before taking this medicine.
- Doses of 10 ml contain 1.3 g of sugar. This should be taken into account if you have diabetes.
- May be harmful to teeth if used for periods of longer than 2 weeks.

Diflucan also contains glycerol. Glycerol may cause headache, stomach upset, and diarrhoea.

3. HOW TO TAKE DIFLUCAN

Always take your medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

The usual doses of this medicine for different infections are below.

It is best to take medicine at the same time each day.

Adults

Condition	Dose
To treat cryptococcal meningitis	400 mg on the first day then 200 mg to 400 mg once daily for 6 to 8 weeks or longer if needed. Sometimes doses are increased up to 800 mg
To stop cryptococcal meningitis from coming back	200 mg once daily until you are told to stop
To treat coccidioidomycosis	200 mg to 400 mg once daily from 11 months for up to 24 months or longer if needed. Sometimes doses are increased up to 800 mg
To treat internal fungal infections caused by <i>Candida</i>	800 mg on the first day then 400 mg once daily until you are told to stop

To treat mucosal infections affecting the lining of mouth, throat and denture sore mouth	200 mg to 400 mg on the first day then 100 mg to 200 mg until you are told to stop
To treat mucosal thrush – dose depends on where the infection is located	50 mg to 400 mg once daily for 7 to 30 day until you are told to stop
To stop mucosal infections affecting the lining of the mouth, throat	100 mg to 200 mg once daily, or 200 mg 3 times a week, while you are at risk of getting an infection
To treat genital thrush	150 mg as a single dose
To reduce recurrence of vaginal trush	150 mg every third day for a total of 3 doses (day 1, 4 and 7) and then once a week for 6 months while you are at risk of getting an infection
To treat fungal skin and nail infections	Depending on the site of the infection 50 mg once daily, 150 mg once weekly, 300 to 400 mg once weekly for 1 to 4 weeks (Athlete's foot may be up to 6 weeks, for nail infection treatment until infected nail is replaced)
To stop you from getting an infection caused by <i>Candida</i> (if your immune system is weak and not working properly)	200 mg to 400 mg once daily while you are at risk of getting an infection

Adolescents from 12 to 17 years old

Follow the dose prescribed by your doctor (either adults or children posology).

Children to 11 years old

The maximum dose for children is 400 mg daily.

The dose will be based on the child's weight in kilograms.

Condition	Daily dose
Mucosal thrush and throat infections caused by <i>Candida</i> – dose and duration depends on the severity of the infection and on where the infection is located	3 mg per kg of body weight (6 mg per kg of body weight might be given on the first day)
Cryptococcal meningitis or internal fungal infections caused by <i>Candida</i>	6 mg to 12 mg per kg of body weight
To stop children from getting an infection caused by <i>Candida</i> (if their immune system is not working properly)	3 mg to 12 mg per kg of body weight

Use in children 0 to 4 weeks of age

Use in children of 3 to 4 weeks of age:

- The same dose as above but given once every 2 days. The maximum dose is 12 mg per kg of body weight every 48 hours.

Use in children less than 2 weeks old:

- The same dose as above but given once every 3 days. The maximum dose is 12 mg per kg of body weight every 72 hours.

Doctors sometimes prescribe different doses to these. Always take your medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Elderly

The usual adult dose should be given unless you have kidney problems.

Patients with kidney problems

Your doctor may change your dose, depending on your kidney function.

If you take more Diflucan than you should

Taking too much Diflucan may make you unwell. Contact your doctor or your nearest hospital casualty department at once. The symptoms of a possible overdose may include hearing, seeing, feeling and thinking things that are not real (hallucination and paranoid behaviour). Symptomatic treatment (with supportive measures and gastric lavage if necessary) may be adequate.

If you forget to take Diflucan

Do not take a double dose to make up for a forgotten dose. If you forget to take a dose, take it as soon as you remember. If it is almost time for your next dose, do not take the dose that you missed.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Diflucan can cause side effects, although not everybody gets them

A few people develop **allergic reactions** although serious allergic reactions are rare. If you get any of the following symptoms, **tell your doctor immediately**.

- sudden wheezing, difficulty in breathing or tightness in the chest
- swelling of eyelids, face or lips
- itching all over the body reddening of the skin or itchy red spots
- skin rash
- severe skin reactions such as a rash that causes blistering (this can affect the mouth and tongue).

Diflucan may affect your liver. The signs of liver problems include:

- tiredness
- loss of appetite
- vomiting
- yellowing of your skin or the whites of your eyes (jaundice)

If any of these happen, stop taking Diflucan and **tell your doctor immediately**.

