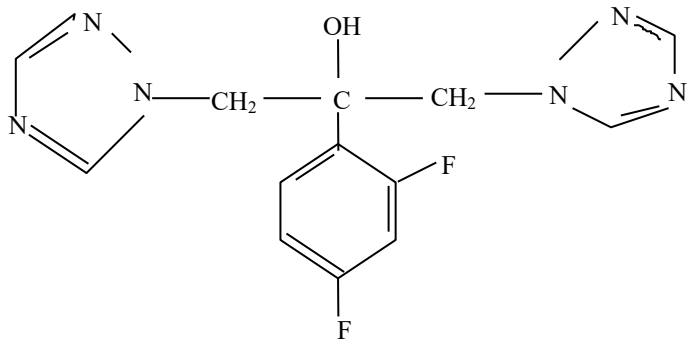
PT. PFIZER INDONESIA
Local Product Document

Generic Name: Fluconazole
Trade Name: Diflucan
CDS Effective Date: March 09, 2022
Supersedes: April 16, 2020

DESCRIPTION

Fluconazole is a bis-triazole: 2-(2,4-difluorophenyl)-1,3-bis (1H-1,2,4-triazol-1yl)-2 propanol.

It has the following structural formula:



Fluconazole is a white to off-white crystalline powder which is sparingly soluble in water and saline. It has a molecular weight of 306.3.

Diflucan for injection is an iso-osmotic, sterile, non-pyrogenic solution of fluconazole in a sodium chloride diluent. Each ml contains 2 mg of fluconazole and 9 mg of sodium chloride. The pH ranges from 4.0 to 8.6. Injection volumes of 100 ml are packaged in glass infusion vials.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

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

Mode of Action

Fluconazole, a triazole antifungal agent, is a potent and specific inhibitor of fungal sterol synthesis.

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 is highly specific for fungal cytochrome P-450 dependent enzymes. Fluconazole 50 mg daily given up to 28 days has been shown not to affect testosterone plasma concentrations in males or steroid concentrations in females of child-bearing age. Fluconazole 200 mg to 400 mg daily has no clinically significant effect on endogenous steroid levels or on adrenocorticotropic hormone (ACTH) stimulated response in healthy male volunteers. Interaction studies with antipyrine indicate that single or multiple doses of fluconazole 50 mg do not affect its metabolism.

Pharmacokinetic/Pharmacodynamic Relationship

In animal studies, there is a correlation between minimum inhibitory concentration (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.

Microbiology

In vitro, fluconazole displays antifungal activity against clinically common *Candida* species (including *C. albicans*, *C. parapsilosis*, *C. tropicalis*). *C. glabrata* shows reduced susceptibility to fluconazole while *C. krusei* is intrinsically resistant to fluconazole. The MICs and EUCAST epidemiological cut-off value (ECOFF) of fluconazole for *C. guilliermondii* are higher than for *C. albicans*. The recently emerging species *C. auris* tends to be relatively resistant to fluconazole.

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

Both orally and intravenously administered fluconazole was active in a variety of animal fungal infection models. Activity has been demonstrated against opportunistic mycoses, such as infections with *Candida* spp., including systemic candidiasis in immunocompromised animals; with *C. neoformans*, including intracranial infections; with *Microsporum* spp.; and with *Trichophyton* spp. Fluconazole has also been shown to be active in animal models of endemic mycoses, including infections with *Blastomyces dermatitidis*; with *Coccidioides immitis*, including intracranial infection; and with *Histoplasma capsulatum* in normal and immunosuppressed animals.

Mechanisms of Resistance

In usually susceptible species of *Candida*, the most commonly encountered mechanism of resistance involves the target enzymes of the azoles, which are responsible for the biosynthesis of ergosterol. Point mutations in the gene (*ERG11*) encoding for the target enzyme lead to an altered target with decreased affinity for azoles. Overexpression of *ERG11* results in the production of high concentrations of the target

enzyme, creating the need for higher intracellular drug concentrations to inhibit all of the enzyme molecules in the cell.

