IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PA0019/044/009
Case No: 2035051

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Pfizer Limited

Ramsgate Road, **Sandwich**, **Kent CT13 9NJ**, **England**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Diflucan Solution for Infusion 2 mg/ml (400mg/200ml)

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **10/05/2007** until **21/08/2009**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Diflucan Solution for Infusion 2 mg/ml (400mg/200ml)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml contains 2mg fluconazole (400mg/200ml).

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion
A clear, sterile, colourless solution.

4 CLINICAL PARTICULARS

4.1 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.

Diflucan is indicated for:

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

2. Mucosal candidiasis. These include oropharyngeal, oesophageal, 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.

3. Systemic candidiasis including candidaemia, disseminated candidiasis and other forms of invasive candidal infection. These include infections of the peritoneum, endocardium and pulmonary and urinary tracts. Candidal infections in patients with malignancy, in intensive care units or those receiving cytotoxic or immunosuppressive therapy, may be treated.

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

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

6. Dermatomycoses including tinea pedis, tinea corporis, tinea cruris, tinea versicolor and candida infections, only where these conditions are resistant to first line therapy or where occurrence is in immunocompromised patients.

4.2 Posology and method of administration

Diflucan may be administered either orally or by intravenous infusion at a rate of approximately 5-10ml/min, the route

being dependent on the clinical state of the patient. On transferring from the intravenous route to the oral route or vice versa, there is no need to change the daily dose.
Diflucan Intravenous Infusion is formulated in 0.9% sodium chloride solution, each 200mg (100 ml bottle) containing 15mmol each of Na^+ and Cl^-.

The daily dose of Diflucan 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 usually require maintenance therapy to prevent relapse.

Use in adults

1. Candidal vaginitis or balanitis. The usual dosage is 150mg as a single dose.

2. Mucosal Candidiasis
   Oropharyngeal candidiasis: The recommended dose is 50mg once daily for 7 to 14 days. Treatment may continue for a longer period if the physician so requires.

Atrophic oral candidiasis associated with dentures: the recommended dose is 50mg once daily for 14 days administered concurrently with local antiseptic measures to the denture.

For other candidal infections of the mucosa, (except genital candidiasis see above), e.g. oesophagitis, non-invasive bronchopulmonary infections, candiduria, mucocutaneous candidiasis etc., the recommended dose is 50mg daily, given for 14 to 30 days.

In unusually difficult cases of mucosal candidal infections the dose may be increased to 100mg daily.

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

4a. For cryptococcal meningitis and cryptococcal infections at other sites: the recommended dose is 400mg on the first day followed by 200mg - 400mg 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.

4b. For the prevention of relapse of cryptococcal meningitis in patients with AIDS, after the patient receives a full course of primary therapy, Diflucan may be administered indefinitely at a daily dose of 100 - 200mg.

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

6. For dermal infections including tinea pedis, corporis, cruris and candida infections the recommended dosage is 150mg once weekly or 50mg 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 50mg once daily for 2 to 4 weeks.

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

For children with impaired renal function, see dosing in 'Use in patients with impaired renal function'.

Children over four weeks of age: Mucosal candidiasis: the recommended dosage of Diflucan is 3mg/kg daily. A loading dose of 6mg/kg may be used on the first day to achieve steady state levels more rapidly.

Systemic candidiasis and cryptococcal infection: the recommended dosage of fluconazole is 6-12mg/kg daily, depending on the severity of disease.

For the prevention of fungal infections in immunocompromised patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, the dose should be 3-12mg/kg daily depending on the extent and duration of the induced neutropenia.(See adult dosing).

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

Use in the elderly: The normal dose should be used if there is no evidence of renal impairment. In patients with renal impairment (creatinine clearance less than 50 ml/min) the dosage schedule should be adjusted as described below.

Use in patients with impaired renal function: Fluconazole is excreted predominantly in the urine as unchanged drug. No adjustments in single dose therapy are required. In patients (including children) with impaired renal function who will receive multiple doses of Diflucan, the normal recommended dose (according to indication) should be given on day 1, followed by a daily dose 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

Compatibility of Intravenous Infusion

Although further dilution is unnecessary Diflucan Intravenous Infusion is compatible with the following administration fluids:

a) Dextrose 20%
b) Ringer's solution
c) Hartmann's solution
d) Potassium chloride in dextrose
e) Sodium bicarbonate 4.2%
f) Aminofusin
g) Peritoneal dialysis solution
h) Normal saline (0.9%)

Diflucan 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 drug prior to infusion is not recommended.

4.3 Contraindications

Diflucan should not be used in patients with known hypersensitivity to fluconazole or to related azole compounds, or any other ingredient in the formulation.

Co-administration of terfenadine is contra-indicated in patients receiving Diflucan at multiple doses of 400mg per day or higher based upon results of a multiple dose interaction study.

Co-administration of cisapride is contraindicated in patients receiving Diflucan. (See 'Interaction with other medicinal products and other forms of interaction').

4.4 Special warnings and precautions for use

In some patients, particularly those with serious underlying diseases such as AIDS and cancer, abnormalities of hepatic, renal, haematological and other biochemical function tests have been observed during treatment with Diflucan but the clinical significance and relationship to treatment is uncertain.

Diflucan has been associated with rare cases of serious hepatic toxicity including fatalities, primarily in patients with serious underlying medical conditions. In cases of Diflucan-associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of patient has been observed. Diflucan hepatotoxicity has usually been reversible on discontinuation of therapy. Patients who develop abnormal liver function tests during Diflucan therapy should be monitored for the development of more serious hepatic injury. Diflucan should be discontinued if clinical signs or symptoms consistent with liver disease develop that may be attributable to Diflucan.

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 drugs. If a rash develops in a patient treated for a superficial fungal infection which is considered attributable to Diflucan, further therapy with this agent should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and Diflucan discontinued if bullous lesions or erythema multiforme develop.

There is little information on safety in long-term use.

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. 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.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Hydrochlorothiazide: In a kinetic 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.

Anticoagulants: In an interaction study, fluconazole increased the prothrombin time (12%) after warfarin administration in healthy males. In post-marketing experiences, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria, and melaena) have been reported, in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. Prothrombin time in patients receiving coumarin-type anticoagulants should be carefully monitiored.

Azithromycin: An open-label, randomised, 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.

Sulphonylureas: Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulphonylureas (chlorpropamide, glibenclamide, glipizide and tolbutamide) in healthy volunteers. Fluconazole and oral sulphonylureas may be co-administered to diabetic patients, but the possibility of a hypoglycaemic episode should be borne in mind.

Phenytoin: Concomitant administration of fluconazole and phenytoin may increase the levels of phenytoin to a clinically 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.

Oral contraceptives: Threekinetic studies with combined oral contraceptives have been performed using multiple doses of fluconazole. There were no relevant effects on either hormone level in the 50mg fluconazole study, while at 200mg daily the AUCs of ethinyl estradiol and levonorgestrel were increased 40% and 24% respectively. In a 300 mg daily fluconazole study, the AUCs of ethinyl estradiol and norethindrone were increased by 24% and 13% respectively. Thus multiple dose use of fluconazole at these doses is unlikely to have an effect on the efficacy of the combined oral contraceptive.

Endogenous steroid: Fluconazole 50mg daily does not affect endogenous steroid levels in females. 200-400 mg daily has no clinically significant effect on endogenous steroid levels or on ACTH stimulated response in healthy male volunteers.

Ciclosporin: A kinetic study in renal transplant patients found fluconazole 200mg daily to slowly increase ciclosporin concentrations. However, in another multiple se study with 100mg daily, fluconazole did not affect ciclosporin levels in patients with bone marrow transplants. Ciclosporin plasma concentration monitoring in patients receiving fluconazole is recommended.

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

Tacrolimus: There have been reports that an interaction exists when fluconazole is administered concomitantly with tacrolimus, leading to increased serum levels of tacrolimus. There have been reports of nephrotoxicity in patients to whom fluconazole and tacrolimus were co-administered. Patients receiving tacrolimus and fluconazole concomitantly should be carefully monitored.

Rifabutin*:* There have been reports that an interaction exists when fluconazole is administered concomitantly with rifabutin, leading to increased serum levels of rifabutin. 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.

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 200mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. Another study at a 400mg and 800mg daily dose of fluconazole demonstrated that fluconazole taken in doses of 400mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. The combined use of fluconazole at doses of 400mg or greater with terfenadine is contra-indicated. (See 'Contra-indications'.) The co-administration of fluconazole at doses lower than 400mg per day with terfenadine should be carefully monitored.

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 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 'Contra-indications'.)

The use of fluconazole in patients concurrently taking astemizole or other drugs metabolised by the cytochrome P450 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.

Zidovudine: Two kinetic studies resulted in increased levels of zidovudine most likely caused by the decreased conversion of zidovudine to its major metabolite. One study determined zidovudine levels in AIDS or ARC patients before and following fluconazole 200mg daily for 15 days. There was a significant increase in zidovudine AUC (20%). A second randomised, two-period, two-treatment cross-over study examined zidovudine levels in HIV infected patients. On two occasions, 21 days apart, patients received zidovudine 200mg every eight hours either with or without fluconazole 400mg daily for seven days.

The AUC of zidovudine significantly increased (74%) during co-administration with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions.

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 that such interactions may occur.

4.6 Pregnancy and lactation

There are no adequate and well controlled studies in pregnant women. There have been reports of multiple congential abnormalities in infants whose mothers were being treated for 3 or more months with high dose (400 - 800mg/day) fluconazole therapy for coccidioidomycosis. The relationship between fluconazole use and these events is unclear.

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 foetus.

Use during lactation: Fluconazole is found in human breast milk at concentrations similar to plasma, hence its use in nursing mothers is not recommended.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Fluconazole is generally well tolerated. The most common undesirable effects observed during clinical trials and associated with fluconazole are:

Nervous System Disorders: Headache.

Skin and Subcutaneous Tissue Disorders: Rash.

Gastrointestinal Disorders: Abdominal pain, diarrhoea, flatulence, nausea.

In some patients, particularly those with serious underlying diseases such as AIDS and cancer, changes in renal and haematological function test results and hepatic abnormalities have been observed during treatment with fluconazole and comparative agents, but the clinical significance and relationship to treatment is uncertain (see Section 4.4 '**Special warnings and precautions for use**").

Hepatobiliary Disorders: Hepatic toxicity including rare cases of fatalities, elevated alkaline phosphatase, elevated bilirubin, elevated serum glutamic-oxaloacetic transaminase, elevated serum glutamic-pyruvic transaminase.

In addition, the following undesirable effects have occurred during post-marketing:

Nervous System Disorders: Dizziness, seizures, taste perversion.

Skin and Subcutaneous Tissue Disorders: Alopecia, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Gastrointestinal Disorders: Dyspepsia, vomiting.

Blood and Lymphatic System Disorders: Leucopenia including neutropenia and agranulocytosis, thrombocytopenia.

Immune System Disorders: Anaphylaxis (including angioedema, face oedema, pruritus, urticaria).

Hepatobiliary Disorders: Hepatic failure, hepatitis, hepatocellular necrosis, jaundice.

Metabolism and Nutrition Disorders: Hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia.

Cardiac Disorders: QT prolongation, torsade de pointes (see section 4.4 **Special warnings and precautions for use**.)

4.9 Overdose

There have been reports of overdosage with fluconazole and in one case a 42 year-old patient infected with human immunodeficiency virus developed hallucinations and exhibited paranoid behaviour after reportedly ingesting 8200mg of fluconazole. The patient was admitted to the hospital and his condition resolved within 48 hours.

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

As 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

Pharmacotherapeutic group: Triazole derivatives, ATC code J02AC.
Fluconazole, a member of the triazole class of antifungal agents, is a potent and selective inhibitor of fungal enzymes necessary for the synthesis of ergosterol. Fluconazole shows little pharmacological activity in a wide range of animal studies. Some prolongation of pentobarbital sleeping times in mice (p.o.), increased mean arterial and left ventricular blood pressure and increased heart rate in anaesthetised cats (i.v.) occurred. Inhibition of rat ovarian aromatase was observed at high concentrations.

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 *Cryptococcus 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 dermatitides;* with *Coccidoides immitis,* including intracranial infection and with *Histoplasma capsulatum* in normal and immunosuppressed animals.

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

Fluconazole is highly specific for fungal cytochrome P-450 dependent enzymes. Fluconazole 50mg 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 200-400 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 50mg do not affect its metabolism.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral routes. 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 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 level by day 2. The apparent volume of distribution approximates to total body water. Plasma protein binding is low (11-12%).

Fluconazole achieves good penetration into 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 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 50mg once daily, the concentration of fluconazole after 12 days was 73 microgram/g and 7 days after cessation of treatment the concentration was still 5.8 microgram/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 genital candidiasis and once-daily dosing in the treatment of all other indicated fungal infections.

A study compared the saliva and the plasma concentrations of a single fluconazole 100mg dose administration 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 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.

Pharmacokinetics in Children

In children, the following pharmacokinetic data have been reported:

Age studied	**Dose (mg/kg)**	**Half-life (hours)**	**AUC (microgram.h/ml)**
11 days - 11 months	Single-IV 3mg/kg	23	110.1
9 months - 13 years	Single-Oral 2mg/kg	25.0	94.7
9 months - 13 years	Single-Oral 8mg/kg	19.5	362.5
5 years - 15 years	Multiple-IV 2mg/kg	17.4*	67.4
5 years - 15 years	Multiple-IV 4mg/kg	15.2*	139.1
5 years - 15 years	Multiple-IV 8mg/kg	17.6*	196.7
Mean Age 7 Years	Multiple-Oral 3mg/kg	15.5	41.6

*Denotes final day

In premature new-borns (gestational age around 28 weeks), intravenous administration of fluconazole of 6mg/kg was given every third day for a maximum of five doses while the premature new-borns remained in the intensive care unit.

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 which 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 mcg/ml and occurred at 1.3 hours post dose. The mean AUC was 76.4 ± 20.3 mcg·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 AUC or C_{max}. In addition, creatinine clearance (74 ml/min), the percent of drug 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 characteristic of this group. A plot of each subject's terminal elimination half-life versus creatinine clearance compared with 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 observed in the elderly subjects compared with normal young male volunteers are due to the decreased kidney function that is expected in the elderly.

5.3 Preclinical safety data

Reproductive toxicity: There were no fetal effects at 5 or 10mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50mg/kg and higher doses. At doses ranging from 80mg/kg (approximately 20-60x the recommended human dose) to 320 mg/kg embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate and abnormal cranio-facial ossification. These effects are consistent with the inhibition of oestrogen sysnthesis in rats and may be a result of known effects of lowered oestrogen on pregnancy, organogenesis and parturition.

Carcinogenesis Fluconazole showed no evidence of carcinogenic potential in mice and rats treated orally for 24 months at doses of 2.5, 5 or 10mg/kg/day. Male rats treated with 5 and 10mg/kg/day had an increased incidence of hepatocellular adenomas.

Mutagenesis: Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of *S.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 1000µg/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, 10 or 20mg/kg or with parenteral doses of 5, 25 or 75mg/kg, although the onset of parturition was slightly delayed at 20mg/kg p.o. In an intravenous perinatal study in rats at 5, 20 and 40mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20mg/kg and 40mg/kg, but not at 5mg/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 oestrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections

6.2 Incompatibilities

Although no specific incompatibilities have been noted, mixing with any other drug prior to infusion is not recommended.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

Do not store above 30^{o}C.
Do not freeze.

6.5 Nature and contents of container

250ml, Type I glass infusion vial sealed with a rubber stopper and an aluminium overcap.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Do not freeze. The infusion does not contain any preservative. It is for single use only. Discard any remaining solution.

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 19/44/9

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 August 1989

Date of last renewal: 22 August 2004

10 DATE OF REVISION OF THE TEXT

May 2007