Other side effects:

Additionally, if any of the following side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Common side effects which affect 1 to 10 users in 100 are listed below:

- headache
- stomach discomfort, diarrhoea, feeling sick, vomiting
- increases in blood tests of liver function
- rash

Uncommon side effects which affect 1 to 10 users in 1,000 are listed below:

- reduction in red blood cells which can make skin pale and cause weakness or breathlessness

- decreased appetite
- inability to sleep, feeling drowsy
- fit, dizziness, sensation of spinning, tingling, pricking or numbness, changes in sense of taste
- constipation, difficult digestion, wind, dry mouth
- muscle pain
- liver damage and yellowing of the skin and eyes (jaundice)
- wheals, blistering (hives), itching, increased sweating
- tiredness, general feeling of being unwell, fever

Rare side effects which affect 1 to 10 users in 10,000 are listed below:

- lower than normal white blood cells that help defend against infections and blood cells that help to stop bleeding
- red or purple discoloration of the skin which may be caused by low platelet count, other blood cell changes
- blood chemistry changes (high blood levels of cholesterol, fats)
- low blood potassium
- shaking
- abnormal electrocardiogram (ECG), change in heart rate or rhythm
- liver failure
- allergic reactions (sometimes severe), including widespread blistering rash and skin peeling, severe skin reactions, swelling of the lips or face
- hair loss

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE DIFLUCAN

- The medicinal product does not require any special storage conditions.
- Keep out of the reach and sight of children.
- Do not use Diflucan after the expiry date which is stated on the bottle after EXP. The expiry date refers to the last day of that month.
- Once opened, Diflucan may be used for a maximum of 30 days.
- Do not use the medicine if you notice signs of deterioration such as unusual odour, product discoloration, visible particles or crystallisation.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Diflucan contains

- The active substance is fluconazole.
- The other ingredients are sucrose, glycerol 85%, purified water, citric acid monohydrate, sodium citrate and cherry Liquid Flavor.

What Diflucan looks like and contents of the pack

Diflucan is a clear, colourless to slightly yellow solution with a viscosity greater than water and is supplied in an amber glass bottle with a screw cap containing 750 mg fluconazole. Pack size 150 ml.

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:

[See Annex I - To be completed nationally]

This leaflet was last approved in

Detailed information on this medicine is available on the web site of {MA/Agency} [To be completed nationally]

PACKAGE LEAFLET: INFORMATION FOR THE USER

Diflucan and associated names (see Annex I) 10 mg/ml powder for oral suspension **Diflucan and associated names (see Annex I) 40 mg/ml powder for oral suspension**

[See Annex I – To be completed nationally]
fluconazole

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Diflucan is and what it is used for
2. Before you take Diflucan
3. How to take Diflucan
4. Possible side effects
5. How to store Diflucan
6. Further information

1. WHAT DIFLUCAN IS AND WHAT IT IS USED FOR

Diflucan is one of a group of medicines called “antifungals”. The active substance is fluconazole.

Diflucan is used to treat infections caused by fungi and may also be used to stop you from getting a candidal infection. The most common cause of fungal infections is a yeast called *Candida*.

Adults

You might be given this medicine by your doctor to treat the following types of fungal infections:

- Cryptococcal meningitis– a fungal infection in the brain
- Coccidioidomycosis– a disease of the bronchopulmonary system
- Infections caused by *Candida* and found in the blood stream, body organs (e.g. heart, lungs) or urinary tract
- Mucosal thrush - infection affecting the lining of the mouth, throat and denture sore mouth
- Genital thrush - infection of the vagina or penis
- Skin infections - e.g. athlete's foot, ringworm, jock itch, nail infection

You might also be given Diflucan to:

- stop cryptococcal meningitis from coming back
- stop mucosal thrush from coming back
- reduce recurrence of vaginal thrush
- stop you from getting an infection caused by *Candida* (if your immune system is weak and not working properly)

Children and adolescents (0 to 17 years old)

You might be given this medicine by your doctor to treat the following types of fungal infections:

- Mucosal thrush - infection affecting the lining of the mouth, throat
- Infections caused by *Candida* and found in the blood stream, body organs (e.g. heart, lungs) or urinary tract
- Cryptococcal meningitis – a fungal infection in the brain

You might also be given Diflucan to:

- stop you from getting an infection caused by *Candida* (if your immune system is weak and not working properly).
- stop cryptococcal meningitis from coming back

2. BEFORE YOU TAKE DIFLUCAN

Do not take Diflucan if you

- are allergic (hypersensitive) to fluconazole, to other medicines you have taken to treat fungal infections or to any of the other ingredients of Diflucan. The symptoms may include itching, reddening of the skin or difficulty in breathing
- are taking astemizole, terfenadine (antihistamine medicines for allergies)
- are taking cisapride (used for stomach upsets)
- are taking pimozide (used for treating mental illness)
- are taking quinidine (used for treating heart arrhythmia)
- are taking erythromycin (an antibiotic for treating infections)

Take special care with Diflucan

Tell your doctor if you

- have liver or kidney problems
- suffer from heart disease, including heart rhythm problems
- have abnormal levels of potassium, calcium or magnesium in your blood.
- develop severe skin reactions (itching, reddening of the skin or difficulty in breathing).