The second major mechanism of drug resistance involves active efflux of fluconazole out of the cell through the activation of two types of multidrug efflux transporters; the major facilitators (encoded by *MDR* genes) and those of the ATP-binding cassette superfamily (encoded by *CDR* genes). Upregulation of the *MDR* gene leads to fluconazole resistance, whereas, upregulation of *CDR* genes may lead to resistance to multiple azoles.

Resistance in *Candida glabrata* usually includes upregulation of *CDR* genes resulting in resistance to multiple azoles.

There have been reports of superinfection with *Candida species* other than *C. albicans*, which often have reduced susceptibility (*C. glabrata*) or resistance to fluconazole (e.g., *C. krusei, C. auris*). Such infections may require alternative antifungal therapy.

Breakpoints

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 rationale document; European Committee on Antimicrobial Susceptibility Testing, Antifungal Agents, Breakpoint tables for interpretation of MICs. 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>) in mg/L						Non-species related breakpoints[A] S≤/R> in mg/L
	Candida albicans	*Candida dubliniensis*	*Candida glabrata*	*Candida krusei*	*Candida parapsilosis*	*Candida tropicalis*	
Fluconazole	2/4	2/4	0.001/16*	--	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.
* = The entire *C. glabrata* is in the I category. MICs against *C. glabrata* should be interpreted as resistant when above 16 mg/L. Susceptible category (≤0.001 mg/L) is simply to avoid misclassification of "I" strains as "S" strains. I - Susceptible, increased exposure: A microorganism is categorised as Susceptible, increased exposure when there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.

Pharmacokinetic Properties

The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral route. 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 with a plasma elimination half-life of approximately 30 hours. Plasma concentrations are proportional to dose. Ninety percent steady-state levels are reached by Days 4 to 5 with multiple once-daily dosing.

Administration of loading dose (on Day 1) of twice the usual daily dose enables plasma levels to approximate to 90% steady-state levels by Day 2. 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 cerebrospinal fluid (CSF) are approximately 80% the corresponding plasma levels.

High skin concentrations 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.

The major route of excretion is renal, with approximately 80% of the administered dose appearing in the urine as unchanged drug. Fluconazole clearance is proportional to creatinine clearance. There is no evidence of circulating metabolites.

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

A study compared the saliva and plasma concentrations of a single fluconazole 100 mg dose administered in a capsule or in an oral suspension by rinsing and retaining in mouth for 2 minutes and swallowing. The maximum concentration of fluconazole in saliva after the suspension was observed 5 minutes after ingestion, and was 182 times higher than the maximum saliva concentration after the capsule which occurred 4 hours after ingestion. After about 4 hours, the saliva concentrations of fluconazole were similar. The mean area under the concentration versus time curve (AUC) (0-96) in saliva was significantly greater after the suspension compared to the capsule. There was no significant difference in the elimination rate from saliva or the plasma pharmacokinetic parameters for the two formulations.

A pharmacokinetic study in 10 lactating women, who had temporarily or permanently stopped breast-feeding their infants, evaluated fluconazole concentrations in plasma and breast milk for 48 hours following a single 150 mg dose of Diflucan. Fluconazole was detected in breast milk at an average concentration of approximately 98% of those in maternal plasma. The mean peak breast milk concentration was 2.61 mg/L at 5.2 hours post-dose.

Pharmacokinetics in Elderly

A pharmacokinetic study was conducted in 22 subjects, 65 years of age or older receiving a single 50 mg oral dose of fluconazole. Ten of these patients were concomitantly receiving diuretics. The C_{max} was 1.54 μg/ml and occurred at 1.3 hours post-dose. The mean AUC was 76.4 ± 20.3 μg.h/ml, and the mean terminal half-life was 46.2 hours. These pharmacokinetic parameter values are higher than analogous values reported for normal young male volunteers. Co-administration of diuretics did not significantly alter the AUC or $C_{max.}$ In addition, creatinine clearance (74 ml/min), the percent of drug recovered unchanged in urine (0-24 hours, 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 characteristic of this group. A plot of each subject's terminal elimination half-life versus creatinine clearance compared to the predicted half-life - creatinine clearance curve derived from normal subjects and subjects with varying degrees of renal insufficiency indicated that 21 of 22 subjects fell within the 95% confidence limit of the predicted half-life - creatinine clearance curves. These results are consistent with the hypothesis that higher values for the pharmacokinetic parameters observed in the elderly subjects compared to normal young male volunteers are due to the decreased kidney function that is expected in the elderly.

