FLUCONAZOLE 2MG/ML SOLUTION FOR INFUSION
PL 14894/0351

UKPAR

TABLE OF CONTENTS

Lay Summary .......................................................... Page 2
Scientific discussion .................................................. Page 3
Steps taken for assessment ......................................... Page 11
Steps taken after authorisation – summary ..................... Page 12
Summary of Product Characteristics .........................
Product Information Leaflet ......................................
Labelling ..................................................................
FLUCONAZOLE 2MG/ML SOLUTION FOR INFUSION
PL 14894/0351

LAY SUMMARY

On 24th February 2010, the MHRA granted Ranbaxy (UK) Limited a Marketing Authorisation (licence) for Fluconazole 2mg/ml Solution for Infusion (PL 14894/0351).

Fluconazole belongs to a group of medicines called antifungals. Fluconazole 2mg/ml Solution for Infusion is used in the treatment of infections caused by Candida, Cryptococci, and other related yeast, in particular:

• Thrush of the mouth and throat, of the swallowing tube that joins the mouth with the stomach (called the oesophagus), of the lining of the lung airways, and Candida infections in the urine in people who have very poor immunity to infections.

• Serious Candida infections that have invaded into the body and the organs. Fluconazole is also used to prevent serious Candida infections in people who have very few white blood cells so are unable to fight off infection. For example, people who have had bone marrow transplants and people who have AIDS.

• A type of meningitis (inflammation of the layers of the brain) caused by a fungus called Cryptococcus. Fluconazole is also used to prevent further infections by this fungus and relapses of cryptococcal meningitis in people with poor immunity to infections.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of using Fluconazole 2mg/ml Solution for Infusion outweigh the risks; hence a Marketing Authorisation has been granted.
**SCIENTIFIC DISCUSSION**

**TABLE OF CONTENTS**

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>4</td>
</tr>
<tr>
<td>Pharmaceutical assessment</td>
<td>5</td>
</tr>
<tr>
<td>Preclinical assessment</td>
<td>8</td>
</tr>
<tr>
<td>Clinical assessment (including statistical assessment)</td>
<td>9</td>
</tr>
<tr>
<td>Overall conclusions and risk benefit assessment</td>
<td>10</td>
</tr>
</tbody>
</table>
INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a Marketing Authorisation for the medicinal product Fluconazole 2mg/ml Solution for Infusion (PL 14894/0351) to Ranbaxy (UK) Limited on 24th February 2010. This prescription only medicine is used for the treatment of mycoses caused by Candida, Cryptococci, and other related yeasts, in particular:

- Mucosal candida infections including oropharyngeal, eosophageal, mucocutaneous and noninvasive bronchopulmonial candidiasis and candiduria in patients with decreased immunological defence.
- Systemic candida infections, including candidemia in non-neutropenic patients.
- Prophylaxis against deep candida- infections (especially Candida albicans) in connection with bone marrow transplantation.
- Acute cryptococcal meningitis in adults, including patients with AIDS, transplanted patients or patients with other causes of immunosuppresion.
- Maintenance treatment to prevent recurrence of cryptococcal meningitis in patients with AIDS.

This application for Fluconazole 2mg/ml Solution for Infusion is submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product to Diflucan Intravenous Infusion 2mg/ml, first authorised in the UK to Pfizer Limited in France in November 1994.

Fluconazole is a member of the triazole class of antifungals 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.

The pharmacovigilance system as described by the applicant fulfils the requirements. It also provides adequate evidence that the applicant has the services of a Qualified Person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring.

The Marketing Authorisation Holder has provided adequate justification for not submitting a risk management plan (RMP).
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Fluconazole

INN: Fluconazole
Chemical name: 2-(2,4-difluorophenyl)-1,3-bis-(1H-1,2,4-triazol-1-yl)-2-propanol.

Structural formula:

![Structural formula of Fluconazole](image)

Physical form: white or almost white, crystalline powder.
Solubility: slightly soluble in water, freely soluble in methanol, soluble in acetone.

Molecular formula: C₁₃H₁₂N₆OF₂
Molecular weight: 306.3

Fluconazole is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture of the active substance fluconazole from its starting materials are controlled by a Certificate of Suitability.

An appropriate retest period has been proposed based on stability data submitted for the active substance fluconazole.

An appropriate specification is provided for the active substance, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specification.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Suitable Certificates of Analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.
DRUG PRODUCT
Other ingredients
Other ingredients consist of pharmaceutical excipients sodium chloride and water for injection. All the ingredients comply with their relevant European Pharmacopoeia monographs.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

Product development
The objective of the development programme was to produce a product that could be considered a generic medicinal product of Diflucan Intravenous Infusion 2mg/ml (Pfizer Limited, November 1994.)

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative impurity profiles have been provided for the finished product versus the reference product Diflucan Intravenous Infusion 2mg/ml (Pfizer Limited).

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

In-process controls are satisfactory based on process validation data and controls on batches of the finished product.

Finished product specification
The finished product specification is satisfactory. 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 for all working standards used have been provided and are satisfactory.

Container-Closure System
The product is packaged in clear, type I, glass vials sealed with bromobutyl stopper and sealed with an aluminium and polypropylene flip-off cap. There is one 100ml vial per pack.

Specifications and Certificates of Analysis for the packaging types used have been provided. All primary product packaging complies with European Pharmacopoeia monograph 3.2.1 (glass containers for pharmaceutical use).

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 4 years has been set with the special precaution for storage ‘Do not freeze’.

ADMINISTRATIVE
Expert Report
A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.
Summary of Product Characteristics (SPC)
This is pharmaceutically satisfactory.

Labelling
These are pharmaceutically satisfactory.

Patient Information Leaflet (PIL)
This is pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

MAA Form
This is pharmaceutically satisfactory.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application.
PRECLINICAL ASSESSMENT

This application for Fluconazole 2mg/ml Solution for Infusion was submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal products of Diflucan Intravenous Infusion 2mg/ml, first authorised to Pfizer Limited in the UK in November 1994.

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

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
No bioequivalence studies have been performed and none are required for this application, as the product is administered as a parental aqueous solution, distributed rapidly in vivo.

EFFICACY
No new data has been provided.

SAFETY
No new data has been provided.

EXPERT REPORTS
The clinical expert report has been written by a suitably qualified person and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
This is consistent with that for the reference product and is satisfactory.

LABELLING
These are satisfactory.

APPLICATION FORM (MAA)
This is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)
This is consistent with that for the reference product and is satisfactory.

DISCUSSION
A bioequivalence study with the reference product is not required for this product, which can be justified as a generic medicinal product considering the quantitative and qualitative composition of the product and the route of administration.

MEDICAL CONCLUSION
The grant of a Marketing Authorisation is recommended for this application.
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 applications of this type.

EFFICACY
Fluconazole is a well-known drug and has been used for many years. No bioequivalence studies have been performed and none are required for this application, as the product is administered as a parental aqueous solution, distributed rapidly \textit{in vivo}.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with those for the reference product Diflucan Intravenous Infusion 2mg/ml.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The data submitted supports the claim that the applicant’s product and the reference product are interchangeable. Extensive clinical experience with fluconazole is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is, therefore, considered to be positive.
FLUCONAZOLE 2MG/ML SOLUTION FOR INFUSION
PL 14894/0351

STEPS TAKEN FOR ASSESSMENT

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation application on 23rd December 2004.</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 15th September 2005.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the application, the MHRA requested further information relating to the quality dossier on 18th April 2008 and 13th November 2008. The MHRA requested further information relating to the clinical dossier on 18th April 2008.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 19th September 2008 and 4th November 2009 for the quality section. The applicant provided further information on 19th September 2008 for the clinical section.</td>
</tr>
<tr>
<td>5</td>
<td>The application was determined on 24th February 2010.</td>
</tr>
</tbody>
</table>
### STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Fluconazole 2mg/ml Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of solution for infusion contains 2 mg Fluconazole.
Each 100 ml vial contains 200 mg Fluconazole.
For Excipients, see Section 6.1.

3 PHARMACEUTICAL FORM
Solution for infusion.
Transparent solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS
Treatment of mycoses caused by Candida, Cryptococci, and other related yeasts, in particular:

- Mucosal candida infections including oropharyngeal, eosophageal, mucocutaneous and noninvasive bronchopulmonial candidiasis and candiduria in patients with decreased immunological defence.
- Systemic candida infections, including candidemia in non-neutropenic patients.
- Prophylaxis against deep candida- infections (especially *Candida albicans*) in connection with bone marrow transplantation.
- Acute cryptococcal meningitis in adults, including patients with AIDS, transplanted patients or patients with other causes of immunosuppresion.
- Maintenance treatment to prevent recurrence of cryptococcal meningitis in patients with AIDS. Consideration should be given to official guidance on the appropriate use of antifungal agents.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
The dose is dependent on the type and severity of infection. Treatment of infections requiring multiple dose treatment should be continued until clinical or laboratory parameters show that the infection has subsided. An inadequate period of treatment may lead to recurrence of the infection.