Taking other medicines

Tell your doctor **immediately** if you are taking astemizole, terfenadine (an antihistamine for treating allergies) or cisapride (used for stomach upsets) or pimozide (used for treating mental illness) or quinidine (used for treating heart arrhythmia) or erythromycin (an antibiotic for treating infections) as these should not be taken with Diflucan (see section: "Do not take Diflucan if you").

There are some medicines that may interact with Diflucan. Make sure your doctor knows if you are taking any of the following medicines:

- rifampicin or rifabutin (antibiotics for infections)
- alfentanil, fentanyl (used as anaesthetic)
- amitriptyline, nortriptyline (used as anti-depressant)
- amphotericin B, voriconazole (anti-fungal)
- medicines that thin the blood to prevent blood clots (warfarin or similar medicines)
- benzodiazepines (midazolam, triazolam or similar medicines) used to help you sleep or for anxiety
- carbamazepine, phenytoin (used for treating fits)
- nifedipine, isradipine, amlodipine felodipine and losartan (for hypertension- high blood pressure)
- ciclosporin, everolimus, sirolimus or tacrolimus (to prevent transplant rejection)
- cyclophosphamide, vinca alkaloids (vincristine, vinblastine or similar medicines) used for treating cancer
- halofantrine (used for treating malaria)
- statins (atorvastatin, simvastatin and fluvastatin or similar medicines) used for reducing high cholesterol levels
- methadone (used for pain)
- celecoxib, flubiprofen, naproxen, ibuprofen, lornoxicam, meloxicam, diclofenac (Non-Steroidal Anti-Inflammatory Drugs (NSAID))
- oral contraceptives
- prednisone (steroid)
- zidovudine, also known as AZT; saquinavir (used in HIV-infected patients)
- medicines for diabetes such as chlorpropamide, glibenclamide, glipizide or tolbutamide

- theophylline (used to control asthma)
- vitamin A (nutritional supplement)

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking Diflucan with food and drink

Diflucan can be taken with or without food.

Pregnancy and breast-feeding

Tell your doctor if you are pregnant, trying to become pregnant or breast-feeding. You should not take Diflucan while you are pregnant or breast-feeding unless your doctor has told you to.

Ask your doctor or pharmacist for advice before taking any medicines.

Driving and using machines

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

Important information about some of the ingredients of Diflucan

Diflucan powder for oral suspension contains sucrose (sugar).

- If you have an intolerance to some sugars, please contact your doctor before taking this medicine.
- Doses of 10 ml contain 5.6 g or more of sugar. This should be taken into account if you have diabetes.
- May be harmful to teeth if used for periods of longer than 2 weeks.

3. HOW TO TAKE DIFLUCAN

Always take your medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

It is best to take medicine at the same time each day.

The usual doses of this medicine for different infections are below:

Adults

Condition	Dose
To treat cryptococcal meningitis	400 mg on the first day then 200 mg to 400 mg once daily for 6 to 8 weeks or longer if needed. Sometimes doses are increased up to 800 mg
To stop cryptococcal meningitis from coming back	200 mg once daily until you are told to stop
To treat coccidioidomycosis	200 mg to 400 mg once daily from 11 months for up to 24 months or longer if needed. Sometimes doses are increased up to 800 mg
To treat internal fungal infections caused by <i>Candida</i>	800 mg on the first day then 400 mg once daily until you are told to stop

To treat mucosal infections affecting the lining of the mouth, throat and denture sore mouth	200 mg to 400 mg on the first day then 100 mg to 200 mg until you are told to stop
To treat mucosal thrush – dose depends on where the infection is located	50 mg to 400 mg once daily for 7 to 30 days until you are told to stop
To stop mucosal infections of mouth and throat from coming back	100 mg to 200 mg once daily, or 200 mg 3 times a week, while you are at risk of getting an infection
To treat genital thrush	150 mg as a single dose
To reduce recurrence of vaginal thrush	150 mg every third day for a total of 3 doses (day 1, 4 and 7) and then once a week for 6 months while you are at risk of getting an infection
To treat fungal skin and nail infections	Depending on the site of the infection 50 mg once daily, 150 mg once weekly, 300 to 400 mg once weekly for 1 to 4 weeks (Athlete's foot may be up to 6 weeks, for nail infection treatment until infected nail is replaced)
To stop you from getting an infection caused by <i>Candida</i> (if your immune system is weak and not working properly)	200 mg to 400 mg once daily while you are at risk of getting an infection

Adolescents from 12 to 17 years old

Follow the dose prescribed by your doctor (either adults or children posology).