PRECLINICAL SAFETY DATA

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.

Mutagenesis
Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in four strains of *Salmonella typhimurium*, and in the mouse lymphoma L5178Y system. Cytogenetic studies *in vivo* (murine bone marrow cells, following oral administration of fluconazole) and *in vitro* (human lymphocytes exposed to fluconazole at 1000 μg/ml) showed no evidence of chromosomal mutations.

Impairment of Fertility
Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5 mg/kg, 10 mg/kg or 20 mg/kg or with parenteral doses of 5 mg/kg, 25 mg/kg or 75 mg/kg, although the onset or parturition was slightly delayed at 20 mg/kg orally. In an intravenous perinatal study in rats at 5 mg/kg, 20 mg/kg and 40 mg/kg, dystocia and prolongation of parturition were observed on a few dams at 20 mg/kg (approximately 5-15 times the recommended human dose) and 40 mg/kg, but not at 5 mg/kg. 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. The effects on parturition in rats are consistent with the species specific estrogen lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole (see section **Pharmacodynamic Properties**).

THERAPEUTIC INDICATIONS

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.

1. Cryptococcosis, including cryptococcal meningitis and infections of other sites (e.g., pulmonary, cutaneous). Normal hosts and patients with AIDS, organ transplants or other causes of immunosuppression may be treated. Fluconazole can be used as maintenance therapy to prevent relapse of cryptococcal disease in patients with AIDS.

2. Systemic candidiasis, including candidemia, disseminated candidiasis and other forms of invasive candidal infections. These include infections of the peritoneum, endocardium, and pulmonary and urinary tracts. Patients with malignancy, in intensive care units, receiving cytotoxic or immunosuppressive therapy, or with other factors predisposing to candidal infection may be treated.

3. Mucosal candidiasis. These include oropharyngeal, esophageal, non-invasive bronchopulmonary infections, candiduria, mucocutaneous and chronic oral atrophic candidiasis (denture sore mouth). Normal hosts and patients with compromised immune function may be treated. Prevention of relapse of oropharyngeal candidiasis in patients with AIDS.

4. Genital candidiasis. Vaginal candidiasis, acute or recurrent, Candidal balanitis.

5. Prevention of fungal infections in patients with malignancy who are predisposed to such infections as a result of cytotoxic chemotherapy or radiotherapy.

6. Dermatomycosis, including tinea pedis, tinea corporis, tinea cruris, tinea versicolor, and dermal *Candida* infections.

CONTRAINDICATIONS

Fluconazole should not be used in patients with known sensitivity to the drug, any of the inert ingredients or to related azole compounds.

Co-administration of terfenadine is contraindicated in patients receiving fluconazole at multiple doses of 400 mg/day or higher based upon result of a multiple-dose interaction study. Co-administration of other drugs known to prolong the QT interval and which are metabolized via the enzyme CYP3A4 such as cisapride, astemizole, erythromycin, pimozide and quinidine are contraindicated in patients receiving fluconazole (see section **SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE** and section **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**).

Co-administration of cisapride is contraindicated in patients receiving fluconazole (see section **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**).

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

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

Effective contraceptive measures should be considered in women of child-bearing potential and should continue throughout the treatment period and for approximately 1 week (5 to 6 half-lives) after the final dose. (see section **FERTILITY, PREGNANCY AND LACTATION**).

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

Fluconazole 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 should be monitored for the development of more serious hepatic injury. Fluconazole should be discontinued if clinical signs or symptoms consistent with liver disease develop that may be attributable to fluconazole.

Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson Syndrome and toxic epidermal necrolysis, during treatment with Fluconazole. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported. AIDS patients are more prone to the development of severe cutaneous reactions to many drugs. If a rash, which is considered attributable to fluconazole, develops in a patient treated for a superficial fungal infection, further therapy with this agent 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.