Oral pharmaceutical forms and solutions for infusion are available for therapy. Patients should be switched from intravenous to oral administration as soon as possible. The daily dose need not be altered when changing from intravenous to oral administration or vice versa.

**Dosage in adults:**

_Mucosal Candidia:_

- Oropharyngeal candidiasis –
  The normal dose is 50mg daily, also in patients with impaired immune function. Administered for 7-14 days. The dose may be increased to 100mg if necessary. In patients with severely impaired immune response, the treatment may be continued for a longer period.

- Oesophageal mucotaneous, non-invasive bronchopulmonial candidiasis and candiduria –
  The normal dose is 50mg daily for 14-30 days. In severe cases, the dose may be increased to 100mg.

_Systemic Candida infections:_
The dose in candidaemia and other invasive candida infections is 400-800 mg on the first day and 200-400 mg daily thereafter. The dose depends on the type and severity of the infection.

In most cases a loading dose of 800 mg on the first day followed by 400 mg daily thereafter may be preferable. The duration of treatment, often up to several weeks, is determined by the clinical response.

_Prophylaxis against deep Candida infections in patients with neutropenia due to bone marrow transplantation:_
400 mg once daily. Prophylaxis with fluconazole should be initiated several days before anticipated neutropenia and should continue for 7 days after neutrophilic values have increased to >1 x 10^9/l.

**Cryptococcal meningitis:**
The normal dose is 400 mg on the first day then 200 mg-400 mg daily thereafter. The duration of treatment for cryptococcal infections depends on the clinical response, but is usually at least 6-8 weeks for cryptococcal meningitis.

A daily dose of 100-200 mg is recommended in maintenance treatment to prevent relapse of cryptococcal meningitis in AIDS patients.

The duration of the maintenance treatment of AIDS-patients should be considered with regard to increased risk of resistance to fluconazole.

**Dosage in children and adolescents:**
As with similar infections in adults, the duration of treatment is based on the clinical response. The maximum daily dose of 400mg should not be exceeded in children.

**Mucosal Candida infections:**
3 mg/kg once daily. 6 mg/kg may be given on day 1 in order to reach steady-state concentration more rapidly.

**Prophylaxis against deep Candida infections in patients with neutropenia due to bone marrow transplantation:**
The recommended dose is 3-12 mg/kg once daily. The dosage is dependent on the extent and duration of the neutropenia

**Prevention of relapse of cryptococcal meningitis:**
The recommended dose is 3-12 mg/kg daily, depending on the degree of severity of the infection.

**Systemic Candida infections:**
The recommended dose is 6-12 mg/kg daily, depending on the degree of severity of the infection.

**Children four weeks of age and younger:**
Fluconazole is excreted more slowly in neonates than in older children. The same dose in mg/kg should be used, but the dose interval extended. For premature newborn infants and neonates up to 2 weeks of age, the dose should be administered every 3rd day (72 hour interval), for children 2-4 weeks old, on alternate days (48 hour interval).

**Use in the elderly:**
The normal adult dose should be given if there is no evidence of renal impairment.

**Renal impairment in adults and children:**
With repeated dosing, the normal dose is given on day 1; thereafter the dose interval or the daily dose is adjusted in relation to creatinine clearance as follows:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>Normal dose regime (100%)</td>
</tr>
<tr>
<td>11-50</td>
<td>Half normal daily dose (50%)</td>
</tr>
<tr>
<td>Patients receiving dialysis</td>
<td>One dose after every dialysis session</td>
</tr>
</tbody>
</table>

**Patients with liver insufficiency:**
Fluconazole should only be administered with special care and under careful monitoring in patients with liver insufficiency (see section 4.4).

**Administration:**
For intravenous infusion only.
Fluconazole is dissolved in isotonic saline solution, with an electrolyte content of Na+ 150 mmol and Cl- 150 mmol per 1000ml, and may be administered directly as an infusion.
The infusion rate should not exceed 20mg (10ml)/minute for adults. For children, it is recommended that the infusion rate not exceed 10mg (5ml)/min. for premature infants, the infusion time should be no less than 15 minutes. In patients requiring sodium or fluid restriction, the rate of administration should be taken into consideration as Fluconazole consists of a salt solution. In such cases the infusion should be given over a longer period.

4.3 CONTRAINDICATIONS
Fluconazole should not be used in patients with known hypersensitivity to fluconazole or to relatedazole compounds or any other ingredient in the formulation.
Fluconazole should not be co-administered with drugs both known to prolong QT-interval and metabolised by CYP3A4 such as cisapride, astemizole, terfenadine, pimozide and quinidine (see Section 4.5 Interactions with other medicinal products and other forms of interaction).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Severe liver toxicity, including death, has been reported in rare cases, most often in patients with serious underlying illnesses. No obvious connection, however, has been found between daily dose, duration of treatment, gender or age. Patients that develop abnormal liver function tests or significant increases from already abnormal levels during treatment should be carefully monitored.

Treatment should be discontinued if clinical signs of liver disease, with possible connection to fluconazole, develop. The liver toxicity has most often been reversible following withdrawal of the treatment. The benefits of the treatment should be evaluated against the risks of developing serious liver damage if therapy is continued in patients whose liver enzyme values rise during fluconazole treatment.

Certain azoles, including fluconazole, have been associated with prolongation of the QT interval. Rare cases of torsade de pointes have been reported during treatment with fluconazole. Although the association of fluconazole and QT-prolongation has not been fully established, fluconazole should be used with caution in patients with potentially proarrythmic conditions such as:
- Congenital or documented acquired QT prolongation
- Cardiomyopathy, in particular when heart failure is present
- Sinus bradycardia
- Existing symptomatic arrythmias
- Concomitant medication known to prolong QT interval (see Section 4.5 “Interactions with other medicinal products and other forms of interaction”)

Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalaemia should be corrected prior to initiation of fluconazole treatment.

In rare cases patients have developed exfoliative skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis in treatment with fluconazole. AIDS-patients have a higher tendency for the development of serious skin reactions from various drugs. Where patients with minor fungal infections that are being treated with fluconazole develop a skin rash, considered to be connected to treatment with fluconazole, the treatment should be stopped.

If patients who are being treated for invasive fungal infections or systemic infections develop a skin rash, they should be closely monitored and the treatment discontinued if bullous skin reactions or erythema multiforme develop.

Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4. Patients who receive concomitant treatment with fluconazole and drugs which have a narrow therapeutic interval (e.g. warfarin and phenytoin) and which are metabolised via CYP2C9 and/or CYP3A4 should be closely monitored (see sections 4.3 Contraindications and 4.5 Interactions with other medicinal products and other forms of interaction).

Fluconazole may lengthen the prothrombin time following administration of warfarin. Close monitoring of the prothrombin time is recommended.

Rare instances of anaphylactic reactions have been reported (see section 4.8 Undesirable effects).
For dosage in renal impairment, see section 4.2 Posology and method of administration.

Fertile women undergoing long-term treatment with fluconazole should use adequate methods of contraception (see section 4.6 Pregnancy and lactation).

Data regarding efficacy and safety of fluconazole in children and adolescents less than 16 years of age are still limited. Therefore the benefits of the treatment with fluconazole should be carefully evaluated against the risks.

Important information about some of the ingredients of Fluconazole
Your medicine contains 3.54 mg of sodium per ml. To be taken into consideration by patients on a controlled sodium diet.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

The following combinations are contraindicated:

- **Astemizole** (CYP3A4-substrate): Astemizole overdoses have led to prolonged QT interval a severe ventricular arrhythmia, torsade de pointes and cardiac arrest. Concomitant administration of astemizole and fluconazole is contraindicated due to the potential for serious, potentially fatal, cardiac effects.

- **Cisapride** (CYP3A4-substrate): Cardiovascular effects, including torsade de pointes, have been reported in patients having received concomitant treatment with fluconazole and cisapride. In one controlled study, where 200 mg fluconazole was administered once daily concomitantly with cisapride 20 mg four times daily, a significant increase in plasma levels of cisapride and prolongation of the QTc-interval where achieved. Concurrent treatment with cisapride and fluconazole is contraindicated (see 4.3 Contraindications).