Children to 11 years old

The maximum dose for children is 400 mg daily.

The dose will be based on the child's weight in kilograms.

Condition	Daily dose
Mucosal thrush and throat infections caused by <i>Candida</i> – dose and duration depends on the severity of the infection and on where the infection is located	3 mg per kg of body weight (6 mg per kg of body weight might be given on the first day)
Cryptococcal meningitis or internal fungal infections caused by <i>Candida</i>	6 mg to 12 mg per kg of body weight
To stop children from getting an infection caused by <i>Candida</i> (if their immune system is not working properly)	3 mg to 12 mg per kg of body weight

Use in children 0 to 4 weeks of age

Use in children of 3 to 4 weeks of age:

- The same dose as above but given once every 2 days. The maximum dose is 12 mg per kg of body weight every 48 hours.

Use in children less than 2 weeks old:

- The same dose as above but given once every 3 days. The maximum dose is 12 mg per kg of body weight every 72 hours.

Doctors sometimes prescribe different doses to these. Always take your medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Elderly

The usual adult dose should be given unless you have kidney problems.

Patients with kidney problems

Your doctor may change your dose, depending on your kidney function.

Instructions to make up the suspension:

It is recommended that your pharmacist makes up Diflucan powder for oral suspension before giving it to you. Instructions are provided in a section of this leaflet for healthcare professionals.

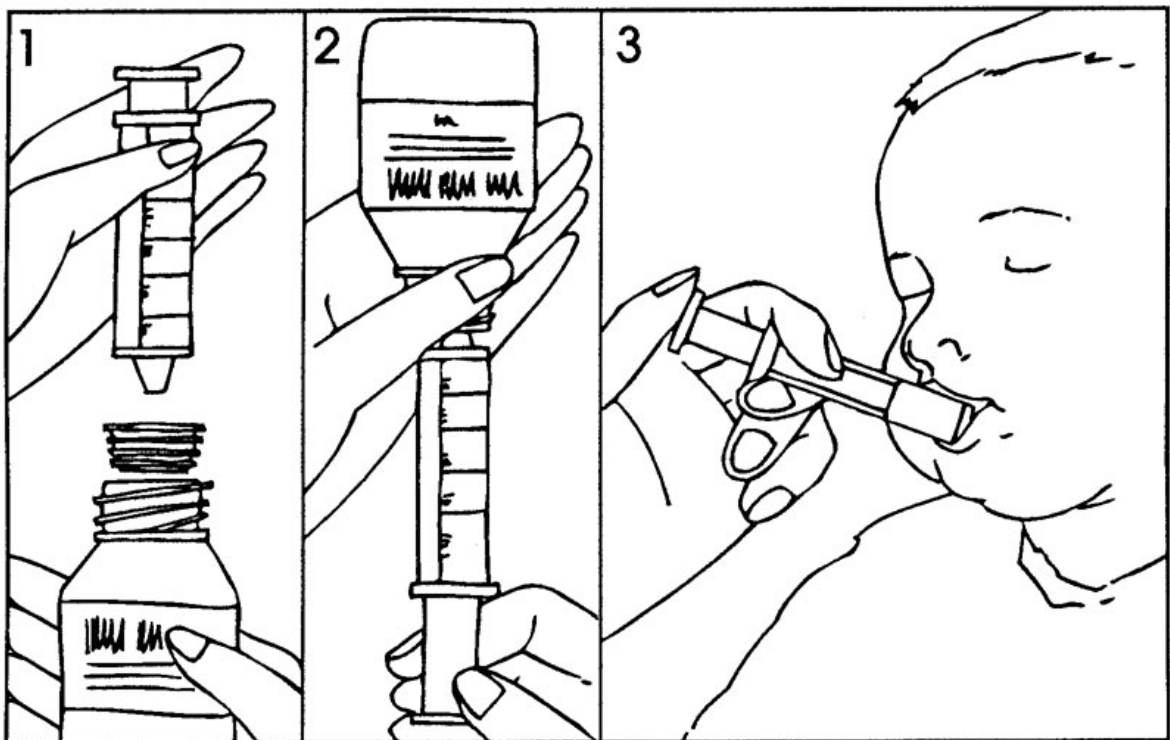
Instructions for use:

Shake the closed bottle of the suspension every time before using.

Instructions to use the paediatric syringe: (Applicable only if marketed in your country)

Shake the prepared suspension well.