The co-administration of fluconazole at doses lower than 400 mg/day with terfenadine should be carefully monitored (see section **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**).

In rare cases, as with other azoles, anaphylaxis has been reported.

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. Fluconazole causes QT prolongation via the inhibition of Rectifier Potassium Channel current (Ikr). The QT prolongation caused by other medicinal products (such as amiodarone) may be amplified via the inhibition of cytochrome P450 (CYP) 3A4 (see section **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**). During post-marketing surveillance, there have been very rare cases of QT prolongation and torsade de pointes in patients taking fluconazole. These reports included seriously ill patients with multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities and concomitant medications that may have been contributory. Patients with hypokalemia and advanced cardiac failure are at an increased risk for the occurrence of life-threatening ventricular arrhythmias and *torsades de pointes*.

Fluconazole should be administered with caution to patients with these potentially proarrhythmic conditions.

Fluconazole should be administered with caution to patients with renal dysfunction (see section **POSOLOGY AND METHOD OF ADMINISTRATION**).

Fluconazole is a moderate CYP2C9 inhibitor and a moderate CYP3A4 inhibitor. Fluconazole is also an inhibitor of the isoenzyme CYP2C19. Fluconazole-treated patients who are concomitantly treated with drugs with a narrow therapeutic window metabolized through CYP2C9, CYP2C19 and CYP3A4 should be monitored (see section **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**).

Adrenal insufficiency has been reported in patients receiving other azoles (e.g., ketoconazole).

Reversible cases of adrenal insufficiency were reported in patients receiving fluconazole.

<u>Candidiasis</u>

Studies have shown an increasing prevalence of infections with *Candida* species other than *C. albicans*. These are often resistant (e.g., *C. krusei* and *C. auris*) or show reduced susceptibility to fluconazole (*C. glabrata*). Such infections may require alternative antifungal therapy secondary to treatment failure. Therefore, prescribers are advised to take into account the prevalence of resistance in various *Candida* species to fluconazole (see section **Pharmacodynamic Properties**).

UNDESIRABLE EFFECTS

Fluconazole is generally well tolerated.

Summary of safety profile

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in association with fluconazole treatment (see section **SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE**).

In some patients, particularly those with serious underlying diseases such as AIDS and cancer, changes in renal and hematological function test results and hepatic abnormalities (see section **SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE**) have been observed during treatment with fluconazole and comparative agents, but the clinical significance and relationship to treatment is uncertain.

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

System Organ Class	Frequency	Undesirable Effects
Blood and lymphatic system disorders	Rare	Agranulocytosis, leukopenia, neutropenia, thrombocytopenia
Immune system disorders	Rare	Anaphylaxis, angioedema
Metabolism and nutrition disorders	Rare	Hypertriglyceridaemia, hypercholesterolaemia, hypokalaemia
Psychiatric disorders	Uncommon	Insomnia, somnolence
Nervous system disorders	Common	Headache
	Uncommon	Seizures, dizziness, paraesthesia, taste perversion
	Rare	Tremor
Ear and labyrinth disorders	Uncommon	Vertigo
Cardiac disorders	Rare	Torsade de pointes, QT prolongation
Gastrointestinal disorders	Common	Abdominal pain, diarrhoea, nausea, vomiting
	Uncommon	Dyspepsia, flatulence, dry mouth
Hepatobiliary disorders	Common	Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased
	Uncommon	Cholestasis, jaundice, bilirubin increased
	Rare	Hepatic toxicity, including rare cases of fatalities, hepatic failure, hepatocellular necrosis, hepatitis, hepatocellular damage

System Organ Class	Frequency	Undesirable Effects
Skin and subcutaneous tissue disorders	Common	Rash
	Uncommon	Pruritus, urticaria, increased sweating, drug eruption[a]
	Rare	Toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, dermatitis exfoliative, face oedema, alopecia
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and connective tissue disorders	Uncommon	Myalgia
General disorders and administration site conditions	Uncommon	Fatigue, malaise, asthenia, fever

[a] including Fixed Drug Eruption

Pediatric Population

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

POSOLOGY AND METHOD OF ADMINISTRATION

The daily dose of fluconazole should be based on the nature and severity of the fungal infection. Most cases of vaginal candidiasis respond to single dose therapy.

