FLUCONAZOLE 50MG CAPSULES
PL 17871/0002

FLUCONAZOLE 100MG CAPSULES
PL 17871/0003

FLUCONAZOLE 150MG CAPSULES
PL 17871/0004 & 0006

FLUCONAZOLE 200MG CAPSULES
PL 17871/0005

(FLUCONAZOLE)

UK Public Assessment Report

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FLUCONAZOLE 50MG, 100MG, 150MG & 200MG CAPSULES (FLUCONAZOLE) PL 17871/0002 - 0006

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Jenson Pharmaceutical Service Limited Marketing Authorisations (licences) for the medicinal products Fluconazole 50mg Capsules (PL 17871/0002), Fluconazole 100mg Capsules (PL 17871/0003), Fluconazole 150mg Capsules (PL 17871/0004 & 0006), and Fluconazole 200mg Capsules (PL 17871/0005) on 9th October 2008.

Fluconazole 50mg, 100mg and 200mg Capsules are prescription-only medicines. Fluconazole 150mg Capsules are licensed as prescription-only medicines (PL 17871/0004) and P medicines, available from pharmacies (PL 17871/0006).

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 150mg Capsules (P licence) are used to treat genital *Candida* infections. Fluconazole 50mg, 100mg, 150mg and 200mg capsules (POM licence) may be prescribed to you by your doctor to treat fungal infections such as thrush of the mouth or throat, skin infections, internal 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 17871/0002 - 0006

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Jenson Pharmaceutical Service Limited Marketing Authorisations (licences) for the medicinal products Fluconazole 50mg Capsules (PL 17871/0002), Fluconazole 100mg Capsules (PL 17871/0003), Fluconazole 150mg Capsules (PL 17871/0004 & 0006), and Fluconazole 200mg Capsules (PL 17871/0005) on 9th October 2008. Fluconazole 50mg, 100mg and 200mg Capsules are prescription-only medicines (POM). Fluconazole 150mg Capsules are licensed as POM (PL 17871/0004) and P medicines (PL 17871/0006).

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 products 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 17871/0006 – P licensed) 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.
- 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 were extrapolated to the other capsule strengths.

PHARMACEUTICAL ASSESSMENT

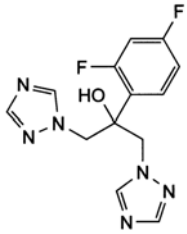
ACTIVE SUBSTANCE

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. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary packaging 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 a suitable retest period has been set.

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), indigo carmine (E132) in the capsule shell; and the 100mg and 150mg strength capsules contain 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 two of the excipients making up the capsule shell - yellow iron oxide (E172) and indigo carmine (E132), which comply with the USP (US Pharmacopoeia) / NF (National Formulary) and French Pharmacopoeia specifications respectively. 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 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 PVC (polyvinylchloride) / aluminium blister strips, which are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons. The 50mg, 100mg and 200mg strength products are packaged in carton pack sizes of 7 capsules. The 150mg strength products are packaged in carton pack sizes of 1 capsule.

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 24 months has been set, which is satisfactory. Storage conditions are “Do not store above 30°C. Store in the original packaging.”

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.

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 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.

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 17871/0006 – P licensed) 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.

- 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. In human studies, plasma testosterone is not affected by 28 days of continuous treatment with 25-50mg of fluconazole. Doses of 50mg per day do not alter oestradiol levels in healthy females.

Pharmacokinetics

Fluconazole is well absorbed following oral administration, bioavailability from the oral route being 90% or more of that from the intravenous route. Mean peak plasma concentrations of 6.72mcg per ml have been reported in healthy subjects following a 400mg oral dose. Peak concentrations are reached within 1 to 2 hours of oral administration. Plasma concentrations are proportional to the dose over a range of 50

to 400mg. Multiple dosing leads to increases in peak plasma concentrations: steady-state concentrations are reached in 6 to 10 days but may be attained on day 2 if a loading dose is given.

Fluconazole is widely distributed and the apparent volume of distribution is close to that of total body water. Concentrations in breast milk, joint fluid, saliva, sputum, vaginal fluids, and peritoneal fluid are similar to those achieved in plasma, Concentrations in the cerebrospinal fluid range from 50 to 90% of the plasma concentrations, even in the absence of meningeal inflammation. Protein binding is about 12%.

Eighty percent or more of fluconazole is excreted unchanged in the urine; about 11% is excreted as metabolites. The elimination half-life of fluconazole is about 30 hours and is increased in patients with impaired renal function. Fluconazole is removed by dialysis.

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 of 14 days. Plasma samples were analysed for fluconazole using an appropriate, validated method.

An adequate statistical plan was provided. The test product was compared to the reference product with respect to the pharmacokinetic variables C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ using ANOVA.

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.

VARIABLE	Unit	Diflucan (Ref.)		Fluconazole(Test)		Mean Ratio (%)*	90% Confidence Interval (%)**
		Mean	SD	Mean	SD		
C_{max}	(ng.h/ml)	**4515**	1.19	**4167**	1.18	**92.2**	86.3;98.5
$AUC(0\text{-}t_{last})$	(ng.h/ml)	**201441**	1.11	**202717**	1.13	**101**	97.8;103
AUC(0- ∞)	(ng.h/ml)	**212351**	1.13	**213572**	1.14	**101**	97.4;104

* : Point estimate of “test/reference” mean ratio from analysis of log-transformed data.
** : 90% Conventional confidence interval for “test/reference” mean ratio from analysis of variance of log-transformed data.

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%.

The linear pharmacokinetics of fluconazole makes it likely that the lower-dose fluconazole formulations are also bioequivalent to their respective marketed brand formulations, although bioequivalence has not been assessed explicitly.

No subject withdrew from the study due to adverse events. There were no reports of serious adverse events.

Overall conclusions on pharmacokinetics

The 90% confidence intervals for the test/reference 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. No new safety issues have been identified. The clinical safety of fluconazole is well established following many years of 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 detailed in the SmPCs).

No new data are submitted and none are required for these types of application. The reference products are established and the applications depend upon the ability to demonstrate bioequivalence.

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 PILs are in line with the approved SmPCs and are 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.

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.

Package leaflets have 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 leaflets are well-structured and organised, easy to understand and written in a comprehensive manner. The tests show that the patients/users are able to act upon the information that the leaflets contain.

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.

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 17871/0002 - 0006

STEPS TAKEN FOR ASSESSMENT

1 The MHRA received the marketing authorisation applications on 23rd April 2002

2 Following standard checks and communication with the applicant the MHRA considered the applications valid on 26th April 2002

3 Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 5th September 2002, 9th June 2003, 12th February 2007 and 26th June 2007 and further information relating to the clinical dossiers on 6th December 2002

4 The applicant responded to the MHRA's requests, providing further information for the quality sections on 27th November 2002, 8th January 2007, 1st June 2007 and 1st October 2007 respectively and further information for the clinical sections on 3rd January 2003

5 The applications were determined on 9th October 2008

FLUCONAZOLE 50MG, 100MG, 150MG & 200MG CAPSULES (FLUCONAZOLE) PL 17871/0002 - 0006

STEPS TAKEN AFTER AUTHORISATION

Not applicable

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Fluconazole 50mg Capsules (PL 17871/0002) is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Fluconazole 50 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains 50mg fluconazole.

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Hard gelatin white-green coloured capsule, size 4.

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 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.

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

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

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

Cryptococcosis, including cryptococcal meningitis and infections of other sites (e.g. pulmonary, cutaneous). Normal hosts, and patients with AIDS, organ transplants or other causes of immunosuppression may be treated. Fluconazole 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.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Capsules for oral administration. The daily dose of Fluconazole Capsules 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.

In Adults

Candidal vaginitis or balanitis:

150mg as a single oral dose.

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.

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.

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.

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.

Candidaemia, disseminated candidiasis and other invasive candidal infections:

The usual dose is 400mg on the first day followed by 200mg daily. Depending on the clinical response the dose may be increased to 400mg daily. Duration of treatment is based upon the clinical response.

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.

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

Prevention of fungal infections in immunocompromised patients:

The recommended daily dose for patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, should be 50 to 400mg, 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 (e.g. during bone marrow transplantation) the recommended dose is 400mg once daily. Administration of Fluconazole Capsules should start several days before the anticipated onset of neutropenia, and continue for 7 days after the neutrophil count rises above 1000 cells per mm^3.

In children aged between 2 and 11 years and adolescents aged between 12 and 18 years:

Where treatment of Fluconazole Capsules is appropriate and as with similar infections in adults, the duration of treatment is based on the clinical and mycological response. Fluconazole Capsules 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”.

The recommended dose of Fluconazole Capsules 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 infection, 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 and adolescents.

There are limited data available on the use of Fluconazole Capsules for genital candidiasis in adolescents and children below 16 years. Treatment is not recommended unless antifungal treatment is imperative and no suitable agent exists.

In the Elderly

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

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 with impaired renal function who will receive multiple doses of Fluconazole Capsules, 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	50%
Regular dialysis	100% after each dialysis.

4.3 CONTRAINDICATIONS

Fluconazole 50 mg 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 contraindicated in patients receiving Fluconazole Capsules. (See section 4.5 Interaction with other Medicinal products and other forms of Interaction)

Fluconazole Capsules should not be used during pregnancy, or in women of childbearing potential unless adequate contraception is employed. Use in nursing mothers is also not recommended.

Fluconazole Capsules are contraindicated for the treatment of genital candidiasis in adolescents and children below 16 years. Treatment is not recommended unless antifungal treatment is imperative and no suitable agent exists.

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 Capsules but the clinical significance and relationship to treatment is uncertain.

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

As a causal relationship with Fluconazole Capsules cannot be excluded, patients who develop abnormal liver function tests during Fluconazole Capsules therapy should be monitored for the development of more serious hepatic injury. Fluconazole Capsules should be discontinued if clinical signs or symptoms consistent with liver disease develop during treatment with Fluconazole Capsules

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, which is considered attributable to Fluconazole Capsules, further therapy with this agent is not recommended.

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

This medicine contains lactose. 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 has not yet been established.

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

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

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

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

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

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

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. Co-administration of cisapride is contraindicated in patients receiving fluconazole. (See Contraindications.)

Zidovudine: Two kinetic studies resulted in increased levels of zidovudine most likely caused by the decreased conversion of zidovudine to its major metabolite. One study determined zidovudine levels in AIDS or ARC patients before and following Fluconazole 200mg daily for 15 days. There was a significant increase in zidovudine AUC (20%). A second randomised, two-period, two-treatment crossover study examined zidovudine levels in HIV infected patients. On two occasions, 21 days apart, patients received zidovudine 200mg every eight hours either with or without fluconazole 400mg daily for seven days. The AUC of zidovudine significantly increased (74%) during co-administration with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions.

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.

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

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

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

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

4.8 UNDESIRABLE EFFECTS

Fluconazole is generally well tolerated. The most common side effects observed are:

Central and Peripheral Nervous System

Headache, dizziness, seizures

Dermatological

Rash, alopecia, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrosis

Gastrointestinal

Abdominal pain, diarrhoea, flatulence, nausea, dyspepsia, vomitting

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, the clinical significance and relationship to treatment is uncertain.

Liver/Biliary

Hepatic toxicity including rare cases of fatalities, hepatic failure, hepatitis, hepatocellular necrosis, jaundice, elevated alkaline phosphatase, elevated bilirubin, elevated SGOT and elevated SGPT.

Metabolic/nutritional

Hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia

Other senses

Taste perversion

4.9 OVERDOSE

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

As fluconazole is largely excreted in the urine, forced volume diuresis would probably increase the elimination rate. A three hour haemodialysis session decreases plasma levels by approximately 50%.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

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 (i.v.) occurred. Inhibition of rat ovarian aromatase was observed at high concentrations.

Both orally and intraveneously 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 immunocompromised animals.

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

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

5.2 PHARMACOKINETIC PROPERTIES

After oral administration fluconazole is well absorbed. Oral absorption is not affected by concomitant food intake. Peak plasma concentrations in the fasting state occur between 0.5 and 1.5 hours post-dose with a plasma elimination half-life of approximately 30 hours. Plasma concentrations are proportional to dose. Ninety percent steady-state levels are reached by day 4-5 with multiple once daily dosing.

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

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

High skin concentrations of fluconazole, above serum concentrations, are achieved in the stratum corneum, epidermis-dermis and eccrine sweat. Fluconazole accumulates in the stratum corneum. At a dose of 50mg once daily, the concentration of fluconazole after 12 days was 73mcg/g and 7 days after cessation of treatment the concentration was still 5.8mcg/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 creatine clearance. There is no evidence of circulating metabolites.

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

Pharmacokinetics in Children

In children, the following pharmacokinetic data have been reported:

Age studied	Dose (mg/kg)	Half-life (hours)	AUC(mg.h/ml)
9 months-13 years	Single-Oral 2mg/kg	25	94.7
9 months-13 years	Single-Oral 8mg/kg	19.5	362.5
5 years – 15 years	Multiple-Oral 2mg/kg	17.4*	67.4
5 years – 15 years	Multiple-Oral 4mg/kg	15.2*	139.1
5 years – 15 years	Multiple-Oral 8mg/kg	17.6*	196.1
5 years – 15 years	Multiple-IV 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 20-60x 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 1000μg/ml) showed no evidence of chromosomal mutations.

Impairment of Fertility

Fluconazole did not affect the fertility of male or female rats treated orally with daily doses of 5, 10 or 20mg/kg or with parenteral doses of 5, 25 or 75mg/kg, although the onset of parturition was slightly delayed at 20mg/kg p.o. In an intravenous perinatal study in rats at 5, 20 and 40mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20mg/kg and 40mg/kg, but not at 5mg/kg. The disturbances in parturition were reflected by a slight increase in the number of stillborn 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

Sodium lauryl sulfate

Silica, colloidal anhydrous

Magnesium stearate

Capsule shell:

Body composition:

Titanium dioxide (E171)

Gelatin

Cap composition:

Titanium dioxide (E171)

Yellow iron oxide (E172)

Indigo Carmine (E132)

Gelatin

6.2 INCOMPATIBILITIES

No specific incompatibilities have been noted

6.3 SHELF LIFE

24 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30ºC. Store in the original packaging.

6.5 NATURE AND CONTENTS OF CONTAINER

PVC blisters with aluminium foil in a cardboard carton containing 7 capsules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services/Jenson Chemicals

Carradine House

237 Regent's Park Road

Finchley

London

N3 3LF

8 MARKETING AUTHORISATION NUMBER(S)

PL 17871 / 0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09/10/2008

10 DATE OF REVISION OF THE TEXT

09/10/2008

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Fluconazole 100mg Capsules (PL 17871/0003) is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Fluconazole 100 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains 100mg fluconazole.

For excipients, see section 6.1

3 PHARMACEUTICAL FORM

Hard gelatin white-light blue coloured capsule, size 2.

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 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.

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

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

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

Cryptococcosis, including cryptococcal meningitis and infections of other sites (e.g. pulmonary, cutaneous). Normal hosts, and patients with AIDS, organ transplants or other causes of immunosuppression may be treated. Fluconazole 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.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Capsules for oral administration. The daily dose of Fluconazole Capsules 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.

In Adults

Candidal vaginitis or balanitis:

150mg as a single oral dose.

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.

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.

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.

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.

Candidaemia, disseminated candidiasis and other invasive candidal infections:

The usual dose is 400mg on the first day followed by 200mg daily. Depending on the clinical response the dose may be increased to 400mg daily. Duration of treatment is based upon the clinical response.

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.

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

Prevention of fungal infections in immunocompromised patients:

The recommended daily dose for patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, should be 50 to 400mg, 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 (e.g. during bone marrow transplantation) the recommended dose is 400mg once daily. Administration of Fluconazole Capsules should start several days before the anticipated onset of neutropenia, and continue for 7 days after the neutrophil count rises above 1000 cells per mm^3.

In children aged between 2 and 11 years and adolescents aged between 12 and 18 years:

Where treatment of Fluconazole Capsules is appropriate and as with similar infections in adults, the duration of treatment is based on the clinical and mycological response. Fluconazole Capsules 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”.

The recommended dose of Fluconazole Capsules 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 infection, 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 and adolescents.

There are limited data available on the use of Fluconazole Capsules for genital candidiasis in adolescents and children below 16 years. Treatment is not recommended unless antifungal treatment is imperative and no suitable agent exists.

In the Elderly

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

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 with impaired renal function who will receive multiple doses of Fluconazole Capsules, 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	50%
Regular dialysis	100% after each dialysis.

4.3 CONTRAINDICATIONS

Fluconazole 100 mg 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 contraindicated in patients receiving Fluconazole Capsules. (See section 4.5 Interaction with other Medicinal products and other forms of Interaction)

Fluconazole Capsules should not be used during pregnancy, or in women of childbearing potential unless adequate contraception is employed. Use in nursing mothers is also not recommended.

Fluconazole Capsules are contraindicated for the treatment of genital candidiasis in adolescents and children below 16 years. Treatment is not recommended unless antifungal treatment is imperative and no suitable agent exists.

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 Capsules but the clinical significance and relationship to treatment is uncertain.

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

As a causal relationship with Fluconazole Capsules cannot be excluded, patients who develop abnormal liver function tests during Fluconazole Capsules therapy should be monitored for the development of more serious hepatic injury. Fluconazole Capsules should be discontinued if clinical signs or symptoms consistent with liver disease develop during treatment with Fluconazole Capsules

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, which is considered attributable to Fluconazole Capsules, further therapy with this agent is not recommended.

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

This medicine contains lactose. 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 has not yet been established.

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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. Co-administration of cisapride is contraindicated in patients receiving fluconazole. (See Contraindications.)

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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.

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

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

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

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

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

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Fluconazole is generally well tolerated. The most common side effects observed are:

Central and Peripheral Nervous System

Headache, dizziness, seizures

Dermatological

Rash, alopecia, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrosis

Gastrointestinal

Abdominal pain, diarrhoea, flatulence, nausea, dyspepsia, vomitting

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, the clinical significance and relationship to treatment is uncertain.

Liver/Biliary

Hepatic toxicity including rare cases of fatalities, hepatic failure, hepatitis, hepatocellular necrosis, jaundice, elevated alkaline phosphatase, elevated bilirubin, elevated SGOT and elevated SGPT.

Metabolic/nutritional

Hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia

Other senses

Taste perversion

4.9 OVERDOSE

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

As fluconazole is largely excreted in the urine, forced volume diuresis would probably increase the elimination rate. A three hour haemodialysis session decreases plasma levels by approximately 50%.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

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 (i.v.) occurred. Inhibition of rat ovarian aromatase was observed at high concentrations.

Both orally and intraveneously 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 immunocompromised animals.

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

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

5.2 PHARMACOKINETIC PROPERTIES

After oral administration fluconazole is well absorbed. Oral absorption is not affected by concomitant food intake. Peak plasma concentrations in the fasting state occur between 0.5 and 1.5 hours post-dose with a plasma elimination half-life of approximately 30 hours. Plasma concentrations are proportional to dose. Ninety percent steady-state levels are reached by day 4-5 with multiple once daily dosing.

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

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

High skin concentrations of fluconazole, above serum concentrations, are achieved in the stratum corneum, epidermis-dermis and eccrine sweat. Fluconazole accumulates in the stratum corneum. At a dose of 50mg once daily, the concentration of fluconazole after 12 days was 73mcg/g and 7 days after cessation of treatment the concentration was still 5.8mcg/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 creatine clearance. There is no evidence of circulating metabolites.

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

Pharmacokinetics in Children

In children, the following pharmacokinetic data have been reported:

Age studied	Dose (mg/kg)	Half-life (hours)	AUC(mg.h/ml)
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5 years – 15 years	Multiple-IV 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 20-60x 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.

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

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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 stillborn 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

Sodium lauryl sulfate

Silica, colloidal anhydrous

Magnesium stearate

Capsule shell:

Body composition:

Titanium dioxide (E171)

Gelatin

Cap composition:

Titanium dioxide (E171)

Patent Blue V (E131)

Gelatin

6.2 INCOMPATIBILITIES

No specific incompatibilities have been noted

6.3 SHELF LIFE

24 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30ºC. Store in the original packaging

6.5 NATURE AND CONTENTS OF CONTAINER

PVC blisters with aluminium foil in a cardboard carton containing 7 capsules

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services/Jenson Chemicals

Carradine House

237 Regent's Park Road

Finchley

London

N3 3LF

8 MARKETING AUTHORISATION NUMBER(S)

PL 17871 / 0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09/10/2008

10 DATE OF REVISION OF THE TEXT

09/10/2008

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Fluconazole 200mg Capsules (PL 17871/0005) is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Fluconazole 200 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains 200 mg fluconazole

For excipients, see section 6.1

3 PHARMACEUTICAL FORM

Hard gelatin white-white coloured capsule, size 0.

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 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.

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

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

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

Cryptococcosis, including cryptococcal meningitis and infections of other sites (e.g. pulmonary, cutaneous). Normal hosts, and patients with AIDS, organ transplants or other causes of immunosuppression may be treated. Fluconazole 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.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Capsules for oral administration. The daily dose of Fluconazole Capsules 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.

In Adults

Candidal vaginitis or balanitis:

150mg as a single oral dose.

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.

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.

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.

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.

Candidaemia, disseminated candidiasis and other invasive candidal infections:

The usual dose is 400mg on the first day followed by 200mg daily. Depending on the clinical response the dose may be increased to 400mg daily. Duration of treatment is based upon the clinical response.

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.

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

Prevention of fungal infections in immunocompromised patients:

The recommended daily dose for patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, should be 50 to 400mg, 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 (e.g. during bone marrow transplantation) the recommended dose is 400mg once daily. Administration of Fluconazole Capsules should start several days before the anticipated onset of neutropenia, and continue for 7 days after the neutrophil count rises above 1000 cells per mm^3.

In children aged between 2 and 11 years and adolescents aged between 12 and 18 years:

Where treatment of Fluconazole Capsules is appropriate and as with similar infections in adults, the duration of treatment is based on the clinical and mycological response. Fluconazole Capsules 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”.

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

For the treatment of systemic candidiasis and cryptococcal infection, the recommended dosage is 6-12 mg/kg daily, depending on the severity of the disease.

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

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

There are limited data available on the use of Fluconazole Capsules for genital candidiasis in adolescents and children below 16 years. Treatment is not recommended unless antifungal treatment is imperative and no suitable agent exists.

In the Elderly

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

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 with impaired renal function who will receive multiple doses of Fluconazole Capsules, 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	50%
Regular dialysis	100% after each dialysis.

4.3 CONTRAINDICATIONS

Fluconazole 200 mg 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 contraindicated in patients receiving Fluconazole Capsules. (See section 4.5 Interaction with other medicinal products and other forms of interaction).

Fluconazole Capsules should not be used during pregnancy, or in women of childbearing potential unless adequate contraception is employed. Use in nursing mothers is also not recommended.

Fluconazole Capsules are contraindicated for the treatment of genital candidiasis in adolescents and children below 16 years. Treatment is not recommended unless antifungal treatment is imperative and no suitable agent exists.

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 Capsules but the clinical significance and relationship to treatment is uncertain.

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

As a causal relationship with Fluconazole Capsules cannot be excluded, patients who develop abnormal liver function tests during Fluconazole Capsules therapy should be monitored for the development of more serious hepatic injury. Fluconazole Capsules should be discontinued if clinical signs or symptoms consistent with liver disease develop during treatment with Fluconazole Capsules

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, which is considered attributable to Fluconazole Capsules, further therapy with this agent is not recommended.

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

This medicine contains lactose. 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 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. Prothrombin time in patients receiving coumarin-type anti-coagulants should be carefully monitored.

Benzodiazepines (Short Acting) Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dosage and the patient should be appropriately monitored.

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

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

Oral contraceptives: Two 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 200 mg daily the AUCs of ethinyloestradiol and levonorgestrel were increased 40% and 24% respectively. Thus multiple dose use of fluconazole at these doses is unlikely to have an effect on the efficacy of the combined oral contraceptive.

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

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

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

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

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. Co-administration of cisapride is contraindicated in patients receiving fluconazole. (See Contraindications.)

Zidovudine: Two kinetic studies resulted in increased levels of zidovudine most likely caused by the decreased conversion of zidovudine to its major metabolite. One study determined zidovudine levels in AIDS or ARC patients before and following Fluconazole 200mg daily for 15 days. There was a significant increase in zidovudine AUC (20%). A second randomised, two-period, two-treatment crossover study examined zidovudine levels in HIV infected patients. On two occasions, 21 days apart, patients received zidovudine 200mg every eight hours either with or without fluconazole 400mg daily for seven days. The AUC of zidovudine significantly increased (74%) during co-administration with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions.

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.

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

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

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

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

4.8 UNDESIRABLE EFFECTS

Fluconazole is generally well tolerated. The most common side effects observed are:

Central and Peripheral Nervous System

Headache, dizziness, seizures

Dermatological

Rash, alopecia, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrosis

Gastrointestinal

Abdominal pain, diarrhoea, flatulence, nausea, dyspepsia, vomitting

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, the clinical significance and relationship to treatment is uncertain.

Liver/Biliary

Hepatic toxicity including rare cases of fatalities, hepatic failure, hepatitis, hepatocellular necrosis, jaundice, elevated alkaline phosphatase, elevated bilirubin, elevated SGOT and elevated SGPT.

Metabolic/nutritional

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Other senses

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

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6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lactose monohydrate

Maize starch

Sodium lauryl sulfate

Silica, colloidal anhydrous

Magnesium stearate

Capsule shell:

Body composition:

Titanium dioxide (E171)

Gelatin

Cap composition:

Titanium dioxide (E171)

Gelatin

6.2 INCOMPATIBILITIES

No specific incompatibilities have been noted

6.3 SHELF LIFE

24 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30ºC. Store in the original packaging.

6.5 NATURE AND CONTENTS OF CONTAINER

PVC blisters with aluminium foil in a cardboard carton containing 7 capsules

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements

7 MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services/Jenson Chemicals

Carradine House

237 Regent's Park Road

Finchley

London

N3 3LF

8 MARKETING AUTHORISATION NUMBER(S)

PL 17871 / 0005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09/10/2008

10 DATE OF REVISION OF THE TEXT

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SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Fluconazole 150mg Capsules (PL 17871/0004 – POM licensed) is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Fluconazole 150 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains 150 mg fluconazole.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard gelatin light blue-light blue coloured capsule, size 1.

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 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.

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

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

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

Cryptococcosis, including cryptococcal meningitis and infections of other sites (e.g. pulmonary, cutaneous). Normal hosts, and patients with AIDS, organ transplants or other causes of immunosuppression may be treated. Fluconazole 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.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Capsules for oral administration. The daily dose of Fluconazole Capsules 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.

In Adults

Candidal vaginitis or balanitis:

150mg as a single oral dose.

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.

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.

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.

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.

Candidaemia, disseminated candidiasis and other invasive candidal infections:

The usual dose is 400mg on the first day followed by 200mg daily. Depending on the clinical response the dose may be increased to 400mg daily. Duration of treatment is based upon the clinical response.

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.

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

Prevention of fungal infections in immunocompromised patients:

The recommended daily dose for patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, should be 50 to 400mg, 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 (e.g. during bone marrow transplantation) the recommended dose is 400mg once daily. Administration of Fluconazole Capsules should start several days before the anticipated onset of neutropenia, and continue for 7 days after the neutrophil count rises above 1000 cells per mm^3.

In children aged between 2 and 11 years and adolescents aged between 12 and 18 years:

Where treatment of Fluconazole Capsules is appropriate and as with similar infections in adults, the duration of treatment is based on the clinical and mycological response. Fluconazole Capsules 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”.

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

For the treatment of systemic candidiasis and cryptococcal infection, the recommended dosage is 6-12 mg/kg daily, depending on the severity of the disease.

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

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

There are limited data available on the use of Fluconazole Capsules for genital candidiasis in adolescents and children below 16 years. Treatment is not recommended unless antifungal treatment is imperative and no suitable agent exists.

In the Elderly

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

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 with impaired renal function who will receive multiple doses of Fluconazole Capsules, 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	50%
Regular dialysis	100% after each dialysis.

4.3 CONTRAINDICATIONS

Fluconazole 150 mg 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 contraindicated in patients receiving Fluconazole Capsules. (See section 4.5 Interaction with other medicinal products and other forms of interaction).

Fluconazole Capsules should not be used during pregnancy, or in women of childbearing potential unless adequate contraception is employed. Use in nursing mothers is also not recommended.

Fluconazole Capsules are contraindicated for the treatment of genital candidiasis in adolescents and children below 16 years. Treatment is not recommended unless antifungal treatment is imperative and no suitable agent exists.

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 Capsules but the clinical significance and relationship to treatment is uncertain.

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

As a causal relationship with Fluconazole Capsules cannot be excluded, patients who develop abnormal liver function tests during Fluconazole Capsules therapy should be monitored for the development of more serious hepatic injury. Fluconazole Capsules should be discontinued if clinical signs or symptoms consistent with liver disease develop during treatment with Fluconazole Capsules.

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, which is considered attributable to Fluconazole Capsules, further therapy with this agent is not recommended.

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

This medicine contains lactose. 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 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. Prothrombin time in patients receiving coumarin-type anti-coagulants should be carefully monitored.

Benzodiazepines (Short Acting) Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dosage and the patient should be appropriately monitored.

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

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

Oral contraceptives: Two 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 50 mg fluconazole study, while at 200 mg 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 50 mg daily does not affect endogenous steroid levels in females: 200-400 mg daily has no clinically significant effect on endogenous steroid levels or on ACTH stimulated response in healthy male volunteers.

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

Theophylline: In a placebo controlled interaction study, the administration of fluconazole 200 mg 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 200 mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. Another study at a 400 mg and 800 mg daily dose of fluconazole demonstrated that fluconazole, taken in multiple doses of 400 mg 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 Contraindications).

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. Co-administration of cisapride is contraindicated in patients receiving fluconazole. (See Contraindications.)

Zidovudine: Two kinetic studies resulted in increased levels of zidovudine most likely caused by the decreased conversion of zidovudine to its major metabolite. One study determined zidovudine levels in AIDS or ARC patients before and following fluconazole 200 mg daily for 15 days. There was a significant increase in zidovudine AUC (20%). A second randomised, two-period, two-treatment crossover study examined zidovudine levels in HIV infected patients. On two occasions, 21 days apart, patients received zidovudine 200 mg every eight hours either with or without fluconazole 400 mg daily for seven days. The AUC of zidovudine significantly increased (74%) during co-administration with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions.

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

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

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

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

During pregnancy

There are no adequate and well controlled studies in pregnant women. There have been reports of multiple congenital abnormalities in infants whose mothers were being treated for 3 or more months with high dose (400-800 mg/day) fluconazole therapy for coccidioidomycosis. The relationship between fluconazole and these events is unclear. Accordingly, Fluconazole Capsules should not be used in pregnancy or in women of childbearing potential unless adequate contraception is employed.

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

4.8 UNDESIRABLE EFFECTS

Fluconazole is generally well tolerated. The most common side effects observed are:

Central and Peripheral Nervous System

Headache, dizziness, seizures

Dermatological

Rash, alopecia, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrosis

Gastrointestinal

Abdominal pain, diarrhoea, flatulence, nausea, dyspepsia, vomitting

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, the clinical significance and relationship to treatment is uncertain.

Liver/Biliary

Hepatic toxicity including rare cases of fatalities, hepatic failure, hepatitis, hepatocellular necrosis, jaundice, elevated alkaline phosphatase, elevated bilirubin, elevated SGOT and elevated SGPT.

Metabolic/nutritional

Hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia

Other senses

Taste perversion

4.9 OVERDOSE

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

As fluconazole is largely excreted in the urine, forced volume diuresis would probably increase the elimination rate. A three hour haemodialysis session decreases plasma levels by approximately 50%.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

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 (i.v.) occurred. Inhibition of rat ovarian aromatase was observed at high concentrations.

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

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

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

5.2 PHARMACOKINETIC PROPERTIES

After oral administration fluconazole is well absorbed. Oral absorption is not affected by concomitant food intake. Peak plasma concentrations in the fasting state occur between 0.5 and 1.5 hours post-dose with a plasma elimination half-life of approximately 30 hours. Plasma concentrations are proportional to dose. Ninety percent steady-state levels are reached by day 4-5 with multiple once daily dosing.

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

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

High skin concentrations of fluconazole, above serum concentrations, are achieved in the stratum corneum, epidermis-dermis and eccrine sweat. Fluconazole accumulates in the stratum corneum. At a dose of 50mg once daily, the concentration of fluconazole after 12 days was 73 mcg/g and 7 days after cessation of treatment the concentration was still 5.8 mcg/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 creatine clearance. There is no evidence of circulating metabolites.

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

Pharmacokinetics in Children

In children, the following pharmacokinetic data have been reported:

Age studied	Dose (mg/kg)	Half-life (hours)	AUC(mg.h/ml)
9 months – 3 years	Single-Oral 2 mg/kg	25	94.7
9 months – 13 years	Single-Oral 8 mg/kg	19.5	362.5
5 years – 15 years	Multiple-Oral 2 mg/kg	17.4*	67.4
5 years – 15 years	Multiple-Oral 4 mg/kg	15.2*	139.1
5 years – 15 years	Multiple-Oral 8 mg/kg	17.6*	196.1
5 years – 15 years	Multiple-IV 3 mg/kg	15.5	41.6

*Denotes final day

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 50 mg/kg and higher doses. At doses ranging from 80 mg/kg (approximately 20-60x the recommended human dose) to 320 mg/kg embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate and abnormal cranio-facial ossification. These effects are consistent with the inhibition of oestrogen 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 10 mg/kg/day. Male rats treated with 5 and 10 mg/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 1000 μg/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 20 mg/kg or with parenteral doses of 5, 25 or 75 mg/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 40 mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg and 40 mg/kg, but not at 5 mg/kg. The disturbances in parturition were reflected by a slight increase in the number of stillborn 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

Sodium lauryl sulfate

Silica, colloidal anhydrous

Magnesium stearate

Capsule shell:

Body composition:

Titanium dioxide (E171)

Patent Blue V (E131)

Gelatin

Cap composition:

Titanium dioxide (E171)

Patent Blue V (E131)

Gelatin

6.2 INCOMPATIBILITIES

No specific incompatibilities have been noted.

6.3 SHELF LIFE

24 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30ºC. Store in the original packaging

6.5 NATURE AND CONTENTS OF CONTAINER

PVC blisters with aluminium foil in a cardboard carton containing 1 capsule

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements

7 MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services/Jenson Chemicals

Carradine House

237 Regent's Park Road

Finchley

London

N3 3LF

8 MARKETING AUTHORISATION NUMBER(S)

PL 17871/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09/10/2008

10 DATE OF REVISION OF THE TEXT

09/10/2008

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Fluconazole 150mg Capsules (PL 17871/0006 – P licensed) is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Fluconazole 150 mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains 150 mg fluconazole.

For excipients, see 6.1

3 PHARMACEUTICAL FORM

Hard gelatin light blue-light blue coloured capsule, size 1

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

Vaginal candidiasis, acute or recurrent; or candidal balanitis associated with vaginal candidiasis.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

In adolescents and adults aged 16-60 years:

Vaginal candidiasis or candidal balanitis 150 mg as a single oral dose.

In children and the elderly:

Fluconazole 150 mg Capsules are not recommended for use in adolescents and children under the age of 16 years and patients over the age of 60 years.

In Renal Impairment

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

4.3 CONTRAINDICATIONS

Fluconazole 150 mg Capsules should not be used in patients with known hypersensitivity to the drug or to related azole compounds or any other ingredient in the formulation.

Co-administration of terfenadine or cisapride is contraindicated in patients receiving Fluconazole Capsules. (See section 4.5 Interaction with other Medicinal products and other forms of Interaction)

Fluconazole Capsules should not be used during pregnancy or in women of childbearing potential unless adequate contraception is employed. Use in nursing mothers is also not recommended.

Fluconazole Capsules are contraindicated for the treatment of genital candidiasis in adolescents and children below 16 years and patients over the age of 60 years.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The product intended for pharmacy availability without prescription will carry a leaflet which will advise the patient: “Do not use Fluconazole 150 mg Capsules without first consulting your doctor”:

If you are under 16 or over 60 years of age.

If you are allergic to any of the ingredients in Fluconazole 150 mg Capsules or other antifungals and other thrush treatments.

If you are taking the antihistamine terfenadine or the prescription medicine cisapride.

If you have any disease or illness affecting your liver or kidneys or have had unexplained jaundice.

If you suffer from any other chronic disease or illness.

If you or your partner have had exposure to a sexually transmitted disease.

If you are experiencing lower abdominal pain or burning on passing urine.

Women only:

If you have had thrush more than twice in the last six months.

If you are pregnant or plan to become pregnant or if are breast feeding.

If you have any abnormal or irregular vaginal bleeding or a blood stained discharge.

If you have vulval or vaginal sores, ulcers or blisters.

Men only:

If your sexual partner does not have thrush

If you have penile sores, ulcers or blisters

If you have an abnormal penile discharge (leakage)

If your penis has started to smell

The product should never be used again if the patient experiences a rash or anaphylaxis follows the use of the drug.

Recurrent use: Patients should be advised to consult their physician if the symptoms have not been relieved within 7 days of taking Fluconazole 150 mg Capsules. Fluconazole 150 mg Capsules can be used if the candidal infection returns after 7 days. However, if the candidal infection recurs more than twice within six months, patients should be advised to consult their doctor.

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 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. Prothrombin time in patients receiving coumarin-type anti-coagulants should be carefully monitored.

Benzodiazepines (Short Acting) Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dosage and the patient should be appropriately monitored.

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

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

Oral contraceptives: Two 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 50 mg fluconazole study, while at 200 mg 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 50 mg daily does not affect endogenous steroid levels in females: 200-400 mg daily has no clinically significant effect on endogenous steroid levels or on ACTH stimulated response in healthy male volunteers.

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

Theophylline: In a placebo controlled interaction study, the administration of fluconazole 200 mg 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 200 mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. Another study at a 400 mg and 800 mg daily dose of fluconazole demonstrated that fluconazole taken in multiple doses of 400 mg 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 Contraindications).

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. Co-administration of cisapride is contraindicated in patients receiving fluconazole. (See Contraindications.)

Zidovudine: Two kinetic studies resulted in increased levels of zidovudine most likely caused by the decreased conversion of zidovudine to its major metabolite. One study determined zidovudine levels in AIDS or ARC patients before and following Fluconazole 200 mg daily for 15 days. There was a significant increase in zidovudine AUC (20%). A second randomised, two-period, two-treatment crossover study examined zidovudine levels in HIV infected patients. On two occasions, 21 days apart, patients received zidovudine 200 mg every eight hours either with or without fluconazole 400 mg daily for seven days. The AUC of zidovudine significantly increased (74%) during co-administration with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions.

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

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

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

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

Pregnancy

There are no adequate and well controlled studies in pregnant women. There have been reports of multiple congenital abnormalities in infants whose mothers were being treated for 3 or more months with high dose (400-800 mg/day) fluconazole therapy for coccidioidomycosis. The relationship between fluconazole and these events is unclear. Accordingly, Fluconazole Capsules should not be used in pregnancy or in women of childbearing potential unless adequate contraception is employed.

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

4.8 UNDESIRABLE EFFECTS

Fluconazole is generally well tolerated. The most common side effects observed are:

Central and Peripheral Nervous System

Headache, dizziness, seizures

Dermatological

Rash, alopecia, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrosis

Gastrointestinal

Abdominal pain, diarrhoea, flatulence, nausea, dyspepsia, vomiting

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, the clinical significance and relationship to treatment is uncertain.

Liver/Biliary

Hepatic toxicity including rare cases of fatalities, hepatic failure, hepatitis, hepatocellular necrosis, jaundice, elevated alkaline phosphatase, elevated bilirubin, elevated SGOT and elevated SGPT.

Metabolic/nutritional

Hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia

Other senses

Taste perversion

4.9 OVERDOSE

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

As fluconazole is largely excreted in the urine, forced volume diuresis would probably increase the elimination rate. A three hour haemodialysis session decreases plasma levels by approximately 50%.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

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 (i.v.) occurred. Inhibition of rat ovarian aromatase was observed at high concentrations.

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

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

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

5.2 PHARMACOKINETIC PROPERTIES

After oral administration fluconazole is well absorbed. Oral absorption is not affected by concomitant food intake. Peak plasma concentrations in the fasting state occur between 0.5 and 1.5 hours post-dose with a plasma elimination half-life of approximately 30 hours. Plasma concentrations are proportional to dose. Ninety percent steady-state levels are reached by day 4-5 with multiple once daily dosing.

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

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

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

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 50 mg/kg and higher doses. At doses ranging from 80 mg/kg (approximately 20-60x the recommended human dose) to 320 mg/kg embryolethality in rats was increased and fetal abnormalities included wavy ribs, cleft palate and abnormal cranio-facial ossification. These effects are consistent with the inhibition of oestrogen 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 10 mg/kg/day. Male rats treated with 5 and 10 mg/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 1000 μg/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 20 mg/kg or with parenteral doses of 5, 25 or 75 mg/kg, although the onset of parturition was slightly delayed at 20 mg/kg p.o. In an intravenous perinatal study in rats at 5, 20 and 40 mg/kg, dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg and 40 mg/kg, but not at 5 mg/kg. The disturbances in parturition were reflected by a slight increase in the number of stillborn 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

Sodium lauryl sulfate

Silica, colloidal anhydrous

Magnesium stearate

Capsule shell:

Body composition:

Titanium dioxide (E171)

Patent Blue V (E131)

Gelatin

Cap composition:

Titanium dioxide (E171)

Patent Blue V (E131)

Gelatin

6.2 INCOMPATIBILITIES

No specific incompatibilities have been noted.

6.3 SHELF LIFE

24 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 30ºC. Store in the original packaging.

6.5 NATURE AND CONTENTS OF CONTAINER

PVC blisters with aluminium foil in a cardboard carton containing 1 capsule

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Jenson Pharmaceutical Services Limited

Carradine House

237 Regent's Park Road

London

N3 3LF

United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 17871/0006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

09/10/2008

10 DATE OF REVISION OF THE TEXT

09/10/2008

PATIENT INFORMATION LEAFLETS

PIL for Fluconazole 50mg, 100mg and 200mg capsules (PL 17871/0002-3 & 0005)

PACKAGE LEAFLET: INFORMATION FOR THE USER

Fluconazole 50mg Capsules
Fluconazole 100mg Capsules
Fluconazole 200mg Capsules

(Fluconazole)

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 get 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
2. Before you take Fluconazole Capsules
3. How to take Fluconazole Capsules
4. Possible side effects
5. How to store Fluconazole Capsules
6. Further information

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

Your medicine contains the active substance fluconazole, which is one of a group of medicines called antifungal agents.

Fluconazole is used to treat infections caused by fungi or yeasts. It may also be used to prevent you from getting a fungal infection. The most common cause of fungal infections is a yeast called Candida.

You may be given this medicine by your doctor to treat fungal infections such as:
- thrush of the mouth or throat (mucosal infections). Thrush is commonly caused by Candida
- skin infections - e.g. athlete's foot, ringworm
- internal (systemic) fungal infections caused by Candida - e.g. infections of the bloodstream, urinary tract or other body organs
- internal (systemic) fungal infections caused by

- a medicine to control epilepsy called phenytoin
- medicines to prevent transplant rejection (such as ciclosporin, or tacrolimus)
- a medicine to control asthma called theophylline
- medicines to treat HIV (such as didanosine or zidovudine also known as AZT)
- oral contraceptives
- medicines to relieve migraines known as ergot alkaloids
- medicines to lower blood cholesterol known as statins (such as atorvastatin or fluvastatin)
- a medicine to treat an irregular heart beat called quinidine
- medicines known as benzodiazepines such as diazepam (used to treat anxiety) or midazolam (used to help people sleep)
- medicines to treat angina and/or high blood pressure (such as losartan or nifedipine)
- a medicine to treat pneumonia called trimetrexate

Cryptococcus - e.g. cryptococcal meningitis and infections of other sites such as the lungs and skin
- genital Candida infections, e.g. vaginal thrush or candidal balanitis (inflammation of the end of the penis and/or foreskin).

You may also be given fluconazole 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
- if you are allergic to any of the other ingredients of Fluconazole Capsules (these are listed in section 6, Further Information)
- if you are taking medicines called terfenadine or astemizole (antihistamines)
- if you are taking a medicine called cisapride (used for stomach upsets)
- if you have heart disease including heart rhythm problems
- if your doctor has told you that you have low levels of potassium or magnesium in your blood

Taking other medicines
Tell your doctor if you are taking any of the following medicines:
- an antibiotic called rifampicin or rifabutin
- a medicine to treat water retention and high blood pressure known as hydrochlorothiazide
- medicines to prevent and/or treat blood clots known as anticoagulants (such as warfarin)
- medicines to treat diabetes known as sulphonylureas (such as tolbutamide)
- an anti-depressant called amitriptyline
- a medicine to treat arthritis called celecoxib
- a medicine to treat fungal infections called amphotericin

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

Pregnancy and breast-feeding
Fluconazole Capsules should only be taken if your doctor decides that it is absolutely necessary. Tell your doctor if you are pregnant, trying to become pregnant or think you may be pregnant.

This medicine can be passed into breast milk. You should not take Fluconazole Capsules whilst breast-feeding, unless you are told to by your doctor.

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

Driving and using machines
Occasionally dizziness or fits can occur in people taking Fluconazole Capsules. If you are affected in this way, you should avoid driving or using machines.

Important information about some of the ingredients of Fluconazole Capsules
These capsules contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

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.

Take your capsules at the same time each day. Swallow the capsules whole with a glass of water (do not chew).

How many capsules should you take?
The usual dose of Fluconazole Capsules is different for different infections, as listed in the table below: In all cases your doctor will tell you what dose you should be taking.

Adults:	
• To treat thrush (mucosal infections) of the mouth	The usual daily dose is 50-100mg for 7-14 days
• To treat thrush (mucosal infections) of the throat or else where	The usual daily dose is 50-100mg for 14-30 days
• To treat genital thrush (Candida) infections	Usually a single dose of 150mg
• To treat fungal skin infections	The usual daily dose is 50mg for 2-4 weeks Athletes foot may need up to six weeks treatment
• To treat internal fungal infections caused by Candida	The usual dose is 400-800mg on the first day then a daily dose of 200-400mg until you are better
• To treat internal fungal infections caused by Cryptococcus	The usual dose is 400mg on the first day then a daily dose of 200-400mg for 6-8 weeks
• To prevent fungal infections caused by Cryptococcus from coming back	The usual daily dose is 100-200mg indefinitely
• To stop you from getting a fungal infection	The usual daily dose is 50-400mg until you are no longer at risk of getting an infection.
Children: Children should not be given a daily dose of more than 400mg.	
• To treat mucosal infections	The usual daily dose is 3mg/kg. The first dose

4.POSSIBLE SIDE EFFECTS

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

You should tell your doctor immediately if you experience sudden wheeziness, difficulty in breathing or tightness in the chest or you notice swelling of the eyelids, face, lips or throat, or a rash or itching especially affecting the whole body.

The most common side effects reported are: -
- nausea and/or vomiting (feeling and/or being sick)
- stomach discomfort
- diarrhoea
- flatulence (wind)
- indigestion
- rash, painful skin or blistering
- hair loss
- headache, dizziness and fits

In some patients, particularly those suffering from a serious ongoing illness such as cancer or AIDS the following side affects have been reported:
- a decrease in the number of red cells (which carry oxygen around the body), white cells (which help to fight infection) and platelets (which help with clotting)
- allergic reactions
- liver problems
- changes in blood, liver function, urine and other biochemical tests
- changes in your sense of taste

If any of the side effects get 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 use after the expiry date stated on the carton after Exp:. The expiry date refers to the last day of that month.

	may sometimes be 6mg/kg
• To treat internal fungal infections caused by Candida or Cryptococcus	The usual daily dose is 6–12mg/kg
• To stop them from getting a fungal infection	The usual daily dose is 3-12mg/kg until your child is no longer at risk of getting an infection.

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

Patients with kidney problems
- Your doctor may adjust your dose depending on how well your kidneys are working. The normal adult dose is usually given on the first day of treatment and then reduced to half the daily dose.
- People on dialysis are normally given the usual adult dose after each dialysis session.

If you take more Fluconazole Capsules than you should
You may start to feel sick or unwell. If you (or someone else) has taken too many capsules, contact your doctor or go to the nearest hospital casualty department immediately.

Remember to take this leaflet or the packaging with you so that the doctor knows what you have taken.

If you forget to take Fluconazole Capsules
If you forget to take a dose of your medicine, take the next dose when it is due. Do not take a double dose to make up for the one you missed.

If you stop taking Fluconazole Capsules
You should complete your course of treatment to make sure that any infection has gone. Do not stop taking Fluconazole Capsules without speaking to your doctor first.

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

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 protect the environment.

6.FURTHER INFORMATION

What Fluconazole Capsules contain
- The active substance is fluconazole 50 mg, 100 or 200 mg.
- The other ingredients are lactose monohydrate, maize starch, sodium lauryl sulfate, silica (colloidal anhydrous), magnesium stearate, titanium dioxide (E171) and gelatine. The 50mg capsule contains titanium dioxide (E171), yellow iron oxide (E172) and indigo carmine (E132) the 100mg capsule contains patent blue V (E131) and the 200mg capsules contain titanium dioxide (E171) as colouring agents.

What Fluconazole Capsules look like and contents of the pack
Your medicine is in the form of a capsule. There are three strengths available in blister packs of 7 capsules:
- The 50mg capsules have a white body with a green cap
- The 100mg capsules have a white body with a blue cap
- The 200mg capsules have a white body with a white cap

Marketing Authorisation Holder and Manufacturer
Jenson Pharmaceutical Services / Jenson Chemicals, Carradine House, 237 Regents Park Road, Finchley, London, N3 3LF

This leaflet was last approved in: {mm/yyyy}

Item code

PIL for Fluconazole 150mg capsules (PL 17871/0004) POM classification

PACKAGE LEAFLET: INFORMATION FOR THE USER

Fluconazole 150mg Capsules

(Fluconazole)

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 get 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
2. Before you take Fluconazole Capsules
3. How to take Fluconazole Capsules
4. Possible side effects
5. How to store Fluconazole Capsules
6. Further information

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

Your medicine contains the active substance fluconazole, which is one of a group of medicines called antifungal agents. Fluconazole is used to treat infections caused by fungi or yeasts.

The most common cause of fungal infections is a yeast called *Candida*. Vaginal thrush or candidal balanitis (inflammation of the end of the penis and/or foreskin) are caused by *Candida*. Fluconazole is used to treat genital *Candida* infections.

2. BEFORE YOU TAKE FLUCONAZOLE CAPSULES

Do not take Fluconazole Capsules

- if you are allergic (hypersensitive) to fluconazole
- if you are allergic to any of the other ingredients of Fluconazole Capsules (these are listed in section 6, Further Information)
- if you are taking medicines called terfenadine or astemizole (antihistamines)
- if you are taking a medicine called cisapride (used for stomach upsets)

Pregnancy and breast-feeding

Fluconazole Capsules should only be taken if your doctor decides that it is absolutely necessary. Tell your doctor if you are pregnant, trying to become pregnant or think you may be pregnant.

This medicine can be passed into breast milk. You should not take Fluconazole Capsules whilst breast-feeding, unless you are told to by your doctor.

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

Driving and using machines

Occasionally dizziness or fits can occur in people taking Fluconazole Capsules. If you are affected in this way, you should avoid driving or using machines.

Important information about some of the ingredients of Fluconazole Capsules

These capsules contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE FLUCONAZOLE CAPSULES

- if you are taking a medicine called cisapride (used for stomach upsets)
- if you have heart disease including heart rhythm problems
- if your doctor has told you that you have low levels of potassium or magnesium in your blood

Taking other medicines
Tell your doctor if you are taking any of the following medicines:

- an antibiotic called rifampicin or rifabutin
- a medicine to treat water retention and high blood pressure known as hydrochlorothiazide
- medicines to prevent and/or treat blood clots known as anticoagulants (such as warfarin)
- medicines to treat diabetes known as sulphonylureas (such as tolbutamide)
- a medicine to control epilepsy called phenytoin
- medicines to prevent transplant rejection (such as ciclosporin, or tacrolimus)
- a medicine to control asthma called theophylline
- medicines to treat HIV (such as didanosine or zidovudine also known as AZT)
- oral contraceptives
- medicines to relieve migraines known as ergot alkaloids
- medicines to lower blood cholesterol known as statins (such as atorvastatin or fluvastatin)
- a medicine to treat an irregular heart beat called quinidine
- medicines known as benzodiazepines such as diazepam (used to treat anxiety) or midazolam (used to help people sleep)
- medicines to treat angina and/or high blood pressure (such as losartan or nifedipine)
- a medicine to treat pneumonia called trimetrexate
- an anti-depressant called amitriptyline
- a medicine to treat arthritis called celecoxib
- a medicine to treat fungal infections called amphotericin

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

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.

Swallow the capsules whole (do not chew), with a glass of water.

How many capsules should you take?
The usual dose for vaginal thrush or candidal balanitis is one Fluconazole 150mg Capsule.

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

Patients with kidney problems
Your doctor may adjust your dose depending on how well your kidneys are working.

People on dialysis are normally given the usual adult dose after a dialysis session.

In all cases your doctor will tell you what dose you should be taking.

If you take more Fluconazole Capsules than you should
You may start to feel sick or unwell. If you (or someone else) has taken too many capsules, contact your doctor or go to the nearest hospital casualty department immediately.

Remember to take this leaflet or the packaging with you so that the doctor knows what you have taken.

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.

You should tell your doctor immediately if you experience sudden wheeziness, difficulty in breathing or tightness in chest or notice swelling of the eyelids, face, lips or throat, or a rash or itching especially affecting the whole body.

The most common side effects reported are: -

- nausea and/or vomiting (feeling and/or being sick)
- stomach discomfort
- diarrhoea
- flatulence (wind)
- indigestion
- rash, painful skin or blistering
- hair loss
- headache, dizziness and fits

In some patients, particularly those suffering from a serious ongoing illness such as cancer or AIDS the following side affects have been reported:

- a decrease in the number of red cells (which carry oxygen around the body), white cells (which help to fight infection) and platelets (which help with clotting)
- allergic reactions
- liver problems
- changes in blood, liver function, urine and other biochemical tests
- changes in your sense of taste

If any of the side effects get 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 use after the expiry date stated on the carton after Exp:.
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 protect the environment.

6.FURTHER INFORMATION

What Fluconazole Capsules contain

- The active substance is fluconazole 150 mg.
- The other ingredients are lactose monohydrate, maize starch, sodium lauryl sulfate, silica (colloidal anhydrous), magnesium stearate, titanium dioxide (E171), patent blue V (E131) and gelatine.

What Fluconazole Capsules look like and contents of the pack

Your medicine is in the form of a capsule with a light blue body and cap. Each capsule contains 150mg of the active ingredient fluconazole.

Marketing Authorisation Holder and Manufacturer

Jenson Pharmaceutical Services / Jenson Chemicals, Carradine House, 237 Regents Park Road, Finchley, London, N3 3LF

This leaflet was last approved in: {mm/yyyy}

PIL for Fluconazole 150mg capsules (PL 17871/0006) P classification

PACKAGE LEAFLET: INFORMATION FOR THE USER

Fluconazole 150mg Capsules

(Fluconazole)

Read all of this leaflet carefully because it contains important information for you.
This medicine is available without prescription. However, you still need to take Fluconazole Capsules carefully to get the best results from it.

- Keep this leaflet. You may need to read it again.
- Ask your pharmacist if you need more information or advice.
- You must contact a doctor if your symptoms worsen or do not improve after 7 days.
- If any of the side effects get serious, or if you notice any side effect 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
2. Before you take Fluconazole Capsules
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6. Further information

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

Your medicine contains the active substance fluconazole, which is one of a group of medicines called antifungal agents. Fluconazole is used to treat infections caused by fungi or yeasts.

The most common cause of fungal infections is a yeast called *Candida*. Vaginal thrush or candidal balanitis (inflammation of the end of the penis and/or foreskin) are caused by *Candida*. Fluconazole is used to treat genital *Candida* infections.

2. BEFORE YOU TAKE FLUCONAZOLE CAPSULES

Do not take Fluconazole Capsules

- if you are allergic (hypersensitive) to fluconazole
- if you are allergic to any of the other ingredients of Fluconazole Capsules (these are listed in section 6, Further Information)
- if you are taking medicines called terfenadine or astemizole (antihistamines)
- if you are taking a medicine called cisapride (used for stomach upsets)

Taking other medicines

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

- an antibiotic called rifampicin or rifabutin
- a medicine to treat water retention and high blood pressure known as hydrochlorothiazide
- medicines to prevent and/or treat blood clots known as anticoagulants (such as warfarin)
- medicines to treat diabetes known as sulphonylureas (such as tolbutamide)
- a medicine to control epilepsy called phenytoin
- medicines to prevent transplant rejection (such as ciclosporin, or tacrolimus)
- a medicine to control asthma called theophylline
- medicines to treat HIV (such as didanosine or zidovudine also known as AZT)
- oral contraceptives
- medicines to relieve migraines known as ergot alkaloids
- medicines to lower blood cholesterol known as statins (such as atorvastatin or fluvastatin)
- a medicine to treat an irregular heart beat called quinidine

- if you have heart disease including heart rhythm problems
- if your doctor has told you that you have low levels of potassium or magnesium in your blood

Take special care with Fluconazole Capsules
Talk to your doctor before taking Fluconazole Capsules if any of the following apply to you:

- if you are under 16 or over 60 years of age
- if you are pregnant, intend to become pregnant, or if you are breast feeding (see section on Pregnancy and breast-feeding, below)
- if you have suffered an allergic reaction to any other antifungal treatment
- if you have any disease or illness affecting your liver or kidneys
- if you have had jaundice (yellowing of the skin or whites of the eyes)
- if you suffer from any long term disease or illness
- if you or your partner have been exposed to a sexually transmitted disease
- if you are experiencing lower stomach pain or burning on passing urine

Women only:

- if you have had thrush more than twice in the last six months
- if you have any abnormal or irregular vaginal bleeding or blood stained discharge
- if you have sores, ulcers or blisters in or around your vagina

Men only:

- if your sexual partner does not have thrush
- if you have sores, ulcers or blisters on your penis
- if you have an abnormal discharge (leakage) from your penis
- if your penis has started to smell

- medicines known as benzodiazepines such as diazepam (used to treat anxiety) or midazolam (used to help people sleep)
- medicines to treat angina and/or high blood pressure (such as losartan or nifedipine)
- a medicine to treat pneumonia called trimetrexate
- an anti-depressant called amitriptyline
- a medicine to treat arthritis called celecoxib
- a medicine to treat fungal infections called amphotericin

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

Pregnancy and breast-feeding
Fluconazole Capsules should only be taken if your doctor decides that it is absolutely necessary. Speak with your doctor if you are pregnant, trying to become pregnant or think you may be pregnant before taking Fluconazole Capsules.

This medicine can be passed into breast milk. You should not take Fluconazole Capsules whilst breast-feeding, unless you are told to by your doctor.

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

Driving and using machines
Occasionally dizziness or fits can occur in people taking Fluconazole Capsules. If you are affected in this way, you should avoid driving or using machines.

Important information about some of the ingredients of Fluconazole Capsules
These capsules contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE FLUCONAZOLE CAPSULES

Swallow the capsules whole (do not chew), with a glass of water.

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

How many capsules should you take?
The usual dose for vaginal thrush or candidal balanitis is one Fluconazole 150mg Capsule.

If your symptoms have not cleared up within 7 days of taking your medicine you should speak with your doctor.

If the infection clears up but then returns after 7 days you can take a Fluconazole 150mg Capsule for a second time. If the candidal infection comes back more than twice within six months, you should speak with your doctor.

If you take more Fluconazole Capsules than you should
You may start to feel sick or unwell. If you (or someone else) has taken too many capsules, contact your doctor or go to the nearest hospital casualty department immediately.

Remember to take this leaflet or the packaging with you so that the doctor knows what you have taken.

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

5.HOW TO STORE FLUCONAZOLE CAPSULES

Keep out of the reach and sight of children.

Do not use after the expiry date stated on the carton after Exp:.
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 protect the environment.

6.FURTHER INFORMATION

What Fluconazole Capsules contain
- The active substance is fluconazole 150 mg.
- The other ingredients are lactose monohydrate, maize starch, sodium lauryl sulfate, silica (colloidal anhydrous), magnesium stearate, titanium dioxide (E171), patent blue V (E131) and gelatine.

What Fluconazole Capsules look like and contents of the pack
Your medicine is in the form of a capsule with a light blue body and cap. Each capsule contains 150mg of the active ingredient fluconazole.

Marketing Authorisation Holder and Manufacturer
Jenson Pharmaceutical Services / Jenson Chemicals, Carradine House, 237 Regents Park Road, Finchley, London, N3 3LF

This leaflet was last approved in: {mm/yyyy}

4.POSSIBLE SIDE EFFECTS

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

You should tell your doctor immediately if you experience sudden wheeziness, difficulty in breathing or tightness in chest or notice swelling of the eyelids, face, lips or throat, or a rash or itching especially affecting the whole body.

The most common side effects reported are: -

- nausea and/or vomiting (feeling and/or being sick)
- stomach discomfort
- diarrhoea
- flatulence (wind)
- indigestion
- rash, painful skin or blistering
- hair loss
- headache, dizziness and fits

In some patients, particularly those suffering from a serious ongoing illness such as cancer or AIDS the following side affects have been reported:

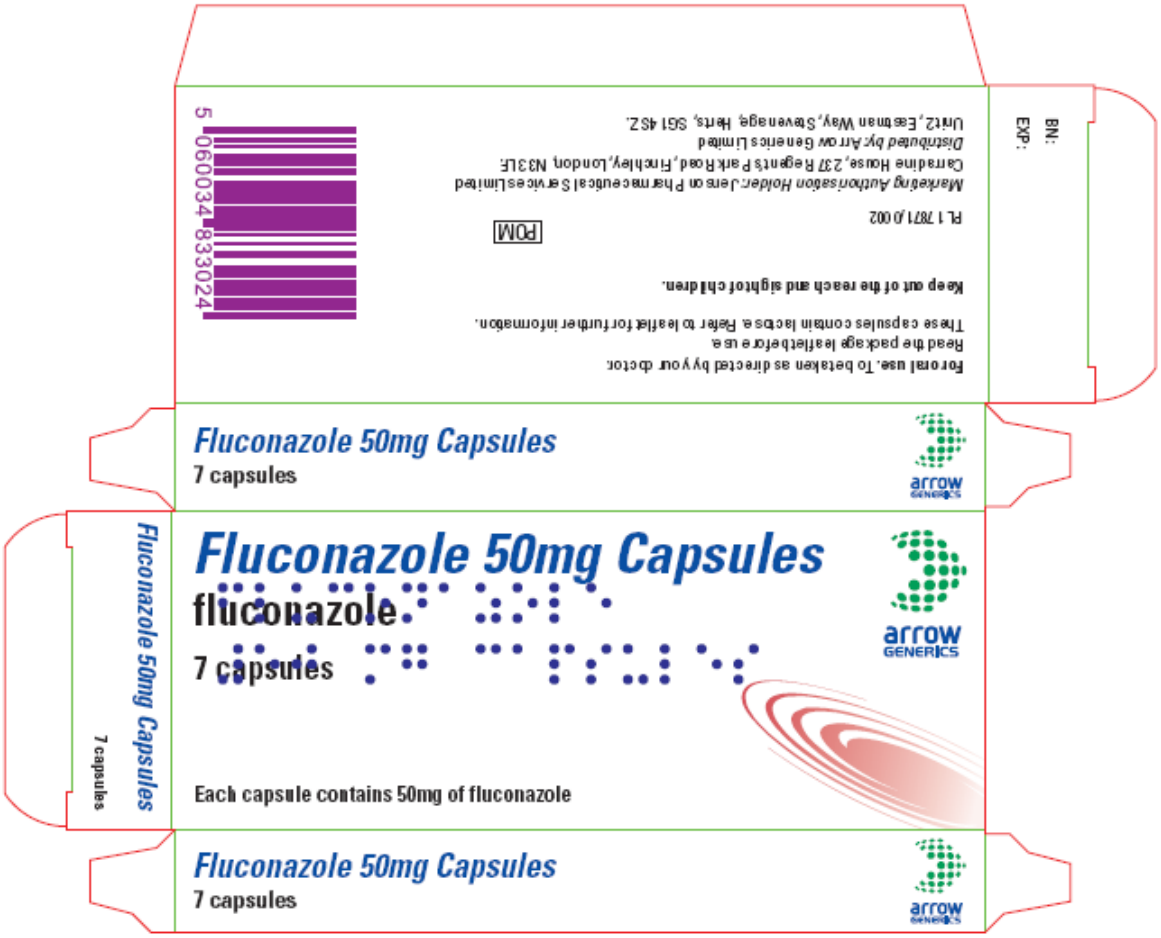
- a decrease in the number of red cells (which carry oxygen around the body), white cells (which help to fight infection) and platelets (which help with clotting)
- allergic reactions
- liver problems
- changes in blood, liver function, urine and other biochemical tests
- changes in your sense of taste

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

LABELLING

Fluconazole 50mg capsules (PL 17871/0002)

Carton for blisters, with braille



Braille translation

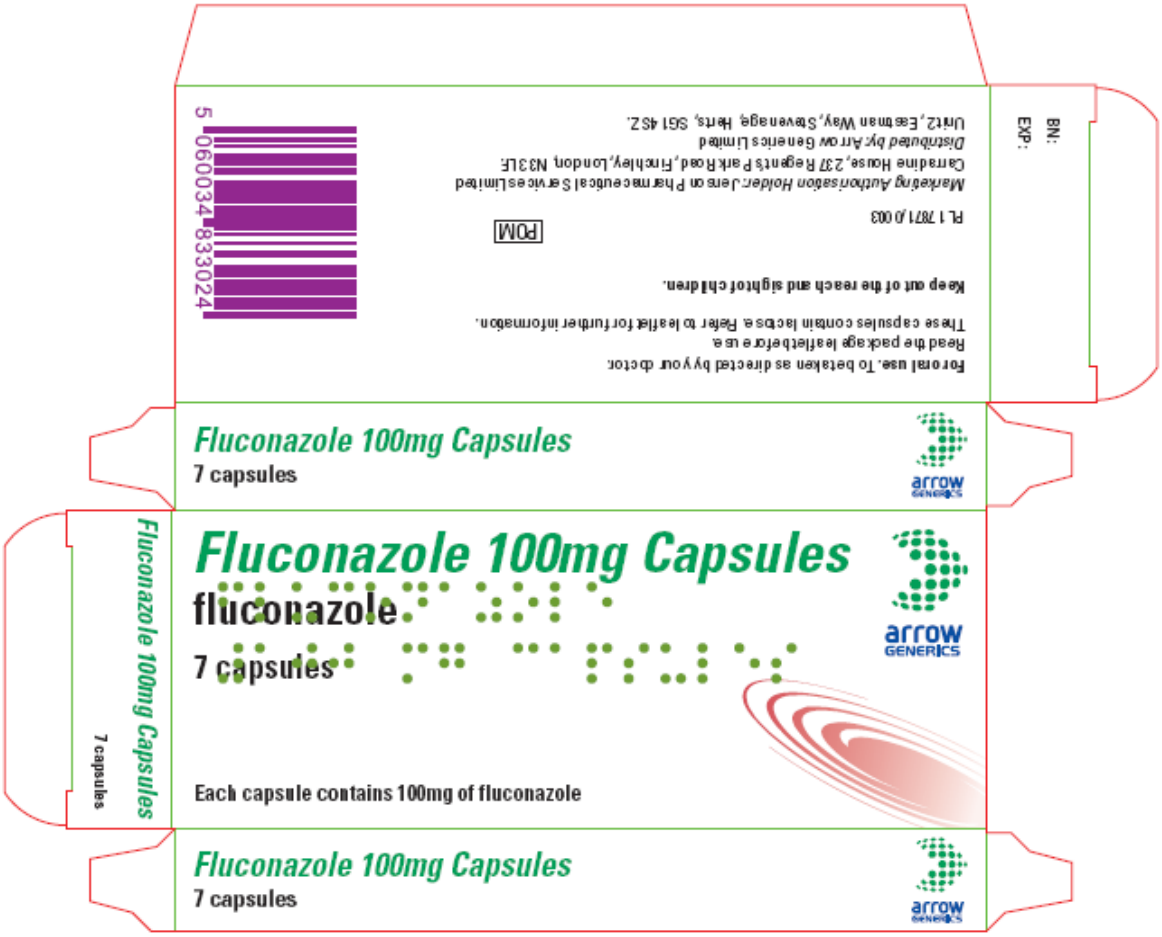
Braille pattern reads as follows ([ls] = letter sign; # = number sign):

f l u c o n a z o l e

5 0 m g c a p s u l e s

Fluconazole 100mg capsules (PL 17871/0003)

Carton for blisters, with braille



Braille translation

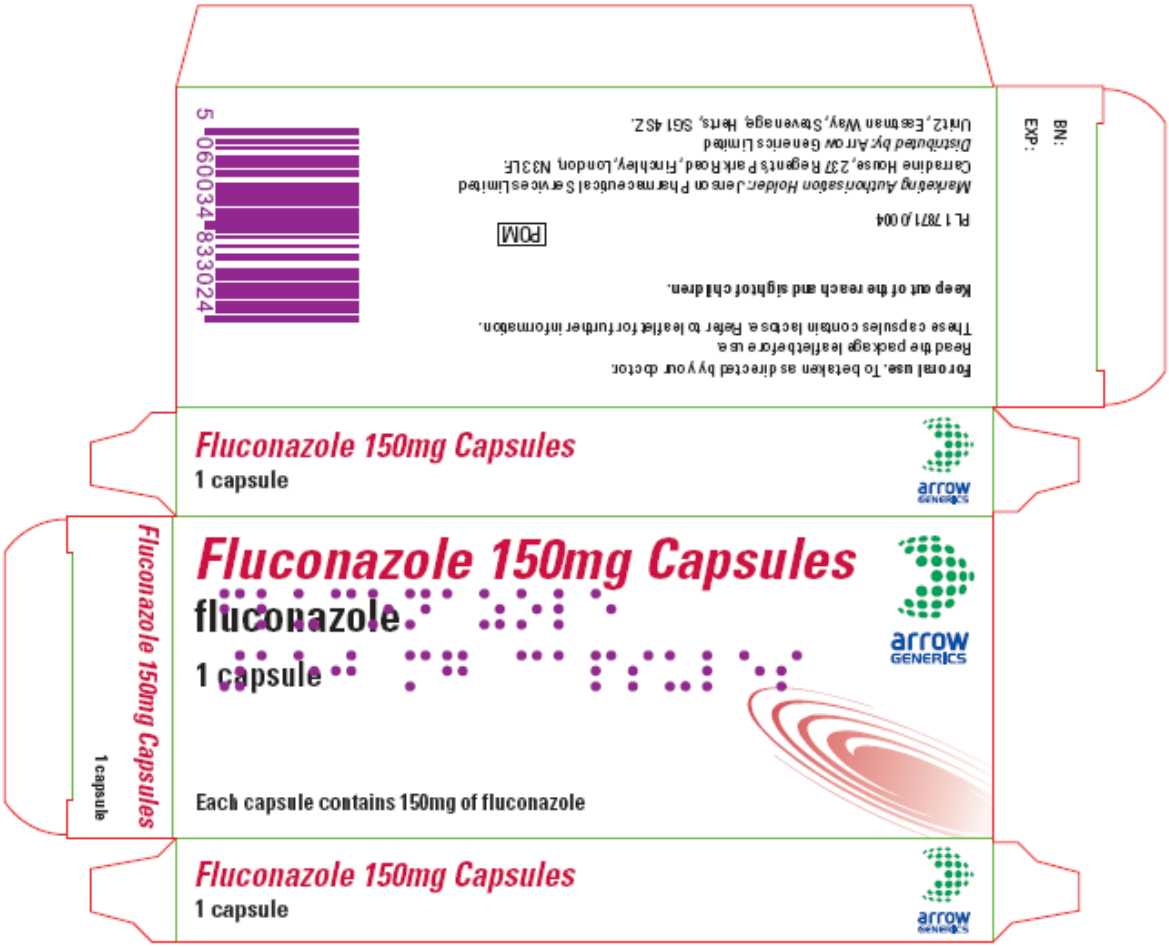
Braille pattern reads as follows ([ls] = letter sign; # = number sign):

f l u c o n a z o l e

1 0 0 m g c a p s u l e s

Fluconazole 150mg capsules (PL 17871/0004) POM classification

Carton for blisters, with braille



Braille translation

Braille pattern reads as follows ([ls] = letter sign; # = number sign):

f l u c o n a z o l e

1 5 0 m g c a p s u l e s

Fluconazole 150mg capsules (PL 17871/0006) P classification

Carton for blisters, with braille

Braille translation

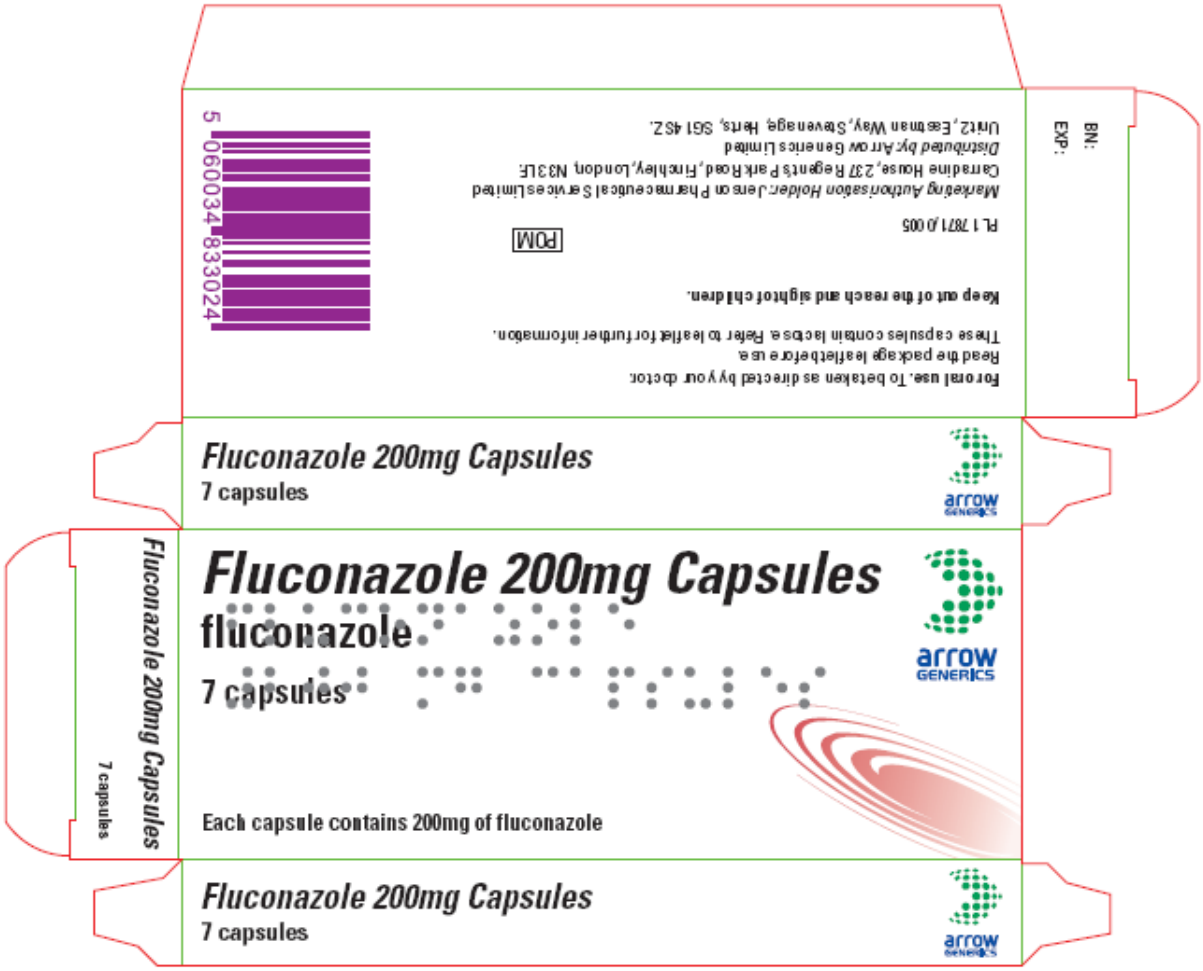
Braille pattern reads as follows ([ls] = letter sign; # = number sign):

f l u c o n a z o l e

1 5 0 m g c a p s u l e s

Fluconazole 200mg capsules (PL 17871/0005)

Carton for blisters, with braille



Braille translation

Braille pattern reads as follows ([ls] = letter sign; # = number sign):

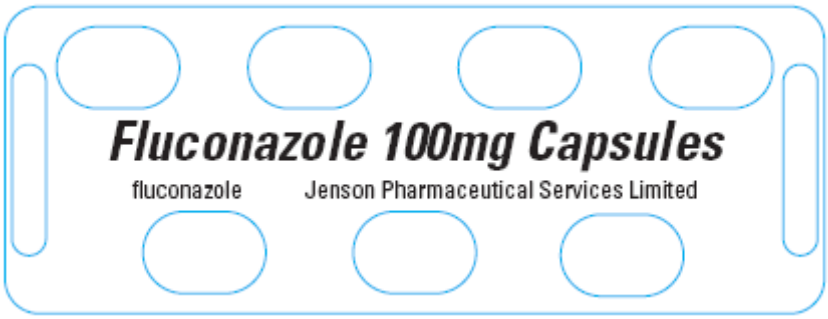
f l u c o n a z o l e

2 0 0 m g c a p s u l e s

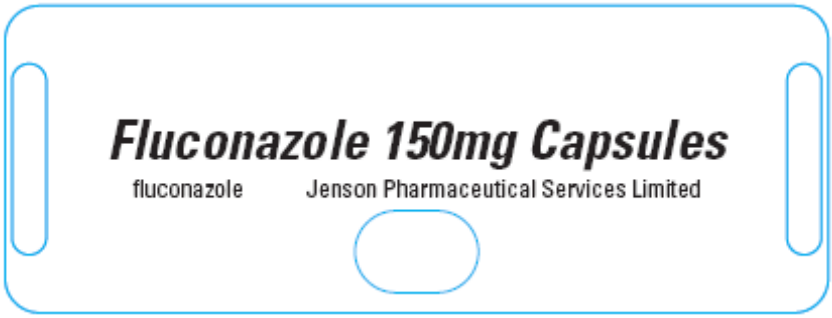
Blisters foils

Fluconazole 50mg capsules (PL 17871/0002)

Fluconazole 100mg capsules (PL 17871/0003)



Fluconazole 150mg capsules (PL 17871/0004 & 0006)



Fluconazole 200mg capsules (PL 17871/0005)