1. Open the bottle (safety cap);
2. Insert the adapter fitted onto the syringe into the bottle neck (Figure 1);
3. Turn the bottle with the syringe upside down and withdraw the quantity of suspension prescribed by the doctor (Figure 2). The marks on the syringe are shown in ml.
The maximum dose for children is 400 mg daily (see section "3. How to take Diflucan").
4. Remove the syringe from the bottle;
5. For younger children, the medicinal product may be given directly into the mouth from the syringe. The child should remain upright during administration. Point the syringe at the inside of the cheek; release the suspension slowly into the child's mouth (Figure 3). For older children, the suspension may be put in a spoon and drunk by the child.
6. Rinse the syringe after use.
7. Close the bottle with the safety cap; the adapter will remain on the bottle neck.



If you take more Diflucan than you should

Taking too much Diflucan may make you unwell. Contact your doctor or your nearest hospital casualty department at once. The symptoms of a possible overdose may include hearing, seeing, feeling and thinking things that are not real (hallucination and paranoid behaviour). Symptomatic treatment (with supportive measures and gastric lavage if necessary) may be adequate.

If you forget to take Diflucan

Do not take a double dose to make up for a forgotten dose. If you forget to take a dose, take it as soon as you remember. If it is almost time for your next dose, do not take the dose that you missed.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Diflucan can cause side effects, although not everybody gets them

A few people develop **allergic reactions** although serious allergic reactions are rare. If you get any of the following symptoms, **tell your doctor immediately**.

- sudden wheezing, difficulty in breathing or tightness in the chest
- swelling of eyelids, face or lips
- itching all over the body reddening of the skin or itchy red spots
- skin rash
- severe skin reactions such as a rash that causes blistering (this can affect the mouth and tongue).

Diflucan may affect your liver. The signs of liver problems include:

- tiredness
- loss of appetite
- vomiting
- yellowing of your skin or the whites of your eyes (jaundice)

If any of these happen, stop taking Diflucan and **tell your doctor immediately**.

Other side effects:

Additionally, if any of the following side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Common side effects which affect 1 to 10 users in 100 are listed below:

- headache
- stomach discomfort, diarrhoea, feeling sick, vomiting
- increases in blood tests of liver function
- rash

Uncommon side effects which affect 1 to 10 users in 1,000 are listed below:

- reduction in red blood cells which can make skin pale and cause weakness or breathlessness
- decreased appetite
- inability to sleep, feeling drowsy
- fit, dizziness, sensation of spinning, tingling, pricking or numbness, changes in sense of taste
- constipation, difficult digestion, wind, dry mouth
- muscle pain
- liver damage and yellowing of the skin and eyes (jaundice)
- wheals, blistering (hives), itching, increased sweating
- tiredness, general feeling of being unwell, fever

Rare side effects which affect 1 to 10 users in 10,000 are listed below:

- lower than normal white blood cells that help defend against infections and blood cells that help to stop bleeding

- red or purple discoloration of the skin which may be caused by low platelet count, other blood cell changes
- blood chemistry changes (high blood levels of cholesterol, fats)
- low blood potassium,
- shaking
- abnormal electrocardiogram (ECG), change in heart rate or rhythm
- liver failure
- allergic reactions (sometimes severe), including widespread blistering rash and skin peeling, severe skin reactions, swelling of the lips or face
- hair loss

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE DIFLUCAN

- Keep out of the reach and sight of children.
- Do not use Diflucan after the expiry date which is stated on the pack after EXP. The expiry date refers to the last day of that month.
- **Powder for oral suspension (60 ml bottle):**
- Keep the bottle tightly closed. Store below 25°C
- **Powder for oral suspension (175 ml bottle):**
- Store the powder below 25°C. Keep the bottle tightly closed.
- Once reconstituted, store the suspension below 30°C, do not freeze.
- The shelf life of the reconstituted suspension is 28 days.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Diflucan contains

- The active substance is fluconazole.
- The other ingredients are: sucrose, silica colloidal anhydrous, titanium dioxide (E 171), xanthan gum, sodium citrate, citric acid anhydrous, sodium benzoate and natural orange flavour (containing orange oil and maltodextrin).

What Diflucan 10 mg/ml and 40 mg/ml powder for oral suspension look like and contents of the pack:

For the 60 ml bottle:

- Diflucan 10 mg/ml and 40 mg/ml powder for oral suspension is a dry white to off-white powder. After adding water to the powder (as instructed in the leaflet for healthcare professionals) an orange flavoured suspension containing the equivalent of 10 mg or 40 mg of fluconazole per ml is produced.
- In each bottle the mixture of powder and water makes 35 ml of suspension.
- A 5 ml measuring spoon and/or a 5 ml graduated syringe with a press-in bottle adaptor might also be provided to measure the correct dose.