Therapy for those types of infections requiring multiple dose treatment should be continued until clinical parameters or laboratory tests indicate that active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection. Patients with AIDS and cryptococcal meningitis or recurrent oropharyngeal candidiasis usually require maintenance therapy to prevent relapse.

Use in Adults

1. For cryptococcal meningitis and cryptococcal infections at other sites, the usual dose is 400 mg on the first day followed by 200 mg to 400 mg once daily. Duration of treatment for cryptococcal infections will depend on the clinical and mycological response, but is usually at least 6 to 8 weeks for cryptococcal meningitis.

   For the prevention of relapse of cryptococcal meningitis in patients with AIDS, after the patient receives a full course of primary therapy, fluconazole may be administered indefinitely at a once daily dose of 200 mg.

2. For candidemia, disseminated candidiasis and other invasive candidal infections, the usual dose is 400 mg on the first day followed by 200 mg once daily. Depending on the clinical response, the dose may be increased to 400 mg once daily. Duration of treatment is based upon the clinical response.

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

   For atrophic oral candidiasis associated with dentures, the usual dose is 50 mg once daily for 14 days administered concurrently with local antiseptic measures to the denture.

   For other candidal infections of mucosa except genital candidiasis (see below) (e.g., esophagitis, non-invasive bronchopulmonary infections, candiduria, mucocutaneous candidiasis, etc.), the usual effective dose is 50 mg to 100 mg once daily, given for 14 to 30 days. For the prevention of relapse of oropharyngeal candidiasis in patients with AIDS, after the patient receives a full course of primary therapy, fluconazole may be administered at a 150 mg once-weekly dose.

4. For *Candida balanitis*, fluconazole 150 mg should be administered as a single oral dose.

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

   A higher dose of 100 mg once daily may be used in patients at risk of severe recurrent infections.

6. For dermal infections including tinea pedis, tinea corporis, tinea cruris and *Candida* infections, the recommended dosage is 150 mg once weekly or 50 mg once daily. Duration of treatment is normally 2 to 4 weeks but tinea pedis may require treatment for up to 6 weeks. For tinea versicolor the recommended dose is 50 mg once daily for 2 to 4 weeks. Duration of treatment should not exceed 6 weeks.

7. For the treatment of vaginal candidiasis, fluconazole 150 mg should be administered as a single dose.

Use in Children

As stated in the Precautions section, use in children below the age of 16 years is not recommended. However, when the treating physician considers fluconazole therapy imperative, the following daily doses for children aged 1 year and older with normal renal function are recommended: 1-2 mg/kg once daily for superficial candidal infections and 3-6 mg/kg once daily for systemic candidal/cryptococcal infections. These recommendations approximate the doses used in adults on a mg.kg basis.

However, preliminary data in children aged 5-13, indicate fluconazole elimination may be faster than in adults. Therefore, for serious or life-threatening infections, higher daily doses may be required. Daily doses up to 12 mg/kg once daily have been used in a small number of children. The maximum approved adult daily dose of 400 mg should not be exceeded.

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

Use in Elderly

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

Use in Renal Impairment

Fluconazole is predominantly excreted in the urine as unchanged drug. No adjustments in single-dose therapy are necessary. In patients with impaired renal function who will receive multiple doses of fluconazole, an initial loading dose of 50 mg to 400 mg should be given. After the loading dose, the daily dose (according to indication) should be administered as outlined in Table 2:

Table 2: Daily Dose

Creatinine Clearance (ml/min)	Recommended Dose (%)
>50	100
≤50 (no dialysis)	50
Hemodialysis	100 after each hemodialysis

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

When serum creatinine is the only measure of renal function available, the following formula (based on sex, weight, and age of the patients) should be based on the following table:

$$\text{Males} : \frac{\text{Weight (kg)} \times (140-\text{age})}{72 \times \text{serum creatinine (mg/100 ml)}}$$

Females : 0.85 x above value

Administration

Fluconazole may be administered either orally (Capsules) or by intravenous infusion (Solution for Infusion) at a rate not exceeding 200 mg/hour given as a continuous 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 dosage. Diflucan injection in glass containers are intended only for intravenous administration using sterile equipment. Fluconazole is formulated in 0.9% sodium chloride solution, each 200 mg (100 ml bottle) containing 15 mmol each of Na^+ and Cl^-. Because fluconazole is available as a dilute saline solution, in patients requiring sodium or fluid restriction, consideration should be given to the rate of fluid administration.

OVERDOSE

There have been reports of overdose with fluconazole accompanied by hallucination and paranoid behaviour.

In the event of overdosage, 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 3-hour hemodialysis session decreases plasma levels by approximately 50%.

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 *torsade de pointes* in patients to whom fluconazole and cisapride were co-administered. A controlled study found that concomitant treatment with 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. Co-administration of cisapride is contraindicated in patients receiving fluconazole (see section **CONTRAINDICATIONS**).

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/day or greater significantly increases plasma levels of terfenadine when taken concomitantly. The combined use of fluconazole at doses of 400 mg/day or greater with terfenadine is contraindicated (see section **CONTRAINDICATIONS**). The co-administration of fluconazole at doses lower than 400 mg/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 *torsade de pointes*. Co-administration of fluconazole and astemizole is contraindicated (see section **CONTRAINDICATIONS**).

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 *torsade de pointes*. Co-administration of fluconazole and pimozide is contraindicated (see section **CONTRAINDICATIONS**).

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

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

Concomitant use that should be avoided or used with caution:

Amiodarone: Concomitant administration of fluconazole with amiodarone may increase QT prolongation. Caution must be exercised if the concomitant use of fluconazole and amiodarone is necessary, notably with high-dose fluconazole (800 mg).

Lemborexant: Concomitant administration of fluconazole increased lemborexant C_{max} and AUC by approximately 1.6- and 4.2-fold, respectively which is expected to increase risk of adverse reactions, such as somnolence. Avoid concomitant use of lemborexant.

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

The effect of other medicinal products on fluconazole

Hydrochlorothiazide: In a pharmacokinetic interaction study, co-administration of multiple-dose hydrochlorothiazide to healthy volunteers receiving fluconazole increased plasma concentrations of fluconazole by 40%. An effect of this magnitude should not necessitate a change in the fluconazole dose regimen in subjects receiving concomitant diuretics, although the prescriber should bear it in mind.

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

The effect of fluconazole on other medicinal products

Fluconazole is a moderate inhibitor of cytochrome P450 (CYP) isoenzymes 2C9 and 3A4. Fluconazole is also an inhibitor of the isoenzyme CYP2C19. In addition to the observed/documented interactions mentioned below, there is a risk of increased plasma concentration of other compounds metabolized by CYP2C9, CYP2C19 and CYP3A4 co-administered 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 to 5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole (see section **CONTRAINDICATIONS**).

Abrocitinib: Fluconazole (inhibitor of CYP2C19, 2C9, 3A4) increased exposure of abrocitinib active moiety by 155%. If co-administered with fluconazole, adjust the dose of abrocitinib as instructed in abrocitinib prescribing information.

Alfentanil: A study observed a reduction in clearance and distribution volume as well as prolongation of $t_{½}$ of alfentanil following concomitant treatment with fluconazole. A possible mechanism of action is fluconazole's inhibition of CYP3A4. Dosage 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 1 week. Dosage 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 *Candida albicans*, no interaction in intracranial infection with *Cryptococcus neoformans*, and antagonism of the two drugs in systemic infection with *Aspergillus fumigatus*. The clinical significance of results obtained in these studies is unknown.

Anticoagulants: In an interaction study, fluconazole increased the prothrombin time (12%) after warfarin administration in healthy males. 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.

Prothrombin time in patients receiving coumarin-type or indanedione anticoagulants should be carefully monitored. Dose adjustment of these anticoagulants may be necessary.

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.