- **Terfenadine** (400 mg fluconazole and higher; CYP3A4-substrate): Serious cardiac arrhythmias, secondary to prolonged QTc interval, have occurred in patients treated with anti-fungal medications such as triazolic compounds and terfenadine. Concomitant treatment with 200 mg fluconazole daily showed no prolongation of the QTc-interval. With doses of 400 mg and 800 mg fluconazole daily, the plasma concentration of terfenadine increased significantly. Concomitant treatment with fluconazole 400 mg per day or higher dose is contraindicated. With concomitant treatment with doses below 400 mg per day, the treatment should be closely monitored.

The effects of fluconazole on other drugs:

- **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 cholesteryl sulfate complex.

- Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4. In addition to the interactions given below, there is a risk that elevated serum concentrations of other drugs metabolised via CYP2C9 and CYP3A4 will not be secreted with concomitant administration of fluconazole. Caution should therefore always be observed during combination therapy with medications such as these and the patient closely monitored. The effects may persist for several days due to the long half life of fluconazole.

- **Alfentanil** (CYP3A4-substrate): In concomitant treatment with fluconazole (400 mg) and intravenous alfentanil (20 μg/kg) in healthy volunteers, AUC10 – increased twofold and clearance decreased by 55 % for alfentanil, probably through inhibition of CYP3A4. The combination may require dose adjustment.

- **Amitriptyline** (CYP2D6-substrate): Several case histories have described the development of elevated amitriptyline concentrations and signs of tricyclic toxicity when amitriptyline is used in combination with fluconazole. Concomitant infusion of fluconazole and nortriptyline, the active metabolite of amitriptyline, have been reported to lead to increased nortriptyline levels. Due to the risk of amitriptyline toxicity, monitoring of amitriptyline levels should be considered with dose adjustment where indicated.
• **Anticoagulants** (CYP2C9-substrate): In concomitant treatment with fluconazole and warfarin, the prothrombin time increased up to twofold. This is probably due to an inhibition of the metabolism of warfarin via CYP2C9. The prothrombin time should be monitored closely in patients treated concomitantly with fluconazole and coumarin-type anticoagulants.

• **Benzodiazepines** (CYP3A4-substrate): Fluconazole may inhibit the metabolism of benzodiazepines metabolised via CYP3A4, e.g. midazolam and triazolam. In concomitant oral single dose treatment with fluconazole (400 mg) and midazolam (7.5 mg) AUC increased 3.7 times and the half life of midazolam 2.2 times. The combination should be avoided. Where concomitant treatment is considered necessary, a reduction in the dose of midazolam should be considered and the patient monitored closely. In concomitant treatment with fluconazole (100 mg daily for 4 days) and triazolam (0.25 mg) the AUC and half-life of triazolam increased respectively 2.5 and 1.8 times. Prolonged and enhanced effects from triazolam have been observed. The combination may require reduction in the dose of triazolam.

• **Calcium channel antagonists** (CYP3A4-substrates): Some dihydropyridine calcium channel antagonists, including nifedipine, isradipine, nicardipine, amlodipine, and felodipine, are metabolised via CYP3A4. Literature reports have documented substantial peripheral oedema and/or elevated calcium antagonist serum concentrations during concurrent use of itraconazole and felodipine, isradipine, or nifedipine. An interaction might occur also with fluconazole.

• **Celecoxib** (CYP2C9-substrate): In concomitant treatment with fluconazole (200 mg daily) and celecoxib (200 mg), Cmax and AUC for celecoxib increased by 68 % and 134 % respectively. Halving the dose of celecoxib is recommended in combination therapy with fluconazole.

• **Cyclosporin** (CYP3A4-substrate): Clinically significant interactions between cyclosporin and fluconazole have been observed at doses of fluconazole of 200 mg and higher. In concomitant treatment with 200 mg fluconazole daily and cyclosporin (2.7 mg/kg/day), AUC for cyclosporin increased approximately 1.8 times and clearance was reduced by approximately 55 %. The plasma concentration of cyclosporin should be monitored in concomitant treatment with fluconazole.

• **Didanosine**: Co-administration of didanosine and fluconazole appears to be safe and has little effect on didanosine pharmacokinetics or efficacy. However, it is important to monitor fluconazole response. It may be advantageous to stagger fluconazole dosing to a time prior to didanosine administration.

• **Halofantrin** (CYP3A4-substrate): Drugs which inhibit CYP3A4 lead to an inhibition of halofantrin metabolism.

• **HMG-CoA-reductase-inhibitors** (CYP2C9- or CYP3A4-substrate): The risk of myopathy increases when fluconazole is administered concomitantly with HMG-CoA reductase inhibitors that are metabolised via CYP3A4, e.g. atorvastatin and simvastatin, or via CYP2C9, such as fluvastatin. Caution should be observed where concomitant treatment with fluconazole and HMG-CoA-reductase-inhibitors is considered necessary.

The combination may require dose reduction of the HMG-CoA reductase inhibitors. The patient should be observed with regard to signs of myopathy or rhabdomyolysis. Where myopathy or rhabdomyolysis are suspected, the treatment with HMG-CoA reductase-inhibitors must be discontinued.

• **Losartan** (CYP2C9-substrate): Fluconazole inhibits the conversion of losartan to its active metabolite (E-3174), which is responsible for the most of the angiotensin II receptor antagonism that occurs with losartan therapy. Concomitant treatment with fluconazole might lead to increased concentrations of losartan and decreased concentrations of the active metabolite. It is recommended that patients receiving the combination be monitored for continued control of their hypertension.

• **Oral contraceptive agents** (CYP3A4-substrate): In a kinetic study with combined oral contraceptives and 50 mg fluconazole daily, hormonal levels were not affected. With 200 mg fluconazole daily, AUC for ethinylestradiol increased by 40 % and levonorgestrel by 24 %. Fluconazole at these dosages probably has no effect on combined oral contraceptives.
• **Phenytoin** (CYP2C9-substrate): Concomitant, repeated treatment with 200 mg fluconazole and 250 mg phenytoin intravenously increased AUC24 for phenytoin by 75 % and Cmin by 128 %. In combination treatment, plasma phenytoin concentrations should be monitored and the dose adjusted.

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

• **Rifabutin** (CYP3A4-substrate): In concomitant treatment with fluconazole and rifabutin, the serum concentrations of rifabutin increased. Uveitis has been reported. Patients undergoing concomitant treatment should be monitored closely.

• **Sirolimus and tacrolimus** (3A4-substrate): In concomitant oral treatment with fluconazole and tacrolimus (0.15 mg/kg twice daily) the plasma concentration trough level of tacrolimus increased 1.4 and 3.1 times with a daily fluconazole dose of 100 mg and 200 mg respectively. Nephrotoxicity has been reported. Even though no interaction studies have been performed with fluconazole and sirolimus, a similar interaction can be anticipated. In concomitant treatment with fluconazole and tacrolimus or sirolimus, patients should be closely monitored and an adjustment in dose considered.

• **Sulphonylureas** (CYP2C9-substrate): Fluconazole has displayed prolonged half-life in serum for concomitantly administered sulphonylureas (glibencamide, glipizide, chlorpropamide and tolbutamide) in healthy volunteers. Fluconazole may be administered to diabetics together with sulphonylureas, but the risk of hypoglycemia should be considered.

• **Theophylline**: Fluconazole 200 mg reduces theophylline clearance by 18 %. In patients receiving high doses of theophylline and concomitant treatment with fluconazole, theophylline toxicity should be taken into consideration, and the dose must be adjusted as necessary.

• **Trimetrexate**: Fluconazole may inhibit the metabolism of trimetrexate, leading to increased trimetrexate plasma concentrations. If the combination cannot be avoided, trimetrexate serum levels and toxicity (bone marrow suppression, renal and hepatic dysfunction, and gastro-intestinal ulceration) must be closely monitored.

• **Zidovudine**: In interaction studies, AUC of zidovudine increased significantly by approximately 20 % and 70 % in concomitant treatment with fluconazole 200 mg and 400 mg per day respectively, probably due to inhibited glucuronidation. Patients receiving the combination should be monitored closely with regard to zidovudine related adverse reactions.

*The effects of other drugs on fluconazole:*

• **Hydrochlorthiazide**: The plasma concentration of fluconazole increased by 40 % with concomitant administration of hydrochlorthiazide in healthy volunteers. An increase of this dimension does not necessitate adjustment in the dose of fluconazole capsules in patients undergoing treatment with diuretics, but the prescribing doctor should be aware of the fact.

• **Rifampicin** (CYP450-inducers): Concomitant treatment with fluconazole (200 mg) and rifampicin (600 mg daily) reduced AUC for fluconazole by 23 % in healthy volunteers.

An increase in the dose of fluconazole should be considered in combination treatment.

### 4.6 PREGNANCY AND LACTATION

#### Pregnancy

Data from several hundred pregnant women treated with standard doses of fluconazole (less than 200 mg/day) as a single repeated dose during the first trimester of pregnancy, does not indicate undesirable effects on the foetus.

There are reports on multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in children 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.

Studies in animals have shown reproductive toxicity (see section 5.3 Preclinical safety data), but the potential risk in humans is unknown.

Fluconazole in standard doses and short-term treatment should not be used during pregnancy unless clearly necessary. Fluconazole in high doses or in prolonged regimens should not be used during pregnancy except for life threatening infections.

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

4.7 **EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**
Fluconazole has no or negligible influence on the ability to drive and use machines. However when driving vehicles or operating machines it should be taken into account that occasionally dizziness or seizures may occur.

4.8 **UNDESIRABLE EFFECTS**
In clinical trials, up to 10% have experienced adverse reactions. Approximately 1% discontinued the treatment due to adverse reactions.

The following treatment-related undesirable effects were reported in 4,048 patients receiving fluconazole for 7 or more days in clinical trials:

<table>
<thead>
<tr>
<th>Organ systems</th>
<th>Very common &gt; 1/10</th>
<th>Common &gt; 1/100, &lt; 1/10</th>
<th>Uncommon &gt; 1/1,000, &lt; 1/100</th>
<th>Rare &gt; 1/10,000, &lt; 1/1,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system</td>
<td></td>
<td></td>
<td>Anaemia</td>
<td></td>
</tr>
<tr>
<td>Immune system</td>
<td></td>
<td></td>
<td>Insomnia, somnolence</td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central and peripheral nervous system</td>
<td></td>
<td></td>
<td>Headache</td>
<td>Convulsion, dizziness, paresthesia, tremor, vertigo</td>
</tr>
<tr>
<td>Autonomic nervous system</td>
<td></td>
<td></td>
<td>Dry mouth, increased sweating</td>
<td></td>
</tr>
<tr>
<td>Special senses</td>
<td></td>
<td></td>
<td>Taste perversion</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td>Nausea and vomiting, abdominal pain, diarrhoea</td>
<td>Anorexia, constipation, dyspepsia, flatulence</td>
</tr>
<tr>
<td>Hepato-biliary</td>
<td></td>
<td></td>
<td>Clinically significant increase of AST, ALT and alkaline phosphatase</td>
<td>Cholestasis, hepatocellular damage, jaundice, clinically significant increase of total bilirubin</td>
</tr>
<tr>
<td>Skin and appendages</td>
<td></td>
<td></td>
<td>Skin rash</td>
<td>Pruritus</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
<td>Myalga</td>
<td></td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
<td>Fatigue, malaise, asthenia, fever</td>
<td></td>
</tr>
</tbody>
</table>
Adverse clinical events were reported more frequently in HIV infected patients (21%) than in non-HIV infected patients (13%). However, the patterns of adverse events in HIV infected and non-HIV infected patients were similar.

The following additional adverse events possibly causally related to the use of fluconazole have been observed after the receipt of the marketing authorisation:

*Blood and lymphatic system*
Leucopenia, including neutropenia and agranulocytosis, thrombocytopenia

*Immune system*
Angiooedema, face oedema, itching, urticaria

*Metabolism and nutrition*
Hypercholesterolemia, hypertriglyceridemia, hypokalemia

*Nervous system*
Seizures

*Cardiac*
Prolonged-QT, torsades de pointes (see section 4.4)

*Hepatobiliary*
Hepatic failure, hepatitis

*Skin and appendages*
Alopecia, toxic epidermal necrolysis

### 4.9 OVERDOSE

**Toxicity:**
Experience of overdose is limited for fluconazole. 1000 mg administered to an adult did not result in symptoms. 8200 mg administered to an adult, caused hallucinations and paranoid reaction. The patient was hospitalised and within 48 hours the patient’s condition was normal.

**Symptoms:**
Increased adverse reactions (headache, gastrointestinal symptoms), possibly hallucinations.

**Treatment:**
Where justified, gastric lavage. Symptomatic treatment. Fluconazole is mainly excreted in the urine. Forced volume diuresis will probably increase the elimination rate. A 3-hour hemodialysis session reduced plasma levels by approximately 50 %.

### 5 PHARMACOLOGICAL PROPERTIES

#### 5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives

ATC-code: J02AC01

Fluconazole is a triazole derivative with fungistatic effect, which specifically inhibits synthesis of the fungi’s ergosterol, which leads to defects in the cell membrane. Fluconazole has a high degree of specificity for the fungal cytochrome P-450 dependent enzymes. At a dose of 50 mg daily for 28 days, fluconazole has not been shown to influence serum levels of testosterone in men or the steroid concentration in fertile women.

Fluconazole 200-400 mg daily has no clinically significant effect on endogenous steroid levels or on ACTH stimulated response in healthy male volunteers. Interaction studies with antipyrine indicate that single or multiple doses of fluconazole 50 mg do not affect its metabolism.

The spectrum activity includes a number of pathogens including *Candida albicans* and other *candida*-species, Cryptococcus species and dermatophytes. *Candida krusei* is resistant to fluconazole. *Candida glabrata* has a naturally reduced sensitivity to fluconazole, approximately 40 % of the isolates are
resistant to fluconazole. Infections resulting from *aspergillus*-species should not be treated with fluconazole.

5.2 PHARMACOKINETIC PROPERTIES

Absorption
The pharmacokinetic properties are similar following oral and intravenous administration. The bioavailability of fluconazole following oral administration is in excess of 90%. The degree of absorption is not affected by concomitant food intake. Maximum serum concentration is generally reached after 0.5 to 1.5 hours.

Distribution
The serum concentration is proportional to the dose. Binding to plasma proteins is approximately 12%. The volume of distribution approximates total body water 0.7 l/kg. Clearance is 0.253 ml/min/kg. The half-life is approximately 30 hours, at which steady-state levels are achieved after 4-5 days of repeated dosing.

Where the dose is doubled on the first day of treatment, a steady-state level of approximately 90% is reached on day 2.

Fluconazole has demonstrated good penetration to various body fluids. The concentration in saliva and sputum is equal to that in plasma. The concentration in cerebrospinal fluid is 80% of the plasma level in patients with meningitis resulting from fungal infection.

High skin concentrations of fluconazole, well above serum concentrations, have been achieved in the stratum corneum, epidermis-dermis and in eccrine sweat. Fluconazole accumulates in the stratum corneum. At a dose of 150 mg once weekly, and after two doses of fluconazole, the concentration was 23.4 μg/g and 7.1 μg/g a week later.

Metabolism
Fluconazole is metabolised only to a small degree. Only 11% of a radioactively labelled dose is excreted in urine in changed form.

Elimination
Fluconazole is primarily excreted via the kidneys. 80% of the dose appears, unchanged in the urine. In addition to renal excretion, approximately 10% of the dose is excreted in the form of metabolites.

Fluconazole clearance is proportional to creatinine clearance.

Pharmacokinetics in Children
The plasma elimination half-life of fluconazole is approximately 20 hours in children after the neonatal period, and the distribution volume is approx. 1 l/kg.

Prematures, have a longer fluconazole plasma elimination half-life (approximately 70 hours) and a larger distribution volume (1.2-2.3 l/kg) compared with children born at the calculated date of delivery.

During the first weeks after birth the plasma clearance of fluconazole increases and the plasma elimination half-life decreases.

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 reproduction toxicity studies in rat 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. In reproduction toxicity studies in rabbits, abortions were recorded.
6 PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Sodium chloride
Water for Injections.

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
4 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not freeze

6.5 NATURE AND CONTENTS OF CONTAINER
Solution for infusion in 100ml clear Type 1 transparent glass vials, with bromobutyl stopper and aluminium/polypropylene flip-off cap.
Pack Sizes: One 100ml vial per pack.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
The solution should be visually inspected prior to use and only clear solutions, without particles, should be used.

The infusion contains no preservatives. For single use only. Any remaining solution should be disposed of, in accordance with local requirements.

The infusion is compatible with the following infusion solutions:
- Dextrose 20% solution
- Ringer’s solution
- Ringer’s-lactate solution
- Potassium chloride 1% in 5% dextrose solution
- Sodium bicarbonate 4.2% solution
- Sodium chloride 9 mg/ml (0.9%) solution

7 MARKETING AUTHORISATION HOLDER
Ranbaxy (UK) Limited
Building 4
Chiswick Park
566 Chiswick High Road
London
W4 5YE
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 14894 / 0351

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
24/02/2010

10 DATE OF REVISION OF THE TEXT
24/02/2010
If Fluconazole and certain other medications are taken at the same time, the effect of treatment may be affected. This applies for example to the following:
- certain blood-thinning agents e.g. warfarin
- certain sleeping pills such as midazolam and triazolam
- celecoxib (for inflammation)
- ciclosporin, tacrolimus and sirolimus (used in organ transplantation)
- phenytoin (for epilepsy)
- certain agents that reduce blood lipids such as atorvastatin, simvastatin and fluvastatin
- rifabutin and rifampicin (for tuberculosis and other infections)
- blood sugar lowering agents such as chlorpropamide, glibenclamide, glipizide, tolbutamide
- theophylline (used in the treatment of asthma)
- zidovudine (used for treatment of HIV infection)
- hydrochlorothiazide (diuretic)
- amitriptyline (for depression)
- halofantrine (for malaria)
- amphotericin B (used to treat fungal infections)
- theophylline (for respiratory problems)
- drugs used in the control of heart rhythm and blood pressure (nilfedinone, isradipine, nicardipine, amlodipine and felodipine)
- losartan (for high blood pressure)
- trimethoprim (used in certain types of pneumonia)
- prednisolone (used in inflammation and organ transplants)
- didanosine (treatment used in AIDS)

Using Fluconazole with food and drink
Avoid consuming alcohol until you have discussed this with your doctor.

Pregnancy and breast-feeding
Before starting treatment, you must inform your doctor if you are pregnant or intend to become pregnant. Your doctor will then decide whether you should take Fluconazole.
Women of child-bearing potential should use reliable contraception during long-term treatment with Fluconazole.

Fluconazole enters breast milk, so women are advised not to breast-feed their babies while they are taking Fluconazole.

Driving and using machines
Occasionally dizziness or fits can occur in people taking Fluconazole, so care should be taken when driving or operating machinery (see section 4 of this leaflet for more information on possible side effects).
• A type of meningitis (inflammation of the layers of the brain) caused by a fungus called the Cryptococcus. Fluconazole is also used to prevent further infections with this fungus and relapses of cryptococcal meningitis in people with poor immunity to infections.

2. BEFORE YOU USE FLUCONAZOLE

Do not use Fluconazole if you:
• are allergic (hypersensitive) to Fluconazole, similar substances, or any of the other ingredients of Fluconazole.
• are taking other medicines containing cisapride (commonly used for nausea and vomiting), astemizole (used in seasonal allergies), terfenadine (used in seasonal allergies), pimozide (used in mental disorders) and quinidine (used for malaria treatment and control of heart rhythm). This combination can cause heart problems.

Take special care with Fluconazole
Before you start treatment with Fluconazole, you should tell your doctor if you have:
• impaired liver function
• impaired kidney function
• Heart disease e.g. an irregular heart rhythm or if you are taking any medicines to control your heart rhythm. These medicines may be called amiodarone, sotalol or disopyramide.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Important information about some of the ingredients of Fluconazole
Your medicine contains 3.54mg of sodium per ml. To be taken into consideration by patients on a controlled sodium diet.

3. HOW TO USE FLUCONAZOLE

Fluconazole is administered via intravenous drip by medical personnel.

The dose and the treatment times will be determined by the doctor, who will adjust them especially for you.

Adults:
The usual doses:
• For mucosal infections of the mouth: 50-100 mg daily for 7-14 days
• For mucosal infections of the throat or elsewhere: 50-100 mg once daily for 14-30 days
• For internal fungal infections caused by Candida: 400 mg on the first day then 200-400 mg once daily.
• For internal fungal infections caused by Cryptococcus: 400mg on the first day then 200-400mg 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.
**Children:**
The usual dose for children ranges between 3 and 12 mg/kg bodyweight per day.

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

**Patients with kidney problems:**
Your doctor may need to modify these doses depending on how your kidneys work.

**If you use more Fluconazole than you should**
It is most unlikely that you will be given too much medicine by your nurse or doctor. Your doctor and nurse will be monitoring your progress, and checking the medicine that you are given. Always ask if you are not sure why you are getting a dose of medicine.

**If you forget to use Fluconazole**
Your doctor or nurse have instructions when to give you your medicine. It is most unlikely that you will not be given the medicine as it has been prescribed. If you think that you may have missed a dose then talk to your nurse or doctor.

**If you stop using Fluconazole**
It is important that you keep using Fluconazole until the prescribed course is finished. Do not stop using it just because you feel better. If you stop too soon, the infection may start up again. If you still feel unwell at the end of the course of treatment, tell your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

### 4. POSSIBLE SIDE EFFECTS

Like all medicines, Fluconazole can cause side effects, although not everybody gets them.

- taste perception
- reduced and low white blood cell count e.g. agranulocytosis, low platelet count
- paresthesia (tingling or numbness)
- tremor
- vertigo (a feeling of dizziness or ‘spinning’)
- constipation
- inflammation and damage to the liver, sometimes with jaundice (yellowing of the skin and whites of eyes)

**Rare:**
- raised blood cholesterol and triglycerides
- low blood potassium
- disturbances of heart rhythm
- hair loss
- skin and mucosal changes (including serious ones such as rashes that involve blistering and peeling of the skin that may involve eyes, mouth and genitals)
- serious allergic reaction with symptoms such as oedema (swelling) of the face, breathing difficulties, itching and hives.

There may be changes in the results of certain laboratory tests:
- Abnormal liver function tests
- Abnormal kidney function tests
- Decreased values of blood cell counts
- Increased cholesterol and triglycerides in blood
- Other biochemical abnormalities (such as decreased potassium in serum)

These changes in the laboratory tests may be more marked in patients with HIV infection, cancer and in patients simultaneously taking other drugs which may also affect the results of such tests.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
5. HOW TO STORE FLUCONAZOLE

Keep out of the reach and sight of children.

Do not freeze.

Do not use Fluconazole after the expiry date which is stated on the carton and label, after "EXP". The expiry date refers to the last day of the month.

Do not use Fluconazole if you notice that there are particles present in the solution i.e. the solution is not clear.

Your medicine is for single use only and any remaining solution has to be discarded.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Fluconazole contains
- The active substance is Fluconazole. Each 100ml vial of Fluconazole 2 mg/ml Solution for Infusion contains 200 mg of Fluconazole.
- The other ingredients are sodium chloride and water for injections.

What Fluconazole looks like and contents of the pack
Fluconazole 2 mg/ml Solution for Injection is a clear, transparent solution which is available in packs of one 100ml vial.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder: Ranbaxy (UK) Limited, Building 4, Chiswick Park, 566 Chiswick High Road London W4 5YE

Manufacturer: Laboratory Reig Jofre, Gran Capita, 10-08970 Sant Joan Despi, Barcelona, Spain

This leaflet was last approved in November 2008
The following information is intended for medical or healthcare professionals only

Fluconazole 2 mg/ml Solution for Infusion

TECHNICAL LEAFLET

NAME OF THE MEDICINAL PRODUCT
Fluconazole 2 mg/ml Solution for Infusion

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of solution for infusion contains 2 mg Fluconazole. Each 100 ml vial contains 200 mg Fluconazole. For Excipients, see ‘List of excipients’.

PHARMACEUTICAL FORM
Solution for infusion.

TRANSPARENT SOLUTION

CLINICAL PARTICULARS

Therapeutic indications
Treatment of mycoses caused by Candida, Cryptococcus, and other related yeasts, in particular:
• Mucocutaneous candidiasis including oropharyngeal, esophageal, mucocutaneous, and noninvasive bronchopulmonary candidiasis and candiduria in patients with decreased immunological defense.
• Systemic candidiasis, including candidemia in non-neutropenic patients.
• Prophylaxis against deep candida infections (especially Candida albicans) in connection with bone marrow transplantation.
• Acute cryptococcal meningitis in adults, including patients with AIDS, transplant patients or patients with other causes of immunosuppression.
• Maintenance treatment to prevent recurrence of cryptococcal meningitis in patients with AIDS.

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

Pharmacology and method of administration
The dose is dependent on the type and severity of infection. Treatment of infections requiring multiple dose treatment should be continued until clinical or laboratory parameters show that the infection has subsided. An inadequate period of treatment may lead to recurrence of the infection.

Oral pharmacological forms and solutions for infusion are available for therapy. Patients should be switched from intravenous to oral administration as soon as possible. The daily dose need not be altered when changing from intravenous to oral administration or vice versa.

Dosage in adults
Mucocutaneous Candida
• Oropharyngeal candidiasis – The normal dose is 50mg daily, also in patients with impaired immune function. Administered for 7-14 days. The dose may be increased to 100mg if necessary. In patients with severely impaired immune response, the treatment may be continued for a longer period.
• Esophageal mucocutaneous, non-invasive bronchopulmonary candidiasis and candiduria – The normal dose is 50mg daily for 14-30 days. In severe cases, the dose may be increased to 100mg.

Systemic Candida infections:
The dose in candidemia and other invasive candida infections is 400-800 mg on the first day and 200-400 mg daily thereafter. The dose depends on the type and severity of the infection.

In most cases a loading dose of 800 mg on the first day followed by 400 mg daily thereafter may be preferable. The duration of treatment, often up to several weeks, is determined by the clinical response.

Prophylaxis against deep Candida infections in patients with neutropenia due to bone marrow transplantation:
400 mg once daily. Prophylaxis with fluconazole should be initiated several days before anticipated neutropenia and should continue for 7 days after neutrophilic values have increased to >1x10⁹/l.

Cryptococcal meningitis:
The normal dose is 400 mg on the first day then 200 mg-400 mg daily thereafter. The duration of treatment for cryptococcal infections depends on the clinical response, but is usually at least 6-8 weeks for cryptococcal meningitis.

A daily dose of 100-200 mg is recommended in maintenance treatment to prevent relapse of cryptococcal meningitis in AIDS patients.

The duration of the maintenance treatment of AIDS-patients should be considered with regard to increased risk of resistance to fluconazole.

Dosage in children and adolescents:
As with similar infections in adults, the duration of treatment is based on the clinical response. The maximum daily dose of 400mg should not be exceeded in children.

Mucosal Candida infections:
3 mg/kg once daily. 6 mg/kg may be given on day 1 in order to reach steady-state concentration more rapidly.

Prophylaxis against deep Candida infections in patients with neutropenia due to bone marrow transplantation:
The recommended dose is 3-12 mg/kg once daily. The dosage is dependent on the extent and duration of the neutropenia.

Prevention of relapse of cryptococcal meningitis:
The recommended dose is 3-12 mg/kg daily, depending on the degree of severity of the infection.

Systemic Candida infections:
The recommended dose is 3-12 mg/kg daily, depending on the degree of severity of the infection.

Children four weeks of age and younger:
Fluconazole is excreted more slowly in infants than in older children. The same dose in mg/kg should be used, but the dose interval extended. For premature newborn infants and neonates up to 2 weeks of age, the dose should be administered every 3rd day (72 hour interval), for children 2-4 weeks old, on alternate days (48 hour interval).

Use in the elderly:
The normal adult dose should be given if there is no evidence of renal impairment.

Renal impairment in adults and children:
With repeated dosing, the normal dose is given on day 1; thereafter the dose interval or the daily dose is adjusted in relation to creatinine clearance as follows:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50</td>
<td>Normal dose regime (100%)</td>
</tr>
<tr>
<td>11-50</td>
<td>Half normal daily dose (50%)</td>
</tr>
</tbody>
</table>

Patients receiving dialysis:
One dose after every dialysis session.

Patients with liver insufficiency:
Fluconazole should only be administered with special care and under careful monitoring in patients with liver insufficiency (see ‘Special warnings and precautions for use’).

Administration:
For intravenous use as infusion only.

Fluconazole is dissolved in isotonic saline solution, with an electrolyte content of Na+ 130 mmol and Cl2- 150 mmol per 1000ml, and may be administered directly as an infusion.

The infusion rate should not exceed 20mg (20ml)/minute for adults. For children, it is recommended that the infusion rate not exceed 10mg (5ml)/min. For premature infants, the infusion time should be no less than 15 minutes. In patients requiring sodium or fluid restriction, the rate of administration should be taken into consideration as if fluconazole is part of a salt solution. In such cases the infusion should be given over a longer period.

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

Fluconazole should not be co-administered with drugs both known to prolong QT-interval and metabolised by CYP3A4 such as clozapine, astemizole, terfenadine, pimozide and quinidine (see ‘Interactions with other medicinal products and other forms of interaction’).

Special warnings and precautions for use:
Severe liver toxicity, including death, has been reported in rare cases, most often in patients with serious underlying illnesses. No obvious connection, however, has been found between daily dose, duration of treatment, gender or age. Patients that develop abnormal liver function tests or significant increases from already abnormal levels during treatment should be carefully monitored.
UKPAR Fluconazole 2mg/ml Solution for Infusion PL 14894/0351

Treatment should be discontinued if clinical signs of liver disease, with possible connection to fluconazole, develop. The liver toxicity has most often been reversible following withdrawal of the treatment. The benefits of the treatment should be evaluated against the risks of developing serious liver damage if therapy is continued in patients whose liver enzyme values rise during fluconazole treatment.

Certain azoles, including fluconazole, have been associated with prolongation of the QT interval. Rare cases of torsade de pointes have been reported during treatment with fluconazole. Although the association of fluconazole and QT-prolongation has not been fully established, fluconazole should be used with caution in patients with potentially proarrhythmic conditions such as:
- Congestive or documented acquired QT prolongation
- Cardiomyopathy, in particular when heart failure is present
- Sinus bradycardia
- Existing symptomatic arrhythmias
- Coexistent medication known to prolong QT interval (see "Interactions with other medicinal products and other forms of interaction")

Electrolyte disturbances such as hypokalaemia, hypoglycaemia and hypocapnia should be corrected prior to initiation of fluconazole treatment.

In rare cases patients have developed exfoliative skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis in treatment with fluconazole. AIDS patients have a higher tendency for the development of serious skin reactions from various drugs. Where patients with minor fungal infections are being treated with fluconazole develop a skin rash, considered to be connected to treatment with fluconazole, the treatment should be stopped.

It patients who are being treated for invasive fungal infections or systemic infections develop a skin rash, they should be closely monitored and the treatment discontinued if bulous skin reactions or erythema multiforme develop.

Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4. Patients who receive concomitant treatment with fluconazole and drugs which have a narrow therapeutic interval (e.g. warfarin and phenytoin) and which are metabolised via CYP2C9 and/or CYP3A4 should be closely monitored (see "Contraindications and interactions with other medicinal products and other forms of interaction").

Fluconazole may lengthen the prothrombin time following administration of warfarin. Close monitoring of the prothrombin time is recommended.

Rare instances of anaphylactic reactions have been reported (see "Undesirable effects").

For dosage in renal impairment, see "Posology and method of administration".

Fertile women undergoing long-term treatment with fluconazole should use adequate methods of contraception (see "Pregnancy and lactation").

Data regarding efficacy and safety of fluconazole in children and adolescents less than 16 years of age are still limited. Therefore the benefits of the treatment with fluconazole should be carefully evaluated against the risks.

Important information about some of the ingredients of Fluconazole

Your medicine contains 3.54mg of sodium per ml. To be taken into consideration by patients on a controlled sodium diet.

Interaction with other medicinal products and other forms of interaction

The following combinations are contraindicated:
- Aztreonam (CYP3A4-substrate): Aztreonam overdoses have led to prolonged QT interval in severe ventricular arrhythmia, torsade de pointes and cardiac arrest. Concomitant administration of aztreonam and fluconazole is contraindicated due to the potential for serious, potentially fatal, cardiac effects.
- Cisapride (CYP3A4-substrate): Cardiac effects including torsade de pointes, have been reported in patients having received concurrent treatment with fluconazole and cisapride. In one controlled study, where 200 mg fluconazole was administered once daily concomitantly with cisapride 20 mg four times daily, a significant increase in plasma levels of cisapride and prolongation of the QT-interval where achieved. Concurrent treatment with cisapride and fluconazole is contraindicated (see "Contraindications").
- Terfenadine (400 mg fluconazole and higher; CYP3A4-substrate): Serious cardiac arrhythmias, secondary to prolonged QTc-interval, have occurred in patients treated with anti-fungal medications such as triazolic compounds and terfenadine. Concomitant treatment with 200 mg fluconazole daily showed no prolongation of the QT-interval. With doses of 400 mg and 800 mg fluconazole daily, the plasma concentration of terfenadine increased significantly. Concomitant treatment with fluconazole 400 mg per day or higher dose is contraindicated. With concomitant treatment with doses below 400 mg per day, the treatment should be closely monitored.

The effects of fluconazole on other drugs:
- 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 cholesteryl sulfate complex.
- Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4. In addition to the interactions given below, there is a risk that elevated serum concentrations of other drugs metabolised via CYP2C9 and CYP3A4 will not be secreted with concomitant administration of fluconazole. Caution should therefore always be observed during combination therapy with medications such as these and the patient closely monitored. The effects may persist for several days due to the long half life of fluconazole.
- Allentanil (CYP3A4-substrate): In concomitant treatment with fluconazole (400 mg) and intravenous allentanil (20 µg/kg) in healthy volunteers, AUC10 increased two-fold and clearance decreased by 55 % for allentanil, probably through inhibition of CYP3A4. The combination may require dose adjustment.
- Amtriptyline (CYP2D6-substrate): Several case histories have described the development of elevated amtriptyline concentrations and signs of tricyclic toxicity when amtriptyline is used in combination with fluconazole. Concomitant infusion of fluconazole and nortriptyline, the active metabolite of amtriptyline, have been reported to lead to increased nortriptyline levels. Due to the risk of amtriptyline toxicity, monitoring of amtriptyline levels should be considered with dose adjustment where indicated.
- Anti-coagulants (CYP2C9-substrate): In concomitant treatment with fluconazole and warfarin, the prothrombin time increased up to twofold. This is probably due to an inhibition of the metabolism of warfarin via CYP2C9. The prothrombin time should be monitored closely in patients treated concomitantly with fluconazole and coumarin-type anti-coagulants.
- Benzodiazepines (CYP3A4-substrate): Fluconazole may inhibit the metabolism of benzodiazepines metabolised via CYP3A4, e.g. midazolam and triazolam. In concomitant oral single dose treatment with fluconazole (400 mg) and midazolam (7.5 mg) AUC increased 3.7 times and the half life of midazolam 2.2 times. The combination should be avoided. Where concomitant treatment is considered necessary, a reduction in the dose of midazolam should be considered and the patient monitored closely in concomitant treatment with fluconazole (100 mg daily for 4 days) and triazolam (0.25 mg) the AUC and half-life of triazolam increased respectively 2.5 and 1.8 times. Prolonged and enhanced effects from triazolam have been observed. The combination may require reduction in the dose of triazolam.
- Calcium channel antagonists (CYP3A4-substrates): Some dihydropyridine calcium channel antagonists, including nifedipine, isradipine, nicardipine, amlopidine, and felodipine, are metabolised via CYP3A4. Literature reports have documented substantial peripheral oedema and/or elevated calcium antagonist serum concentrations during concurrent use of fluconazole and felodipine, isradipine, or nifedipine. An interaction might occur also with fluconazole.
- Celecoxib (CYP2C9-substrate): In concomitant treatment with fluconazole (200 mg daily) and celecoxib (200 mg), Cmax and AUC for celecoxib increased by 68 % and 134 % respectively. Halving the dose of celecoxib is recommended in combination therapy with fluconazole.
- Ciclosporin (CYP3A4-substrate): Clinically significant interactions between ciclosporin and fluconazole have been observed at doses of fluconazole of 200 mg and higher. In concomitant treatment with 200 mg fluconazole daily and ciclosporin (2.7 mg/kg/day), AUC for ciclosporin increased approximately 1.5 times and clearance was reduced by approximately 55 %. The plasma concentration of ciclosporin should be monitored in concomitant treatment with fluconazole.
- Didanosine: Co-administration of didanosine and fluconazole appears to be safe and has little effect on didanosine pharmacokinetics or efficacy. However, it is important to monitor fluconazole response. It may be advantageous to stagger fluconazole dosing to a time prior to didanosine administration.
- Balofloxacin (CYP3A4-substrate): Drugs which inhibit CYP3A4 lead to an inhibition of balofloxacin metabolism.
- HMG-CoA-reductase inhibitors (CYP2C9- or CYP3A4-substrate): The risk of myopathy increases when fluconazole is administered concomitantly with HMG-CoA-Reductase inhibitors that are metabolised via CYP3A4, e.g. atorvastatin and simvastatin, or via CYP2C9, such as fluvastatin. Caution
should be observed where concomitant treatment with fluconazole and HMG-CoA reductase-inhibitors is considered necessary. The combination may require dose reduction of the HMG-CoA reductase inhibitors. The patient should be warned about signs of myopathy or rhabdomyolysis. Where myopathy or rhabdomyolysis are suspected, the treatment with HMG-CoA reductase-inhibitors must be discontinued.

- **Losartan** (CYP2C9-substrate): Fluconazole inhibits the conversion of losartan to its active metabolite (E-3174), which is responsible for the most of the angiotensin II receptor antagonism that occurs with losartan therapy. Concomitant treatment with fluconazole might lead to increased concentrations of losartan and decreased concentrations of the active metabolite. It is recommended that patients receiving the combination be monitored for continued control of their hypertension.

- **Oral contraceptives** (CYP3A4-substrate): A kinetic study with combined oral contraceptives and 50 mg fluconazole daily; hormonal levels were not affected. With 200 mg fluconazole daily, AUC for ethinyloestradiol increased by 40 % and levonorgestrel by 24 %. Fluconazole at these dosages probably has no effect on combined oral contraceptives.

- **Phenytoin** (CYP2C9-substrate): Concomitant, repeated treatment with 200 mg fluconazole and 250 mg phenytoin intravenously increased AUC24 for phenytoin by 75 % and Cmin by 128 %. In combination treatment, plasma phenytoin concentrations should be monitored and the dose adjusted.

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

- **Ribavirin** (CYP3A4-substrate): In concomitant treatment with fluconazole and ribavirin, the serum concentrations of ribavirin increased. Elevation has been reported. Patients undergoing concomitant treatment should be monitored closely.

- **Sirolopin** and tacrolimus (3A4-substrate): In concomitant oral treatment with fluconazole and tacrolimus (0.15 mg/kg twice daily) the plasma concentration trough level of tacrolimus increased 1.4 and 3.1 times with a daily fluconazole dose of 100 mg and 200 mg respectively. Nephrotoxicity has been reported. Even though no interaction studies have been performed with fluconazole and sirolimus, a similar interaction can be anticipated. In concomitant treatment with fluconazole and tacrolimus or sirolimus, patients should be closely monitored and an adjustment in dose considered.

- **Salicylates** (CYP2C9-substrate): Fluconazole has displayed prolonged half-life in serum for concomitantly administered sulphasalazine (glibenclamide, glibizide, chlorpropamide and tolbutamide) in healthy volunteers. Fluconazole may be administered to diabetics together with sulphasalazine, but the risk of hypoglycaemia should be considered.

- **Theophylline**: Fluconazole 200 mg reduces theophylline clearance by 28 %. In patients receiving high doses of theophylline and concomitant treatment with fluconazole, theophylline toxicity should be taken into consideration, and the dose must be adjusted as necessary.

- **Trimetrexate**: Fluconazole may inhibit the metabolism of trimetrexate, leading to increased trimetrexate plasma concentrations. If the combination cannot be avoided, trimetrexate serum levels and toxicity (bone marrow suppression, renal and hepatic dysfunction, and gastrointestinal elevation) must be closely monitored.

- **Zidovudine**: In interaction studies, AUC of zidovudine increased significantly by approximately 20 % and 70 % in concomitant treatment with fluconazole 200 mg and 400 mg per day respectively; probably due to inhibited glucuronidation. Patients receiving the combination should be monitored closely with regard to zidovudine related adverse reactions.

**The effects of other drugs on fluconazole**:

- **Hydrochlorothiazide**: The plasma concentration of fluconazole increased by 49 % with concomitant administration of hydrochlorothiazide in healthy volunteers. An increase of this dimension does not necessitate adjustment in the dose of fluconazole capsules in patients undergoing treatment with diuretics, but the prescribing doctor should be aware of the fact.

- **Rifampicin** (CYP450 inducers): Concomitant treatment with fluconazole (200 mg) and rifampicin (600 mg daily) reduced AUC for fluconazole by 23 % in healthy volunteers. An increase in the dose of fluconazole should be considered in combination treatment.

**Pregnancy and lactation**

**Pregnancy**

Data from several hundred pregnant women treated with standard doses of fluconazole (less than 200 mg/day) as a single repeated dose during the first trimester of pregnancy, does not indicate undesirable effects on the foetus.

There are reports on multiple congenital abnormalities (including brachycephaly, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humerous synostosis) in children 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.

Studies in animals have shown reproductive toxicity (see section 5.3 Preclinical safety data), but the potential risk in humans is unknown.

Fluconazole in standard doses and short-term treatment should not be used during pregnancy unless clearly necessary, fluconazole in high doses or in prolonged regimen should not be used during pregnancy except for life threatening infections.

**Breast-feeding**

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

**Effects on ability to drive and use machines**

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

**Undesirable effects**

In clinical trials, up to 10% have experienced adverse reactions. Approximately 1% discontinued the treatment due to adverse reactions. The following treatment-related undesirable effects were reported in 4,048 patients receiving fluconazole for 7 or more days in clinical trials:

- Common > 1/10
- Common > 1/100, < 1/10
- Uncommon > 1/1,000, < 1/100
- Rare > 1/10,000, < 1/1,000

**Blood and lymphatic system**:

- Uncommon: Anemia
- Uncommon: Thrombocytopenia

**Immune system**:

- Rare: Anaphylaxis

**Psychiatric**:

- Uncommon: Insomnia, somnolence

**Central and peripheral nervous system**:

- Common: Headache
- Uncommon: Convulsion, dizziness, paresthesia, tremor, vertigo

**Autonomic nervous system**:

- Uncommon: Dry mouth, increased sweating

**Special senses**:

- Uncommon: Taste perversion

**Gastro-intestinal**:

- Common: Nausea and vomiting, abdominal pain, diarrhoea
- Uncommon: Anorexia, constipation, dyspepsia, flatulence

**Hepato-biliary**:

- Common: Clinically significant increase of AST, ALT and alkaline phosphatase
- Uncommon: Cholestasis, hepatocellular damage, jaundice, clinically significant
- Rare: Hepatic necrosis

**Skin and appendages**:

- Common: Skin rash
- Uncommon: Puerpitis
- Rare: Exfoliative skin disorder

**Musculoskeletal**:

- Uncommon: Myalgia

**General**:

- Uncommon: Fatigue, malaise, asthenia, fever

Adverse clinical events were reported more frequently in HIV infected patients (21%) than in non-HIV infected patients (13%). However, the patterns of adverse events in HIV infected and non-HIV infected patients were similar.
UKPAR Fluconazole 2mg/ml Solution for Infusion

The following additional adverse events possibly causally related to the use of fluconazole have been observed after the receipt of the marketing authorisation:

**Blood and lymphatic system**
Leucopenia, including neutropenia and agranulocytosis, thrombocytopenia

**Immune system**
Angioedema, face oedema, itching, urticaria

**Metabolism and nutrition**
Hypercholesterolaemia, hyperglycaemia, hypokalemia

**Nervous system**
Seizures

**Cardiac**
Prolonged-QT, torsades de pointes (see section 4.4)

**Hepatobiliary**
Hepatic failure, hepatitis

**Skin and appendages**
Alopecia, toxic epidermal necrolysis

**Overtreatment**
Toxicity:
Experience of overtreatment is limited for fluconazole. 1000 mg administered to an adult did not result in symptoms. 8000 mg administered to an adult, caused hallucinations and paranoid reaction. The patient was hospitalised and within 48 hours the patient's condition was normal.

**Symptoms**
Increased adverse reactions (headache, gastrointestinal symptoms), possibly hallucinations.

**Treatment**
Where justified, gastric lavage. Symptomatic treatment. Fluconazole is mainly excreted in the urine. Forced volume diuresis will probably increase the elimination rate. A 3-hour hemodialysis session reduces plasma levels by approximately 50%.

**PHARMACOLOGICAL PROPERTIES**
Pharmacodynamic properties
Pharmaco therapeutic group: Antimycotics for systemic use, triazole derivatives

ATC-code: C02AC01

Fluconazole is a triazole derivative with fungistatic effect, which specifically inhibits synthesis of the fungi's ergosterol, which leads to defects in the cell membrane. Fluconazole has a high degree of specificity for the fungal cytochrome P-450 dependent enzymes. At a dose of 50 mg daily for 28 days, fluconazole has not shown to influence serum levels of testosterone in men or the steroid concentration in fertile women.

Fluconazole 200-400 mg daily has no clinically significant effect on endogenous steroid levels or on ACTH stimulated response in healthy male volunteers. Interactions with antipyrine indicate that single or multiple doses of fluconazole 50 mg do not affect its metabolism.

The spectrum activity includes a number of pathogens including Candida albicans and other Candida species, Cryptococcus species and dermatophytes. Candida krusei is resistant to fluconazole. Candida glabrata has a naturally reduced sensitivity to fluconazole, approximately 40% of the isolates are resistant to fluconazole. Infections resulting from aspergillus species should not be treated with fluconazole.

Pharmacokinetic properties
Absorption
The pharmacokinetic properties are similar following oral and intravenous administration. The bioavailability of fluconazole following oral administration is in excess of 90%. The degree of absorption is not affected by concomitant food intake. Maximum serum concentration is generally reached after 0.5 to 1.5 hours.

Distribution
The serum concentration is proportional to the dose. Binding to plasma proteins is approximately 12%. The volume of distribution approximates total body water 0.7 L/kg. Clearance is 0.255 ml/min/kg. The half-life is approximately 50 hours, at which steady-state levels are achieved after 4-5 days of repeated dosing.

Where the dose is doubled on the first day of treatment, a steady-state level of approximately 90% is reached on day 2.
Fluconazole has demonstrated good penetration to various body fluids. The concentration in saliva and sputum is equal to that in plasma. The concentration in cerebrospinal fluid is 80% of the plasma level in patients with meningitis resulting from fungal infection.

High skin concentrations of fluconazole, well above serum concentrations, have been achieved in the stratum corneum, epidermis-dermis and in occlusive sweat. Fluconazole accumulates in the stratum corneum. At a dose of 150 mg once weekly, and after two doses of fluconazole, the concentration was 23.4 μg/g and 7.1 μg/g a week later.

**Metabolism**
Fluconazole is metabolised only to a small degree. Only 11% of a radioactively labelled dose is excreted in urine in unchanged form.

**Elimination**
Fluconazole is primarily excreted via the kidneys, 80% of the dose appears unchanged in the urine. In addition to renal excretion, approximately 10 of the dose is excreted in the form of metabolites.
Fluconazole clearance is proportional to creatinine clearance.

**Pharmacokinetics in Children**
The plasma elimination half-life of fluconazole is approximately 20 hours in children after the neonatal period, and the distribution volume is approx. 1 L/kg.
Prematures, have a longer fluconazole plasma elimination half-life (approximately 70 hours) and a larger distribution volume (1.2-2.3 L/kg) compared with children born at the calculated date of delivery.
During the first weeks after birth the plasma clearance of fluconazole increases and the plasma elimination half-life decreases.

**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 reproduction toxicity studies in rat an increased incidence of hydrocephalus and extension of renal pelvis was reported and embryonal lethality was increased. An increase in anabrotic variations and delayed ossification was noted as well as prolonged delivery and dystocia. In reproduction toxicity studies in rabbits, abortions were recorded.

**PHARMACEUTICAL PARTICULARS**

List of excipients
- Sodium chloride
- Water for Injections.

Incompatibilities
- This medicinal product must not be mixed with other medicinal products.

Shelf life
- 4 years

Special precautions for use
- Do not freeze

Nature and contents of container
- Solution for infusion in 100ml clear Type 1 transparent glass vials, with bromobutyl stopper and aluminium/polypropylene flip-off cap.

Pack Sizes: One 100ml vial per pack.

Special precautions for disposal and other handling
- The solution should be visually inspected prior to use and only clear solutions, without particles, should be used.
- The infusion contains no preservatives. For single use only. Any remaining solution should be disposed of, in accordance with local requirements.

**MARKETING AUTHORISATION HOLDER**
- Ranbaxy (UK) Limited
- Building 4
- Chiswick Park
- 560 Chiswick High Road
- London
- W4 5YE

**MARKETING AUTHORISATION NUMBER**
- PL 14894 / 0351
Fluconazole 2mg/ml Solution for Infusion

FOR I.V. INFUSION ONLY
Each ml contains 2 mg Fluconazole. Each 100ml vial contains 200mg Fluconazole. Read the enclosed leaflet for details.

MA Holder: Ranbaxy (UK) Limited
Building 4, Chiswick Park, 566 Chiswick High Road
London W4 5YE

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN

2mg/ml Solution for Infusion

Pack contains one 100ml vial
For single use only. Discard any remaining solution.