For the 175 ml bottle:

- Diflucan 10 mg/ml powder for oral suspension is a dry white to off-white powder. After adding water to the powder (as instructed in the leaflet for healthcare professionals) an orange flavoured suspension containing the equivalent of 10 mg of fluconazole per ml is produced.
- In each bottle the mixture of powder and water makes 100 ml of suspension.

- A measuring cup is also provided to measure the correct dose .

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:

[See Annex I - To be completed nationally]

This leaflet was last approved in

Detailed information on this medicine is available on the web site of {MA/Agency} [To be completed nationally]

The following information is intended for medical or healthcare professionals only:

Instructions to make up the suspension:

The reconstituted suspension will provide a white to off-white orange-flavoured suspension after reconstitution.

For the 60 ml bottle:

1. Tap the bottle to release the powder.
2. Add a small quantity of still water and shake it vigorously. Add water up to the level marked on the bottle (this corresponds to adding 24 ml of water)
3. Shake well for one to two minutes to obtain a well mixed suspension.
4. Write the expiry date of the reconstituted suspension on the bottle label (the shelf life of the reconstituted suspension is 28 days). Any unused suspension should be not be used after this date and should be returned to your pharmacist.

For the 175 ml bottle:

1. Tap the bottle to release the powder.
2. Measure 66 ml of still water and add the water to the bottle.
3. Shake well for one to two minutes to obtain a well mixed suspension.
4. Write the expiry date of the reconstituted suspension on the bottle label (the shelf life of the reconstituted suspension is 28 days). Any unused suspension should be not be used after this date and should be returned to your pharmacist.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Diflucan and associated names (see Annex I) 2 mg/ml solution for infusion

[See Annex I – To be completed nationally]

fluconazole

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Diflucan is and what it is used for
2. Before you are given Diflucan
3. How Diflucan is given
4. Possible side effects
5. How to store Diflucan
6. Further information

1. WHAT DIFLUCAN IS AND WHAT IT IS USED FOR

Diflucan is one of a group of medicines called “antifungals”. The active substance is fluconazole.

Diflucan is used to treat infections caused by fungi and may also be used to stop you from getting candidal infection. The most common cause of fungal infections is a yeast called *Candida*.

Adults

You might be given this medicine by your doctor to treat the following types of fungal infections:

- Cryptococcal meningitis – a fungal infection in the brain
- Coccidioidomycosis – a disease of the bronchopulmonary system
- Infections caused by *Candida* and found in the blood stream, body organs (e.g. heart, lungs) or urinary tract
- Mucosal thrush - infection affecting the lining of the mouth, throat and denture sore mouth

You might also be given Diflucan to:

- stop cryptococcal meningitis from coming back
- stop mucosal thrush from coming back
- stop you from getting an infection caused by *Candida* (if your immune system is weak and not working properly)

Children and adolescents (0 to 17 years old)

You might be given this medicine by your doctor to treat the following types of fungal infections:

- Mucosal thrush - infection affecting the lining of the mouth, throat
- Infections caused by *Candida* and found in the blood stream, body organs (e.g. heart, lungs) or urinary tract
- Cryptococcal meningitis – a fungal infection in the brain

You might also be given Diflucan to:

- stop you from getting an infection caused by *Candida* (if your immune system is weak and not working properly)
- stop cryptococcal meningitis from coming back

2. BEFORE YOU ARE GIVEN DIFLUCAN

You should not be treated with Diflucan if you

- are allergic (hypersensitive) to fluconazole, to other medicines you have taken to treat fungal infections or to any of the other ingredients of Diflucan. The symptoms may include itching, reddening of the skin or difficulty in breathing
- are taking astemizole, terfenadine (antihistamine medicines for allergies)
- are taking cisapride (used for stomach upsets)
- are taking pimozone (used for treating mental illness)
- are taking quinidine (used for treating heart arrhythmia)
- are taking erythromycin (an antibiotic for treating infections)

Take special care with Diflucan

Tell your doctor if you

- have liver or kidney problems
- suffer from heart disease, including heart rhythm problems
- have abnormal levels of potassium, calcium or magnesium in your blood.
- develop severe skin reactions (itching, reddening of the skin or difficulty in breathing).

Taking other medicines

Tell your doctor **immediately** if you are taking astemizole, terfenadine (an antihistamine for treating allergies) or cisapride (used for stomach upsets) or pimozone (used for treating mental illness) or quinidine (used for treating heart arrhythmia) or erythromycin (an antibiotic for treating infections) as these should not be taken with Diflucan (see section: "Do not take Diflucan if you").

