

FLUCONAZOLE 2MG/ML SOLUTION FOR INFUSION

PL 19960/0024-5

UKPAR

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FLUCONAZOLE 2MG/ML SOLUTION FOR INFUSION

PL 19960/0024-5

LAY SUMMARY

The MHRA granted Opal Healthcare Limited Marketing Authorisations (licences) for the medicinal products Fluconazole 2mg/ml Solution for Infusion (PL 19960/0024-5). These are prescription-only medicine (POM).

Fluconazole Solution for Infusion belongs to a group of medicines called anti-fungal agents. It is used to treat infections caused by fungi/yeasts. It may also be used to stop you from getting a fungal infection.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Fluconazole 2mg/ml Solution for Infusion outweigh the risks, hence marketing Authorisations have been granted.

FLUCONAZOLE 2MG/ML SOLUTION FOR INFUSION

PL 19960/0024-5

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal products Fluconazole 2 mg/ml, Solution for Infusion (PL 19960/0024-5) to Opal Healthcare Limited on 23rd May 2007. These products are prescription-only medicine (POM).

These are abridged applications for Fluconazole 2mg/ml Solution for Infusion submitted, by Opal Healthcare Limited, under article 10.1 (a) (iii) of Directive 2001/83/EC (first paragraph). These products are claiming to be generic medicinal product of, Diflucan Intravenous Infusion, PL 00057/0315, marketed in the UK by Pfizer Ltd. The reference product marketing authorisation was granted on 31st August 1989 and so the 10-year period of data exclusivity has expired.

Fluconazole is a triazole antifungal indicated for the treatment of a range of candidal and tinea infections and for cryptococcal infections including fungal meningitis. Intravenous administration is used in the treatment of invasive candidal infections and cryptococcal infections, the prevention of relapse of cryptococcal meningitis in AIDS patients and the prevention of fungal infections in immunocompromised patients following cytotoxic chemotherapy or radiotherapy, with doses of 50-400mg daily, according to the severity of infection or infection risk.

PHARMACEUTICAL ASSESSMENT

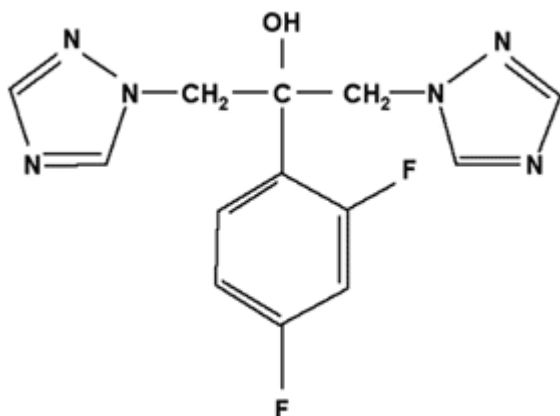
DRUG SUBSTANCE

Nomenclature

INN: Fluconazole

CAS number: 86386-73-4

Structure



Molecular formula: C₁₃H₁₂F₂N₆O

Molecular Weight: 306.27

General Properties

White crystalline powder; slightly soluble in water, freely soluble in methanol. Two crystalline polymorphic forms are reported.

A letter of access has been provided.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

All potential known impurities have been identified and characterised.

Active fluconazole is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data has been generated.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely sodium chloride and water for injections. All excipients used comply with their respective European Pharmacopoeial monograph.

Satisfactory specifications and Certificates of Analysis have been provided for all excipients. No materials of animal or human origin are contained in or used in the manufacture of this product. No genetically modified organisms are included in these products.

Impurity profiles

Satisfactory information was provided on levels of impurities in the proposed product.

Manufacture

A description and flow-chart of the manufacturing method have been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

Product is packaged in Type I clear glass vials, closed with chlorobutyl rubber stoppers (Type I) and sealed with an aluminium overcap and plastic flip-offs. Specifications and Certificates of Analysis for all packaging used have been provided. This is satisfactory. All primary product packaging comply with EU legislation regarding contact with solutions for parenteral and ophthalmic use Directive 2002/72/EC (as amended).

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years and storage conditions of "Store below 30°C" and "Do not Freeze" have been set, which are satisfactory.

SPC, PIL, Labels

The SPC, PIL and labels are acceptable.

The PIL is in compliance with current guidelines. The marketing authorisation holder has provided a commitment to update the marketing authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 1st July 2008.

Conclusion

It is recommended that Marketing Authorisation is granted for these applications.

The proposed products are considered to be generic medicinal products to the reference product with respect to qualitative and quantitative content of the active substance and pharmaceutical form. It was not necessary to demonstrate bioequivalence.

PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none is required for an application of this type.

CLINICAL ASSESSMENT

1 INDICATIONS

These are national marketing authorisations for a medicinal products containing fluconazole, in solution of 2mg/ml for Infusion.

The applications are submitted by Opal Healthcare under Article 10.1 of Directive 2001/83/EC as amended, claiming to be generic medicinal products of the UK brand leader, Diflucan, (Pfizer, PL 00057/0135).

The original product authorised for not less than 6/10 years in the EEA are Diflucan Intravenous Infusion 2mg/ml authorised to Pfizer Ltd in the UK in August 1989.

2 BACKGROUND

Fluconazole is a member of the triazole class of antifungal agents. It is a potent selective inhibitor of fungal enzymes necessary for the synthesis of ergosterol.

It is highly active against a wide range of fungal infections, especially those caused by candida and cryptococci and also against dermatophytes.

3 INDICATIONS

The proposed indications are in line with the reference product.

4 DOSE & DOSE SCHEDULE

The dose advice is fully in line with the SPC for the UK reference product.

5 CLINICAL PHARMACOLOGY

No new data are submitted and none are required for this type of application. A bioequivalence study is not required.

6 EFFICACY

The efficacy profile of fluconazole is well established. No new efficacy data are required for these applications.

7 SAFETY

No new data are submitted and none are required for this type of application.

8 EXPERT REPORTS

A satisfactory expert report is provided by an appropriately qualified individual.

9 PATIENT INFORMATION LEAFLET (PIL)

The PIL is satisfactory.

10 LABELLING

The labelling is satisfactory.

11 SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPC is fully in line with that for the reference product.

12 DISCUSSION

The SPC, PIL and labelling are fully in line with that for the reference product. A bioequivalence study is not required.

13 CONCLUSION

There are no medical objections to the granting of a product licence for this preparation.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Fluconazole 2mg/ml solution for Infusion are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for application of this type.

EFFICACY

There was no need for bioequivalence to be demonstrated between the applicant's Fluconazole 2mg/ml solution for infusion and the originator product.

No new data were submitted and none are required for application of this type.

The SPC, PIL and labelling are satisfactory and consistent with that for reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with Fluconazole is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is considered to be positive.

FLUCONAZOLE 2MG/ML SOLUTION FOR INFUSION**PL 19960/0024-5****STEPS TAKEN FOR ASSESSMENT**

1	The MHRA received the marketing authorisation application on 24 th October 2004
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 12 th November 2004
3	Following assessment of the application the MHRA requested further information relating to the quality dossiers on 22 nd April 2005, 4 th May 2005, 15 th July 2005, 9 th September 2005, 12 th July 2006 and to the clinical dossier on 10 th March 2005, and 2 nd March 2007
4	The applicant responded to the MHRA's requests, providing further information on the quality dossier on 19 th August 2005, 24 th January 2006, and 3 rd April 2007 and clinical dossier 12 th April 2005, and 21 st of March 2007
5	The applications were determined on 23 rd May 2007

FLUCONAZOLE 2MG/ML SOLUTION FOR INFUSION**PL 19960/0024-5****STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

Date submitted	Application type	Scope	Outcome
25/07/2007	Type IB	To amend the specification of the Drug Substance	Approved 27/09/2007
25/07/2007	Type IB	To extend the shelf life	Approved 18/01/2008
25/07/2007	Type II	To introduce new batch size	Approved 22/11/2007
07/06/2007	National	Label and PIL submission for self certification	Approved 27/6/2007

SUMMARY OF PRODUCT CHARACTERISTICS**1 NAME OF THE MEDICINAL PRODUCT**

Fluconazole 2 mg/ml, Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 2mg fluconazole in a 0.9% sodium chloride solution.

Each 50mL bottle contains 100mg fluconazole.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Infusion.

Fluconazole Solution for Infusion is formulated in 0.9% sodium chloride solution.

Each 100mg (50mL infusion vial) contains 7.7 mmol each of Na⁺ and Cl⁻.

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.

Fluconazole Solution for Infusion is indicated for the treatment of the following conditions:

Genital candidiasis. Vaginal candidiasis, acute or recurrent. Candidal balanitis. The treatment of partners who present with symptomatic genital candidiasis should be considered.

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.

Tinea pedis, tinea corporis, tinea cruris, tinea versicolor and dermal *Candida* infections. Fluconazole Solution for Infusion is not indicated for nail infections.

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.

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 Solution for Infusion can be used as maintenance therapy to prevent relapse of cryptococcal disease in patients with AIDS.

For the prevention of fungal infections in immunocompromised patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, including bone marrow transplant patients.

4.2 Posology and method of administration

Fluconazole Solution for Infusion may be administered by intravenous infusion at a rate of approximately 5-10 ml/min. On transferring from the intravenous route to the oral route or *vice versa*, there is no need to change the daily dose.

The daily dose of Fluconazole Solution for Infusion 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:

a) *Mucosal Candidiasis*

Oropharyngeal candidiasis – the usual dose is 50mg once daily for 7-14 days. Treatment should not normally exceed 14 days except in severely immunocompromised patients.

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

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

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

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

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

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

d.2) *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 daily dose of 100-200mg.

e) *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 50 to 400mg 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 such as during bone marrow transplantation, the recommended dose is 400mg once daily. Fluconazole Solution for Infusion 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 mm³.

Use in children:

As with similar infections in adults, the duration of treatment is based on the clinical and mycological response. Fluconazole 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:

The recommended dose of fluconazole for mucosal candidiasis is 3mg/kg daily. A loading dose of 6mg/kg may be used on the first day to achieve steady state levels more rapidly.

For the treatment of systemic candidiasis and cryptococcal infections, the recommended dosage is 6-12 mg/kg daily, depending on the severity of the 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 3-12 mg/kg daily, depending on the extent and duration of the induced neutropenia (see adult dosing).

A maximum dosage of 400mg daily should not be exceeded in children.

Despite extensive data supporting the use of fluconazole in children there are limited data available on the use of fluconazole for genital candidiasis in children below 16 years. Use at present is not recommended unless antifungal treatment is imperative and no suitable alternative agent exists.

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.

A maximum dosage of 12 mg/kg every 72 hours should not be exceeded in children in the first two weeks of life. For children between 3 and 4 weeks of life, 12 mg/kg every 48 hours should not be exceeded.

For children with impaired renal function, the daily dose should be reduced in accordance with the dosing for adults.

To facilitate accurate measurement of doses less than 10mg, fluconazole should preferably be administered to children in hospital using the intravenous infusion, depending on the clinical condition of the child.

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 50ml/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 fluconazole, 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
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> 50	100%
≤ 50 (no dialysis)	50%
Regular dialysis	One dose after each dialysis

Compatibility of intravenous infusion:

Although further dilution is unnecessary Fluconazole Solution for Infusion is compatible with the following administration fluids:

Dextrose Solution 20%
 Ringer's Solution
 Ringer's Lactate Solution
 Potassium Chloride 1% in Dextrose Solution 5%
 Sodium Bicarbonate 4.2%
 Sodium Chloride Solution 0.9%

Fluconazole Solution for Infusion may be infused through an existing line with one of the above listed fluids. No specific incompatibilities have been noted, although mixing with any other drug prior to infusion is not recommended.

4.3 Contraindications

Fluconazole Solution for Infusion 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 or cisapride is contra-indicated in patients receiving Fluconazole Solution for Infusion. (See "Interactions 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 in haematologic, hepatic, renal and other biochemical function test results have been observed during treatment with fluconazole but the clinical significance and relationship to treatment is uncertain.

Very rarely, patients who died with severe underlying disease and who had received multiple doses of fluconazole had post-mortem findings, which included hepatic necrosis. These patients were receiving multiple concomitant medications, some known to be potentially hepatotoxic, and/or had underlying diseases, which could have caused the hepatic necrosis.

In cases of hepatotoxicity, no obvious relationship to total daily dose of fluconazole, duration of therapy, sex or age of the patient has been observed; the abnormalities have usually been reversible on discontinuation of fluconazole therapy.

As a causal relationship with fluconazole cannot be excluded, 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 during treatment with fluconazole.

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 fluconazole, further therapy with this agent should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and Fluconazole Solution for Infusion discontinued if bullous lesions or erythema multiforme develop.

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

4.5 Interaction with other medicinal products and other forms of interaction

The following drug interactions relate to the use of multiple-dose fluconazole, and the relevance to single-dose 150mg fluconazole has not yet been established:

Rifampicin

Concomitant administration of fluconazole and rifampicin 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 experience, 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 monitored.

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

Two kinetics 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 ethinyloestradiol 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.

Endogenous steroid

Fluconazole 50mg daily does not affect endogenous steroid levels in females: 200-400mg 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 dose 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.

Terfenadine

Because of the occurrence of serious dysrhythmias secondary to prolongation of the QTc interval in patients receiving other azole antifungals in conjunction with terfenadine, interactions 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 multiple doses of 400mg per day or greater significantly increased plasma levels of terfenadine when taken concomitantly. There have been spontaneously reported cases of palpitations, tachycardia, dizziness, and chest pain in patients taking concomitant fluconazole and terfenadine where the relationship of the reported adverse events to drug therapy or underlying medical conditions was not clear. Because of the potential seriousness of such an interaction, it is recommended that terfenadine not be taken in combination with fluconazole. (See "Contra-indications")

Cisapride

There have been reports of cardiac events including torsades de pointes in patients to whom fluconazole and cisapride were co-administered. In most of these cases, the patients appear to have been predisposed to arrhythmias or had serious underlying illnesses, and the relationship of the reported events to a possible fluconazole-cisapride drug interaction is unclear. Because of the potential seriousness of such an interaction, co-administration of cisapride is contra-indicated in patients receiving fluconazole. (See "Contra-indications")

Zidovudine

Two kinetics 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 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.

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.

Tacrolimus

There have been reports that an interaction exists when fluconazole is administered concomitantly with tacrolimus, leading to increased serum levels to 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.

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.

Interactions 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

Use during pregnancy

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 (400-800 mg/day) fluconazole therapy for coccidioidomycosis. The relationship between fluconazole and these events is unclear.

Accordingly, Fluconazole Solution for Infusion should not be used in pregnancy, or in women of childbearing potential unless adequate contraception is employed.

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 fluconazole 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 side effects observed during clinical trials and associated with fluconazole are:

Central and Peripheral Nervous System: headache.

Dermatological: rash.

Gastrointestinal: abdominal pain, diarrhoea, flatulence and 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 "Special warnings and special precautions for use")

Liver/Biliary: hepatic toxicity including rare cases of fatalities, elevated alkaline phosphatase, elevated bilirubin, elevated SGOT, elevated SGPT.

In addition, the following adverse events have occurred during post-marketing:

Central and Peripheral Nervous System: dizziness, seizures.

Dermatological: alopecia, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Gastrointestinal: dyspepsia, vomiting.

Haematopoietic and Lymphatic: leukopenia including neutropenia and agranulocytosis, thrombocytopenia.

Immunological Anaphylaxis: (including angiodema, face oedema, pruritus)..

Liver/Biliary: hepatic failure, hepatitis, hepatocellular necrosis, jaundice.

Metabolic/Nutritional: hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia.

Other senses: taste perversion.

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, unverified by his physician. 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**

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.

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 *Microsporium* 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 *Coccidioides 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 childbearing age. Fluconazole 200-400mg daily has no clinically significant effect on endogenous steroid levels or on ACTH stimulated response in healthy male volunteers. Interaction studies with antipyrene 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 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 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. 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% of 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, epidermis-dermis and eccrine sweat. 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 for other indications.

Pharmacokinetics in Children

In children, the following pharmacokinetic data have been reported:

Age studied	Dose (mg/kg)	Half-life (hours)	AUC ($\mu\text{g.h/ml}$)
11 days-11 months	Single – IV 3 mg/kg	23	110.1
9 months –13 years	Single – Oral 2 mg/kg	25.0	94.7
9 months –13 years	Single – Oral 8 mg/kg	19.5	362.5
5 years - 15 years	Multiple – Oral 2 mg/kg	17.4*	67.4
5 years -15 years	Multiple – Oral 4 mg/kg	15.2*	139.1
5 years -15 years	Multiple – Oral 8 mg/kg	17.6*	196.1
5 years -15 years	Multiple – IV 3 mg/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 days 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 ($\mu\text{.h/ml}$) 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 mean of 1184 (range 510-2130) on day 7 and 1328 (range 1040-1680) on day 13.

5.3 Preclinical safety data

Reproductive toxicity: 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 320mg/kg embryoletality 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 synthesis 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
Hydrochloric acid (pH adjuster)

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

3 years.

6.4 Special precautions for storage

Store below 30°C.

Do not freeze.

6.5 Nature and contents of container

Fluconazole Solution for Infusion is supplied in a 50mL clear Type I glass infusion vials, closed with a rubber stopper and sealed with an aluminium overcap and a plastic flip-off.

6.6 Special precautions for disposal

The infusion does not contain any preservative. It is for single use only. Discard any remaining solution according to guidelines of the local authorities.

Do not use if container is found leaking or solution is not clear.

Solutions containing visible solid particles must not be used.

Although further dilution is unnecessary, Fluconazole Solution for Infusion is compatible with the following administration fluids:

Dextrose Solution 20%
Ringer's Solution
Ringer's Lactate Solution
Potassium Chloride 1% in Dextrose Solution 5%
Sodium Bicarbonate 4.2%
Sodium Chloride Solution 0.9%

7 MARKETING AUTHORISATION HOLDER

Opal Healthcare Limited
Kingswood Court Business Park
Long Meadow
South Brent
Devon TQ10 9YS

8 MARKETING AUTHORISATION NUMBER(S)

PL 19960/0024

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/05/2007

10 DATE OF REVISION OF THE TEXT

23/05/2007

1 NAME OF THE MEDICINAL PRODUCT

Fluconazole 2 mg/ml, Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 2mg fluconazole in a 0.9% sodium chloride solution.

Each 100mL bottle contains 200mg fluconazole.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Infusion.

Fluconazole Solution for Infusion is formulated in 0.9% sodium chloride solution.

Each 200mg (100mL infusion vial) contains 15.4 mmol each of Na⁺ and Cl⁻.

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.

Fluconazole Solution for Infusion is indicated for the treatment of the following conditions:

Genital candidiasis. Vaginal candidiasis, acute or recurrent. Candidal balanitis. The treatment of partners who present with symptomatic genital candidiasis should be considered.

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.

Tinea pedis, tinea corporis, tinea cruris, tinea versicolor and dermal *Candida* infections. Fluconazole Solution for Infusion is not indicated for nail infections.

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.

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 Solution for Infusion can be used as maintenance therapy to prevent relapse of cryptococcal disease in patients with AIDS.

For the prevention of fungal infections in immunocompromised patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, including bone marrow transplant patients.

4.2 Posology and method of administration

Fluconazole Solution for Infusion may be administered by intravenous infusion at a rate of approximately 5-10 ml/min. On transferring from the intravenous route to the oral route or *vice versa*, there is no need to change the daily dose.

The daily dose of Fluconazole Solution for Infusion 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:

a) *Mucosal Candidiasis*

Oropharyngeal candidiasis – the usual dose is 50mg once daily for 7-14 days. Treatment should not normally exceed 14 days except in severely immunocompromised patients.

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

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

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

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

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

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

d.2) *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 daily dose of 100-200mg.

e) *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 50 to 400mg 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 such as during bone marrow transplantation, the recommended dose is 400mg once daily. Fluconazole Solution for Infusion 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 mm³.

Use in children:

As with similar infections in adults, the duration of treatment is based on the clinical and mycological response. Fluconazole 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:

The recommended dose of fluconazole for mucosal candidiasis is 3mg/kg daily. A loading dose of 6mg/kg may be used on the first day to achieve steady state levels more rapidly.

For the treatment of systemic candidiasis and cryptococcal infections, the recommended dosage is 6-12 mg/kg daily, depending on the severity of the 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 3-12 mg/kg daily, depending on the extent and duration of the induced neutropenia (see adult dosing).

A maximum dosage of 400mg daily should not be exceeded in children.

Despite extensive data supporting the use of fluconazole in children there are limited data available on the use of fluconazole for genital candidiasis in children below 16 years. Use at present is not recommended unless antifungal treatment is imperative and no suitable alternative agent exists.

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.

A maximum dosage of 12 mg/kg every 72 hours should not be exceeded in children in the first two weeks of life. For children between 3 and 4 weeks of life, 12 mg/kg every 48 hours should not be exceeded.

For children with impaired renal function, the daily dose should be reduced in accordance with the dosing for adults.

To facilitate accurate measurement of doses less than 10mg, fluconazole should preferably be administered to children in hospital using the intravenous infusion, depending on the clinical condition of the child.

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 50ml/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 fluconazole, 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	One dose after each dialysis

Compatibility of intravenous infusion:

Although further dilution is unnecessary Fluconazole Solution for Infusion is compatible with the following administration fluids:

Dextrose Solution 20%
Ringer's Solution
Ringer's Lactate Solution
Potassium Chloride 1% in Dextrose Solution 5%
Sodium Bicarbonate 4.2%
Sodium Chloride Solution 0.9%

Fluconazole Solution for Infusion may be infused through an existing line with one of the above listed fluids. No specific incompatibilities have been noted, although mixing with any other drug prior to infusion is not recommended.

4.3 Contraindications

Fluconazole Solution for Infusion 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 or cisapride is contra-indicated in patients receiving Fluconazole Solution for Infusion. (See "Interactions 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 in haematologic, hepatic, renal and other biochemical function test results have been observed during treatment with fluconazole but the clinical significance and relationship to treatment is uncertain.

Very rarely, patients who died with severe underlying disease and who had received multiple doses of fluconazole had post-mortem findings, which included hepatic necrosis. These patients were receiving multiple concomitant medications, some known to be potentially hepatotoxic, and/or had underlying diseases, which could have caused the hepatic necrosis.

In cases of hepatotoxicity, no obvious relationship to total daily dose of fluconazole, duration of therapy, sex or age of the patient has been observed; the abnormalities have usually been reversible on discontinuation of fluconazole therapy.

As a causal relationship with fluconazole cannot be excluded, 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 during treatment with fluconazole.

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 fluconazole, further therapy with this agent should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and Fluconazole Solution for Infusion discontinued if bullous lesions or erythema multiforme develop.

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

4.5 Interaction with other medicinal products and other forms of interaction

The following drug interactions relate to the use of multiple-dose fluconazole, and the relevance to single-dose 150mg fluconazole has not yet been established:

Rifampicin

Concomitant administration of fluconazole and rifampicin 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 experience, 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 monitored.

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

Two kinetics 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 ethinyloestradiol 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.

Endogenous steroid

Fluconazole 50mg daily does not affect endogenous steroid levels in females: 200-400mg 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 dose 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.

Terfenadine

Because of the occurrence of serious dysrhythmias secondary to prolongation of the QTc interval in patients receiving other azole antifungals in conjunction with terfenadine, interactions 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 multiple doses of 400mg per day or greater significantly increased plasma levels of terfenadine when taken concomitantly. There have been spontaneously reported cases of palpitations, tachycardia, dizziness, and chest pain in patients taking concomitant fluconazole and terfenadine where the relationship of the reported adverse events to drug therapy or underlying medical conditions was not clear. Because of the potential seriousness of such an interaction, it is recommended that terfenadine not be taken in combination with fluconazole. (See “Contra-indications”)

Cisapride

There have been reports of cardiac events including torsades de pointes in patients to whom fluconazole and cisapride were co-administered. In most of these cases, the patients appear to have been predisposed to arrhythmias or had serious underlying illnesses, and the relationship of the reported events to a possible fluconazole-cisapride drug interaction is unclear. Because of the potential seriousness of such an interaction, co-administration of cisapride is contra-indicated in patients receiving fluconazole. (See “Contra-indications”)

Zidovudine

Two kinetics 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 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.

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.

Tacrolimus

There have been reports that an interaction exists when fluconazole is administered concomitantly with tacrolimus, leading to increased serum levels to 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.

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.

Interactions 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**

Use during pregnancy

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 (400-800 mg/day) fluconazole therapy for coccidioidomycosis. The relationship between fluconazole and these events is unclear.

Accordingly, Fluconazole Solution for Infusion should not be used in pregnancy, or in women of childbearing potential unless adequate contraception is employed.

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 fluconazole 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 side effects observed during clinical trials and associated with fluconazole are:

Central and Peripheral Nervous System: headache.

Dermatological: rash.

Gastrointestinal: abdominal pain, diarrhoea, flatulence and 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 "Special warnings and special precautions for use")

Liver/Biliary: hepatic toxicity including rare cases of fatalities, elevated alkaline phosphatase, elevated bilirubin, elevated SGOT, elevated SGPT.

In addition, the following adverse events have occurred during post-marketing:

Central and Peripheral Nervous System: dizziness, seizures.

Dermatological: alopecia, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Gastrointestinal: dyspepsia, vomiting.

Haematopoietic and Lymphatic: leukopenia including neutropenia and agranulocytosis, thrombocytopenia.

Immunological Anaphylaxis: (including angioedema, face oedema, pruritus)..

Liver/Biliary: hepatic failure, hepatitis, hepatocellular necrosis, jaundice.

Metabolic/Nutritional: hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia.

Other senses: taste perversion.

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, unverified by his physician. 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

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.

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 *Coccidioides 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 childbearing age. Fluconazole 200-400mg 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 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 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. 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% of 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, epidermis-dermis and eccrine sweat. 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 for other indications.

Pharmacokinetics in Children

In children, the following pharmacokinetic data have been reported:

Age studied	Dose (mg/kg)	Half-life (hours)	AUC ($\mu\text{g.h/ml}$)
11 days-11 months	Single – IV 3 mg/kg	23	110.1
9 months –13 years	Single – Oral 2 mg/kg	25.0	94.7
9 months –13 years	Single – Oral 8 mg/kg	19.5	362.5
5 years - 15 years	Multiple – Oral 2 mg/kg	17.4*	67.4
5 years -15 years	Multiple – Oral 4 mg/kg	15.2*	139.1
5 years -15 years	Multiple – Oral 8 mg/kg	17.6*	196.1
5 years -15 years	Multiple – IV 3 mg/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 days 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 ($\mu\text{.h/ml}$) 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 mean of 1184 (range 510-2130) on day 7 and 1328 (range 1040-1680) on day 13.

5.3 Preclinical safety data

Reproductive toxicity: 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 320mg/kg embryoletality 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 synthesis 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
Hydrochloric acid (pH adjuster)

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

3 years.

6.4 Special precautions for storage

Store below 30°C.

Do not freeze.

6.5 Nature and contents of container

Fluconazole Solution for Infusion is supplied in a 100mL clear Type I glass infusion vials, closed with a rubber stopper and sealed with an aluminium overcap and a plastic flip-off.

6.6 Special precautions for disposal

The infusion does not contain any preservative. It is for single use only. Discard any remaining solution according to guidelines of the local authorities.

Do not use if container is found leaking or solution is not clear.

Solutions containing visible solid particles must not be used.

Although further dilution is unnecessary, Fluconazole Solution for Infusion is compatible with the following administration fluids:

Dextrose Solution 20%
Ringer's Solution
Ringer's Lactate Solution
Potassium Chloride 1% in Dextrose Solution 5%
Sodium Bicarbonate 4.2%

Sodium Chloride Solution 0.9%

7 MARKETING AUTHORISATION HOLDER

Opal Healthcare Limited
Kingswood Court Business Park
Long Meadow
South Brent
Devon TQ10 9YS

8 MARKETING AUTHORISATION NUMBER(S)

PL 19960/0025

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/05/2007

10 DATE OF REVISION OF THE TEXT

23/05/2007

Opal Healthcare Ltd.

Fluconazole

2mg/ml Solution for Infusion

PATIENT INFORMATION LEAFLET

Fluconazole 100 mg/50 ml
Fluconazole 200 mg/100 ml

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 further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet

- What is Fluconazole Solution for Infusion and what is it used for?
- Before you take Fluconazole Solution for Infusion
- How to take Fluconazole Solution for Infusion
- Possible side effects
- Storing Fluconazole Solution for Infusion
- Further information

1. WHAT FLUCONAZOLE SOLUTION FOR INFUSION IS AND WHAT IS IT USED FOR?

Each ml of solution contains 2 mg fluconazole, which is the active substance. The solution also contains the following inactive ingredients: Water for injections and 0.9% sodium chloride (the 100 mg / 50 ml vial contains 7.7 mmol sodium and the 200 mg / 100 ml vial contains 15.4 mmol sodium). Hydrochloric acid is used to adjust the acidity of the injection.

Fluconazole Solution for Infusion is available in two pack sizes: 100 mg / 50 ml and 200 mg / 100 ml.

Fluconazole Solution for Infusion belongs to a group of medicines called anti-fungal agents.

Fluconazole Solution for Infusion is used to treat infections caused by fungi/yeasts. It may also be used to stop you from getting a fungal infection. The most common cause of fungal infections is a yeast called *Candida*.

You may be given Fluconazole Solution for Infusion by your doctor to treat fungal infections such as:

- Thrush of the mouth or throat (mucosal infections). Thrush is commonly caused by *Candida*.
- Skin infections e.g. athlete's foot, ring worm.
- Internal (systemic) fungal infections caused by *Candida*, e.g. infections of the blood stream, urinary tract or other body organs.
- Internal (systemic) fungal infections caused by *Cryptococcus*, e.g. cryptococcal meningitis and infections of other sites such as the lungs and skin.
- Genital *Candida* infections, e.g. vaginal thrush or candidal balanitis (inflammation of the end of the penis and/or foreskin).

You may also be given Fluconazole Solution for Infusion to:

- Stop you from getting a fungal infection (if your immune system is not working properly).
- Stop an infection caused by *Cryptococcus* from coming back (in AIDS patients).

2. BEFORE YOU TAKE FLUCONAZOLE SOLUTION FOR INFUSION

Tell your doctor **immediately** if your answer is **YES** to any of following situations:

- You are pregnant or trying to become pregnant.
- You are breast-feeding.
- You have liver or kidney problems.
- You ever have had an allergic reaction to any of the ingredients of Fluconazole Solution for Infusion or other medicines, which you may have taken to treat a fungal infection. This may have been itching, reddening of the skin or difficulty in breathing.
- You are taking either terfenadine (an antihistamine) or cisapride (used for stomach upsets).
- You have ever had any form of cancer.
- You have AIDS.
- You are on a low-sodium diet. Your medicine contains the following amounts of sodium and may not be suitable for you:

Fluconazole 100 mg / 50 ml Solution for Infusion: 7.7 mmol sodium

Fluconazole 200 mg / 100 ml Solution for Infusion: 15.4 mmol sodium

Inform your doctor if you are taking any of the following medicines:

- Warfarin or coumarin drugs (to prevent blood clots).
- Oral sulphonylureas such as chlorpropamide, glibenclamide, glipizide or tolbutamide (to control diabetes).
- Diuretics, such as hydrochlorothiazide, used to treat fluid retention and high blood pressure.
- Benzodiazepines (used as tranquilizers).
- Phenytoin (used to control epilepsy).
- Rifampicin or rifabutin (antibiotics).
- Ciclosporin or tacrolimus (used to affect the immune response).
- Theophylline (used to control asthma).
- Astemizole (an antihistamine).
- Zidovudine, also known as AZT (used in HIV-infected patients).

Tell your doctor of any medicines you are taking including those that were not prescribed for you that you may have bought.

3. HOW TO TAKE FLUCONAZOLE SOLUTION FOR INFUSION

This medicine is normally given in hospital by your doctor or nurse as an intravenous infusion over approximately 30 minutes.

Fluconazole Solution for Infusion is supplied as solution. It is unnecessary to dilute it further.

This medicine should not be mixed with any other drug before infusion.

Your first dose will depend on the type and severity of your infection, your age, weight and kidney function.

Check with your doctor or nurse if you are not sure why you are being given Fluconazole Solution for Infusion.

The usual doses of Fluconazole Solution for Infusion for different infections are below:

Adults

Mucosal infections of mouth	50-100 mg once daily for 7-14 days
Mucosal infections of throat or elsewhere	50-100 mg once daily for 14-30 days
Fungal skin infections	50mg once daily for 2-4 weeks. Athlete's foot may need up to 6 weeks treatment
Internal fungal infections caused by <i>Candida</i>	400 mg on the first day then 200-400 mg once daily
Internal fungal infections caused by <i>Cryptococcus</i>	400 mg on the first day then 200-400 mg once daily for 6-8 weeks
To stop you from getting a fungal infection	50-400 mg once daily while you are at risk of getting an infection
To prevent a cryptococcal infection from coming back	100-200 mg once daily indefinitely
To treat genital <i>Candida</i> infection	150 mg as a single dose

Children

4 weeks to 15 years old	
Mucosal infections	3 mg/kg once daily.
Internal fungal infections caused by <i>Candida</i> or <i>Cryptococcus</i>	6-12 mg/kg once daily.
Prevention of fungal infections	3-12 mg/kg once daily while at risk of getting an infection.

2-4 weeks old

Same dose as above but given once every 2 days. A maximum dose of 12 mg/kg every 2 days.

Less than 2 weeks old

Same dose as above but given once every 3 days. A maximum dose of 12 mg/kg every 3 days.

A maximum dosage of 400 mg daily should not be exceeded in children.

Use of Fluconazole Solution for Infusion for treating genital *Candida* infections in children under 16 years old is not recommended.

Elderly

The usual adult dose should be given unless you have kidney problems.

Patients with kidney problems

Your doctor may modify your dose, depending on your kidney function.

Doctors sometimes prescribe different doses to those listed above. If your kidneys are not working properly you may be given a different dose. Ask your doctor or nurse if you want to know what doses you are being given.

If you have the impression that the effect of Fluconazole Solution for Infusion is too strong or too weak, talk to your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Fluconazole Solution for Infusion can have side effects.

The most common undesirable effects are:

- Nausea
- Stomach discomfort

- Diarrhoea
- Wind (flatulence)
- Rash
- Headache

The following have occurred rarely in patients being given this medicine but they may not all be due to the drug:

- Itching
- Vomiting
- Seizure
- Abnormalities in blood/liver function/urine or other biochemical tests
- Liver toxicity
- Severe skin reactions
- Hair loss
- Dizziness
- Swelling of the face
- Altered sense of taste

A few people develop allergic reactions to medicines. If you develop any of the following undesirable effects tell your doctor or nurse **immediately**:

- Sudden wheeziness, difficulty in breathing or tightness in chest
- Swelling of eyelids, face, lips or blood vessels under the skin
- Severe rash, skin lumps or itchy red spots
- Itch all over body

AIDS patients should be warned that they are likely to be prone to skin reactions to many drugs, including Fluconazole Solution for Infusion.

Tell your doctor or nurse if you become unwell or have any other discomfort you do not understand.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING FLUCONAZOLE SOLUTION FOR INFUSION

Keep out of the reach and sight of children.

Store below 30°C (unopened packaging). The solution for infusion should not be frozen.

The doctor or nurse will check that the expiry date on the label has not passed.

Once open, any unused infusion will be discarded, since the solution contains no preservatives.

6. FURTHER INFORMATION

This leaflet does not contain all the information about this medicine. If you have any questions or are not sure about anything, ask your doctor or nurse.

For any information about this medicinal product, please contact the Marketing Authorisation Holder / Manufacturer or its local representative:

Marketing Authorisation Holder
Opal Healthcare Limited
Kingswood Court Business Park
Long Meadow
South Brent
Devon
TQ10 9YS UK

Manufacturer
Hikma Farmacéutica (Portugal), S.A.
Estrada do Rio da Mò 8
8A e 8B Ferveça
2705-906 Terrugem SNT
Portugal

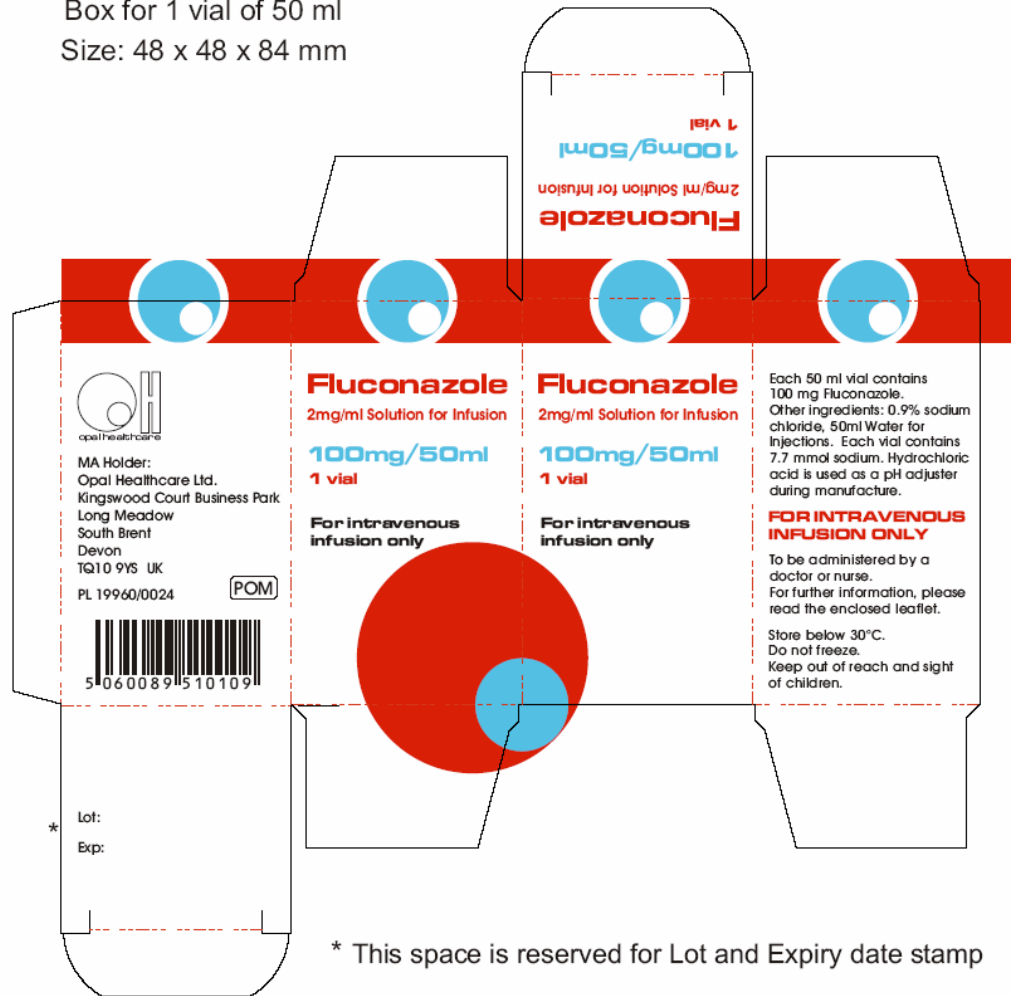
Tel: +351 21 960 84 10
Fax: +351 21 961 51 02

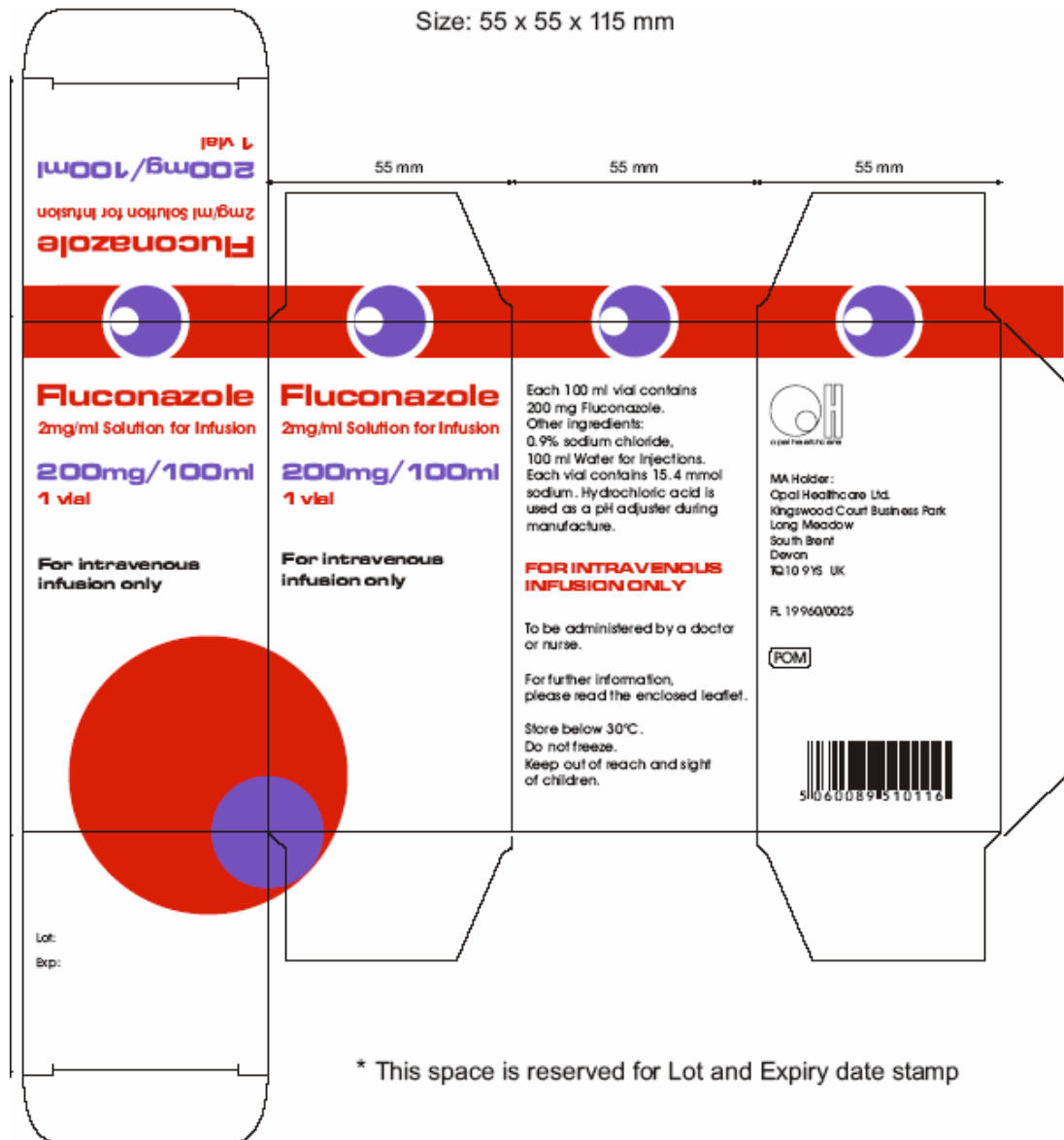
Product licence number
PL 19960/0024
PL 19960/0025

This leaflet was last approved in:
May 2007

LABELLING

Box for 1 vial of 50 ml
Size: 48 x 48 x 84 mm





Fluconazole
2mg/ml Solution for Infusion
200mg/100ml

Each 100 ml vial contains 200 mg Fluconazole. Other ingredients: 0.9% sodium chloride, 100ml Water for injections. Each vial contains 15.4 mmol sodium. Hydrochloric acid is used as a pH adjuster during manufacture.

(POM)

PL 19960/0025

Store below 30°C. Do not freeze. Keep out of reach and sight of children.

MA Holder: Opal Healthcare Ltd., Kingswood Court Business Park
Long Meadow, South Brent, Devon, TQ10 9YS UK

Lot: Exp: