# FLUCONAZOLE 50MG CAPSULES
# PL 12762/0136

# FLUCONAZOLE 100MG CAPSULES
# PL 12762/0137

# FLUCONAZOLE 150MG CAPSULES
# PL 12762/0138

# FLUCONAZOLE 200MG CAPSULES
# PL 12762/0139

# (FLUCONAZOLE)

# UK Public Assessment Report

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# FLUCONAZOLE 50MG, 100MG, 150MG & 200MG CAPSULES (FLUCONAZOLE) PL 12762/0136 - 0139

## LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Goldshield Pharmaceuticals Limited Marketing Authorisations (licences) for the medicinal products Fluconazole 50mg Capsules (PL 12762/0136), Fluconazole 100mg Capsules (PL 12762/0137), Fluconazole 150mg Capsules (PL 12762/0138), and Fluconazole 200mg Capsules (PL 12762/0139) on 8th January 2009. Fluconazole Capsules are prescription-only medicines used to treat a variety of infections.

Fluconazole Capsules contain the active ingredient fluconazole, which is one of a group of medicines called anti-fungal agents. Fluconazole is used to treat infections caused by fungi and yeasts. The most common cause of fungal infections is a yeast called *Candida*.

Fluconazole 50mg, 100mg, 150mg and 200mg capsules may be prescribed to you by your doctor to treat fungal infections such as thrush of the mouth or throat, skin infections, internal (systemic) fungal infections (caused by *Candida* or *Cryptococcu*s), and genital *Candida* infections. You may also be given fluconazole to stop you from getting a fungal infection (if your immune system is not working properly) or to stop an infection caused by *Cryptococcu*s from coming back (in AIDS patients).

These applications are based on reference products with valid UK licences. No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Fluconazole 50mg, 100mg, 150mg and 200mg Capsules outweigh the risk; hence Marketing Authorisations have been granted.

# FLUCONAZOLE 50MG, 100MG, 150MG & 200MG CAPSULES (FLUCONAZOLE) PL 12762/0136 - 0139

## SCIENTIFIC DISCUSSION

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# INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Goldshield Pharmaceuticals Limited Marketing Authorisations (licences) for the medicinal products Fluconazole 50mg Capsules (PL 12762/0136), Fluconazole 100mg Capsules (PL 12762/0137), Fluconazole 150mg Capsules (PL 12762/0138), and Fluconazole 200mg Capsules (PL 12762/0139) on 8th January 2009. These are prescription-only medicines.

These are abridged, national applications for Fluconazole 50mg, 100mg, 150mg and 200mg Capsules. These are four strengths of fluconazole, submitted under Article 10.1 of Directive 2001/83/EC, as amended, claiming to be generic medicinal versions of the reference products, Diflucan Capsules 50mg, 100mg, 150mg and 200mg (PL 00057/0289, 0316, 0290 & 0317 respectively), authorised to Pfizer Ltd in June 1988 (50mg and 150mg strengths) and August 1989 (100mg and 200mg strengths). These are the innovator products and have been authorised in the UK for more than 10 years, thus the period of data exclusivity has expired.

The active ingredient, fluconazole, is a member of the triazole class of antifungal agents, and is a potent and selective inhibitor of fungal enzymes necessary for the synthesis of ergosterol. Fluconazole Capsules are indicated for the treatment of the following conditions:

- Genital candidiasis. Vaginal candidiasis, acute or recurrent. Candidal balanitis. Fluconazole 150mg Capsules (PL 12762/0138) are only used for this indication.
- Mucosal candidiasis. These include oropharyngeal, oesophageal, non-invasive bronchopulmonary infections, candiduria, mucocutaneous and chronic oral atrophic candidiasis (denture sore mouth).
- Tinea pedis, tinea corporis, tinea cruris, tinea versicolor and dermal Candida infections. Fluconazole capsules are not indicated for nail infections.
- Systemic candidiasis including candidaemia, disseminated candidiasis and other forms of invasive candidal infection. These include infections of the peritoneum, endocardium and pulmonary and urinary tracts.
- Cryptococcosis, including cryptococcal meningitis and infections of other sites (e.g. pulmonary, cutaneous). Fluconazole Capsules can be used as maintenance therapy to prevent relapse of cryptococcal disease in patients with AIDS.
- For the prevention of fungal infections in immunocompromised patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, including bone marrow transplant patients.

These applications for Fluconazole 50mg, 100mg, 150mg and 200mg Capsules are supported by the single bioequivalence study presented comparing the applicant's 200mg product with the Pfizer Ltd reference product, Diflucan 200mg Capsules. As the test products, Fluconazole 50mg, 100mg, 150mg and 200mg Capsules, were deemed to meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 200mg strength product were extrapolated to the other capsule strengths.

# PHARMACEUTICAL ASSESSMENT

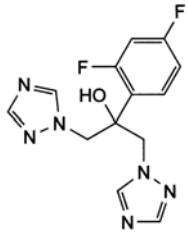
## ACTIVE SUBSTANCE

### Fluconazole

Nomenclature:

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

Structure:




| | |
|---|---|
| Molecular formula: | $C_{13}H_{12}N_6OF_2$ |
| Molecular weight: | 306.3 |
| CAS No: | 86386-73-4 |
| Physical form: | White or almost white crystalline powder |
| Solubility: | Fluconazole is slightly soluble in water, freely soluble in methanol, soluble in acetone. |
| Stereochemistry: | No chiral centre, therefore no optical isomerism. |

The active substance, fluconazole, is the subject of a European Pharmacopoeia (EP) monograph.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal or biological origin, and therefore comply with the TSE requirements.

An appropriate specification has been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. It is packed in double polyethylene bags, which are placed into a fibre drum. Specifications and Certificates of Analysis have been provided for the packaging materials used. The polyethylene bags in direct contact with the active substance satisfies Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and support a retest period of 3 years.

## DRUG PRODUCT

### Description and Composition

The drug products are presented as hard gelatin capsules of different colours (see individual SPCs / patient information leaflets for full descriptions of capsules). Each capsule contains 50mg, 100mg, 150mg, or 200mg of the active ingredient fluconazole.

Other ingredients consist of pharmaceutical excipients, namely maize starch, lactose monohydrate, magnesium stearate, colloidal anhydrous silica, and sodium lauryl sulfate comprising the capsule contents; and titanium dioxide (E171) and gelatin making up the capsule shell. In addition, the 50mg strength capsules contain the excipients yellow iron oxide (E172) and indigo carmine (E132) in the capsule shell; and the 100mg and 150mg strength capsules contain the excipient patent blue V (E131) in the capsule shell. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs, with the exception of three of the excipients making up the capsule shell - yellow iron oxide (E172), which complies with the USP (US Pharmacopoeia), and indigo carmine (E132) and patent blue V (E131), which comply with the French Pharmacopoeia specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

There are three excipients used that contain material of animal or human origin – magnesium stearate, lactose monohydrate, and gelatin. Appropriate statements or certification were submitted for magnesium stearate and gelatin. For lactose monohydrate, the applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

There were no novel excipients used and no overages.

### Dissolution profiles

Satisfactory comparative dissolution data were provided for the 4 strengths of the test and reference products. The dissolution profiles were found to be similar.

### Pharmaceutical development

Details of the pharmaceutical development of the drug products have been supplied and are satisfactory.

## Manufacture

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

In-process controls have been provided and are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are satisfactory.

## Finished product specification

The finished product specifications are acceptable, and provide an assurance of the quality and consistency of the finished products. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any reference standards used.

## Container Closure System

The finished products are licensed for marketing in aluminium / PVC (polyvinylchloride) laminate blister strips, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The product is packaged in pack sizes of 1, 7, 14, 28 and 56 capsules.

Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

## Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. Storage conditions are “Do not store above 25°C. Store in the original package.”

## Bioequivalence Study

A single bioequivalence study was submitted comparing the test product, Fluconazole 200mg Capsules, to the reference product, Diflucan 200mg Capsules (Pfizer Ltd, UK).

An evaluation of the bioequivalence study is found in the Clinical Assessment section.

## Quality Overall Summary

A satisfactory QOS is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

## Product Information

The approved SmPCs, leaflets, and labelling are satisfactory. Colour mock-ups of the labelling have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

## Conclusion

The drug products correspond to the current EU definition of a generic medicinal product because they comply with the criteria of having the same qualitative and quantitative composition in terms of the active substance and pharmaceutical form. On this basis, and considering the bioequivalence data provided, the applicant's claim that Fluconazole 200mg Capsules is a generic medicinal product of Diflucan 200mg Capsules appears justified. As the test products, Fluconazole 50mg, 100mg, 150mg and 200mg Capsules, meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 200mg strength product were extrapolated to the 50mg, 100mg and 150mg strength capsules.

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. It was, therefore, recommended that Marketing Authorisations be granted.

# PRECLINICAL ASSESSMENT

These abridged applications are for Fluconazole 50mg, 100mg, 150mg and 200mg capsules and were submitted under Article 10.1 of Directive 2001/83/EC, as amended.

No new preclinical data have been supplied with these applications and none are required for applications of this type. A preclinical overview has been written by a suitably qualified expert and is satisfactory. An appropriate CV for the expert has been supplied.

# CLINICAL ASSESSMENT

## INDICATIONS

Fluconazole Capsules are indicated for the treatment of the following conditions:

- Genital candidiasis. Vaginal candidiasis, acute or recurrent. Candidal balanitis. Fluconazole 150mg Capsules (PL 12762/0138) are only used for this indication.
- Mucosal candidiasis. These include oropharyngeal, oesophageal, non-invasive bronchopulmonary infections, candiduria, mucocutaneous and chronic oral atrophic candidiasis (denture sore mouth).
- Tinea pedis, tinea corporis, tinea cruris, tinea versicolor and dermal Candida infections. Fluconazole capsules are not indicated for nail infections.
- Systemic candidiasis including candidaemia disseminated candidiasis and other forms of invasive candidal infection. These include infections of the peritoneum, endocardium and pulmonary and urinary tracts.
- Cryptococcosis, including cryptococcal meningitis and infections of other sites (e.g. pulmonary, cutaneous). Fluconazole Capsules can be used as maintenance therapy to prevent relapse of cryptococcal disease in patients with AIDS.
- For the prevention of fungal infections in immunocompromised patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, including bone marrow transplant patients.

The indications are consistent with those for the cross-reference products and are satisfactory.

## POSOLOGY AND METHOD OF ADMINISTRATION

The posology is consistent with that for the reference products.

## TOXICOLOGY

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

## CLINICAL PHARMACOLOGY

### Pharmacodynamics

Fluconazole is a triazole antifungal agent which is a highly selective inhibitor of fungal sterol synthesis without effect on mammalian or human steroid synthesis. It is a potent and selective inhibitor of fungal enzymes necessary for the synthesis of ergosterol. Both orally and intravenously administered fluconazole was active in a variety of animal fungal infection models.

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

Fluconazole is highly specific for fungal cytochrome P-450 dependant enzymes. Fluconazole 50mg daily given up to 28 days has been shown not to affect testosterone plasma concentrations in males or steroid concentrations in females of child-bearing age. Fluconazole 200-400mg daily has no clinically significant effect on endogenous steroid levels or on ACTH stimulated response in healthy male volunteers.

## Pharmacokinetics

The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral route. After oral administration, fluconazole is well absorbed and plasma levels (and systemic bioavailability) are over 90% of the levels achieved after intravenous administration. Oral absorption is not affected by concomitant food intake. Peak plasma concentrations in the fasting state occur between 0.5 and 1.5 hours post-dose with a plasma elimination half-life of approximately 30 hours. Plasma concentrations are proportional to dose. Ninety percent steady-state levels are reached by day 4-5 with multiple once daily dosing.

Fluconazole achieves good penetration in all body fluids studied. The levels of fluconazole in saliva and sputum are similar to plasma levels. In patients with fungal meningitis, fluconazole levels in the CSF are approximately 80% of the corresponding plasma levels.

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

The long plasma elimination half-life provides the basis for single dose therapy for genital candidiasis and once daily dosing for other indications.

## Pharmacokinetics - Bioequivalence study

The applicant presented a single bioequivalence study comparing the test product, Fluconazole 200mg Capsules, to the reference product, Diflucan 200mg capsules (Pfizer Ltd). The study was conducted in accordance with current standards of Good Clinical Practice.

The design was a randomised, open label, two-treatment, two-period, crossover, single dose bioequivalence study, performed in healthy, adult, male, human volunteers. Single oral doses were separated by an adequate washout period. Plasma samples were analysed for fluconazole using an appropriate, validated LC/ tandem MS method.

Statistical evaluation was performed for the primary pharmacokinetic parameters for this study; $\mathbf{C}_{max}$, $AUC_{0-t}$, and $AUC_{0-\infty}$. Bioequivalence of the test product versus the reference product was concluded if the 90% CI fell within the acceptance range, 0.80-1.25 (80%-125%), for log-transformed $C_{max}$, $AUC_{0-t}$, and $AUC_{0-\infty}$.

Biostudy outcome and results:

The data from an adequate number of subjects were evaluated statistically. The results for the main pharmacokinetic parameters are reported as follows.

| **Parameter** | **Reference Prod Diflucan® 200** | **Test Prod Fluconazole 200** | **90% CI** |
|---|---|---|---|
| Cmax (ng/ml) | 4579 ± 823 | 4224 ± 720 | 92.2 (86.3 - 98.5) |
| AUC(0-t) ng*h/ml | 202526 ±21023 | 203992 ± 22309 | 101 (97.8 - 103) |
| AUC (0-∞) ng*h/ml | 213869 ±25571 | 215289 ±26672 | 101 (97.4 - 104) |

These data confirm the bioequivalence of the two formulations with the 90% CI of primary variables ($C_{max}$ & AUC) being within the conventionally acceptable bioequivalence range of 80% to 125%.

There were no reports of serious adverse events during the study.

**Overall conclusions on pharmacokinetics**

The 90% confidence intervals for the test/reference products lie within the accepted 80-125% bioequivalence range. Bioequivalence of the test product to the reference formulation has been satisfactorily demonstrated in accordance with CHMP criteria.

The multiple dose waiver criteria are met and hence this study is accepted as demonstrating bioequivalence for the other product strengths.

## EFFICACY

Efficacy is reviewed in the clinical overview. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence.

No new data are submitted and none are required for these types of application.

## SAFETY

Safety is reviewed in the clinical overview. The applicant has provided a safety review of fluconazole. The clinical safety of fluconazole is well established following many years of use. Whilst adverse reactions are noted with use of fluconazole, no major safety issues have arisen associated with its use. The most commonly reported side effects relate to the gastro-intestinal tract and include nausea, abdominal discomfort, flatulence and diarrhoea. However, a small proportion of treated patients subsequently discontinue fluconazole therapy mostly due to rare side effects such as Steven-Johnson syndrome, seizures and anaphylaxis (all of these side effects are already detailed in the SmPCs).

No new data are submitted and none are required for these types of application.

## EXPERT REPORT

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

## PRODUCT INFORMATION:

### Summary of Product Characteristics

The approved SmPCs are consistent with those for the innovator products and are acceptable.

### Patient Information Leaflet

The final PIL is in line with the approved SmPCs and is satisfactory.

### Labelling

Colour mock-ups of the labelling have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

## CONCLUSIONS

All issues have been adequately addressed by the applicant. The bioequivalence study was of an appropriate design and bioequivalence of the 200mg strength test and reference products was shown with 90% Confidence Intervals within general acceptance limits. The conditions, as detailed in CPMP/EWP/QWP/1401/98, for a single bioequivalence study to cover multiple strengths of a product have been met, so the results and conclusions of this bioequivalence study were extrapolated to the 50mg, 100mg and 150mg strength capsules. It is therefore concluded that the 50mg, 100mg and 150mg strength formulations are bioequivalent to their corresponding marketed brand formulations, despite bioequivalence not being assessed explicitly.

Sufficient clinical information has been submitted to support these applications. When used as indicated, fluconazole has a favourable benefit-to-risk ratio. The grant of Marketing Authorisations was, therefore, recommended on medical grounds.

# OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

## QUALITY

The important quality characteristics of Fluconazole 50mg, 100mg, 150mg and 200mg Capsules 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

Bioequivalence has been demonstrated between the applicant's Fluconazole 200mg Capsules, and the reference product Diflucan 200mg Capsules (Pfizer Ltd, UK). As the test products were deemed to meet the criteria specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 200mg strength were extrapolated to the 50mg, 100mg and 150mg capsule strengths. Thus, no separate bioequivalence studies were necessary for these strengths.

No new or unexpected safety concerns arise from these applications.

## PRODUCT LITERATURE

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

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. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The testing shows that the patients/users are able to act upon the information that the leaflet contains.

The approved labelling artwork complies with statutory requirements. In line with current legislation, the name of the product in Braille appears on the outer packaging and sufficient space has been included for a standard UK pharmacy dispensing label.

Labelling artworks have been approved and included in this report for the 28 capsule pack size. The MA Holder has committed to submit mock-up packaging for all other pack sizes (1, 7, 14 and 56) for assessment before they are commercially marketed.

## RISK BENEFIT ASSESSMENT

The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study and the valid extrapolation of its results and conclusions support the claim that the applicant's products and their respective reference products are interchangeable. Extensive clinical experience with fluconazole is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

# FLUCONAZOLE 50MG, 100MG, 150MG & 200MG CAPSULES (FLUCONAZOLE) PL 12762/0136 - 0139

## STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the marketing authorisation applications on 15th January 2003

2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 4th March 2003

3 Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 4th June 2003 (1), 6th February 2004 (2), and 20th July 2006 (3); and further information relating to the quality dossiers on 21st August 2003 (1), 18th November 2004 (2), 7th January 2005 (3), 7th July 2006 (4), 11th October 2007 (5), 12th October 2007 (6), 27th February 2008 (7) and 8th October 2008 (8)

4 The applicant responded to the MHRA's requests, providing further information for the clinical sections on 5th August 2003 (1), 20th June 2006 (2), and 2nd April 2007 (3); and further information for the quality sections on 20th June 2006 (3), 5th October 2007 (4), 12th October 2007 (5), 15th February 2008 (6), 9th September 2008 (7) and 28th October 2008 (8)

5 The applications were determined on 8th January 2009

# FLUCONAZOLE 50MG, 100MG, 150MG & 200MG CAPSULES (FLUCONAZOLE) PL 12762/0136 - 0139

## STEPS TAKEN AFTER AUTHORISATION

Not applicable

# SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Fluconazole 50mg Capsules (PL 12762/0136) is as follows:

## 1 NAME OF THE MEDICINAL PRODUCT

Fluconazole 50mg capsules

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains fluconazole 50mg.

Excipients: Lactose monohydrate 52.39mg, for a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Capsule, hard

Fluconazole 50mg capsules are green and white.

## 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 50mg capsules are indicated for the treatment of the following conditions:

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

2. Mucosal candidiasis. These include oropharyngeal, oesophageal, non-invasive bronchopulmonary infections, candiduria, mucocutaneous and chronic oral atrophic candidiasis (denture sore mouth). Normal hosts and patients with compromised immune function may be treated.

3. Tinea pedis, tinea corporis, tinea cruris, tinea versicolor and dermal Candida infections. Fluconazole 50mg capsules are not indicated for nail infections.

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

5. Cryptococcosis, including cryptococcal meningitis and infections of other sites (e.g. pulmonary, cutaneous). Normal hosts and patients with AIDS, organ transplants or other causes of immunosuppression may be treated. Fluconazole 50mg capsules can be used as maintenance therapy to prevent relapse of cryptococcal disease in patients with AIDS.

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

### 4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Fluconazole may be administered either orally or by intravenous infusion at a rate of approximately 5-10ml/min, the route being dependent on the clinical state of the patient. On transferring from the intravenous route to the oral route or vice versa, there is no need to change the daily dose.The daily dose fluconazole should be based on the nature and severity of the fungal infection. Most cases of vaginal candidiasis respond to single dose therapy. Therapy for those types of infections requiring multiple dose treatment should be continued until clinical parameters or laboratory tests indicate that active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection. Patients with AIDS and cryptococcal meningitis usually require maintenance therapy to prevent relapse.

**Use in Adults**

1. Candidal vaginitis or balanitis – 150mg single oral dose.

2. Mucosal Candidiasis.

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

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

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

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

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

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

5a For cryptococcal meningitis and cryptococcal infections at other sites, the usual dose is 400mg on the first day followed by 200mg – 400mg once daily. Duration of treatment for cryptococcal infections will depend on the clinical and mycological response, but is usually at least 6 – 8 weeks for cryptococcal meningitis.

5b For the prevention of relapse of cryptococcal meningitis in patients with AIDS, after the patient receives a full course of primary therapy, fluconazole may be administered at a daily dose of 100 – 200mg.

6. For the prevention of fungal infections in immunocompromised patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, the dose should be 50 to 400mg once daily, based on the patient's risk for developing fungal infection. For patients at high risk of systemic infection, e.g. patients who are anticipated to have profound or prolonged neutropenia such as during bone marrow transplantation, the recommended dose is 400mg once daily. Fluconazole administration should start several days before the anticipated onset of neutropenia, and continued for 7 days after the neutrophil count rises above 1000 cells per $mm^3$.

**Use in Children**

As with similar infections in adults, the duration of treatment is based on the clinical and mycological response. Fluconazole is administered as a single daily dose each day.

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

Children over four weeks of age: The recommended dose of fluconazole for mucosal candidiasis is 3mg/kg daily. A loading dose of 6mg/kg may be used on the first day to achieve steady state levels more rapidly. For the treatment of systemic candidiasis and cryptococcal infections, the recommended dosage is 6 – 12mg/kg daily, depending on the severity of the disease.

For the prevention of fungal infections in immunocompromised patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, the dose should be 3 – 12mg/kg daily, depending on the extent and duration of the induced neutropenia (see adult dosing). A maximum dosage of 400mg daily should not be exceeded in children.

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

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

A maximum dosage of 12mg/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, 12mg/kg every 48 hours should not be exceeded. To facilitate accurate measurement of doses less than 10mg, fluconazole should only be

administered to children in hospital using the 50mg/5ml suspension orally or the intraveneous infusion, depending on the clinical condition of the child.

**Use in the Elderly**

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

**Use in patients with impaired renal function**

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

| Creatinine clearance (ml/min) | Percent of recommended dose |
|---|---|
| >50 | 100% |
| ≤50 (no dialysis) (11-50) | 50% |
| Regular dialysis | 100% after each dialysis |

Fluconazole capsules should be swallowed whole.

## 4.3 CONTRAINDICATIONS

Fluconazole 50mg capsules should not be used in patients with known hypersensitivity to fluconazole or to related azole compounds or any other ingredient in the formulation.

Co-administration of terfenadine or cisapride is contra-indicated in patients receiving fluconazole. (See "Interactions with other medicinal products and other forms of interaction").

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In some patients, particularly those with serious underlying diseases such as AIDS and cancer, abnormalities in 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.

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and torsade de pointes in patients taking fluconazole. 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 arrhythmias
- Concomitant medication not metabolized by CY34A but known to prolong QT interval
- Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia

(See Section 4.5 Interactions with other medical products and other forms of interaction).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## 4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

The following drug interactions relate to the use of multiple-dose fluconazole, and the relevance to single-dose fluconazole 50mg capsules has not yet been established.

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

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

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

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

**Sulphonylureas**: Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulphonylureas (chlorpropamide, glibenclamide, glipizide and tolbutamide) in healthy volunteers. Fluconazole and oral sulphonylureas may be co-administered to diabetic patients, but the possibility of a hypoglycaemic episode should be borne in mind. Blood glucose levels must therefore be monitored and the dose of sulphonylurea adjusted accordingly.

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

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

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

**Ciclosporin**: A pharmacokinetic study conducted on kidney transplant patients showed that a daily dose of 200 mg of fluconazole slightly increased the concentrations of ciclosporin. However, another multiple-dose study using 100 mg daily of fluconazole showed that levels of ciclosporin were not affected in patients following bone marrow transplants.Metabolism of ciclosporin is inhibited, leading to an increase in its plasma concentration when co-administered with fluconazole. Hence, ciclosporin plasma concentration monitoring is recommended in patients receiving fluconazole.

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

**Terfenadine**: Because of the occurrence of serious dysrhythmias secondary to prolongation of the QTc interval in patients receiving other azole antifungals in conjunction with terfenadine, interactions studies have been performed. One study at a 200mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. Another study at a 400mg and 800mg daily dose of fluconazole demonstrated that fluconazole taken in multiple doses of 400mg per day or greater significantly increased plasma levels of terfenadine when taken concomitantly. There have been spontaneously reported cases of palpitations, tachycardia, dizziness, and chest pain in patients taking concomitant fluconazole and terfenadine where the relationship of the reported adverse events to drug therapy or underlying medical conditions was not clear. Because of the potential seriousness of such an interaction, it is recommended that terfenadine not be taken in combination with fluconazole. (See "Contra-indications".)

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

**Zidovudine**: Increased levels of zidovudine most likely caused by the decreased conversion of zidovudine to its major metabolite are known to occur with concomitant fluconazole administration. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions.

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

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

**Bosentan**: Concomitant administration of fluconazole and bosentan increased the plasma concentration of bosentan; hence concomitant use should be avoided.

**Celecoxib**: Increase in plasma concentration of celecoxib has been reported with concomitant fluconazole use and it is recommended that the dose of celecoxib be halved, when these two drugs are given concurrently.

**Parecoxib**: Increase in plasma concentration of parecoxib has been reported with concomitant fluconazole use and it is recommended that the dose of parecoxib be reduced, when these two drugs are given concurrently.

**Valdecoxib**: Increase in plasma concentration of valdecoxib has been reported with concomitant fluconazole use and it is recommended that the initial dose of valdecoxib be reduced, when these two drugs are given concurrently.

The use of fluconazole in patients concurrently taking astemizole, rifabutin, tacrolimus, or other drugs metabolised by the cytochrome P450 system may be associated with elevations in serum levels of these drugs. In the absence of definitive information, caution should be used when co-administering fluconazole. Patients should be carefully monitored.

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

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

## 4.6 PREGNANCY AND LACTATION

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

Accordingly, fluconazole 50mg capsules should not be used in pregnancy or in women of childbearing potential unless adequate contraception is employed.

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

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Experience with fluconazole 50mg capsules indicates that therapy is unlikely to impair a patient's ability to drive or use machinery.

## 4.8 UNDESIRABLE EFFECTS

The most common undesirable effects observed during clinical trials and associated with fluconazole are:

**Blood and lymphatic system disorders** – Leukopenia including neutropenia and agranulocytosis, thrombocytopenia.

Cardiac Disorders - QT prolongation, torsade de pointes (see section 4.4 Special Warnings and Special Precautions for Use).

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

**Hepatobiliary disorders** – Hepatic failure, hepatitis, hepatocellular necrosis, jaundice. Hepatic toxicity including rare cases of fatalities, elevated alkaline phosphatase, elevated bilirubin, elevated SGOT, elevated SGPT.

**Immune system disorders** – Anaphylaxis (including angioedema, face oedema, pruritus), urticaria.

**Metabolism and nutrition disorders** – Hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia.

**Nervous system disorders** - Taste perversion, Headache, Dizziness, seizures

**Skin and subcutaneous tissue disorders** – Rash, Alopecia, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrolysis.

## 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

ATC CODE: JO2AC01

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

Fluconazole shows little pharmacological activity in a wide range of animal studies. Some prolongation of pentobarbitone sleeping times in mice (p.o.), increased mean arterial and left ventricular blood pressure and increased heart rate in anaesthetised cats (iv) occurred. Inhibition of rat ovarian aromatase was observed at high concentrations.

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

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

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

## 5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral route. After oral administration, fluconazole is well absorbed and plasma levels (and systemic bioavailability) are over 90% of the levels achieved after intravenous administration. Oral absorption is not affected by concomitant food intake. Peak plasma concentrations in the fasting state occur between 0.5 and 1.5 hours post-dose with a plasma elimination half-life of approximately 30 hours. Plasma concentrations are proportional to dose. Ninety percent steady-state levels are reached by day 4-5 with multiple once daily dosing.

Administration of a loading dose (on day 1) of twice the usual dose enables plasma levels to approximate to 90% steady-state levels by day 2. The apparent volume of distribution approximates to total body water. Plasma protein binding is low (11-12%).

Fluconazole achieves good penetration in all body fluids studied. The levels of fluconazole in saliva and sputum are similar to plasma levels. In patients with fungal meningitis, fluconazole levels in the CSF are approximately 80% of the corresponding plasma levels.

High skin concentrations of fluconazole, above serum concentrations, are achieved in the stratum corneum, epidermis-dermis and eccrine sweat. Fluconazole accumulates in the stratum corneum. At a dose of 50mg once daily, the concentration of fluconazole after 12 days was 73 microgram/g and 7 days after cessation of treatment the concentrations was still 5.8 microgram/g.

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

The long plasma elimination half-life provides the basis for single dose therapy for genital candidiasis and once daily dosing for other indications.

A study compared the saliva and plasma concentrations of a single fluconazole 100mg dose administration in a capsule or in an oral suspension by rinsing and retaining in mouth for 2 minutes and swallowing. The maximum concentration of fluconazole in saliva after the suspension was observed 5 minutes after ingestion, and was 182 times higher than the maximum saliva concentration after the

capsule which occurred 4 hours after ingestion. After about 4 hours, the saliva concentrations of fluconazole were similar. The mean AUC (0-96) in saliva was significantly greater after the suspension compared to the capsule. There was no significant difference in the elimination rate from saliva or the plasma pharmacokinetic parameters for the two formulations.

**Pharmacokinetics in Children**

In children, the following pharmacokinetic data have been reported:

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

* Denotes final day

## 5.3 PRECLINICAL SAFETY DATA

Reproductive Toxicity: Increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50mg/kg and higher doses. At doses ranging from 80mg/kg (approximately 20-60 x the recommended human dose) to 320mg/kg embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate and abnormal cranio-facial ossification. These effects are consistent with the inhibition of oestrogen synthesis in rats and may be a result of known effects of lowered oestrogen on pregnancy, organogenesis and parturition.

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

**Mutagenesis**: Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of S.typhimurium and in the mouse lymphoma L5178Y system. Cytogenetic studies in vivo (murine bone marrow cells, following oral administration of fluconazole) and in vitro (human lymphocytes exposed to fluconazole at 1000ug/ml) showed no evidence of chromosomal mutations.

**Impairment of fertility**: Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10 or 20mg/kg or with parenteral doses of 5, 25 or 75mg/kg, although the onset of parturition was slightly delayed at 20mg/kg p.o. In an intravenous perinatal study in rats at 5, 20 and 40mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20mg/kg and 40mg/kg, but not at 5mg/kg. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal survival at these dose levels. The effects on parturition in rats are consistent with the species specific oestrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

Lactose monohydrate

Maize Starch

Colloidal Anhydrous Silica

Magnesium Stearate

Sodium Lauril sulfate

In addition, capsule shells contain:

Titanium, dioxide (E171)

Gelatin

Yellow Iron Oxide (E172)

Indigo Carmine (E132)

### 6.2 INCOMPATIBILITIES

Not applicable.

### 6.3 SHELF LIFE

2 years

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C

Store in the original package.

### 6.5 NATURE AND CONTENTS OF CONTAINER

Fluconazole capsules will be supplied in aluminium/PVC laminate blister packs. Packs of 1, 7, 14, 28 and 56 capsules.

### 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused product or waste material should be disposed of in accordance with local requirements.

## 7 MARKETING AUTHORISATION HOLDER

Goldshield Pharmaceuticals Limited

NLA Tower

12-16 Addiscombe Road

Croydon

Surrey

CR0 0XT

United Kingdom

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 12762/0136

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/01/2009

## 10 DATE OF REVISION OF THE TEXT

08/01/2009

# SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Fluconazole 100mg Capsules (PL 12762/0137) is as follows:

## 1 NAME OF THE MEDICINAL PRODUCT

Fluconazole 100mg capsules

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains fluconazole 100mg.

Excipients: Lactose monohydrate 104.78mg, for a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Capsule, hard

Fluconazole 100mg capsules are light blue and white.

## 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 100mg capsules are indicated for the treatment of the following conditions:

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

2. Mucosal candidiasis. These include oropharyngeal, oesophageal, non-invasive bronchopulmonary infections, candiduria, mucocutaneous and chronic oral atrophic candidiasis (denture sore mouth). Normal hosts and patients with compromised immune function may be treated.

3. Tinea pedis, tinea corporis, tinea cruris, tinea versicolor and dermal Candida infections. Fluconazole 100mg capsules are not indicated for nail infections.

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

5. Cryptococcosis, including cryptococcal meningitis and infections of other sites (e.g. pulmonary, cutaneous). Normal hosts and patients with AIDS, organ transplants or other causes of immunosuppression may be treated. Fluconazole 100mg capsules can be used as maintenance therapy to prevent relapse of cryptococcal disease in patients with AIDS.

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

### 4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Fluconazole may be administered either orally or by intravenous infusion at a rate of approximately 5-10ml/min, the route being dependent on the clinical state of the patient. On transferring from the intravenous route to the oral route or vice versa, there is no need to change the daily dose.The daily dose fluconazole should be based on the nature and severity of the fungal infection. Most cases of vaginal candidiasis respond to single dose therapy. Therapy for those types of infections requiring multiple dose treatment should be continued until clinical parameters or laboratory tests indicate that active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection. Patients with AIDS and cryptococcal meningitis usually require maintenance therapy to prevent relapse.

**Use in Adults**

1. Candidal vaginitis or balanitis – 150mg single oral dose.

2. Mucosal Candidiasis.

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

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

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

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

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

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

5a For cryptococcal meningitis and cryptococcal infections at other sites, the usual dose is 400mg on the first day followed by 200mg – 400mg once daily. Duration of treatment for cryptococcal infections will depend on the clinical and mycological response, but is usually at least 6 – 8 weeks for cryptococcal meningitis.

5b For the prevention of relapse of cryptococcal meningitis in patients with AIDS, after the patient receives a full course of primary therapy, fluconazole may be administered at a daily dose of 100 – 200mg.

6. For the prevention of fungal infections in immunocompromised patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, the dose should be 50 to 400mg once daily, based on the patient's risk for developing fungal infection. For patients at high risk of systemic infection, e.g. patients who are anticipated to have profound or prolonged neutropenia such as during bone marrow transplantation, the recommended dose is 400mg once daily. Fluconazole administration should start several days before the anticipated onset of neutropenia, and continued for 7 days after the neutrophil count rises above 1000 cells per $mm^3$.

**Use in Children**

As with similar infections in adults, the duration of treatment is based on the clinical and mycological response. Fluconazole is administered as a single daily dose each day.

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

Children over four weeks of age: The recommended dose of fluconazole for mucosal candidiasis is 3mg/kg daily. A loading dose of 6mg/kg may be used on the first day to achieve steady state levels more rapidly. For the treatment of systemic candidiasis and cryptococcal infections, the recommended dosage is 6 – 12mg/kg daily, depending on the severity of the disease.

For the prevention of fungal infections in immunocompromised patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, the dose should be 3 – 12mg/kg daily, depending on the extent and duration of the induced neutropenia (see adult dosing). A maximum dosage of 400mg daily should not be exceeded in children.

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

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

A maximum dosage of 12mg/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, 12mg/kg every 48 hours should not be exceeded. To facilitate accurate measurement of doses less than 10mg, fluconazole should only be

administered to children in hospital using the 50mg/5ml suspension orally or the intraveneous infusion, depending on the clinical condition of the child.

**Use in the Elderly**

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

**Use in patients with impaired renal function**

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

| Creatinine clearance (ml/min) | Percent of recommended dose |
|---|---|
| >50 | 100% |
| ≤50 (no dialysis) (11-50) | 50% |
| Regular dialysis | 100% after each dialysis |

Fluconazole capsules should be swallowed whole.

## 4.3 CONTRAINDICATIONS

Fluconazole 50mg capsules should not be used in patients with known hypersensitivity to fluconazole or to related azole compounds or any other ingredient in the formulation.

Co-administration of terfenadine or cisapride is contra-indicated in patients receiving fluconazole. (See "Interactions with other medicinal products and other forms of interaction").

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In some patients, particularly those with serious underlying diseases such as AIDS and cancer, abnormalities in 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.

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and torsade de pointes in patients taking fluconazole. 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 arrhythmias
- Concomitant medication not metabolized by CY34A but known to prolong QT interval
- Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia

(See Section 4.5 Interactions with other medical products and other forms of interaction).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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The following drug interactions relate to the use of multiple-dose fluconazole, and the relevance to single-dose fluconazole 100mg capsules has not yet been established.

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

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

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

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

**Sulphonylureas**: Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulphonylureas (chlorpropamide, glibenclamide, glipizide and tolbutamide) in healthy volunteers. Fluconazole and oral sulphonylureas may be co-administered to diabetic patients, but the possibility of a hypoglycaemic episode should be borne in mind. Blood glucose levels must therefore be monitored and the dose of sulphonylurea adjusted accordingly.

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

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

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

**Ciclosporin**: A pharmacokinetic study conducted on kidney transplant patients showed that a daily dose of 200 mg of fluconazole slightly increased the concentrations of ciclosporin. However, another multiple-dose study using 100 mg daily of fluconazole showed that levels of ciclosporin were not affected in patients following bone marrow transplants.Metabolism of ciclosporin is inhibited, leading to an increase in its plasma concentration when co-administered with fluconazole. Hence, ciclosporin plasma concentration monitoring is recommended in patients receiving fluconazole.

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

**Terfenadine**: Because of the occurrence of serious dysrhythmias secondary to prolongation of the QTc interval in patients receiving other azole antifungals in conjunction with terfenadine, interactions studies have been performed. One study at a 200mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. Another study at a 400mg and 800mg daily dose of fluconazole demonstrated that fluconazole taken in multiple doses of 400mg per day or greater significantly increased plasma levels of terfenadine when taken concomitantly. There have been spontaneously reported cases of palpitations, tachycardia, dizziness, and chest pain in patients taking concomitant fluconazole and terfenadine where the relationship of the reported adverse events to drug therapy or underlying medical conditions was not clear. Because of the potential seriousness of such an interaction, it is recommended that terfenadine not be taken in combination with fluconazole. (See "Contra-indications".)

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

**Zidovudine**: Increased levels of zidovudine most likely caused by the decreased conversion of zidovudine to its major metabolite are known to occur with concomitant fluconazole administration. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions.

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

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

**Bosentan**: Concomitant administration of fluconazole and bosentan increased the plasma concentration of bosentan; hence concomitant use should be avoided.

**Celecoxib**: Increase in plasma concentration of celecoxib has been reported with concomitant fluconazole use and it is recommended that the dose of celecoxib be halved, when these two drugs are given concurrently.

**Parecoxib**: Increase in plasma concentration of parecoxib has been reported with concomitant fluconazole use and it is recommended that the dose of parecoxib be reduced, when these two drugs are given concurrently.

**Valdecoxib**: Increase in plasma concentration of valdecoxib has been reported with concomitant fluconazole use and it is recommended that the initial dose of valdecoxib be reduced, when these two drugs are given concurrently.

The use of fluconazole in patients concurrently taking astemizole, rifabutin, tacrolimus, or other drugs metabolised by the cytochrome P450 system may be associated with elevations in serum levels of these drugs. In the absence of definitive information, caution should be used when co-administering fluconazole. Patients should be carefully monitored.

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

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

## 4.6 PREGNANCY AND LACTATION

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

Accordingly, fluconazole 100mg capsules should not be used in pregnancy or in women of childbearing potential unless adequate contraception is employed.

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

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Experience with fluconazole 100mg capsules indicates that therapy is unlikely to impair a patient's ability to drive or use machinery.

## 4.8 UNDESIRABLE EFFECTS

The most common undesirable effects observed during clinical trials and associated with fluconazole are:

**Blood and lymphatic system disorders** – Leukopenia including neutropenia and agranulocytosis, thrombocytopenia.

Cardiac Disorders - QT prolongation, torsade de pointes (see section 4.4 Special Warnings and Special Precautions for Use).

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

**Hepatobiliary disorders** – Hepatic failure, hepatitis, hepatocellular necrosis, jaundice. Hepatic toxicity including rare cases of fatalities, elevated alkaline phosphatase, elevated bilirubin, elevated SGOT, elevated SGPT.

**Immune system disorders** – Anaphylaxis (including angioedema, face oedema, pruritus), urticaria.

**Metabolism and nutrition disorders** – Hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia.

**Nervous system disorders** - Taste perversion, Headache, Dizziness, seizures

**Skin and subcutaneous tissue disorders** – Rash, Alopecia, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrolysis.

## 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

ATC CODE: JO2AC01

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

Fluconazole shows little pharmacological activity in a wide range of animal studies. Some prolongation of pentobarbitone sleeping times in mice (p.o.), increased mean arterial and left ventricular blood pressure and increased heart rate in anaesthetised cats (iv) occurred. Inhibition of rat ovarian aromatase was observed at high concentrations.

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

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

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

## 5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral route. After oral administration, fluconazole is well absorbed and plasma levels (and systemic bioavailability) are over 90% of the levels achieved after intravenous administration. Oral absorption is not affected by concomitant food intake. Peak plasma concentrations in the fasting state occur between 0.5 and 1.5 hours post-dose with a plasma elimination half-life of approximately 30 hours. Plasma concentrations are proportional to dose. Ninety percent steady-state levels are reached by day 4-5 with multiple once daily dosing.

Administration of a loading dose (on day 1) of twice the usual dose enables plasma levels to approximate to 90% steady-state levels by day 2. The apparent volume of distribution approximates to total body water. Plasma protein binding is low (11-12%).

Fluconazole achieves good penetration in all body fluids studied. The levels of fluconazole in saliva and sputum are similar to plasma levels. In patients with fungal meningitis, fluconazole levels in the CSF are approximately 80% of the corresponding plasma levels.

High skin concentrations of fluconazole, above serum concentrations, are achieved in the stratum corneum, epidermis-dermis and eccrine sweat. Fluconazole accumulates in the stratum corneum. At a dose of 50mg once daily, the concentration of fluconazole after 12 days was 73 microgram/g and 7 days after cessation of treatment the concentrations was still 5.8 microgram/g.

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

The long plasma elimination half-life provides the basis for single dose therapy for genital candidiasis and once daily dosing for other indications.

A study compared the saliva and plasma concentrations of a single fluconazole 100mg dose administration in a capsule or in an oral suspension by rinsing and retaining in mouth for 2 minutes and swallowing. The maximum concentration of fluconazole in saliva after the suspension was observed 5 minutes after ingestion, and was 182 times higher than the maximum saliva concentration after the

capsule which occurred 4 hours after ingestion. After about 4 hours, the saliva concentrations of fluconazole were similar. The mean AUC (0-96) in saliva was significantly greater after the suspension compared to the capsule. There was no significant difference in the elimination rate from saliva or the plasma pharmacokinetic parameters for the two formulations.

**Pharmacokinetics in Children**

In children, the following pharmacokinetic data have been reported:

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

* Denotes final day

## 5.3 PRECLINICAL SAFETY DATA

Reproductive Toxicity: Increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50mg/kg and higher doses. At doses ranging from 80mg/kg (approximately 20-60 x the recommended human dose) to 320mg/kg embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate and abnormal cranio-facial ossification. These effects are consistent with the inhibition of oestrogen synthesis in rats and may be a result of known effects of lowered oestrogen on pregnancy, organogenesis and parturition.

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

**Mutagenesis**: Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of S.typhimurium and in the mouse lymphoma L5178Y system. Cytogenetic studies in vivo (murine bone marrow cells, following oral administration of fluconazole) and in vitro (human lymphocytes exposed to fluconazole at 1000ug/ml) showed no evidence of chromosomal mutations.

**Impairment of fertility**: Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10 or 20mg/kg or with parenteral doses of 5, 25 or 75mg/kg, although the onset of parturition was slightly delayed at 20mg/kg p.o. In an intravenous perinatal study in rats at 5, 20 and 40mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20mg/kg and 40mg/kg, but not at 5mg/kg. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal survival at these dose levels. The effects on parturition in rats are consistent with the species specific oestrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

Lactose monohydrate

Maize Starch

Colloidal Anhydrous Silica

Magnesium Stearate

Sodium Lauril sulfate

In addition, capsule shells contain:

Titanium, dioxide (E171)

Gelatin

Patent blue V (E131)

### 6.2 INCOMPATIBILITIES

Not applicable.

### 6.3 SHELF LIFE

2 years

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C

Store in the original package.

### 6.5 NATURE AND CONTENTS OF CONTAINER

Fluconazole capsules will be supplied in aluminium/PVC laminate blister packs. Packs of 1, 7, 14, 28 and 56 capsules.

### 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused product or waste material should be disposed of in accordance with local requirements.

## 7 MARKETING AUTHORISATION HOLDER

Goldshield Pharmaceuticals Limited

NLA Tower

12-16 Addiscombe Road

Croydon

Surrey

CR0 0XT

United Kingdom

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 12762/0137

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/01/2009

## 10 DATE OF REVISION OF THE TEXT

08/01/2009

# SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Fluconazole 150mg Capsules (PL 12762/0138) is as follows:

## 1 NAME OF THE MEDICINAL PRODUCT

Fluconazole 150mg capsules

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains fluconazole 150mg.

Excipients: Lactose monohydrate 151.17mg, for a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Capsule, hard

Fluconazole 150mg capsules are blue and blue.

## 4 CLINICAL PARTICULARS

### 4.1 THERAPEUTIC INDICATIONS

Fluconazole 150mg capsules are indicated for the treatment of the following conditions:

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

### 4.2 POSOLOGY AND METHOD OF ADMINISTRATION

**In Adults**

Vaginal candidiasis or candidal balanitis – 150mg single oral dose.

**In Children**

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

**Use in Elderly**

The normal adult dose should be used.

**Use in renal impairment**

Fluconazole is excreted predominantly in the urine as unchanged drug. No adjustments in single dose therapy are required.

Fluconazole capsules should be swallowed whole.

### 4.3 CONTRAINDICATIONS

Fluconazole 50mg capsules should not be used in patients with known hypersensitivity to fluconazole or to related azole compounds or any other ingredient in the formulation.

Co-administration of terfenadine or cisapride is contra-indicated in patients receiving fluconazole. (See “Interactions with other medicinal products and other forms of interaction”).

### 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In some patients, particularly those with serious underlying diseases such as AIDS and cancer, abnormalities in 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.

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and torsade de pointes in patients taking fluconazole. 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 arrhythmias
- Concomitant medication not metabolized by CY34A but known to prolong QT interval
- Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia.

(See Section 4.5 Interactions with other medical products and other forms of interaction).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## 4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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

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

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

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

**Benzodiazepines (Short Acting)**: Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. This effect on midazolam

appears to be more pronounced following oral administration of fluconazole than with fluconazole administered intravenously. If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dosage and the patients should be appropriately monitored.

**Sulphonylureas**: Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulphonylureas (chlorpropamide, glibenclamide, glipizide and tolbutamide) in healthy volunteers. Fluconazole and oral sulphonylureas may be co-administered to diabetic patients, but the possibility of a hypoglycaemic episode should be borne in mind. Blood glucose levels must therefore be monitored and the dose of sulphonylurea adjusted accordingly.

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

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

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

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

**Terfenadine**: Because of the occurrence of serious dysrhythmias secondary to prolongation of the QTc interval are known to occur in patients receiving other azole antifungals in conjunction with terfenadine, interactions studies have been performed. One study at a 200mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. Another study at a 400mg and 800mg daily dose of fluconazole demonstrated that fluconazole taken in multiple doses of 400mg per day or greater significantly increased plasma levels of terfenadine when taken concomitantly.There have been spontaneously reported cases of palpitations, tachycardia, dizziness and chest pain in patients taking concomitant fluconazole and terfenadine where the relationship of the reported adverse events to drug therapy or underlying medical conditions was not clear. Because of the potential seriousness of such an interaction, it is recommended that terfenadine not be taken in combination with fluconazole. (See "Contra-indications").

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Accordingly, fluconazole 150mg capsules should not be used in pregnancy or in women of childbearing potential unless adequate contraception is employed.

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**Hepatobiliary disorders** – Hepatic failure, hepatitis, hepatocellular necrosis, jaundice. Hepatic toxicity including rare cases of fatalities, elevated alkaline phosphatase, elevated bilirubin, elevated SGOT, elevated SGPT.

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**Metabolism and nutrition disorders** – Hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia.

**Nervous system disorders** - Taste perversion, Headache, Dizziness, seizures

**Skin and subcutaneous tissue disorders** – Rash, Alopecia, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrolysis.

### 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

ATC CODE: JO2AC01

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

Fluconazole shows little pharmacological activity in a wide range of animal studies. Some prolongation of pentobarbitone sleeping times in mice (P.O.) increased mean arterial and left ventricular blood pressure and increased heart rate in anaesthetised cats (IV) occurred. Inhibition of rat ovarian aromatase was observed at high concentrations.

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

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

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

### 5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral route. After oral administration, fluconazole is well absorbed and plasma levels (and systemic bioavailability) are over 90% of the levels achieved after intravenous administration. Oral absorption is not affected by concomitant food intake. Peak plasma concentrations in the fasting state occur between 0.5 and 1.5 hours post-dose with a plasma elimination half-life of approximately 30 hours. Plasma

concentrations are proportional to dose. Ninety percent steady-state levels are reached by day 4-5 with multiple once daily dosing.

Administration of a loading dose (on day 1) of twice the usual dose enables plasma levels to approximate to 90% steady-state levels by day 2. The apparent volume of distribution approximates to total body water. Plasma protein binding is low (11-12%).

Fluconazole achieves good penetration in all body fluids studied. The levels of fluconazole in saliva and sputum are similar to plasma levels. In patients with fungal meningitis, fluconazole levels in the CSF are approximately 80% of the corresponding plasma levels.

High skin concentrations of fluconazole, above serum concentrations, are achieved in the stratum corneum, epidermis-dermis and eccrine sweat. Fluconazole accumulates in the stratum corneum. At a dose of 50mg once daily, the concentration of fluconazole after 12 days was 73 microgram/g and 7 days after cessation of treatment the concentrations was still 5.8 microgram/g.

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

The long plasma elimination half-life provides the basis for single dose therapy for genital candidiasis and once daily dosing for other indications.

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

**Pharmacokinetics in Children**

In children, the following pharmacokinetic data have been reported:

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

* Denotes final day

## 5.3 PRECLINICAL SAFETY DATA

Reproductive Toxicity: Increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50mg/kg and higher doses. At doses ranging from 80mg/kg (approximately 20-60 x the recommended human dose) to 320mg/kg embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate and abnormal cranio-facial ossification. These effects are consistent with the inhibition of oestrogen synthesis in rats and may be a result of known effects of lowered oestrogen on pregnancy, organogenesis and parturition.

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

**Mutagenesis**: Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of S.typhimurium and in the mouse lymphoma L5178Y system. Cytogenetic studies in vivo (murine bone marrow cells, following oral administration of fluconazole) and in vitro (human lymphocytes exposed to fluconazole at 1000ug/ml) showed no evidence of chromosomal mutations.

**Impairment of fertility**: Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10 or 20mg/kg or with parenteral doses of 5, 25 or 75mg/kg, although the onset of parturition was slightly delayed at 20mg/kg p.o. In an intravenous perinatal study in rats at 5, 20 and 40mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20mg/kg and 40mg/kg, but not at 5mg/kg. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal survival at these dose levels. The effects on parturition in rats are consistent with the species specific oestrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 LIST OF EXCIPIENTS

Lactose monohydrate

Maize Starch

Colloidal Anhydrous Silica

Magnesium Stearate

Sodium Lauril sulfate

In addition, capsule shells contain:

Titanium, dioxide (E171)

Gelatin

Patent blue V (E131)

### 6.2 INCOMPATIBILITIES

Not applicable.

### 6.3 SHELF LIFE

2 years

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C

Store in the original package.

### 6.5 NATURE AND CONTENTS OF CONTAINER

Fluconazole capsules will be supplied in aluminium/PVC laminate blister packs. Packs of 1, 7, 14, 28 and 56 capsules.

### 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused product or waste material should be disposed of in accordance with local requirements.

## 7 MARKETING AUTHORISATION HOLDER

Goldshield Pharmaceuticals Limited

NLA Tower
12-16 Addiscombe Road
Croydon
Surrey
CR0 0XT
United Kingdom

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 12762/0138

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/01/2009

## 10 DATE OF REVISION OF THE TEXT

08/01/2009

# SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Fluconazole 200mg Capsules (PL 12762/0139) is as follows:

## 1 NAME OF THE MEDICINAL PRODUCT

Fluconazole 200mg capsules

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains fluconazole 200mg.

Excipients: Lactose monohydrate 209.56mg, for a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Capsule, hard

Fluconazole 200mg capsules are white and white.

## 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 200mg capsules are indicated for the treatment of the following conditions:

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

2. Mucosal candidiasis. These include oropharyngeal, oesophageal, non-invasive bronchopulmonary infections, candiduria, mucocutaneous and chronic oral atrophic candidiasis (denture sore mouth). Normal hosts and patients with compromised immune function may be treated.

3. Tinea pedis, tinea corporis, tinea cruris, tinea versicolor and dermal Candida infections. Fluconazole 200mg capsules are not indicated for nail infections.

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

5. Cryptococcosis, including cryptococcal meningitis and infections of other sites (e.g. pulmonary, cutaneous). Normal hosts and patients with AIDS, organ transplants or other causes of immunosuppression may be treated. Fluconazole 200mg capsules can be used as maintenance therapy to prevent relapse of cryptococcal disease in patients with AIDS.

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

### 4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Fluconazole may be administered either orally or by intravenous infusion at a rate of approximately 5-10ml/min, the route being dependent on the clinical state of the patient. On transferring from the intravenous route to the oral route or vice versa, there is no need to change the daily dose.The daily dose fluconazole should be based on the nature and severity of the fungal infection. Most cases of vaginal candidiasis respond to single dose therapy. Therapy for those types of infections requiring multiple dose treatment should be continued until clinical parameters or laboratory tests indicate that active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection. Patients with AIDS and cryptococcal meningitis usually require maintenance therapy to prevent relapse.

**Use in Adults**

1. Candidal vaginitis or balanitis – 150mg single oral dose.

2. Mucosal Candidiasis.

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

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

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

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

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

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

5a For cryptococcal meningitis and cryptococcal infections at other sites, the usual dose is 400mg on the first day followed by 200mg – 400mg once daily. Duration of treatment for cryptococcal infections will depend on the clinical and mycological response, but is usually at least 6 – 8 weeks for cryptococcal meningitis.

5b For the prevention of relapse of cryptococcal meningitis in patients with AIDS, after the patient receives a full course of primary therapy, fluconazole may be administered at a daily dose of 100 – 200mg.

6. For the prevention of fungal infections in immunocompromised patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, the dose should be 50 to 400mg once daily, based on the patient's risk for developing fungal infection. For patients at high risk of systemic infection, e.g. patients who are anticipated to have profound or prolonged neutropenia such as during bone marrow transplantation, the recommended dose is 400mg once daily. Fluconazole administration should start several days before the anticipated onset of neutropenia, and continued for 7 days after the neutrophil count rises above 1000 cells per $mm^3$.

**Use in Children**

As with similar infections in adults, the duration of treatment is based on the clinical and mycological response. Fluconazole is administered as a single daily dose each day.

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

Children over four weeks of age: The recommended dose of fluconazole for mucosal candidiasis is 3mg/kg daily. A loading dose of 6mg/kg may be used on the first day to achieve steady state levels more rapidly. For the treatment of systemic candidiasis and cryptococcal infections, the recommended dosage is 6 – 12mg/kg daily, depending on the severity of the disease.

For the prevention of fungal infections in immunocompromised patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, the dose should be 3 – 12mg/kg daily, depending on the extent and duration of the induced neutropenia (see adult dosing). A maximum dosage of 400mg daily should not be exceeded in children.

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

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

A maximum dosage of 12mg/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, 12mg/kg every 48 hours should not be exceeded. To facilitate accurate measurement of doses less than 10mg, fluconazole should only be

administered to children in hospital using the 50mg/5ml suspension orally or the intraveneous infusion, depending on the clinical condition of the child.

**Use in the Elderly**

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

**Use in patients with impaired renal function**

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

| Creatinine clearance (ml/min) | Percent of recommended dose |
|---|---|
| >50 | 100% |
| ≤50 (no dialysis) (11-50) | 50% |
| Regular dialysis | 100% after each dialysis |

Fluconazole capsules should be swallowed whole.

## 4.3 CONTRAINDICATIONS

Fluconazole 200mg capsules should not be used in patients with known hypersensitivity to fluconazole or to related azole compounds or any other ingredient in the formulation.

Co-administration of terfenadine or cisapride is contra-indicated in patients receiving fluconazole. (See "Interactions with other medicinal products and other forms of interaction").

## 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

In some patients, particularly those with serious underlying diseases such as AIDS and cancer, abnormalities in 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.

Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and torsade de pointes in patients taking fluconazole. 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 arrhythmias
- Concomitant medication not metabolized by CY34A but known to prolong QT interval
- Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia

(See Section 4.5 Interactions with other medical products and other forms of interaction).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

## 4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

The following drug interactions relate to the use of multiple-dose fluconazole, and the relevance to single-dose fluconazole 200mg capsules has not yet been established.

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

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

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

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

**Sulphonylureas**: Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulphonylureas (chlorpropamide, glibenclamide, glipizide and tolbutamide) in healthy volunteers. Fluconazole and oral sulphonylureas may be co-administered to diabetic patients, but the possibility of a hypoglycaemic episode should be borne in mind. Blood glucose levels must therefore be monitored and the dose of sulphonylurea adjusted accordingly.

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

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

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

**Ciclosporin**: A pharmacokinetic study conducted on kidney transplant patients showed that a daily dose of 200 mg of fluconazole slightly increased the concentrations of ciclosporin. However, another multiple-dose study using 100 mg daily of fluconazole showed that levels of ciclosporin were not affected in patients following bone marrow transplants.Metabolism of ciclosporin is inhibited, leading to an increase in its plasma concentration when co-administered with fluconazole. Hence, ciclosporin plasma concentration monitoring is recommended in patients receiving fluconazole.

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

**Terfenadine**: Because of the occurrence of serious dysrhythmias secondary to prolongation of the QTc interval in patients receiving other azole antifungals in conjunction with terfenadine, interactions studies have been performed. One study at a 200mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. Another study at a 400mg and 800mg daily dose of fluconazole demonstrated that fluconazole taken in multiple doses of 400mg per day or greater significantly increased plasma levels of terfenadine when taken concomitantly. There have been spontaneously reported cases of palpitations, tachycardia, dizziness, and chest pain in patients taking concomitant fluconazole and terfenadine where the relationship of the reported adverse events to drug therapy or underlying medical conditions was not clear. Because of the potential seriousness of such an interaction, it is recommended that terfenadine not be taken in combination with fluconazole. (See "Contra-indications".)

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

**Zidovudine**: Increased levels of zidovudine most likely caused by the decreased conversion of zidovudine to its major metabolite are known to occur with concomitant fluconazole administration. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions.

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

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

**Bosentan**: Concomitant administration of fluconazole and bosentan increased the plasma concentration of bosentan; hence concomitant use should be avoided.

**Celecoxib**: Increase in plasma concentration of celecoxib has been reported with concomitant fluconazole use and it is recommended that the dose of celecoxib be halved, when these two drugs are given concurrently.

**Parecoxib**: Increase in plasma concentration of parecoxib has been reported with concomitant fluconazole use and it is recommended that the dose of parecoxib be reduced, when these two drugs are given concurrently.

**Valdecoxib**: Increase in plasma concentration of valdecoxib has been reported with concomitant fluconazole use and it is recommended that the initial dose of valdecoxib be reduced, when these two drugs are given concurrently.

The use of fluconazole in patients concurrently taking astemizole, rifabutin, tacrolimus, or other drugs metabolised by the cytochrome P450 system may be associated with elevations in serum levels of these drugs. In the absence of definitive information, caution should be used when co-administering fluconazole. Patients should be carefully monitored.

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

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

## 4.6 PREGNANCY AND LACTATION

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

Accordingly, fluconazole 200mg capsules should not be used in pregnancy or in women of childbearing potential unless adequate contraception is employed.

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

## 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Experience with fluconazole 200mg capsules indicates that therapy is unlikely to impair a patient's ability to drive or use machinery.

## 4.8 UNDESIRABLE EFFECTS

The most common undesirable effects observed during clinical trials and associated with fluconazole are:

**Blood and lymphatic system disorders** – Leukopenia including neutropenia and agranulocytosis, thrombocytopenia.

Cardiac Disorders - QT prolongation, torsade de pointes (see section 4.4 Special Warnings and Special Precautions for Use).

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

**Hepatobiliary disorders** – Hepatic failure, hepatitis, hepatocellular necrosis, jaundice. Hepatic toxicity including rare cases of fatalities, elevated alkaline phosphatase, elevated bilirubin, elevated SGOT, elevated SGPT.

**Immune system disorders** – Anaphylaxis (including angioedema, face oedema, pruritus), urticaria.

**Metabolism and nutrition disorders** – Hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia.

**Nervous system disorders** - Taste perversion, Headache, Dizziness, seizures

**Skin and subcutaneous tissue disorders** – Rash, Alopecia, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrolysis.

## 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

ATC CODE: JO2AC01

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

Fluconazole shows little pharmacological activity in a wide range of animal studies. Some prolongation of pentobarbitone sleeping times in mice (p.o.), increased mean arterial and left ventricular blood pressure and increased heart rate in anaesthetised cats (iv) occurred. Inhibition of rat ovarian aromatase was observed at high concentrations.

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

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

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

## 5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral route. After oral administration, fluconazole is well absorbed and plasma levels (and systemic bioavailability) are over 90% of the levels achieved after intravenous administration. Oral absorption is not affected by concomitant food intake. Peak plasma concentrations in the fasting state occur between 0.5 and 1.5 hours post-dose with a plasma elimination half-life of approximately 30 hours. Plasma concentrations are proportional to dose. Ninety percent steady-state levels are reached by day 4-5 with multiple once daily dosing.

Administration of a loading dose (on day 1) of twice the usual dose enables plasma levels to approximate to 90% steady-state levels by day 2. The apparent volume of distribution approximates to total body water. Plasma protein binding is low (11-12%).

Fluconazole achieves good penetration in all body fluids studied. The levels of fluconazole in saliva and sputum are similar to plasma levels. In patients with fungal meningitis, fluconazole levels in the CSF are approximately 80% of the corresponding plasma levels.

High skin concentrations of fluconazole, above serum concentrations, are achieved in the stratum corneum, epidermis-dermis and eccrine sweat. Fluconazole accumulates in the stratum corneum. At a dose of 50mg once daily, the concentration of fluconazole after 12 days was 73 microgram/g and 7 days after cessation of treatment the concentrations was still 5.8 microgram/g.

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

The long plasma elimination half-life provides the basis for single dose therapy for genital candidiasis and once daily dosing for other indications.

A study compared the saliva and plasma concentrations of a single fluconazole 100mg dose administration in a capsule or in an oral suspension by rinsing and retaining in mouth for 2 minutes and swallowing. The maximum concentration of fluconazole in saliva after the suspension was observed 5 minutes after ingestion, and was 182 times higher than the maximum saliva concentration after the

capsule which occurred 4 hours after ingestion. After about 4 hours, the saliva concentrations of fluconazole were similar. The mean AUC (0-96) in saliva was significantly greater after the suspension compared to the capsule. There was no significant difference in the elimination rate from saliva or the plasma pharmacokinetic parameters for the two formulations.

**Pharmacokinetics in Children**

In children, the following pharmacokinetic data have been reported:

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

* Denotes final day

## 5.3 PRECLINICAL SAFETY DATA

Reproductive Toxicity: Increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50mg/kg and higher doses. At doses ranging from 80mg/kg (approximately 20-60 x the recommended human dose) to 320mg/kg embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate and abnormal cranio-facial ossification. These effects are consistent with the inhibition of oestrogen synthesis in rats and may be a result of known effects of lowered oestrogen on pregnancy, organogenesis and parturition.

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

**Mutagenesis**: Fluconazole, with or without metabolic activation, was negative in tests for mutagenicity in 4 strains of S.typhimurium and in the mouse lymphoma L5178Y system. Cytogenetic studies in vivo (murine bone marrow cells, following oral administration of fluconazole) and in vitro (human lymphocytes exposed to fluconazole at 1000ug/ml) showed no evidence of chromosomal mutations.

**Impairment of fertility**: Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10 or 20mg/kg or with parenteral doses of 5, 25 or 75mg/kg, although the onset of parturition was slightly delayed at 20mg/kg p.o. In an intravenous perinatal study in rats at 5, 20 and 40mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20mg/kg and 40mg/kg, but not at 5mg/kg. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal survival at these dose levels. The effects on parturition in rats are consistent with the species specific oestrogen-lowering property produced by high doses of fluconazole. Such a hormone change has not been observed in women treated with fluconazole.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 LIST OF EXCIPIENTS

Lactose monohydrate

Maize Starch

Colloidal Anhydrous Silica

Magnesium Stearate
Sodium Lauril sulfate
In addition, capsule shells contain:
Titanium, dioxide (E171)
Gelatin

### 6.2 INCOMPATIBILITIES

Not applicable.

### 6.3 SHELF LIFE

2 years

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C
Store in the original package.

### 6.5 NATURE AND CONTENTS OF CONTAINER

Fluconazole capsules will be supplied in aluminium/PVC laminate blister packs.
Packs of 1, 7, 14, 28 and 56 capsules.

### 6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused product or waste material should be disposed of in accordance with local requirements.

## 7 MARKETING AUTHORISATION HOLDER

Goldshield Pharmaceuticals Limited
NLA Tower
12-16 Addiscombe Road
Croydon
Surrey
CR0 0XT
United Kingdom

## 8 MARKETING AUTHORISATION NUMBER(S)

PL 12762/0137

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08/01/2009

## 10 DATE OF REVISION OF THE TEXT

08/01/2009

# PATIENT INFORMATION LEAFLET

## Patient Information Leaflet

## FLUCONAZOLE 50mg, 100mg, 150mg, and 200mg CAPSULES

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

**In this leaflet:**



### 1. WHAT FLUCONAZOLE CAPSULES ARE AND WHAT THEY ARE USED FOR

Fluconazole is one of a group of medicines called antifungal agents.

Fluconazole is used to treat infections caused by fungi/yeasts.
The most common cause of fungal infections is yeast called Candida.

**You may be given Fluconazole to treat fungal infections such as:**
- Thrush of the mouth or throat (mucosal infections).
- Skin infections (e.g. athlete's foot, ringworm).
- 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 like vaginal thrush or candidal balanitis (inflammation of the end of the penis and/or foreskin).

**You may also be given Fluconazole to:**
- Stop you from getting a fungal infection (if your immune system is not working properly).
- Stop an infection caused by Cryptococcus from coming back (in AIDS patients).

### 2. BEFORE YOU TAKE FLUCONAZOLE CAPSULES

**Do not take Fluconazole Capsules if you:**
- are allergic (hypersensitive) to fluconazole, or another drug from the same group of antifungal drugs,or any of the other ingredients of Fluconazole Capsules
- are taking another drug called terfenadine (an antihistamine) or cisapride (a drug used to treat acid reflux, indigestion or decreased gastric motility)

If any of the above apply to you and you have not already discussed this with your doctor or pharmacist, you should do so as soon as possible and before taking Fluconazole Capsules.

**Take special care with Fluconazole Capsules if you:**
- suffer from liver problems
- suffer from kidney problems
- suffer from heart problems which increase the QT interval as tested by your doctor or are taking medicines which may increase the QT interval such as terfenadine
- have imbalances in the salt levels in your blood
- have AIDS
- have cancer

If you have any of these conditions and you have not already discussed this with your doctor or pharmacist, you should do so as soon as possible and before taking Fluconazole Capsules.

**Taking other medicines**

Please tell your doctor or pharmacist if you are taking any of the following medicines:
- terfenadine or astemizole (types of antihistamines)
- rifampicin or rifabutin (types of antibiotics, often used for the treatment of tuberculosis)
- hydrochlorothiazide (a type of diuretic or 'water tablet')
- any drugs which thin the blood (known as anticoagulants e.g. warfarin)
- any medicines to help you sleep (such as benzodiazepines e.g. midazolam)
- medicines to treat diabetes known as sulphonylureas e.g. chlorpropamide, glibenclamide, glipizide or tolbutamide
- phenytoin (used to treat epilepsy)
- an oral contraceptive (the 'Pill')
- ciclosporin (drugs which suppress the immune system, which are commonly used following organ transplants)
- theophylline (a drug used to treat asthma)
- zidovudine (AZT), nevirapine, tipranavir, saquinavir (antiviral drugs, used to treat HIV)
- cisapride (a drug used to treat acid reflux, indigestion or decreased gastric motility)
- celecoxib & valdecoxib (used as pain killers)
- bosentan (used to control high blood pressure)

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

**Taking Fluconazole Capsules with food and drink**

The capsules should always be taken with plenty of water. They can be taken with or without food.

**Pregnancy and breast-feeding**

Fluconazole should not be used in pregnancy or in women of childbearing potential unless adequate contraception is used.

Breast-feeding is not recommended whilst using fluconazole.

Ask your doctor or pharmacist for advice before taking any medicine.

**Driving and using machines**

Fluconazole Capsules are unlikely to affect your ability to drive or use machinery.

**Important information about some of the ingredients of Fluconazole Capsules**

Fluconazole Capsules contain lactose monohydrate, a type of sugar. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

### 3. HOW TO TAKE FLUCONAZOLE CAPSULES

Always take Fluconazole Capsules exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Your dose will be dependent on the type and severity of your infection, your age, weight and kidney function. Your doctor will choose the best dose for you.

**Adults**

The usual dose for the treatment of genital thrush is one 150mg single dose.

To treat mucosal thrush of the mouth or throat, the usual dose is 50mg-100mg once daily for up to 14 days. In other types of mucosal thrush, this may be continued for up to 30 days. If you have oral thrush associated with the use of dentures, you may be given a local antiseptic to use at the same time.

To treat fungal skin infections (e.g. athlete's foot, ringworm), the usual dose is 50mg once daily for up to 6 weeks.

For systemic infections, the usual dose is 400mg on the first day, followed by 200mg – 400mg daily.

In cryptococcal infections (e.g meningitis), this may be continued for up to 8 weeks.

To prevent fungal infections in patients with poor immune systems, the usual dose is 50-400mg once daily, depending on the risk of infection. To prevent cryptococcal infections coming back in AIDS patients, a usual dose of 100-200mg daily may be given indefinitely.

**Elderly**

Your doctor will decide what dose to give you. This may be lower than the usual adult dose depending on your kidney function.

**Kidney problems**

Your doctor will decide what dose to give you depending on your kidney function.

**Children**

The capsules formulation may be unsuitable for children under 5-6 years of age.

**Children over 4 weeks of age**

Your doctor will calculate an appropriate dose based on body weight. The usual dose for mucosal infections is 3mg/kg body weight daily. A dose of 6mg/kg may be given on the first day. For internal infections and cryptococcal infections, the usual dose is 6-12mg/kg daily, depending on the severity of the infection. To prevent fungal infections in patients with poor immune systems, a dose of 3-12mg/kg should be given daily, depending on the risk of infection.

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

**If you take more Fluconazole Capsules than you should**

It is important to stick to the dose on the label of your medicine. If you or someone else swallows several of these capsules all together, contact your doctor, pharmacist or hospital emergency department immediately. Always take any capsules left over with you and also the box, as this will allow easier identification of the capsules.

**If you forget to take Fluconazole Capsules**

If you forget to take a dose, take it as soon as you remember.

Do not take a double dose to make up for a forgotten dose if it is almost time for your next dose.

**If you stop taking Fluconazole Capsules**

Even when you start to feel better it is important for you to keep on taking your capsules for as long as your doctor tells you. If you stop too soon, the infection may start up again.

Sometimes your doctor may want you to continue taking your capsules to prevent your infection from coming back.

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 Capsules can cause side effects, although not everybody gets them.

If any of the following symptoms occur soon after taking your capsules, stop taking the capsules and tell your doctor immediately. This kind of reaction is rare and may mean you are suffering from an allergic reaction (anaphylaxis) to the capsules:

- Severe rash, itching, a lumpy skin rash ('hives') or fever
- Sudden wheeziness or tightness of the chest
- Swelling of the eyelids, face, lips or blood vessels in the skin

**The most common side effects, which may occur, are listed below:**

- Headache
- Rash
- Stomach pain or discomfort
- Diarrhoea
- Flatulence (wind)
- Nausea (feeling sick)

These side effects are usually mild. However, if you suffer from any of these and they are severe or prolonged, please inform your doctor or pharmacist.

**Other possible side effects, which may occur, include:**

- Abnormalities in blood, liver or kidney function, or other biochemical tests (especially if you have a serious underlying disease such as AIDS or cancer)
- Increase in your cholesterol and/or lipids and decrease in potassium levels. Your doctor may want to monitor you.
- Dizziness, vertigo
- Seizures or convulsions (fits)
- Hair loss (alopecia)
- Severe skin disorders or itching (e.g. Stevens-Johnson Syndrome)
- Indigestion (dyspepsia)
- Sickness (vomiting)
- Swelling of the face, lips, mouth or throat (angioedema)
- Changes to your sense of taste
- Change in heart rate or rhythm
- Liver disease. Your liver may stop working properly, or, damage or death (necrosis) of liver cells may occur.
  You may experience a yellowing of the skin and/or eyes (jaundice).

Your doctor may monitor liver function during your treatment with fluconazole capsules, and if you are found to have a toxicity reaction, you may have to stop taking fluconazole capsules.

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 CAPSULES

Keep out of the reach and sight of children. Do not store above 25°C. Store in the original package.

Do not use Fluconazole Capsules after the expiry date which is stated on the carton after expiry date. The expiry date refers to the last day of that month.

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 Capsules contain**

- The active substance is fluconazole. Each capsule contains either 50mg, 100mg, 150mg, or 200mg fluconazole.
- The other ingredients are lactose monohydrate, maize starch, sodium laurilsulfate, colloidal anhydrous silica and magnesium stearate.

**The capsule shell contains:**

50mg: titanium dioxide (E171), yellow iron oxide (E172), indigo carmine (E132) and gelatin.

100mg and 150mg: titanium dioxide (E171), patent blue V(E131) and gelatin.

200mg: titanium dioxide (E171) and gelatin.

**What Fluconazole Capsules look like and contents of the pack**

50mg: green and white capsules.

100mg: blue and white capsules.

150mg: blue capsules.

200mg: white capsules.

Fluconazole Capsules are available in blister packs of:

1,7,14,28 or 56 capsules. Not all pack sizes maybe marketed.

**Marketing Authorisation Holder and Manufacturer:**

Goldshield Pharmaceuticals Ltd.,

NLA Tower, 12-16 Addiscombe Road, Croydon, Surrey, CR0 0XT, UK.

**Distributed by:**

Forley Generics Limited.

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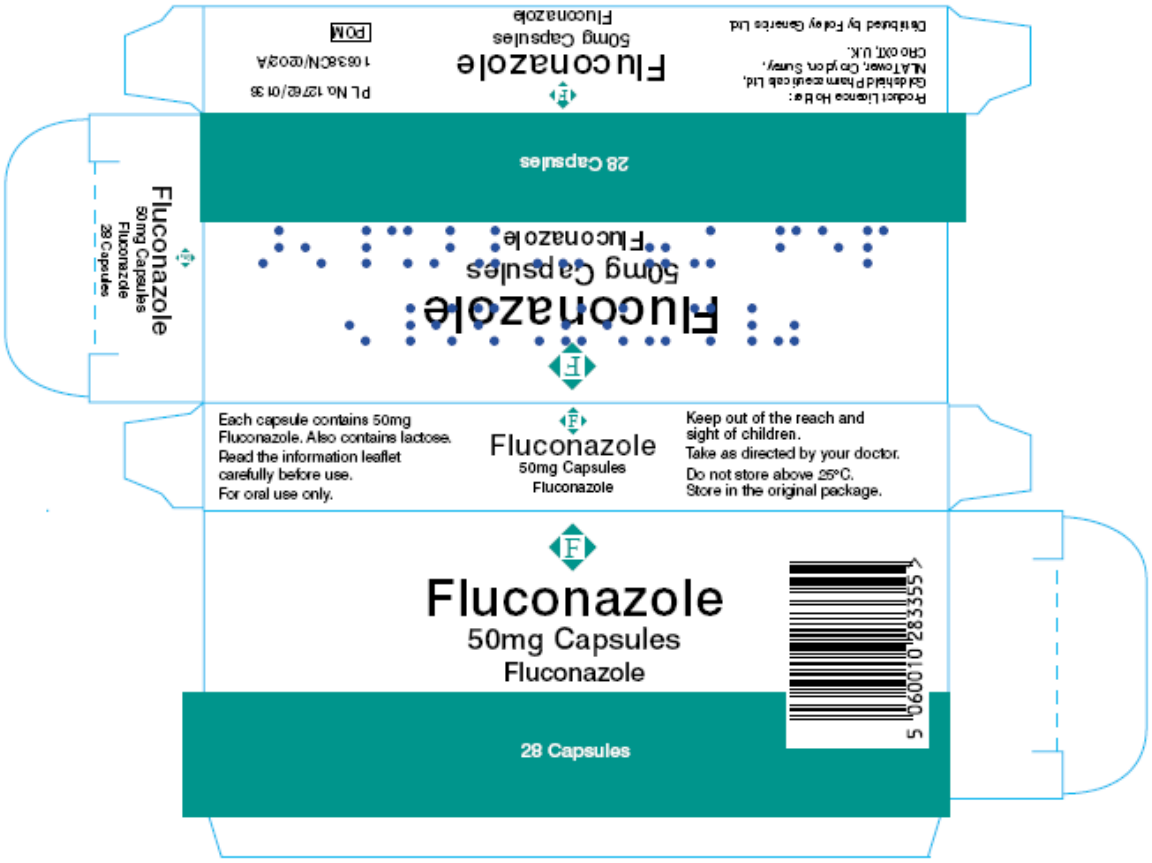
10638-41/LF/A

# LABELLING

## Fluconazole 50mg capsules (PL 12762/0136)

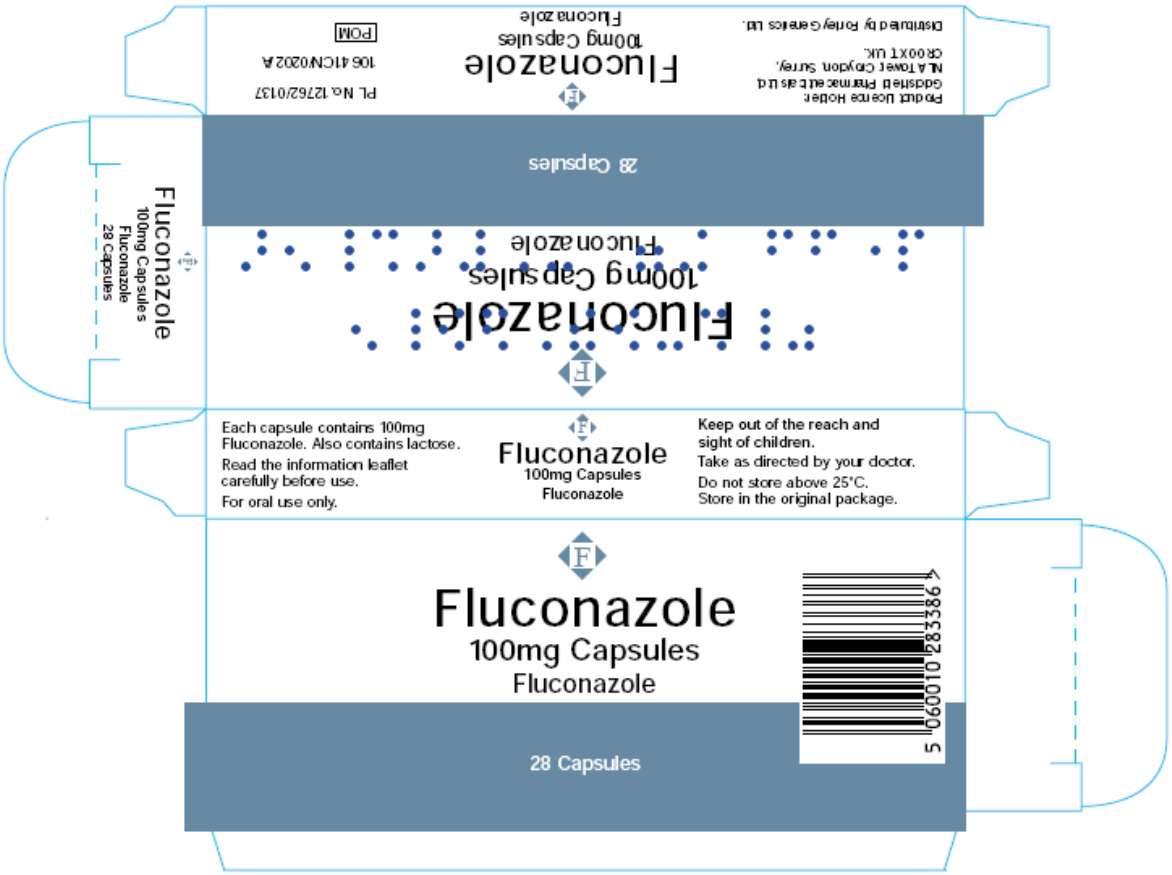
Carton for blisters, with braille




Blister foil

## Fluconazole 100mg capsules (PL 12762/0137)

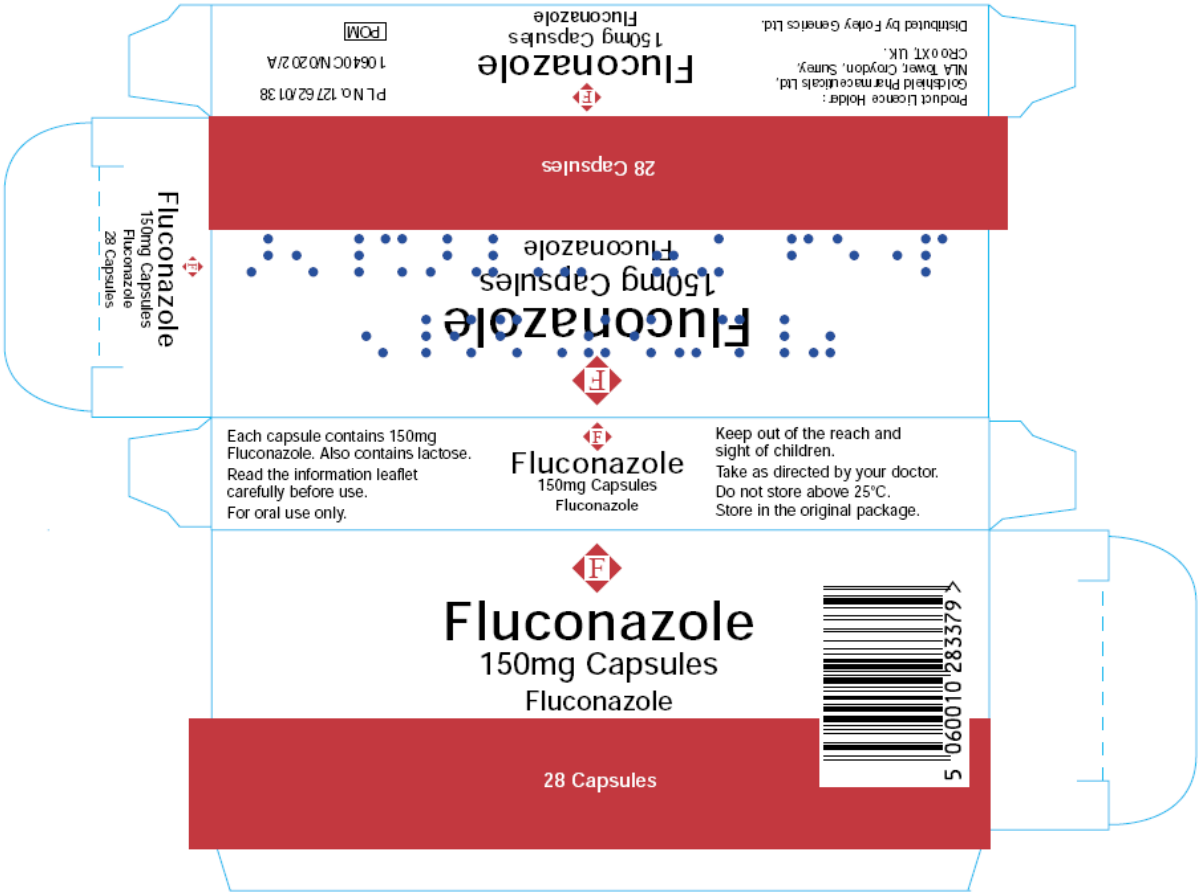
Carton for blisters, with braille




Blister foil

## Fluconazole 150mg capsules (PL 12762/0138)

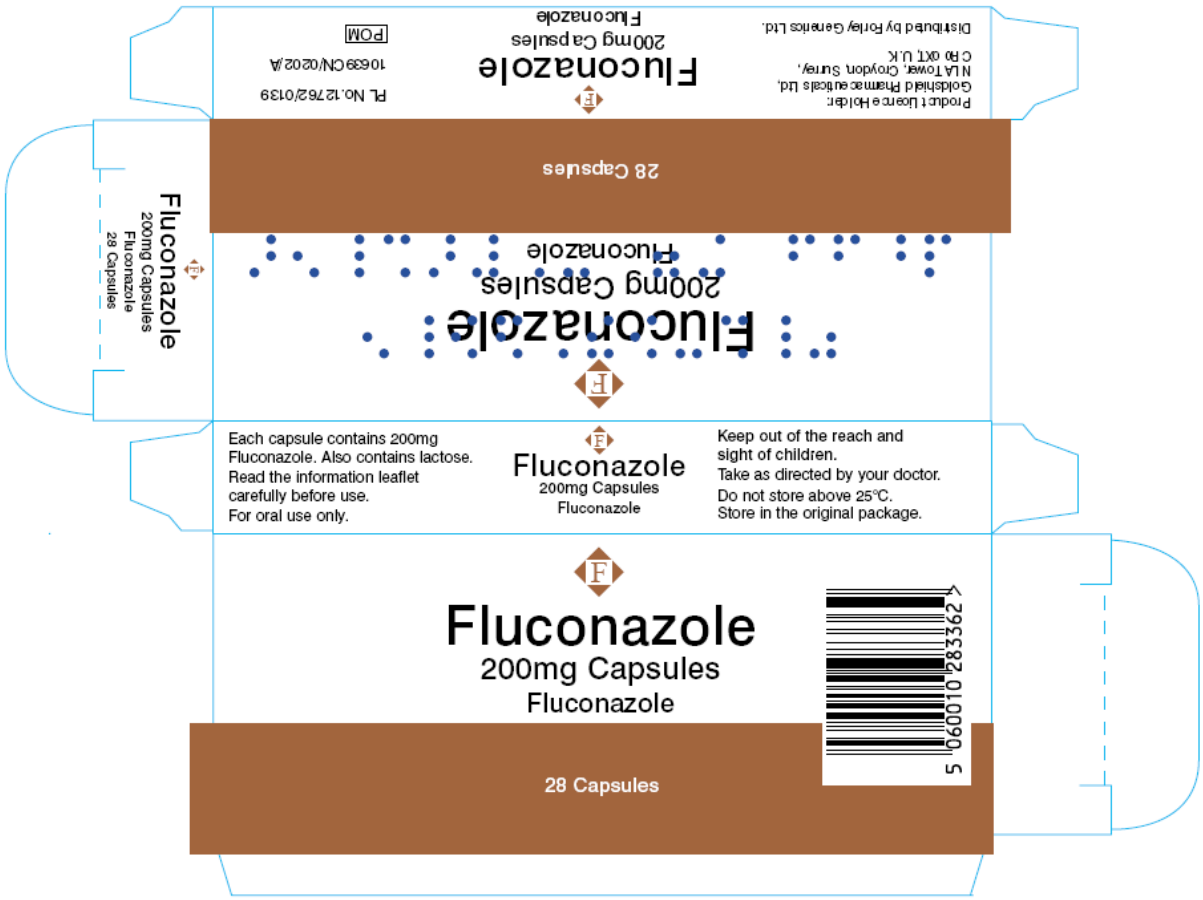
Carton for blisters, with braille




Blister foil

## Fluconazole 200mg capsules (PL 12762/0139)

Carton for blisters, with braille




Blister foil