There are some medicines that may interact with Diflucan. Make sure your doctor knows if you are taking any of the following medicines:

- rifampicin or rifabutin (antibiotics for infections)
- alfentanil, fentanyl (used as anaesthetic)
- amitriptyline, nortriptyline (used as anti-depressant)
- amphotericin B, voriconazole (anti-fungal)
- medicines that thin the blood to prevent blood clots (warfarin or similar medicines)
- benzodiazepines (midazolam, triazolam or similar medicines) used to help you sleep or for anxiety
- carbamazepine, phenytoin (used for treating fits)
- nifedipine, isradipine, amlodipine felodipine and losartan (for hypertension- high blood pressure)
- ciclosporin, everolimus, sirolimus or tacrolimus (to prevent transplant rejection)
- cyclophosphamide, vinca alkaloids (vincristine, vinblastine or similar medicines) used for treating cancer
- halofantrine (used for treating malaria)
- statins (atorvastatin, simvastatin and fluvastatin or similar medicines) used for reducing high cholesterol levels
- methadone (used for pain)
- celecoxib, flurbiprofen, naproxen, ibuprofen, lornoxicam, meloxicam, diclofenac (Non-Steroidal Anti-Inflammatory Drugs (NSAID))
- oral contraceptives
- prednisone (steroid)
- zidovudine, also known as AZT; saquinavir (used in HIV-infected patients)
- medicines for diabetes such as chlorpropamide, glibenclamide, glipizide or tolbutamide
- theophylline (used to control asthma)
- vitamin A (nutritional supplement)

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding

Tell your doctor if you are pregnant, trying to become pregnant or breast-feeding and your doctor will decide whether you should be given Diflucan.

Ask your doctor or pharmacist for advice before taking any medicines.

Driving and using machines

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

Important information about some of the ingredients of Diflucan

Diflucan contains 0.154 mmol sodium per ml. To be taken into consideration by patients on a controlled sodium diet.

3. HOW DIFLUCAN IS GIVEN

This medicine will be given by your doctor or nurse as a slow injection (infusion) into your vein. Diflucan is supplied as a solution. It will not be diluted further. There is more information for healthcare professionals in a section at the end of the leaflet

The usual doses of this medicine for different infections are below. Check with your doctor or nurse if you are not sure why you are being given Diflucan.

Adults

Condition	Dose
To treat cryptococcal meningitis	400 mg on the first day then 200 mg to 400 mg once daily for 6 to 8 weeks or longer if needed. Sometimes doses are increased up to 800 mg
To stop cryptococcal meningitis from coming back	200 mg once daily until you are told to stop
To treat coccidioidomycosis	200 mg to 400 mg once daily from 11 months for up to 24 months or longer if needed. Sometimes doses are increased up to 800 mg
To treat internal fungal infections caused by <i>Candida</i>	800 mg on the first day then 400 mg once daily until you are told to stop
To treat mucosal infections affecting the lining of mouth, throat and denture sore mouth	200 mg to 400 mg on the first day then 100 mg to 200 mg until you are told to stop
To treat mucosal thrush – dose depends on where the infection is located	50 mg to 400 mg once daily for 7 to 30 days until you are told to stop
To stop mucosal infections affecting the lining of mouth, throat	100 mg to 200 mg once daily, or 200 mg 3 times a week, while you are at risk of getting an infection
To stop you from getting an infection caused by <i>Candida</i> (if your immune system is weak and not working properly)	200 mg to 400 mg once daily while you are at risk of getting an infection

Adolescents from 12 to 17 years old

Follow the dose prescribed by your doctor (either adults or children posology).

Children to 11 years old

The maximum dose for children is 400 mg daily.

The dose will be based on the child's weight in kilograms.

Condition	Daily dose
Mucosal thrush and throat infections caused by <i>Candida</i> – dose and duration depends on the severity of the infection and on where the infection is located	3 mg per kg of body weight (6 mg per kg of body weight might be given on the first day)
Cryptococcal meningitis or internal fungal infections caused by <i>Candida</i>	6 mg to 12 mg per kg of body weight
To stop children from getting an infection caused by <i>Candida</i> (if their immune system is not working properly)	3 mg to 12 mg per kg of body weight

Use in children 0 to 4 weeks of age

Use in children of 3 to 4 weeks of age:

- The same dose as above but given once every 2 days. The maximum dose is 12 mg per kg of body weight every 48 hours.

Use in children less than 2 weeks old:

- The same dose as above but given once every 3 days. The maximum dose is 12 mg per kg of body weight every 72 hours.

Doctors sometimes prescribe different doses to these. Always take your medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Elderly

The usual adult dose should be given unless you have kidney problems.

Patients with kidney problems

Your doctor may change your dose, depending on your kidney function.

If you receive more Diflucan than you should

If you are concerned that you may have been given too much Diflucan, tell your doctor or nurse immediately. The symptoms of a possible overdose may include hearing, seeing, feeling and thinking things that are not real (hallucination and paranoid behaviour).