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

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

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. Dosage adjustment of carbamazepine may be necessary depending on concentration measurements/effect.

Calcium channel blockers: Certain calcium channel antagonists (nifedipine, isradipine, amlodipine, verapamil and felodipine) are metabolized by CYP3A4. 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.

Cyclosporin: Fluconazole significantly increases the concentration and AUC of cyclosporin. This combination may be used by reducing the dosage of cyclosporin depending on cyclosporin concentration.

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 possible fentanyl-fluconazole interaction was reported. The author judged that the patient died from fentanyl intoxication. Furthermore, in a randomized crossover study with 12 healthy volunteers, it was shown that fluconazole delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to respiratory depression.

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

HMG-CoA reductase inhibitors: The risk of myopathy and rhabdomyolysis increases (dose-dependent) when fluconazole is co-administered with HMG-CoA reductase inhibitors metabolized through CYP3A4, such as atorvastatin and simvastatin, or through CYP2C9, such as fluvastatin (decreased hepatic metabolism

of the statin). If concomitant therapy is necessary, the patient should be observed for symptoms of myopathy and rhabdomyolysis and creatine kinase should be monitored. HMG-CoA reductase inhibitors should be discontinued if a marked increase in creatine kinase is observed or myopathy/rhabdomyolysis is diagnosed or suspected. Lower doses of HMG-CoA reductase inhibitors may be necessary as instructed in the statins prescribing information.

Ibrutinib: Moderate inhibitors of CYP3A4 such as fluconazole increase plasma ibrutinib concentrations and may increase risk of toxicity. If the combination cannot be avoided, reduce the dose of ibrutinib prescribing information and provide close clinical monitoring.

Ivacaftor (alone or combined with drugs in the same therapeutic class): Coadministration with ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, increased ivacaftor exposure by 3-fold and hydroxymethyl-ivacaftor (M1) exposure by 1.9-fold. A reduction of the ivacaftor (alone or combined) dose is necessary as instructed in the ivacaftor (alone or combined) prescribing information.

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

Lurasidone: Moderate inhibitors of CYP3A4 such as fluconazole may increase lurasidone plasma concentrations. If concomitant use cannot be avoided, reduce the dose of lurasidone as instructed in the lurasidone prescribing information.

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

Non-steroidal anti-inflammatory drugs: The C_{max} and AUC of flurbiprofen were increased by 23% and 81%, respectively, when co-administered with fluconazole compared to administration of flurbiprofen alone. Similarly, the C_{max} and AUC of the pharmacologically active isomer [S-(+)-ibuprofen] were increased by 15% and 82%, respectively, when fluconazole was co-administered 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 non-steroidal anti-inflammatory drugs (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 dosage of NSAIDs may be needed.

Olaparib: Moderate inhibitors of CYP3A4 such as fluconazole increase olaparib plasma concentrations; concomitant use is not recommended. If the combination cannot be avoided, limit the dose of olaparib to 200 mg twice daily.

Oral contraceptives: Two kinetic studies with a combined oral contraceptive have been performed using multiple doses of fluconazole. There were no relevant effects on either 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.

Phenytoin: Concomitant administration of fluconazole and phenytoin may increase the levels of phenytoin to a clinical significant degree. If it is necessary to administer both drugs concomitantly, phenytoin levels should be monitored and the phenytoin dose adjusted to maintain therapeutic levels.

Fluconazole inhibits the hepatic metabolism of phenytoin. 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 3-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: There have been reports that an interaction exists when fluconazole is administered concomitantly with rifabutin, leading to increased serum levels of rifabutin up to 80%. There have been reports of uveitis in patients to whom fluconazole and rifabutin were co-administered. Patients receiving rifabutin and fluconazole concomitantly should be carefully monitored.

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

Sirolimus: 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 dosage adjustment of sirolimus depending on the effect/concentration measurements.

Sulfonylureas: Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulfonylureas (chlorpropamide, glibenclamide, glipizide and tolbutamide) in healthy volunteers. Fluconazole and oral sulfonylureas may be co-administered to diabetic patients, but the possibility of a hypoglycemic episode should be borne in mind. Frequent monitoring of blood glucose and appropriate reduction of sulfonylurea dosage are recommended during co-administration.

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. Dosage of orally administered tacrolimus should be decreased depending on tacrolimus concentration.

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, and therapy modified appropriately if signs of toxicity develop.

Tofacitinib: Exposure of tofacitinib is increased when tofacitinib is co-administered with medications that result in both moderate inhibition of CYP3A4 and inhibition of CYP2C19 (e.g., fluconazole). Dosage adjustment of tofacitinib may be necessary.

Tolvaptan: Exposure to tolvaptan is significantly increased (200% in AUC; 80% in C_{max}) when tolvaptan, a CYP3A4 substrate, is co-administered with fluconazole, a moderate CYP3A4 inhibitor, with risk of significant increase in adverse effects particularly significant diuresis, dehydration and acute renal failure. In case of concomitant use, the tolvaptan dose should be reduced and the patient managed cautiously.

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, central nervous system (CNS)-related undesirable effects have developed in the form of pseudotumor cerebri, which disappeared after discontinuation of fluconazole treatment. This combination may be used but the incidence of CNS-related undesirable effects should be borne in mind.

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

Zidovudine: Fluconazole increases the C_{max} and AUC of zidovudine by 84% and 74%, respectively, due to an approximately 45% decrease in oral zidovudine clearance. The half-life of zidovudine was likewise prolonged by approximately 128% following combination therapy with fluconazole.

Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions. Dosage reduction of zidovudine may be considered.

The use of fluconazole in patients concurrently taking astemizole or other drugs metabolized by the cytochrome P-450 system may be associated with elevations in serum levels of these drugs. In the absence of definitive information, caution should be used when co-administering fluconazole. Patients should be carefully monitored.

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

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

FERTILITY, PREGNANCY AND LACTATION

Use During Pregnancy

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

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

There have been reports of spontaneous abortion and congenital abnormalities in infants whose mothers were treated with 150 mg of fluconazole as a single or repeated dose in the first trimester.

There are no adequate and well controlled studies in pregnant women. There have been reports of multiple congenital abnormalities in infants whose mothers were being treated for 3 or more months with high-dose (400 mg/day to 800 mg/day) fluconazole therapy for coccidioidomycosis. The relationship between fluconazole use and these events is unclear. Adverse fetal effects have been seen in animals only at high-dose levels associated with maternal toxicity. There were no fetal effects at 5 mg/kg or 10 mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 mg/kg and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg (approximately 20-60 times the recommended human dose) to 320 mg/kg embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate and abnormal craniofacial ossification. These effects are consistent with the inhibition of estrogen synthesis in rats and may be a result of known effects of lowered estrogen on pregnancy, organogenesis and parturition.

Case reports describe a distinctive and a rare pattern of birth defects among infants whose mothers received high-dose (400-800 mg/day) fluconazole during most or all of the first trimester of pregnancy. The features seen in these infants include: brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital heart disease.

Use During Lactation

Fluconazole is found in human breast milk at concentrations similar to plasma (see section **Pharmacokinetic Properties**). The elimination half-life from breast milk approximates the plasma elimination half-life of 30 hours. The estimated daily infant dose of fluconazole from breast milk (assuming mean milk consumption of 150 ml/kg/day) based on the mean peak milk concentration is 0.39 mg/kg/day, which is approximately 40% of the recommended neonatal dose (<2 weeks of age) or 13% of the recommended infant dose for mucosal candidiasis.

Breast-feeding may be maintained after a single dose of 150 mg fluconazole. Breast-feeding is not recommended after repeated use or after high-dose fluconazole. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for Diflucan and any potential adverse effects on the breastfed child from Diflucan or from the underlying maternal condition.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Experience with fluconazole indicates that therapy is unlikely to impair a patient ability to drive or use machinery.

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

SUPPLY

Diflucan® is available as:
IV Infusion (2 mg/ml) Box of 1 glass infusion vials @ 100 ml
Reg. No. DKI9590400243A1

STORE IN DRY PLACE BELOW 30°C.

HARUS DENGAN RESEP DOKTER

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