Public Assessment Report

Fluconazole 2mg/ml Solution for Infusion

Fluconazole

PL 20395/0012

Relonchem Limited

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Lay Summary

The MHRA granted a National Marketing Authorisation (licence) to Relonchem for the medicinal product Fluconazole 2mg/ml solution for infusion on 16th October 2006.

Fluconazole 2mg/ml solution is an antifungal treatment used in the treatment of a number of fungal infections. No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Fluconazole 2mg/ml solution for infusion outweigh the risks, hence a Marketing Authorisation has been granted.

Scientific Discussion

INTRODUCTION

This Public Assessment Report is based on the Assessment Report for an abridged application for a Marketing Authorisation for a 2mg/ml presentation of Fluconazole solution for infusion. The application was submitted, by Relonchem Ltd, under article 10.1 (a) (iii) of Directive 2001/83/EC (first paragraph), claiming essential similarity to the innovator product, Diflucan Intravenous Infusion, PL 00057/0315, marketed in the UK by Pfizer Ltd. The reference product marketing authorisation was granted on 31st August 1989. A Marketing Authorisation was granted to Relonchem Ltd on 16th October 2006.

Fluconazole is a triazole antifungal indicated for the treatment of a range of candidal and tineal 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. The SPC for the current application refers to all indications (both oral and intravenous routes of administration).

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

The drug substance is the subject of a Drug Master File (DMF). The latest version of the DMF has been assessed and accepted.

General information

Fluconazole was not described in a pharmacopoeial monograph at the time of assessment or approval. A draft monograph was published in Pharmeuropa in March 1998.

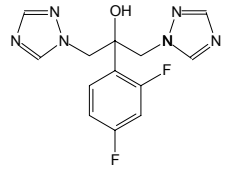
Nomenclature

INN: Fluconazole

Chemical names: 2,4-Difluoro-α,α-bis(1H-1,2,4-triazol-1-ylmethyl) benzylalcohol
α-(2,4-Difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)-1H-1,2,4-triazol-1-ethanol
2-(2,4-Difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1yl) propan-2-ol

CAS number: 86386-73-4

Structure



Molecular formula: $C_{13}H_{12}F_2N_6O$
MWt: 306.27

General properties

A white to off-white crystalline powder.

Manufacture

The applicant's part of the DMF presented in the application contains a summary of the synthetic route; full details of the process are contained in the closed part of the DMF. A letter of access to the closed DMF was included in the application. This is acceptable.

Impurities

Five related substances are listed in the drug substance specification as potentially occurring in Fluconazole, manufactured as described in the DMF. Structures have been provided for each of these. This has been accepted previously.

Residual solvents are specified in the drug substance specification and controlled to limits that are tighter than those prescribed by the ICH.

Control of Drug Substance

Specification

The Active Ingredient Manufacturer's (AIM's) specification for the drug substance has been assessed and approved previously. Proposed acceptance limits are comparable with (or tighter than) those outlined in the draft fluconazole monograph published in Pharmeuropa in 1998.

Analytical Procedures

The methods employed by the AIM have been assessed and approved previously.

Validation of Analytical Procedures

The validation of methods employed by the AIM has been assessed and approved previously in relation to the DMF. Analytical procedures followed by the finished product manufacturer for testing of the drug substance have been provided.

Batch Analyses

Certificates of analysis for 3 representative batches of drug substance are included in the applicant's part of the DMF in Part IIC. These have been seen previously in the assessment of the DMF. Representative certificates of analysis documenting routine testing on the active substance performed by the finished product manufacturer were provided.

Justification of Specification

The specification applied by the AIM has been previously accepted as justified.

Reference Standards or Materials

Details of the AIM's reference standards are included in the DMF.

Container Closure System

The drug substance is packaged in double polyethylene bags, with a silica gel desiccant, and stored in cardboard or polyethylene drums. This packaging system has been assessed and accepted previously.

Stability

The drug substance stability has been reviewed previously in relation to the original DMF assessment. The proposed retest period of 5 years, when stored in well-closed containers, has been accepted before.

DRUG PRODUCT

Description and Composition of the Drug Product

The composition of the product is given in Table 1, below:

Table 1: Composition of Fluconazole 2mg/ml Solution for Infusion

Ingredient	Quantity (mg/ml)	**Function**	**Reference to standard**
Fluconazole	2.0	Active substance	Quimica's specification
Sodium chloride		Tonicity adjuster	Ph Eur
Water for Injection		Solvent	Ph Eur

Container:
The product is filled into colourless glass (hydrolytic class I) infusion bottles of 3 sizes (50ml, 100ml and 250ml [for 400mg/200ml fill volume]). These are sealed with chlorobutyl rubber closures and aluminium caps.

Clinical trial formula:
Since this application is for a parenteral product, no bioequivalence study is required and no clinical trials have been carried out. This is acceptable.

Pharmaceutical Development

A brief overview of the formulation, covering properties of the active substance and the role of excipients and making reference to the brandleader and other approved fluconazole products, was provided. Given the simplicity of the formulation, this information is adequate. Adequate justification of the proposed manufacturing process/method of sterilisation is given.

Manufacture

A flow-chart depicting the manufacturing process, with in-process controls indicated, was provided.

Batch Formula

The proposed maximum manufacturing batch size is 100L, corresponding to 500, 1000 or 2000 units of the 200ml, 100ml and 50ml fill volumes, respectively. A typical batch formula was provided.

Control of Critical Steps and Intermediates

A summary table of the in-process controls is provided that indicates the frequency at which they are routinely performed. These are satisfactory to guarantee control over the manufacturing process. Representative IPC results for 3 batches were provided.

Process Validation and/or Evaluation

A process validation report was provided. All stages of manufacture were encompassed by this validation. The parameters monitored at each critical stage were indicated, along with satisfactory acceptance limits/ranges: fluconazole content was determined during mixing and after filtration and sterilisation, the bioburden of raw materials was measured, along with the pre- and post-filtration bioburden and the sterility of the product was evaluated.

Results are provided for three batches of product. The batch size was 1000 units of the 100mL fill volume, corresponding to maximum production scale. The results for the validation at this fill volume may be extrapolated to the 50ml and 200ml fill volumes.

The report indicates that the method is consistently capable of yielding sterile product of the required quality. The filtration and sterilisation operations/conditions have been demonstrated to have no adverse effect on fluconazole content. Further validation reports have been provided for the filtration and sterilisation methods and for the WFI preparation/distribution system.

Control of Excipients

Specifications

Sodium chloride and water for injections are controlled according to their Ph Eur monograph specifications. Microbiological quality of the sodium chloride is not determined, but this is not considered critical, given the subsequent sterilisation steps that take place. Sample certificates of analysis are provided.

A specification for nitrogen gas used during filtration and filling was provided together with a Certificate of Analysis from the supplier.

Analytical Procedures

Pharmacopoeial methodology is employed.

Validation of Analytical Procedure

No validation is necessary.

Justification of Specification

Pharmacopoeial specifications are employed, therefore no further validation is necessary.

Excipients of Human or Animal Origin

There are none.

Novel Excipients

There are none.

Control of Drug Product

Specification

A satisfactory finished product specification for the product was provided.

Analytical Procedures

Two identification tests are included in the finished product specification. Full details of these methods were provided. A titration method is used to determine sodium chloride content.

Validation of Analytical Procedures

The HPLC method for determination of purity has been satisfactorily validated in terms of selectivity, precision (system and method), accuracy, linearity over 30-150% of limit concentration and robustness. System suitability is routinely determined, with appropriate parameters set. Limits of detection and quantification have been defined for impurities. The HPLC assay method has been satisfactorily validated in terms of selectivity, precision, linearity, accuracy and robustness. System suitability is routinely evaluated.

Forced degradation studies were performed to demonstrate that the HPLC methods used for assay and related substances are stability indicating. The method for determination of sodium chloride has also been satisfactorily validated. The Ph Eur

tests for sterility and determination of bacterial endotoxins have both been validated for the applicant's product.

Batch Analyses

Certificates of analysis have been presented for 3 batches of each fill volume. All of the batches meet the proposed release specification.

Characterisation of Impurities

No information on impurities, further to that provided in the DMF, has been provided. This may be accepted.

Justification of Specification

The Finished Product Specification was tightened during assessment in line with batch analytical and stability data.

Reference Standards or Materials

Batch numbers and potency values are stated for the reference standards used in the validation of the analytical methods. Since fluconazole was a non-pharmacopoeial substance at the time of assessment and approval, there were no official standards available.

Container Closure System

The product is filled into clear, type I borosilicate glass bottles. It is confirmed that they meet the Ph Eur requirements for hydrolytic resistance and arsenic. The stoppers are constructed from chlorobutyl rubber, and are stated to meet Ph Eur type I requirements. Satisfactory specifications and representative certificates of analysis have been provided for both of these container components.

Stability

Satisfactory stability data was provided under normal and accelerated conditions. The stability data support the shelf-life of 3 years.

Assessor's Comments On The SPC, Labels And Package Leaflet

Minor changes were requested to the SPC, labels and package leaflet and these changes were carried out.

Bioavailability, bioequivalence

Since this product is for parenteral administration as an intravenous infusion/injection, no bioavailability/bioequivalence studies are required.

Essential similarity

No bioequivalence study is required for this application. The formulation can be accepted as pharmaceutically equivalent to the reference product and, thus, the claim of essential similarity is supported.

Comment on Expert report

A satisfactory pharmaceutical expert report was written with a CV provided which indicates that the expert is adequately qualified to perform this role. The report is a suitably critical evaluation of the pharmaceutical data presented in the dossier.

ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

A Marketing Authorisation was granted.

MEDICAL ASSESSMENT

1. INTRODUCTION

Fluconazole belongs to the group of triazole antimycotics. It specifically inhibits fungal ergosterol synthesis, the pharmacokinetic properties being identical after both intravenous and oral administration.

2. BACKGROUND

The national product licence application by Relonchem Ltd was for a 2mg/ml intravenous infusion of fluconazole, cross-referred to the original product Diflucan Intravenous Infusion 2mg/ml first authorised to Pfizer Limited in the Republic of Ireland on 22-08-1989, the reference product in the UK being Diflucan Intravenous Infusion PL 00057/0315.

3. INDICATIONS

Fluconazole is indicated for the treatment of the following infections when caused by fungi that are known or are likely to be fluconazole-susceptible:

- *Acute or recurrent vaginal candidiasis; or candidal balanitis associated with vaginal candidiasis.*
- *Mucous membrane candidiasis including oropharyngeal, oesophageal, mucocutaneous and non-invasive bronchopulmonary candidiasis and candiduria in patients with immunosuppression.*
- *Systemic candidiasis (candidaemia, disseminated deep candidiasis, peritonitis).*
- *Prevention of Candida infections in neutropenic patients (eg. AIDS, bone marrow transplantation).*
- *Treatment and maintenance treatment of cryptococcal meningitis in immunosuppressed patients.*
- *Verified fungal skin infections caused either by dermatophytes or other species (tinea corporis/cruris/pedis/versicolor) or Candida when local treatment has failed or is considered inappropriate. Fluconazole should be used to treat Tinea versicolor only when the infection is resistant to first line therapy or when the patient is immunosuppressed.*

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

4. DOSE & DOSE SCHEDULE

The daily dose depends on the type and severity of the infection and can be found in the Summary of Product Characteristics (SPC) below. Considerable changes to the dosing posology in the SPC were needed to conform with current requirements.

5. TOXICOLOGY

No formal data are presented under this heading and none are required for this application.

6. CLINICAL PHARMACOLOGY

6.1 PHARMACODYNAMICS

Fluconazole inhibits synthesis of ergosterol that is an essential component of fungal cell well. The azole ring nitrogen blinds to lanosterol-14 alpha-demethylase and cytochrome P450, and inhibits conversion of lanosterol to ergosterol. Impaired ergosterol synthesis results in accumulation of non-functioning sterols, alteration in normal membrane functions including chitin formation, disturbed binding capacity of membrane sterols, and impaired cell wall permeability.

It is available for systemic but not topical administration.

6.2 PHARMACOKINETICS

The bioavailability of oral fluconazole is 90% when compared to intravenous fluconazole. It is well distributed in body tissues. 80% is renally eliminated as unchanged fluconazole. There are, however, a number of potentially dangerous drug interactions because of its effect on cytochrome P450.

No bioequivalence study has been performed, as the product is for intravenous infusion, the clinical expert providing a literature search of all clinical trials up to the year 2000.

7. EFFICACY

No formal data are presented under this heading and none are required for this application. The clinical expert has provided an adequate review of the different clinical uses of fluconazole.

8. SAFETY

No new data are presented and none are required for this indication. The adverse events that can be expected are listed in the Summary of Product Characteristics.

9. EXPERT REPORTS

There is an adequate clinical expert report written by a suitably qualified clinical expert. A satisfactory curriculum vitae was included, as are those for the preclinical and pharmaceutical assessors.

10. SUMMARY OF PRODUCT CHARACTERISTICS

The Summary of Product Characteristics needed considerable changes to bring it into line with current requirements. The current SPC can be found on page 15.

11 PATIENT INFORMATION LEAFLET (PIL)

The patient information leaflet needed some revisions and additions and the PIL can be found on page 28 of this Public Assessment Report.

12. LABELLING

The labelling was mostly satisfactory and minor changes only were required. Full colour mock-up of the revised carton can be found on page 31.

13. MAA

The MAA was satisfactory

14. DISCUSSION

Relonchem Ltd have applied for a product licence for their 2mg/ml infusion solution of fluconazole. Considerable changes were required in the Summary of Product Characteristics and, subsequently, the Patient Information Leaflet for these to satisfy current requirements. The rest of the application, however, was largely satisfactory.

15. RECOMMENDATION

The necessary amendments to the SPC and PIL were made and a Marketing Authorisation was granted.

Overall Conclusion and Risk/Benefit Analysis

Quality

The quality aspects of Fluconazole 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.

Pre-Clinical

No new pre-clinical data were presented or were required for this type of application.

Clinical

No formal data on clinical efficacy or safety was presented for this application and none were required. Changes were made to the Summary of Product Characteristics, PIL and packaging to satisfy current requirements.

Risk/Benefit Analysis

The quality of the product, Fluconazole 2mg/ml solution for infusion, is acceptable and the product is essentially similar to the reference product which has a positive risk/benefit assessment. A Marketing Authorisation was granted.

Steps Taken During Assessment

1	The MHRA received the application on 25th June 2003.
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 15th September 2003.
3	Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on10th June 2004, and 15th April 2005 and on the medical assessment on 18th May 2004.
4	The applicant provided further information in regard to the quality assessment on 28th February 2005 and 31st August 2006 and on the medical assessment on 26th October 2004.
5	The application was determined on 16th October 2006.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Fluconazole 2 mg/ml Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fluconazole 2mg/ml.
Each 50 ml bottle contains 100 mg of fluconazole
Each 100 ml contains 200 mg of fluconazole
Each 200 ml contains 400 mg fluconazole

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Solution for infusion.
Clear, 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.

Fluconazole is indicated for the treatment of the following infections when caused by fungi that are known or are likely to be fluconazole-susceptible.

- Acute or recurrent vaginal candidiasis; or candidal balanitis associated with vaginal candidiasis.
- Mucous membrane candidiasis including oropharyngeal, oesophageal, mucocutaneous and non-invasive bronchopulmonary candidiasis and candiduria in patients with immunosuppression.
- Systematic candidiasis (candidaemia, disseminated deep candidiasis, peritonitis).
- Prevention of Candida infections in neutropenic patients (eg. AIDS, bone marrow transplantation.
- Treatment and maintenance treatment of cryptococcal meningitis in immunosuppressed patients.
- Verified fungal skin infections caused either by dermatophytes or other species (Tinea corporis/cruris/pedis/veriscolor) or Candida when local treatment has failed or is considered inappropriate. Fluconazole should be used to treat Tinea versicolor only when the infection is resistant to first line therapy or when the patient is immunosuppressed.

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

4.2. Posology and method of administration

For intravenous infusion use.

Fluconazole is administered by intravenous infusion at a rate of approximately 5-10ml/min, 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. Fluconazole Solution for Infusion is formulated in 0.9% sodium chloride solution, each 200 mg (100 ml bottle) containing 15 mmol each of Na^+ and Cl^-.

The daily dose of fluconazole should be based on the nature and severity of the fungal infection. Most cases of vaginal candidiasis respond to single dose therapy. Therapy for those types of infections requiring multiple dose treatment should be continued until clinical parameters or laboratory tests indicate that active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection.

Adults

1. Vaginal candidiasis - 150 mg single oral dose.
2. Oropharyngeal candidiasis - 50 mg once daily. In severe or recurrent cases the dose may be increased to100 mg once daily. Duration of treatment: 1-2 weeks. In order to prevent relapse treatment may be given for longer periods (6–8 weeks)

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

For other candidal infections of mucosa except genital candidiasis (see above), e.g. oesophagitis, non-invasive bronchopulmonary infections, candiduria, mucocutaneous candidiasis etc., the usual effective dose is 50 mg daily, given for 2 - 4 weeks. In difficult cases the dose may be increased to 100 mg daily. In order to prevent relapse, treatment may be given for longer periods (6-8 weeks)

3 Systemic candidiasis: usually, a single 400 mg loading dose should be administered on Day 1, followed by 200 mg once daily thereafter. The dose may be increased to 400mg once daily. The duration of treatment depends on the clinical response.

4. Prevention of candida infections in neutropenic patients: 50-400 mg once daily according to the risk of infection. In patients with high risk of systemic infection, such as patients with or likely to develop severe or prolonged neutropenia, 400 mg once daily is recommended. Treatment should begin a few days before the appearance of neutropenia and should continue until 7 days after the neutrophil counts have reached >1000/mm^3.

5. Treatment and maintenance treatment of cryptococcal meningitis in immunosuppressed patients: 400 mg once daily initially. Thereafter 200-400 mg daily for at least 6-8 weeks. A 100-200 mg daily dose is recommended to prevent recurrence of cryptococcal meningitis. Duration of maintenance treatment in AIDS

patients should be carefully justified, because of the increased risk of resistance to fluconazole.

6.. Fungal skin infections (tinea corporis, tinea cruris, tinea versicolor, tinea pedis): 50 mg fluconazole once daily. Duration of treatment: 2-4 weeks, except that Tinea pedis may require up to 6 weeks.

Children

As with similar infections in adults, the duration of treatment is based on the clinical and mycological response. The maximum daily dose in children is 400 mg as a single dose and this dose should not be exceeded.

Children over 4 weeks of age:
1. Mucous membrane candidiasis: the recommended dose is 3 mg/kg daily. A loading dose of 6 mg/kg may be used on the first day to achieve steady state levels more rapidly.
2. Systemic candidiasis and cryptococcal infections: 6-12 mg/kg daily, depending on the severity of the disease.
3. Prevention of candida infections in neutropenic children: 3-12 mg/kg daily, depending on the extent and duration neutropenia (see adult dosing).

Despite extensive data supporting the use of fluconazole in children there are limited data available on the use 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.

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

Elderly
The normal adult dose should be given 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 mainly excreted unchanged in the urine. No change in dose is needed if treatment consists of a single dose.
For patients with impaired renal function who require multiple doses, the normal recommended dose for the indication should be given on day 1, followed by a daily dose according to the following table:

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

For information regarding administration and incompatibilities, see sections 6.2 and 6.6.

4.3. Contraindications

Fluconazole must not be used in:
1. patients with known hypersensitivity to fluconazole or to related triazole antifungal agents or any other ingredient in the formulation.
2. patients who are taking cisapride, terfenadine or astemizole. (see sections 4.4 and 4.5).
3. patients with congenital or documented acquired QT prolongation
4. patients who are taking other medicinal products that prolong the QT interval such as antiarrhythmics of classes IA and III.
5. patients with electrolyte disturbance, particularly hypokalaemia and hypomagnesaemia.
6. patients with clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

4.4. Special warnings and precautions for use

In some patients, particularly those with serious underlying diseases such as AIDS and cancer, abnormalities in haematological, 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 discontinued if bullous lesions or erythema multiforme develop.

In rare cases, as with other azoles, anaphylaxis has been reported (see section 4.8).

The dose of fluconazole must be reduced when the creatinine clearance is below 50 ml/min.

4.5. Interactions with other medicinal products and other forms of interaction

Terfenadine (400 mg or higher, CYP3A4 substrate): Due to occurrence of serious cardiac dysrhythmias secondary to prolongation of the QTc interval in patients receiving azole antifungals in conjunction with terfenadine, interaction studies have been performed. One study at a 200 mg daily dose of fluconazole did not show any prolongation in QTc interval. Another study at a 400 mg and 800 mg daily dose of fluconazole showed that fluconazole 400 mg or more daily significantly increases plasma levels of terfenadine when taken concomitantly. Concomitant administration of fluconazole and terfenadine is contraindicated.

Cisapride (CYP3A4 substrate): There have been reports of cardiac events including torsades de pointes in patients receiving fluconazole concomitantly with cisapride. Concomitant administration of fluconazole and cisapride is contra-indicated.

Astemizole overdoses have led to prolonged QT interval and severe ventricular arrhythmia, torsades de pointes and cardiac arrest. Concomitant administration of astemizole and fluconazole is contraindicated due to the potential for serious, potentially fatal, cardiac effects.

Medicinal products affecting the metabolism and/or excretion of fluconazole

Hydrochlorothiazide: In a pharmacokinetic interaction study with healthy volunteers who concomitantly received fluconazole and multiple doses of hydrochlorothiazide the plasma concentrations of fluconazole increased by 40%. An effect of this size should not necessitate a change in the fluconazole dose regimen in patients who are concomitantly treated with diuretics, although the prescriber should bear this in mind.

Rifampicin (CYP450 inducer): Concomitant intake of fluconazole and rifampicin resulted in a 25% reduction in the AUC and 20% reduction in the half-life of fluconazole. An increase in the dose of fluconazole should be considered in patients concomitantly receiving rifampicin.

Rifabutin (CYP450 inducer): There have been reports that concomitant administration of rifabutin and fluconazole results in increased serum levels of rifabutin. Uveitis has been reported in patients treated concomitantly with fluconazole and rifabutin were co-administered. Patients receiving rifabutin and fluconazole concomitantly should be carefully monitored.

Effects of fluconazole on the metabolism of other medicinal products

Fluconazole is potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4. Besides the following observed interactions there is a

risk of increased plasma concentrations of other medicinal products metabolised by CYP2C9 or CYP3A4 (i.e. ergot-alkaloids, HMG-CoA reductase inhibitors, quinidine) when co-administered with fluconazole. Therefore, care should always be taken when using these combinations and the patients should be carefully monitored. The effect may persist for 4-5 days after the end of fluconazole treatment due to the long fluconazole half-life.

Anticoagulants: (CYP2C9 substrate): Concomitant intake of fluconazole during warfarin treatment may prolong the prothrombin time up to 2 fold. As for other azoles there have been reports of bleeding (bruises, nose bleeding, gastrointestinal bleeding, blood in the urine and faeces) in connection with an increase of prothrombin time in patients concomitantly treated with warfarin. The prothrombin time must be closely monitored in patients on treatment with fluconazole and coumarin derivatives.

Phenytoin (CYP2C9 substrate and potent CYP450 inducer): Intake of fluconazole 200 mg concomitantly with phenytoin 250 mg intravenously increased the phenytoin AUC by 75% and C_{min} by 128%. If it is necessary to administer both substances concomitantly, the phenytoin concentration must be controlled by dose adjustment in order to maintain therapeutic but non-toxic plasma concentrations.

Benzodiazepines (CYP3A4 substrate): Concomitant intake of fluconazole 400 mg and midazolam 7.5 mg orally increased the midazolam AUC and half-life 3.7-fold and 2.2-fold, respectively and also the psychomotor effects. Fluconazole 100mg daily and triazolam 0.25mg increased the triazolam AUC and half-life 2.5-fold and 1.8-fold with potentiated and prolonged effects. If it is necessary to treat patients with a benzodiazepine concomitantly with fluconazole, consideration should be given to decreasing the dose of the benzodiazepine. Patients should be closely followed.

Fluvastatin: Up to 200% increases in the area under the curve (AUC) of fluvastatin may occur as a result of the interaction between fluvastain and fluconazole. An individual patient using fluvastatin 80 mg daily may be exposed to considerable fluvastatin concentrations if treated with high doses of fluconazole. Caution should be exercised when fluconazole or other potent cytochrome P450 2C9 (CYP2C9) inhibitors are prescribed to patients who are also taking fluvastatin. The clinical significance of increased plasma concentrations and prolonged elimination of fluvastatin remains unclear.

Calcium channel antagonists: CYP3A4 is involved in the metabolism of some dihydropyridine calcium channel antagonists, including nifedipine, isradipine, nicardipine, amlodipine and felodipine. There have been published reports of marked peripheral oedema and/or elevated calcium antagonist serum concentrations during concurrent use of itraconazole and felodipine, isradipine or nifedipine. This interaction would be expected to occur with other triazole antifungal agents. Consideration should be given to reducing the dose of the calcium antagonist.

Sulphonyl urea (CYP2C9 substrate): It has been demonstrated that fluconazole prolongs the plasma half-life of concomitantly administered sulphonyl urea drugs (chlorpropamide, glibenclamide, glipizide and tolbutamide) in healthy volunteers. Fluconazole and oral sulphonyl urea derivatives may be used concomitantly to diabetics, but patients should be warned about the possibility of hypoglycaemia.

Celecoxib: A clinical study with Celecoxib has demonstrated a two-fold increase in celecoxib plasma concentrations when given concurrently with fluconazole 200 mg. this interaction is believed to be due to inhibition of cytochrome P450 2C9-mediated

metabolism of celecoxib. Celecoxib therapy should be commenced at the lowest recommended dose in patients who are also receiving fluconazole.

Losartan: Due to inhibition of CYP2C9 by fluconazole, there is decreased conversion of losartan to its active metabolite (E-3174) which is responsible for most of the angiotensin II receptor antagonism that occurs with losartan therapy. The patient should be monitored for continued control of their hypertension.

Chemotherapeutic agents

Didanosine: Although co-administration of didanosine and fluconazole appears to have little effect on the pharmacokinetics of efficacy of didanosine, the response to fluconazole should be monitored. It may be advantageous to administer fluconazole at some time prior to didanosine.

Trimetrexate: medicinal products such as fluconazole that inhibit the P450 enzyme system may cause interactions that increase trimetrexate plasma concentrations. If it is not possible to avoid concomitant administration of trimetrexate and fluconazole, trimetrexate serum levels and trimetrexate toxicity (bone marrow suppression, renal and hepatic dysfunction and gastrointestinal ulceration) must be monitored carefully.

Zidovudine: Interaction studies showed increased zidovudine AUC by approximately 20% and 70% when taken concomitantly with fluconazole 200 mg or 400 mg daily, respectively, probably due to inhibition of glucuronidation. Patients receiving this combination must be monitored for zidovudine related side-effects.

Immunosuppressants

Ciclosporin (CYP 3A4 substrate): In a pharmacokinetic study with renal transplant patients 200 mg daily of fluconazole slowly increased plasma concentrations of ciclosporin. However, in another study, multiple dosing with fluconazole 100mg daily did not influence ciclosporine concentrations in patients after bone marrow transplants. Ciclosporin plasma concentrations should be monitored during concomitant treatment with fluconazole.

Prednisone: A liver transplant recipient receiving prednisone experienced an Addisonian crisis when a three month course of fluconazole was discontinued. The withdrawal of fluconazole caused an increase in CYP3A4 activity, leading to an increase in the degradation of prednisone and the precipitation of an Addisonian crisis. Patients receiving long-term therapy with fluconazole and prednisone should be closely monitored for signs of adrenal insufficiency when fluconazole is withdrawn.

Tacrolimus and sirolimus: Concomitant intake of fluconazole and tacrolimus 0.15 mg/kg b.i.d increased C_{min} 1.4 and 3.1-fold with fluconazole doses of 100mg and 200mg respectively. Renal toxicity has been reported in patients concomitantly receiving fluconazole and tacrolimus. Although no interaction studies have been conducted with fluconazole and sirolimus, it is recommended that sirolimus levels should be monitored because an adjustment of the dose may be required. Patients who receive tacrolimus or sirolimus and fluconazole concomitantly must be closely monitored for increased toxicity (anaemia, leucopenia, thrombocytopenia, hypokalaemia, diarrhoea).

Other drugs

Oral contraceptives: Two pharmacokinetic studies have been performed with a combined oral contraceptive and multiple dosing of fluconazole. 50mg fluconazole did not influence any of the hormone concentrations, but 200mg daily increased AUC of ethinylestradiol and levonorgestrel with 40 and 24% respectively. Thus fluconazole at these doses is unlikely to impair the efficacy of combined oral contraceptive pills.

Amitriptyline: Several case reports have described the development of increased amitripyline concentrations and signs of tricyclic toxicity when amitriptyline was used in combination with fluconazole. Co-administration of fluconazole with nortriptyline, the active metabolite of amitriptyline has been reported to result in increased nortriptyline levels. Due to the risk of amitriptyline toxicity, consideration should be given to monitoring amitriptyline levels and making dose adjustments as may be necessary.

Theophylline: In a placebo controlled interaction study, intake of fluconazole 200mg for 14 days resulted in 18% decrease in the mean plasma clearance of theophylline. Patients on treatment with high doses of theophylline or with any other reason to be at increased risk of theophylline toxicity should be observed carefully during concomitant treatment with fluconazole and the dose of theophylline must be adjusted as necessary.

Other types of interactions

Amphotericin B: In-vitro and in-vivo animal studies have found antagonism between amphotericin B and azole derivatives. The mechanism of action of imidazoles is to inhibit ergosterol synthesis in fungal cell membranes. Amphotericin B acts by binding to sterols in the cell membrane and changing membrane permeability. Clinical effects of this antagonism are to date unknown. A similar effect may occur with amphotericin B cholesterol sulphate complex.

HMG-CoA: The risk of myopathy or rhabdomyolysis is increased when azole antifungals are administered concurrently with HMG-CoA reductase inhibitors such as atorvastatin. If concurrent therapy is required patients should be monitored for signs and symptoms of myopathy or rhabdomyolysis (muscle pain, tenderness or weakness), and creatine kinase (CK) levels. HMG-CoA therapy should be discontinued if CK levels show a marked increase, or if myopathy or rhabdomyolysis is diagnosed or suspected.

Interaction studies have shown that no clinically significant change in absorption of fluconazole occurs with oral use together with food, cimetidine, antacids or after radiation therapy of the whole body in connection with bone marrow transplantation.

4.6. Pregnancy and lactation

Pregnancy

There are no adequate data from the use of fluconazole studies in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk to humans is unknown. Data from a few hundred pregnant women treated with a single low dose of fluconazole during early pregnancy do not indicate any

undesirable effects on the foetus. There are reports on multiple congenital abnormalities in infants whose mothers were being treated for 3 months or longer with high doses of fluconazole (400-800 mg/day) for coccidioidomycosis. The relation between these effects and treatment with fluconazole is not clear.

Fluconazole should only be used in pregnancy in patients with serious or potential life-threatening infections and when the expected benefit to the mother has been weighed against the potential risk for the foetus

Lactation
Fluconazole passes into breast milk in quantities comparable to those in plasma. Fluconazole is therefore not recommended to breastfeeding women or alternatively, breast-feeding should be discontinued during therapy with fluconazole.

4.7. Effects on ability to drive and use machines

Fluconazole has no or negligible influence on the ability to drive or use machinery. However when driving vehicles or operating machines it should be taken into account that occasionally dizziness or seizures may occur.

4.8. Undesirable effects

The most common side effects observed during clinical trials in connection with fluconazole are:

Central and Peripheral Nervous System: Headache, dizziness and seizures.

Dermatological: Skin Rash accompanied by eosinophilia and pruritus has been reported in approximately 5 % of patients receiving fluconazole

Gastrointestinal: 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).

Liver/Biliary: Liver toxicity including rare cases of fatalities, elevated alkaline phosphatase, elevated bilirubin, elevated alanine aminotransferase (ALAT), elevated aspartate aminotransferase (ASAT).

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

Allergic Reactions: anaphylaxis (including angioedema, facial oedema and pruritus

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

Gastrointestinal: Dyspepsia, vomiting.

Haematopoietic and Lymphatic: Leucopenia (including neutropenia and agranulocytosis), thrombocytopenia.

*Liver/Biliary***:** Liver impairment, hepatitis, hepatocellular necrosis, jaundice.

Metabolic/Nutritional: Hypercholesterolemia, hypertriglyceridaemia, hypokalaemia.

Other: Changes in Taste.

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

Pharmacodynamic Group: Antimycotics for systemic use
ATC code: J02A C01

Fluconazole, belongs to the group of triazole antimycotics, specifically inhibiting fungal ergosterol synthesis.

5.2. Pharmacokinetic properties

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

Absorption
After administration of 200 mg fluconazole, Cmax is around 4.6 mg/l and plasma concentrations obtained at steady state after 15 days are around 10 mg/l

After administration of 400 mg of fluconazole, Cmax is around 9 mg/l and plasma concentrations obtained at steady state after 15 days are around 18 mg/l

The intake of a double dose on day 1 results in plasma concentrations that are approximately 90% of steady state on day 2

Distribution
The volume of distribution corresponds to total body water. The protein binding in plasma is low (11-12%).

Fluconazole is distributed over the total body water. The concentration in saliva is similar to plasma levels. In patients with fungal meningitis, the concentration of fluconazole in the cerebrospinal fluid is approximately 80% of the corresponding plasma levels.

In the stratum corneum, epidermis-dermis and eccrine sweat higher concentrations of fluconazole are reached compared to those in the serum. Fluconazole is accumulated in the stratum corneum. At a dose of 150 mg once weekly, the concentration of fluconazole in the stratum corneum after 2 doses was 23.4 microgram/g and 7 days after second dosing the concentration was still 7.1 microgram/g.

Elimination
Fluconazole is mainly renally excreted. Approximately 80% of the administered dose is excreted in the urine in the non metabolised form. Fluconazole clearance is proportional to creatinine clearance. Circulating metabolites have not been demonstrated.

The half-life in plasma is approximately 30 hours, which allows for single dose treatment in vaginal candidiasis and once daily dosing and once weekly dosing in connection with other indications.

Children, metabolise fluconazole more rapidly. Accordingly the half life in children of 5-15 years is between 15.2-17.6 hours, about half of that of adults

It has been demonstrated that fluconazole 50 mg daily given for up to 28 days does not influence plasma concentrations in women of childbearing age. Fluconazole 200-400 mg daily has no clinically significant effect on endogenous steroid levels or on ACTH stimulated responses in healthy, male volunteers.

5.3. Preclinical safety data

Preclinical data from conventional studies on repeat-dose/general toxicity, genotoxicity or carcinogenicity indicate no special hazard for humans not already considered in other sections of the SPC.

In reproductive toxicity studies in rats an increased incidence of hydronephrosis and extension of renal pelvis was reported and embryonal lethality was increased. An increase in anatomical variations and delayed ossification was noted as well as prolonged delivery and dystocia, effects consistent with inhibition of estrogen synthesis in rats. In reproduction toxicity studies in the rabbit, abortions were recorded.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium chloride
Water for Injection.

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.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4. Special precautions for storage

Keep container in the outer carton.

6.5. Nature and contents of container

Glass vial with a rubber stopper and aluminium overseal.

Pack sizes: 50 ml, 100 ml and 200 ml.

6.6. Instruction for use and handling (and disposal)

For single use only. Discard any remaining solution.

Although further dilution is unnecessary, Fluconazole Solution for Infusion is compatible with the following administration fluids:
Dextrose 20%
Ringers solution
Hartmann's solution
Sodium bicarbonate 4.2%
Normal Saline 0.9%

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

ADMINISTRATIVE DATA

7. MARKETING AUTHORISATION HOLDER

Relonchem Limited,

27 Old Gloucester Street,
London WC1 3XX.

8. MARKETING AUTHORISATION NUMBER

PL 20395/0012

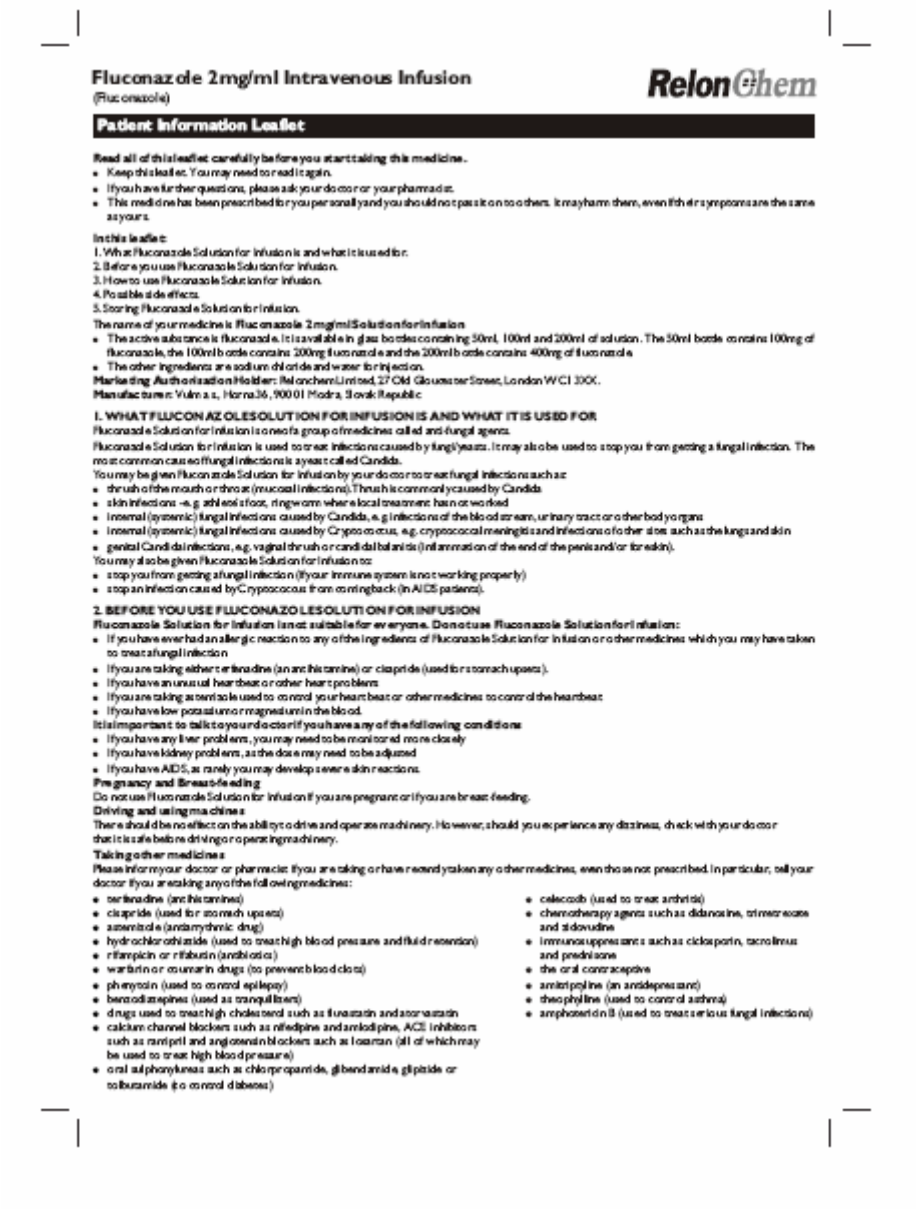
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/10/2006

10 DATE OF REVISION OF THE TEXT

16/10/2006

Labels and Leaflet



Fluconazole 2mg/ml Intravenous Infusion

(Fluconazole)

RelonChem

Patient Information Leaflet

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:
1. What Fluconazole Solution for Infusion is and what it is used for.
2. Before you use Fluconazole Solution for Infusion.
3. How to use Fluconazole Solution for Infusion.
4. Possible side effects.
5. Storing Fluconazole Solution for Infusion.

The name of your medicine is Fluconazole 2mg/ml Solution for Infusion
- The active substance is fluconazole. It is available in glass bottles containing 50ml, 100ml and 200ml of solution. The 50ml bottle contains 100mg of fluconazole, the 100ml bottle contains 200mg fluconazole and the 200ml bottle contains 400mg of fluconazole.
- The other ingredients are sodium chloride and water for injection.

Marketing Authorisation Holder: Relonchem Limited, 27 Old Gloucester Street, London WC1 3XX.
Manufacturer: Vulm a.s., Horna 36, 90001 Modra, Slovak Republic

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

Fluconazole Solution for Infusion is one of 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, ringworm where local treatment has not worked
- 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 USE FLUCONAZOLE SOLUTION FOR INFUSION

Fluconazole Solution for Infusion is not suitable for everyone. Do not use Fluconazole Solution for Infusion:
- If you have ever 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
- If you are taking either terfenadine (an antihistamine) or cisapride (used for stomach upsets).
- If you have an unusual heartbeat or other heart problems
- If you are taking an antiarrhythmic used to control your heartbeat or other medicines to control the heartbeat
- If you have low potassium or magnesium in the blood.

It is important to talk to your doctor if you have any of the following conditions:
- If you have any liver problems, you may need to be monitored more closely
- If you have kidney problems, as the dose may need to be adjusted
- If you have AIDS, as rarely you may develop severe skin reactions.

Pregnancy and Breast-feeding

Do not use Fluconazole Solution for Infusion if you are pregnant or if you are breast-feeding.

Driving and using machines

There should be no effect on the ability to drive and operate machinery. However, should you experience any dizziness, check with your doctor that it is safe before driving or operating machinery.

Taking other medicines

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed. In particular, tell your doctor if you are taking any of the following medicines:
- terfenadine (an antihistamine)
- cisapride (used for stomach upsets)
- astemizole (an antiarrhythmic drug)
- hydrochlorothiazide (used to treat high blood pressure and fluid retention)
- rifampicin or rifabutin (antibiotics)
- warfarin or coumarin drugs (to prevent blood clots)
- phenytoin (used to control epilepsy)
- benzodiazepines (used as tranquillisers)
- drugs used to treat high cholesterol such as fluvastatin and atorvastatin
- calcium channel blockers such as nifedipine and amlodipine, ACE inhibitors such as ramipril and angiotensin blockers such as losartan (all of which may be used to treat high blood pressure)
- oral sulphonylureas such as chlorpropamide, glibenclamide, glipizide or tolbutamide (to control diabetes)
- celecoxib (used to treat arthritis)
- chemotherapy agents such as didanosine, trimetrexate and zidovudine
- immunosuppressants such as ciclosporin, tacrolimus and prednisone
- the oral contraceptive
- amitriptyline (an antidepressant)
- theophylline (used to control asthma)
- amphotericin B (used to treat serious fungal infections)

3. HOW TO USE FLUCONAZOLE SOLUTION FOR INFUSION

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

Fluconazole Solution for Infusion is supplied as a solution. It is unnecessary to dilute it further. This medicine should not be mixed with any other drug before infusion.

The usual doses of Fluconazole Solution for Infusion for different infections are below. Check with your doctor or nurse if you are not sure why you are being given Fluconazole Solution for Infusion.

Duration of Treatment: the length of treatment will depend on the type and severity of infection being treated and how well you respond to the treatment.

ADULTS

- **Thrush infections of mouth and throat:** The usual dose is 50mg(25ml) once daily for 1-2 weeks.
- **Vaginal thrush infections:** A single dose of 150mg(75ml).
- **Other Mucosal thrush infections:** 50-100mg (25-50ml) once daily for 2-4 weeks.
- **Internal (Systemic) thrush:** A single dose of 400mg(200ml) on the first day followed by a daily dose of 200mg(100ml).
- **To prevent thrush infections in patients with a poor immune system due to low numbers of white blood cells (neutropenic patients):** 50-400 mg (25-200ml) once daily depending on your risk of infection.
- **To treat cryptococcal meningitis in patients with a poor immune system:** A single dose of 400mg (200ml) on the first day followed by a daily dose of 200-400mg (100-200ml) for 6-8 weeks. To prevent repeat infection a daily dose of 100-200mg (50-100ml) is recommended.
- **Fungal skin infections:** 50mg (25ml) once daily for 2-4 weeks. Athlete's foot may need up to 6 weeks treatment.

CHILDREN

4 weeks to 15 years old

The maximum daily dose for children is 400mg. For children over 4 weeks old, the dose is based on their body weight.

- For infections of the body surfaces: 3mg/kg for every kg of body weight daily. The first dose may sometimes be 6mg per kg.
- For treatment of infections that have invaded the body and for cryptococcal meningitis, a dose of 6-12mg per kg of body weight daily.
- For prevention of infection in children with a poor immune system, due to low numbers of white blood cells (neutropenic patients): a dose of 3- 12mg per kg daily, depending on the severity of the neutropenia.

2-4 weeks old

The maximum daily dose for infants 2-4 weeks is 12mg per kg of body weight every 2 days. The dosage is the same as for children but to be given once every 2 days.

Less than 2 weeks old

The maximum daily dose for infants 2-4 weeks is 12mg per kg of body weight every 3 days. The dosage is the same as for children but to be given once every 3 days.

Use of fluconazole 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. If you are on dialysis the recommended dose as detailed above can be given after dialysis. If you have poor kidney function but are not on dialysis then the dose will be halved if appropriate.

If you are unsure about the dose being given ask your doctor or nurse to explain.

4. POSSIBLE SIDE EFFECTS

Like all medicines, fluconazole Solution for Infusion can have side effects. The most common side effects are nausea, stomach pain, diarrhoea, wind, headache, dizziness, fits and skin rashes.

Some people may have an allergic reaction to fluconazole.

- An allergic reaction (angioedema): swelling of the face, lips, tongue or throat, or difficulty breathing or swallowing.
- Severe skin reactions such as large fluid filled blisters, ulceration in the mouth and throat, around the anus and genital region. These symptoms are usually accompanied by sickness, headache and fever.

This is a very serious but rare side effect. You may need urgent medical attention.

Other side effects that have occurred rarely in patients being given this medicine include:

Gastrointestinal disorders: heartburn, being sick, changes in taste.

Skin disorders: itchy redness and skin rashes, hair loss, severe skin reactions including blistering and ulcers.

Liver disorders: yellowing of the skin as a result of liver problems including inflammation of liver and liver toxicity.

Blood changes: increased blood triglycerides and cholesterol and decreased potassium, decrease in the number of white blood cells and decrease in the number of platelets which may make you more prone to infections.

AIDS patients should be warned that they are likely to be prone to skin reactions to many drugs, including fluconazole.

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

5. STORING FLUCONAZOLE SOLUTION FOR INFUSION

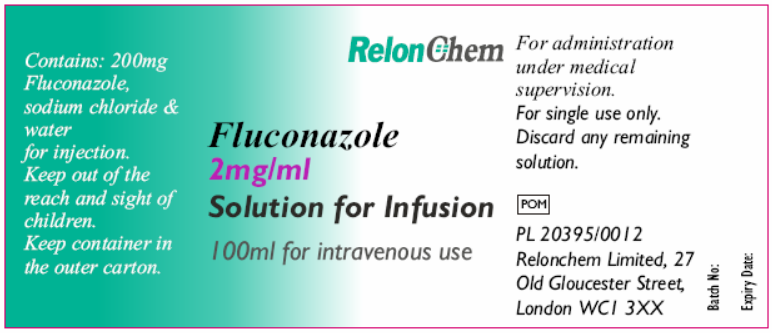
Keep container in the outer carton.

Keep out of the reach and sight of children.

Do not use after the expiry date stated on the label.

This leaflet was last approved in January 2006

28 x 130 mm



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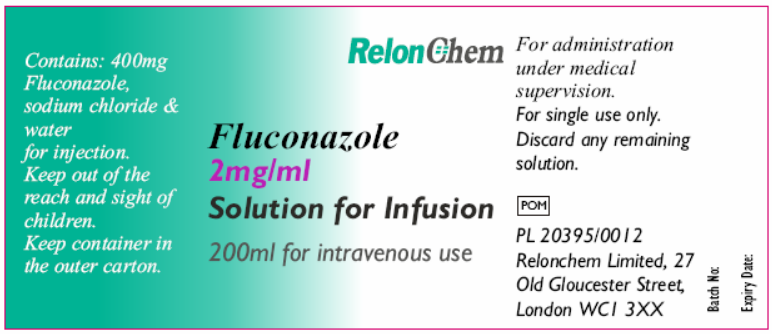

55 x 130 mm


RelonChem
Fluconazole
2mg/ml
Solution for
Infusion
For intravenous use
50ml solution
for infusion
Contains:
Fluconazole 100
mg.
Also contains:
sodium chloride,
water for injection.
Keep out of the
reach and sight of
children.
Keep container in
the outer carton.
For single use only.
Discard any
remaining solution.
RelonChem
Fluconazole
2mg/ml
Solution for
Infusion
For intravenous use
50ml solution
for infusion
Batch No:
Expiry Date :
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patient information
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London, WC1 3XX.
For administration
under medical
supervision.