If a dose of Diflucan has been forgotten

As you will be given this medicine under close medical supervision, it is unlikely that a dose would be missed. However tell your doctor or pharmacist if you think that a dose has been forgotten.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Diflucan can cause side effects, although not everybody gets them

A few people develop **allergic reactions** although serious allergic reactions are rare. If you get any of the following symptoms, **tell your doctor immediately**.

- sudden wheezing, difficulty in breathing or tightness in the chest
- swelling of eyelids, face or lips

- itching all over the body reddening of the skin or itchy red spots
- skin rash
- severe skin reactions such as a rash that causes blistering (this can affect the mouth and tongue).

Diflucan may affect your liver. The signs of liver problems include:

- tiredness
- loss of appetite
- vomiting
- yellowing of your skin or the whites of your eyes (jaundice)

If any of these happen, stop taking Diflucan and **tell your doctor immediately.**

Other side effects:

Additionally, if any of the following side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Common side effects which affect 1 to 10 users in 100 are listed below:

- headache
- stomach discomfort, diarrhoea, feeling sick, vomiting
- increases in blood tests of liver function
- rash

Uncommon side effects which affect 1 to 10 users in 1,000 are listed below:

- reduction in red blood cells which can make skin pale and cause weakness or breathlessness
- decreased appetite
- inability to sleep, feeling drowsy
- fit, dizziness, sensation of spinning, tingling, pricking or numbness, changes in sense of taste
- constipation, difficult digestion, wind, dry mouth
- muscle pain
- liver damage and yellowing of the skin and eyes (jaundice)
- wheals, blistering (hives), itching, increased sweating
- tiredness, general feeling of being unwell, fever

Rare side effects which affect 1 to 10 users in 10,000 are listed below:

- lower than normal white blood cells that help defend against infections and blood cells that help to stop bleeding
- red or purple discoloration of the skin which may be caused by low platelet count, other blood cell changes
- blood chemistry changes (high blood levels of cholesterol, fats)
- shaking
- low blood potassium
- abnormal electrocardiogram (ECG), change in heart rate or rhythm
- liver failure
- allergic reactions (sometimes severe), including widespread blistering rash and skin peeling, severe skin reactions, swelling of the lips or face
- hair loss

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, pharmacist or nurse.

5. HOW TO STORE DIFLUCAN

- Keep out of the reach and sight of children.
- Do not use after the expiry date which is stated on the pack after EXP. The expiry date refers to the last day of that month.
- Glass vials: Do not freeze.

- **Plasticised PVC bags: Store below 30°C.** Do not freeze. This medicinal product is for single use. Once opened, any unused infusion should be discarded.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Diflucan solution for infusion contains

- The active substance is fluconazole.
- Each ml contains 2 mg of fluconazole.
- The other ingredients are: sodium chloride, water for injections and sodium hydroxide (for pH adjustment).

What Diflucan solution for infusion looks like and contents of the pack

- Diflucan is a clear, colourless solution with no visible particles.
- It comes in either a glass vial containing a total of 50 mg, 100 mg, 200 mg or 400 mg fluconazole or 1, 5, 10 and 20 plasticised PVC bag(s) containing a total of 200 mg or 400 mg fluconazole. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

[See Annex I - To be completed nationally]

This medicinal product is authorised in the Member States of the EEA under the following names:

[See Annex I - To be completed nationally]

This leaflet was last approved in

[To be completed nationally]

Detailed information on this medicine is available on the web site of {MA/Agency} [To be completed nationally]

The following information is intended for medical or healthcare professionals only:

Intravenous infusion should be administered at a rate not exceeding 10 ml/minute. Diflucan is formulated in sodium chloride 9 mg/ml (0.9%) solution for infusion, each 200 mg (100 ml bottle) containing 15 mmol each of Na⁺ and Cl⁻. Because Diflucan is available as a dilute sodium chloride solution, in patients requiring sodium or fluid restriction, consideration should be given to the rate of fluid administration.

Fluconazole intravenous infusion is compatible with the following administration fluids:

- a) Dextrose 5% and 20%
- b) Ringer's solution
- c) Hartmann's solution
- d) Potassium chloride in dextrose
- e) Sodium bicarbonate 4.2% and 5%
- f) Aminosyn 3.5%
- g) Sodium chloride 9 mg/ml (0.9%)
- h) Dialaflex (interperitoneal dialysis Soln 6.36%)

Fluconazole may be infused through an existing line with one of the above listed fluids. Although no specific incompatibilities have been noted, mixing with any other medicinal products prior to infusion is not recommended.

The solution for infusion is for single use only.

From a microbiological point of view, the dilutions should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 ° C, unless dilution has taken place in controlled and validated aseptic conditions.

The dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements