FLUCONAZOLE 50MG CAPSULES
PL 18909/0372

FLUCONAZOLE 100MG CAPSULES
PL 18909/0373

FLUCONAZOLE 150MG CAPSULES
PL 18909/0374 & 0376

FLUCONAZOLE 200MG CAPSULES
PL 18909/0375

(FLUCONAZOLE)

UK Public Assessment Report

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FLUCONAZOLE 50MG, 100MG, 150MG & 200MG CAPSULES
(FLUCONAZOLE)
PL 18909/0372-6

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 Cryptococcus), 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 Cryptococcus 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.

A subsequent Change of Ownership (CoA) was granted for these products on 01 December 2009, to change the Marketing Authorisation Holder to Arrow Generics Limited (PL 18909/0372-6).
FLUCONAZOLE 50MG, 100MG, 150MG & 200MG CAPSULES
(FLUCONAZOLE)
PL 18909/0372-6

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.
A subsequent Change of Ownership (CoA) was granted for these products on 01 December 2009, to change the Marketing Authorisation Holder to Arrow Generics Limited (PL 18909/0372-6).
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:

![Structure of Fluconazole](image)

Molecular formula: C$_{13}$H$_{12}$N$_6$OF$_2$
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 \( C_{\text{max}} \), \( \text{AUC}_{0-t} \), and \( \text{AUC}_{0-\infty} \) 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.

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

* : 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<sub>max</sub> & 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 18909/0372-6

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 18909/0372-6

**STEPS TAKEN AFTER AUTHORISATION-SUMMARY**

The following table lists non-safety updates to the Marketing Authorisations for these products that have been approved by the MHRA since the products were first licensed. The table includes updates that have been incorporated into the text of this Public Assessment Report (PAR) or added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>04/02/2012</td>
<td>Type 1B</td>
<td>To update sections 4.1 to 4.9 and 5.1 to 5.3 of the SmPC in line with the Article 30 EC decision for products containing the active fluconazole (opinion dated 02/09/2011). As a consequence the Patient Information Leaflet (PIL) has been updated.</td>
<td>Granted 06/07/2012</td>
</tr>
</tbody>
</table>
SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Fluconazole 50mg Capsules (PL 18909/0372) 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 (dentine 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 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:

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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.

**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 ethinylestradiol 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

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 coccidiodomycosis. 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
- Other senses
  - Taste perversion

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

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 *Coccidioides 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:

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

*Denotes final day
6.4 Special precautions for storage
Do not store above 30°C. 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
Arrow Generics Limited
Unit 2 Eastman Way
Stevenage
Hertfordshire
SG1 4SZ
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 18909/0372

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
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 18909/0373) 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 malignany, 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.

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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:

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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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**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, 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 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:

<table>
<thead>
<tr>
<th>Age studied</th>
<th>Dose (mg/kg)</th>
<th>Half-life (hours)</th>
<th>AUC(mg.h/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 months-13 years</td>
<td>Single-Oral</td>
<td>25</td>
<td>94.7</td>
</tr>
<tr>
<td></td>
<td>8mg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 years – 15 years</td>
<td>Multiple-Oral</td>
<td>2mg/kg</td>
<td>17.4*</td>
</tr>
<tr>
<td></td>
<td>4mg/kg</td>
<td></td>
<td>15.2*</td>
</tr>
<tr>
<td></td>
<td>8mg/kg</td>
<td></td>
<td>17.6*</td>
</tr>
<tr>
<td></td>
<td>Multiple-IV</td>
<td>3mg/kg</td>
<td>15.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age studied</th>
<th>Dose (mg/kg)</th>
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</tr>
<tr>
<td>5 years – 15 years</td>
<td>Multiple-Oral</td>
<td>2mg/kg</td>
<td>67.4</td>
</tr>
<tr>
<td></td>
<td>4mg/kg</td>
<td></td>
<td>139.1</td>
</tr>
<tr>
<td></td>
<td>8mg/kg</td>
<td></td>
<td>196.1</td>
</tr>
<tr>
<td>5 years – 15 years</td>
<td>Multiple-Oral</td>
<td>3mg/kg</td>
<td>41.6</td>
</tr>
</tbody>
</table>
5.3 Preclinical safety data

Reproductive Toxicity
Increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 and 50mg/kg and higher doses. At doses ranging from 80mg/kg (approximately 20-60× 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)
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 30°C. 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 AUTHORIZATION HOLDER
Arrow Generics Limited
Unit 2 Eastman Way
Stevenage
Hertfordshire
SG1 4SZ
UK

8 MARKETING AUTHORIZATION NUMBER(S)
PL 18909/0373

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
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 18909/0374-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 mm3.

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:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Percent of recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>100%</td>
</tr>
<tr>
<td>&lt;50</td>
<td>50%</td>
</tr>
<tr>
<td>Regular dialysis</td>
<td>100% after each dialysis</td>
</tr>
</tbody>
</table>

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, 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 dermatitidis*; with *Coccidioides 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:

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<td>15.5</td>
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</table>

*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 30°C. 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**  
Arrow Generics Limited  
Unit 2 Eastman Way  
Stevenage  
Hertfordshire  
SG1 4SZ  
UK

8 **MARKETING AUTHORISATION NUMBER(S)**  
Pl 18909/0374

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 18909/0375) 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:**
Fluconazole 50mg, 100mg, 150mg & 200mg Capsules

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 mm3.

**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:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Percent of recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>100%</td>
</tr>
<tr>
<td>&lt;50</td>
<td>50%</td>
</tr>
<tr>
<td>Regular dialysis</td>
<td>100% after each dialysis.</td>
</tr>
</tbody>
</table>

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 ethinylestradiol 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 coccidiodomycosis. 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, 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 dermatitidis.*
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.

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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:

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<td>Multiple-IV 3mg/kg</td>
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</tr>
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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)
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 AUTHORIZATION HOLDER
Arrow Generics Limited
Unit 2 Eastman Way
Stevenage
Hertfordshire
SG1 4SZ
UK

8 MARKETING AUTHORIZATION NUMBER(S)
PL 18909/0375

9 DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
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 18909/0376-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 ethinylestradiol 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**
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 Coccidioides 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 30°C. 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**
Arrow Generics Limited
Unit 2 Eastman Way
Stevenage
Hertfordshire
SG1 4SZ
UK

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 18909/0376

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
09/10/2008

10 **DATE OF REVISION OF THE TEXT**
09/10/2008
UKPAR Fluconazole 50mg, 100mg, 150mg & 200mg Capsules
PL 18909/0372-6

PATIENT INFORMATION LEAFLETS

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
- ringworm (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 Cryptococcus - e.g. cryptococcal meningitis and infections of other sites such as the lungs and skin
-_geomital 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 4. Further Information)
- If you are taking medicines called terfenadine or astemizole (antihistamines)
- If you are taking a medicine called cisapride (used for stomach upset)
- 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 rifampin or rifabutin
- a medicine to treat water retention and high blood pressure known as hydrochlorothiazide
- a medicine to prevent and/or treat blood clots known as anticoagulants (such as warfarin)
- a medicine 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 stavudine also known as AZT)
- oral contraceptives
- medicines to relieve migraines known as ergot derivatives
- 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 isosorbide or nifedipine)
- a medicine to treat pneumonia called trimethoprim
- 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.

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

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

Driving and using machines
Occasionally dizziness or drowsiness 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).
UKPAR Fluconazole 50mg, 100mg, 150mg & 200mg Capsules
PL 18909/0372-6

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 (infections of the mouth)
The usual daily dose is 50-100mg for 7-14 days.
- To treat thrush (infections of the throat or oesophagus)
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 50-100mg for 2-4 weeks.
Athlete’s foot may need up to 6 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 for 6-8 weeks.
- 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 treat infections caused by Cryptococcus from coming back
The usual daily dose is 100-200mg indefinitely.
- To treat infections caused by Cryptococcus from coming back
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 2mg/kg. The first dose 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 3-6mg/kg up to 4 weeks.

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 usual 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.

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 (looking 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 effects 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.

4. 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 sulphate, talc (corn starch) and magnesium stearate.
- The 50mg capsule contains titanium dioxide (E171) and polysorbate 80 (E380) which may cause allergic reactions (including skin rashes) in some individuals.

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
Aarav Genetics Limited, Unit 7, Eastman Way, Stevenage, Hertfordshire, SG1 4SZ, UK
This leaflet was last approved in: (mm/yyyy)

Item code
UKPAR Fluconazole 50mg, 100mg, 150mg & 200mg Capsules

PL 18909/0372-6

PACKAGE LEAFLET: INFORMATION FOR THE USER

Fluconazole 150mg Capsules
(Imidazole)

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.

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) 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 already taking medicines called tetracainide or astemizole (antihistamines)
- if you are already taking a medicine called cisapride (used for stomach upset)
- 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 hydralazine/amiodarone
- medicines to prevent and treat blood clots known as anticoagulants (such as warfarin)
- medicines to treat diabetes known as sulfonylurea (such as tolbutamide)
- a medicine to control epilepsy called phenytoin
- medicines to prevent transplant rejection (such as cyclosporine, or tacrolimus)
- a medicine to control asthma called theophylline
- medicines to treat HIV (such as dextranose or indomethacin 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 bisaratin or nifedipine)
- a medicine to treat pneumonia called theitomate
- an antidepressant called amitryptiline
- a medicine to treat arthritis called meloxicam
- a medicine to treat fungal infections called amphotericin

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 may 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.

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) have 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.

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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 dizziness, 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 effects 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 gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE FLUCONAZOLE CAPSULES

Keep out of the reach and sight of children.

Do not 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, microcrystalline cellulose, sodium lauryl sulphate, 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 tight blue body and cap. Each capsule contains 150 mg of the active ingredient fluconazole.

Marketing Authorisation Holder and Manufacturer
Arrow Generics Limited, Unit 2, Eastman Way, Stevenage, SG1 4SZ, UK

This leaflet was last approved in: (mm/yyyy)
UKPAR Fluconazole 50mg, 100mg, 150mg & 200mg Capsules

PL 18909/0372-6

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
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. Fluconazole is used to treat vaginal candidiasis (infection of the vagina) and to treat thrush in babies. Candida infections are caused by Candida fluconazole.

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 tetracycline or erythromycin (antibiotics).
- If you are taking a medicine called cisapride (used for stomach upset).
- 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 4. Pregnancy and breast-feeding).
- 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 your or your partner have been exposed to a sexually transmitted disease.
- If you are experiencing lower stomach pain or vomiting on passing urine.

Women:
- If you have had a miscarriage 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.

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 a diuretic (such as hydrochlorothiazide).
- A medicine to prevent and/or treat blood clots known as anticoagulants (such as warfarin).
- A medicine to treat diabetes known as sulphonylureas (such as tolbutamide).
- A medicine to control epilepsy (such as carbamazepine or valproate).
- A medicine to prevent transplant rejection (such as cyclosporine or tacrolimus).
- A medicine to control asthma (such as theophylline).
- A medicine to treat HIV (such as dolutegravir or efavirenz).
- A medicine to control an irregular heartbeat (such as amiodarone).
- A medicine to treat high blood cholesterol known as statins (such as atorvastatin or rosuvastatin).
- A medicine to treat high blood pressure (such as losartan or enalapril).
- An anti-depressant called amitriptyline.
- A medicine to treat arthritis called celecoxib.
- A medicine to treat fungal infections called antifungals.

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 to 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.

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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.

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 effects 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 Expiry.
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 100 mg.
• The other ingredients are lactose monohydrate, maize starch, sodium lauryl sulphate, 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
Aenex Generics Limited, Unit 2, Eastman Way,
Stevenage, SG1 4SZ, UK
This leaflet was last approved in: (mm/yyyy)
UKPAR Fluconazole 50mg, 100mg, 150mg & 200mg Capsules

LABELLING

Carton:

Fluconazole 50mg Capsules
7 capsules

Fluconazole 50mg Capsules
7 capsules
Each capsule contains 50mg of fluconazole

Fluconazole 50mg Capsules
7 capsules

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

Blister:

Fluconazole 50mg Capsules
fluconazole Arrow Generics Limited
UKPAR Fluconazole 50mg, 100mg, 150mg & 200mg Capsules

Carton:

Blister:
Fluconazole 150mg Capsules
1 capsule

One Fluconazole 150mg Capsule is the complete treatment for vaginal thrush and candidal balanitis.

Keep out of the reach and sight of children.
Each capsule contains 150mg of fluconazole

Braille pattern reads as follows (L = letter sign; # = number sign):
fl u c o n a z o l e
# 1 5 0 m g c a p s u l e s

Blister:
Annex 1

Reference: PL 18909/0372-0008
PL 18909/0373-0008
PL 18909/0374-0008
PL 18909/0375-0008
PL 18909/0376-0008

Product: Fluconazole 50 mg Capsules
Fluconazole 100 mg Capsules
Fluconazole 150 mg Capsules
Fluconazole 200 mg Capsules

Marketing Authorisation Holder: Arrow Generics Limited

Active Ingredient(s): Fluconazole

Reason
To update sections 4.1 to 4.9 and 5.1 to 5.3 of the SmPC in line with the Article 30 EC decision for products containing the active fluconazole (opinion dated 02/09/2011). As a consequence the Patient Information Leaflet (PIL) has been updated.

Evaluation
Satisfactory, updated SmPC fragments and PILs were submitted in support of the variation applications. The variations were approved on 06 July 2012 and the following updated SmPC fragments and PILs have been incorporated into the Marketing Authorisations.

Summary of Product Characteristics - updated

The SmPC fragments updated in-line with variations PL 18909/0372-6-0008 are reproduced below:

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fluconazole is indicated in the following fungal infections (see section 5.1).

Fluconazole is indicated in adults for the treatment of:

- Cryptococcal meningitis (see section 4.4).
- Coccidioidomycosis (see section 4.4).
- Invasive candidiasis.
- Mucosal candidiasis including oropharyngeal, oesophageal candidiasis, candiduria and chronic mucocutaneous candidiasis.
- Chronic oral atrophic candidiasis (denture sore mouth) if dental hygiene or topical treatment are insufficient.
- Vaginal candidiasis, acute or recurrent; when local therapy is not appropriate.
- Candidal balanitis when local therapy is not appropriate.
Dermatomycosis including *tinea pedis, tinea corporis, tinea cruris, tinea versicolor* and dermal candida infections when systemic therapy is indicated.
*Tinea unguium (onychomycosis)* when other agents are not considered appropriate.

Fluconazole is indicated in adults for the prophylaxis of:

- Relapse of cryptococcal meningitis in patients with high risk of recurrence.
- Relapse of oropharyngeal or oesophageal candidiasis in patients infected with HIV who are at high risk of experiencing relapse.
- To reduce the incidence of recurrent vaginal candidiasis (4 or more episodes a year). Prophylaxis of candidal infections in patients with prolonged neutropenia (such as patients with haematological malignancies receiving chemotherapy or patients receiving Hematopoietic Stem Cell Transplantation (see section 5.1)).

Fluconazole is indicated in term newborn infants, infants, toddlers, children, and adolescents aged from 0 to 17 years old.

Fluconazole is used for the treatment of mucosal candidiasis (oropharyngeal, oesophageal), invasive candidiasis, cryptococcal meningitis and the prophylaxis of candidal infections in immunocompromised patients. Fluconazole can be used as maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of reoccurrence (see section 4.4). 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.

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

### 4.2 Posology and method of administration

**Posology**

The dose should be based on the nature and severity of the fungal infection. Treatment of infections requiring multiple dosing should be continued until clinical parameters or laboratory tests indicate that active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection.

#### Adults

<table>
<thead>
<tr>
<th>Indications</th>
<th>Posology</th>
<th>Duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cryptococcosis</strong></td>
<td>Loading dose: 400 mg on Day 1</td>
<td>Usually at least 6 to 8 weeks. In life threatening infections the daily dose can be increased to 800 mg</td>
</tr>
<tr>
<td></td>
<td>Subsequent dose: 200 mg to 400 mg daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Maintenance therapy to prevent relapse of cryptococcal meningitis in patients with high risk of recurrence.</td>
<td>Indefinitely at a daily dose of 200 mg</td>
</tr>
<tr>
<td><strong>Coccidioidomycosis</strong></td>
<td>200 mg to 400 mg</td>
<td>11 months up to 24 months or longer depending on the patient. 800 mg daily may be considered for some infections and especially for meningal disease</td>
</tr>
<tr>
<td><strong>Invasive candidiasis</strong></td>
<td>Loading dose: 800 mg on Day 1</td>
<td>In general, the recommended duration of therapy for candidemia is for 2 weeks</td>
</tr>
<tr>
<td></td>
<td>Subsequent dose:</td>
<td></td>
</tr>
<tr>
<td>Indications</td>
<td>Posology</td>
<td>Duration of treatment</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Treatment of mucosal candidiasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Oropharyngeal candidiasis</td>
<td>Loading dose: 200 mg to 400 mg on Day 1</td>
<td>7 to 21 days (until oropharyngeal candidiasis is in remission). Longer periods may be used in patients with severely compromised immune function</td>
</tr>
<tr>
<td></td>
<td>Subsequent dose: 100 mg to 200 mg daily</td>
<td></td>
</tr>
<tr>
<td>- Oesophageal candidiasis</td>
<td>Loading dose: 200 mg to 400 mg on Day 1</td>
<td>14 to 30 days (until oesophageal candidiasis is in remission). Longer periods may be used in patients with severely compromised immune function</td>
</tr>
<tr>
<td></td>
<td>Subsequent dose: 100 mg to 200 mg daily</td>
<td></td>
</tr>
<tr>
<td>- Candiduria</td>
<td>200 mg to 400 mg daily</td>
<td>7 to 21 days. Longer periods may be used in patients with severely compromised immune function.</td>
</tr>
<tr>
<td>Prevention of relapse of mucosal candidiasis in patients infected with HIV who are at high risk of experiencing relapse</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Oropharyngeal candidiasis</td>
<td>100 mg to 200 mg daily or 200 mg 3 times per week</td>
<td>An indefinite period for patients with chronic immune suppression</td>
</tr>
<tr>
<td>- Oesophageal candidiasis</td>
<td>100 mg to 200 mg daily or 200 mg 3 times per week</td>
<td>An indefinite period for patients with chronic immune suppression</td>
</tr>
<tr>
<td>Genital candidiasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Acute vaginal candidiasis</td>
<td>150 mg</td>
<td>Single dose</td>
</tr>
<tr>
<td>- Candidal balanitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Treatment and prophylaxis of recurrent vaginal candidiasis (4 or more episodes a year)</td>
<td>150 mg every third day for a total of 3 doses (day 1, 4, and 7) followed by 150 mg once weekly maintenance dose</td>
<td>Maintenance dose: 6 months.</td>
</tr>
</tbody>
</table>
**Indications**

<table>
<thead>
<tr>
<th>Dermatomycosis</th>
<th>Posology</th>
<th>Duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>- tinea pedis, - tinea corporis, - tinea cruris, - candida infections</td>
<td>150 mg once weekly or 50 mg once daily</td>
<td>2 to 4 weeks, tinea pedis may require treatment for up to 6 weeks</td>
</tr>
<tr>
<td>- tinea versicolor</td>
<td>300 mg to 400 mg once weekly</td>
<td>1 to 3 weeks</td>
</tr>
<tr>
<td></td>
<td>50 mg once daily</td>
<td>2 to 4 weeks</td>
</tr>
<tr>
<td>- tinea unguium (onychomycosis)</td>
<td>150 mg once weekly</td>
<td>Treatment should be continued until infected nail is replaced (uninfected nail grows in). Regrowth of fingernails and toenails normally requires 3 to 6 months and 6 to 12 months, respectively. However, growth rates may vary widely in individuals, and by age. After successful treatment of long-term chronic infections, nails occasionally remain disfigured.</td>
</tr>
</tbody>
</table>

**Prophylaxis of candidal infections in patients with prolonged neutropenia**

<table>
<thead>
<tr>
<th></th>
<th>Posology</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>200 mg to 400 mg</td>
<td>Treatment should start several days before the anticipated onset of neutropenia and continue for 7 days after recovery from neutropenia after the neutrophil count rises above 1000 cells per mm³.</td>
</tr>
</tbody>
</table>

**Special populations**

- **Elderly**
  Dosage should be adjusted based on the renal function (see “Renal impairment”).

- **Renal impairment**
  No adjustments in single dose therapy are necessary. In patients (including paediatric population) with impaired renal function who will receive multiple doses of fluconazole, an initial dose of 50 mg to 400 mg should be given, based on the recommended daily dose for the indication. After this initial loading dose, the daily dose (according to indication) should be based on the following table:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Percent of recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>100%</td>
</tr>
<tr>
<td>≤50 (no dialysis)</td>
<td>50%</td>
</tr>
<tr>
<td>Regular dialysis</td>
<td>100% after each dialysis</td>
</tr>
</tbody>
</table>

Patients on regular dialysis should receive 100% of the recommended dose after each dialysis; on nondialysis days, patients should receive a reduced dose according to their creatinine clearance.

- **Hepatic impairment**
  Limited data are available in patients with hepatic impairment, therefore fluconazole should be administered with caution to patients with liver dysfunction (see sections 4.4 and 4.8).
Paediatric population
A maximum dose of 400 mg daily should not be exceeded in paediatric population.

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

For paediatric patients with impaired renal function, see dosing in “Renal impairment”. The pharmacokinetics of fluconazole has not been studied in paediatric population with renal insufficiency (for “Term newborn infants” who often exhibit primarily renal immaturity please see below).

Infants, toddlers and children (from 28 days to 11 years old):

<table>
<thead>
<tr>
<th>Indication</th>
<th>Posology</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Mucosal candidiasis</td>
<td>Initial dose: 6 mg/kg</td>
<td>Initial dose may be used on the first day to achieve steady state levels more rapidly</td>
</tr>
<tr>
<td></td>
<td>Subsequent dose: 3 mg/kg daily</td>
<td></td>
</tr>
<tr>
<td>- Invasive candidiasis</td>
<td>Dose: 6 to 12 mg/kg daily</td>
<td>Depending on the severity of the disease</td>
</tr>
<tr>
<td>- Cryptococcal meningitis</td>
<td>Dose: 6 mg/kg daily</td>
<td>Depending on the severity of the disease</td>
</tr>
<tr>
<td>- Maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of recurrence</td>
<td>Dose: 6 mg/kg daily</td>
<td>Depending on the severity of the disease</td>
</tr>
<tr>
<td>- Prophylaxis of <em>Candida</em> in immunocompromised patients</td>
<td>Dose: 3 to 12 mg/kg daily</td>
<td>Depending on the extent and duration of the induced neutropenia (see Adults posology)</td>
</tr>
</tbody>
</table>

Adolescents (from 12 to 17 years old):
Depending on the weight and pubertal development, the prescriber would need to assess which posology (adults or children) is the most appropriate. Clinical data indicate that children have a higher fluconazole clearance than observed for adults. A dose of 100, 200 and 400 mg in adults corresponds to a 3, 6 and 12 mg/kg dose in children to obtain a comparable systemic exposure.

Safety and efficacy for genital candidiasis indication in paediatric population has not been established. Current available safety data for other paediatric indications are described in section 4.8. If treatment for genital candidiasis is imperative in adolescents (from 12 to 17 years old), the posology should be the same as adults posology.

Term newborn infants (0 to 27 days):
Neonates excrete fluconazole slowly. There are few pharmacokinetic data to support this posology in term newborn infants (see section 5.2).

<table>
<thead>
<tr>
<th>Age group</th>
<th>Posology</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term newborn infants (0 to 14 days)</td>
<td>The same mg/kg dose as for infants, toddlers and children should be given every 72 hours</td>
<td>A maximum dose of 12 mg/kg every 72 hours should not be exceeded</td>
</tr>
<tr>
<td>Term newborn infants (from 15 to 27 days)</td>
<td>The same mg/kg dose as for infants, toddlers and children should be given every 48 hours</td>
<td>A maximum dose of 12 mg/kg every 48 hours should not be exceeded</td>
</tr>
</tbody>
</table>

Method of administration
Fluconazole may be administered either orally or by intravenous infusion, the route being dependent on the clinical state of the patient. On transferring from the intravenous to the oral route, or vice versa, there is no need to change the daily dose.

The capsules should be swallowed whole and independent of food intake.
4.3 Contraindications

Hypersensitivity to the active substance, to related azole substances, or to any of the excipients (see section 6.1).

Coadministration of terfenadine is contraindicated in patients receiving Fluconazole at multiple doses of 400 mg per day or higher based upon results of a multiple dose interaction study. Coadministration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 such as cisapride, astemizole, pimozide, quinidine and erythromycin are contraindicated in patients receiving fluconazole (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

*Tinea capitis*
Fluconazole has been studied for treatment of *tinea capitis* in children. It was shown not to be superior to griseofulvin and the overall success rate was less than 20%. Therefore, Fluconazole should not be used for *tinea capitis*.

*Cryptococcosis*
The evidence for efficacy of fluconazole in the treatment of cryptococcosis of other sites (e.g. pulmonary and cutaneous cryptococcosis) is limited, which prevents dosing recommendations.

*Deep endemic mycoses*
The evidence for efficacy of fluconazole in the treatment of other forms of endemic mycoses such as *paracoccidioidomycosis*, *lymphocutaneous sporotrichosis* and *histoplasmosis* is limited, which prevents specific dosing recommendations.

*Renal system*
Fluconazole should be administered with caution to patients with renal dysfunction (see section 4.2).

*Hepatobiliary system*
Fluconazole should be administered with caution to patients with liver dysfunction.

Fluconazole has been associated with rare cases of serious hepatic toxicity including fatalities, primarily in patients with serious underlying medical conditions. In cases of fluconazole associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of patient has been observed. Fluconazole hepatotoxicity has usually been reversible on discontinuation of therapy.

Patients who develop abnormal liver function tests during fluconazole therapy must be monitored closely for the development of more serious hepatic injury. The patient should be informed of suggestive symptoms of serious hepatic effect (important asthenia, anorexia, persistent nausea, vomiting and jaundice). Treatment of fluconazole should be immediately discontinued and the patient should consult a physician.

*Cardiovascular system*
Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and *torsades de pointes* in patients taking Fluconazole. These reports included seriously ill patients with multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities and concomitant treatment that may have been contributory.

Fluconazole should be administered with caution to patients with these potentially proarrhythmic conditions. Coadministration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 are contraindicated (see sections 4.3 and 4.5).

*Halofantrine*
Halofantrine has been shown to prolong QTc interval at the recommended therapeutic dose and is a substrate of CYP3A4. The concomitant use of fluconazole and halofantrine is therefore not recommended (see section 4.5).

Dermatological reactions
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 medicinal products. If a rash, which is considered attributable to fluconazole, develops in a patient treated for a superficial fungal infection, further therapy with this medicinal product should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and fluconazole discontinued if bullous lesions or erythema multiforme develop.

Hypersensitivity
In rare cases anaphylaxis has been reported (see section 4.3).

Cytochrome P450
Fluconazole is a potent CYP2C9 inhibitor and a moderate CYP3A4 inhibitor. Fluconazole is also an inhibitor of CYP2C19. Fluconazole treated patients who are concomitantly treated with medicinal products with a narrow therapeutic window metabolised through CYP2C9, CYP2C19 and CYP3A4, should be monitored (see section 4.5).

Terfenadine
The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored (see sections 4.3 and 4.5).

Excipients
Capsules contain lactose monohydrate. 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

Concomitant use of the following other medicinal products is contraindicated:

Cisapride: There have been reports of cardiac events including torsades de pointes in patients to whom fluconazole and cisapride were coadministered. A controlled study found that concomitant fluconazole 200 mg once daily and cisapride 20 mg four times a day yielded a significant increase in cisapride plasma levels and prolongation of QTc interval. Concomitant treatment with fluconazole and cisapride is contraindicated (see section 4.3).

Terfenadine: Because of the occurrence of serious cardiac dysrhythmias secondary to prolongation of the QTc interval in patients receivingazole antifungals in conjunction with terfenadine, interaction 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 doses of 400 mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. The combined use of fluconazole at doses of 400 mg or greater with terfenadine is contraindicated (see section 4.3). The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored.

Astemizole: Concomitant administration of fluconazole with astemizole may decrease the clearance of astemizole. Resulting increased plasma concentrations of astemizole can lead to QT prolongation and rare occurrences of torsades de pointes. Coadministration of fluconazole and astemizole is contraindicated (see section 4.3).

Pimozide: Although not studied in vitro or in vivo, concomitant administration of fluconazole with pimozide may result in inhibition of pimozide metabolism. Increased pimozide plasma
concentrations can lead to QT prolongation and rare occurrences of *torsades de pointes*. Coadministration of fluconazole and pimozide is contraindicated (see section 4.3).

**Quinidine:** Although not studied *in vitro* or *in vivo*, concomitant administration of fluconazole with quinidine may result in inhibition of quinidine metabolism. Use of quinidine has been associated with QT prolongation and rare occurrences of *torsades de pointes*. Coadministration of fluconazole and quinidine is contraindicated (see section 4.3).

**Erythromycin:** Concomitant use of fluconazole and erythromycin has the potential to increase the risk of cardiotoxicity (prolonged QT interval, *torsades de pointes*) and consequently sudden heart death. Coadministration of fluconazole and erythromycin is contraindicated (see section 4.3).

**Concomitant use of the following other medicinal products cannot be recommended:**

**Halofantrine:** Fluconazole can increase halofantrine plasma concentration due to an inhibitory effect on CYP3A4. Concomitant use of fluconazole and halofantrine has the potential to increase the risk of cardiotoxicity (prolonged QT interval, *torsades de pointes*) and consequently sudden heart death. This combination should be avoided (see section 4.4).

**Concomitant use of the following other medicinal products lead to precautions and dose adjustments:**

The effect of other medicinal products on fluconazole

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

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

**The effect of fluconazole on other medicinal products**

Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4. Fluconazole is also an inhibitor of the isozyme CYP2C19. In addition to the observed/documentated interactions mentioned below, there is a risk of increased plasma concentration of other compounds metabolized by CYP2C9 and CYP3A4 coadministered with fluconazole. Therefore caution should be exercised when using these combinations and the patients should be carefully monitored. The enzyme inhibiting effect of fluconazole persists 4-5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole (see section 4.3).

**Alfentanil:** During concomitant treatment with fluconazole (400 mg) and intravenous alfentanil (20 µg/kg) in healthy volunteers the alfentanil AUC increased 2-fold, probably through inhibition of CYP3A4. Dose adjustment of alfentanil may be necessary.

**Amitriptyline, nortriptyline:** Fluconazole increases the effect of amitriptyline and nortriptyline. S-nortriptyline and/or S-amitriptyline may be measured at initiation of the combination therapy and after one week. Dose of amitriptyline/nortriptyline should be adjusted, if necessary

**Amphotericin B:** Concurrent administration of fluconazole and amphotericin B in infected normal and immunosuppressed mice showed the following results: a small additive antifungal effect in systemic infection with *C. albicans*, no interaction in intracranial infection with *Cryptococcus neoformans*, and antagonism of the two medicinal products in systemic infection with *A. fumigatus*. The clinical significance of results obtained in these studies is unknown.
Anticoagulants: In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria, and melena) have been reported, in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. During concomitant treatment with fluconazole and warfarin the prothrombin time was prolonged up to 2-fold, probably due to an inhibition of the warfarin metabolism through CYP2C9. In patients receiving coumarin-type anticoagulants concurrently with fluconazole the prothrombin time should be carefully monitored. Dose adjustment of warfarin may be necessary.

Benzodiazepines (short acting), i.e., midazolam, triazolam: Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. Concomitant intake of fluconazole 200 mg and midazolam 7.5 mg orally increased the midazolam AUC and half-life 3.7-fold and 2.2-fold, respectively. Fluconazole 200 mg daily given concurrently with triazolam 0.25 mg orally increased the triazolam AUC and half-life 4.4-fold and 2.3-fold, respectively. Potentiated and prolonged effects of triazolam have been observed at concomitant treatment with fluconazole. If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dose, and the patients should be appropriately monitored.

Carbamazepine: Fluconazole inhibits the metabolism of carbamazepine and an increase in serum carbamazepine of 30% has been observed. There is a risk of developing carbamazepine toxicity. Dose adjustment of carbamazepine may be necessary depending on concentration measurements/effect.

Calcium channel blockers: Certain calcium channel antagonists (nifedipine, isradipine, amlodipine, verapamil and felodipine) are metabolized by CYP3A4. Fluconazole has the potential to increase the systemic exposure of the calcium channel antagonists. Frequent monitoring for adverse events is recommended.

Celecoxib: During concomitant treatment with fluconazole (200 mg daily) and celecoxib (200 mg) the celecoxib C_max and AUC increased by 68% and 134%, respectively. Half of the celecoxib dose may be necessary when combined with fluconazole.

Cyclophosphamide: Combination therapy with cyclophosphamide and fluconazole results in an increase in serum bilirubin and serum creatinine. The combination may be used while taking increased consideration to the risk of increased serum bilirubin and serum creatinine.

Fentanyl: One fatal case of fentanyl intoxication due to possible fentanyl fluconazole interaction was reported. Furthermore, it was shown in healthy volunteers that fluconazole delayed the elimination of fentanyl significantly. Elevated fentanyl concentration may lead to respiratory depression. Patients should be monitored closely for the potential risk of respiratory depression. Dosage adjustment of fentanyl may be necessary.

HMG CoA reductase inhibitors: The risk of myopathy and rhabdomyolysis increases when fluconazole is coadministered with HMG-CoA reductase inhibitors metabolised through CYP3A4, such as atorvastatin and simvastatin, or through CYP2C9, such as fluvastatin. If concomitant therapy is necessary, the patient should be observed for symptoms of myopathy and rhabdomyolysis and creatinine kinase should be monitored. HMG-CoA reductase inhibitors should be discontinued if a marked increase in creatinine kinase is observed or myopathy/rhabdomyolysis is diagnosed or suspected.

Immunosuppressors (i.e., ciclosporin, everolimus, sirolimus and tacrolimus):

Ciclosporin: Fluconazole significantly increases the concentration and AUC of ciclosporin. During concomitant treatment with fluconazole 200 mg daily and ciclosporin (2.7 mg/kg/day) there was a 1.8-fold increase in ciclosporin AUC. This combination may be used by reducing the dose of ciclosporin depending on ciclosporin concentration.

Everolimus: Although not studied in vivo or in vitro, fluconazole may increase serum concentrations of everolimus through inhibition of CYP3A4.
Sirolimus: Fluconazole increases plasma concentrations of sirolimus presumably by inhibiting the metabolism of sirolimus via CYP3A4 and P-glycoprotein. This combination may be used with a dose adjustment of sirolimus depending on the effect/concentration measurements.

Tacrolimus: Fluconazole may increase the serum concentrations of orally administered tacrolimus up to 5 times due to inhibition of tacrolimus metabolism through CYP3A4 in the intestines. No significant pharmacokinetic changes have been observed when tacrolimus is given intravenously. Increased tacrolimus levels have been associated with nephrotoxicity. Dose of orally administered tacrolimus should be decreased depending on tacrolimus concentration.

Losartan: Fluconazole inhibits the metabolism of losartan to its active metabolite (E-31 74) which is responsible for most of the angiotensin II-receptor antagonism which occurs during treatment with losartan. Patients should have their blood pressure monitored continuously.

Methadone: Fluconazole may enhance the serum concentration of methadone. Dose adjustment of methadone may be necessary.

Non-steroidal anti-inflammatory drugs: The C$_{\text{max}}$ and AUC of flurbiprofen was increased by 23% and 81%, respectively, when coadministered with fluconazole compared to administration of flurbiprofen alone. Similarly, the C$_{\text{max}}$ and AUC of the pharmacologically active isomer [S-(+)-ibuprofen] was increased by 15% and 82%, respectively, when fluconazole was coadministered with racemic ibuprofen (400 mg) compared to administration of racemic ibuprofen alone.

Although not specifically studied, fluconazole has the potential to increase the systemic exposure of other NSAIDs that are metabolized by CYP2C9 (e.g. naproxen, lornoxicam, meloxicam, diclofenac). Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Adjustment of dose of NSAIDs may be needed.

Phenytoin: Fluconazole inhibits the hepatic metabolism of phenytoin. Concomitant repeated administration of 200 mg fluconazole and 250 mg phenytoin intravenously, caused an increase of the phenytoin AUC$_{24}$ by 75% and C$_{\text{min}}$ by 128%. With coadministration, serum phenytoin concentration levels should be monitored in order to avoid phenytoin toxicity.

Prednisone: There was a case report that a liver-transplanted patient treated with prednisone developed acute adrenal cortex insufficiency when a three month therapy with fluconazole was discontinued. The discontinuation of fluconazole presumably caused an enhanced CYP3A4 activity which led to increased metabolism of prednisone. Patients on long-term treatment with fluconazole and prednisone should be carefully monitored for adrenal cortex insufficiency when fluconazole is discontinued.

Rifabutin: Fluconazole increases serum concentrations of rifabutin, leading to increase in the AUC of rifabutin up to 80%. There have been reports of uveitis in patients to whom fluconazole and rifabutin were coadministered. In combination therapy, symptoms of rifabutin toxicity should be taken into consideration.

Saquinavir: Fluconazole increases the AUC and C$_{\text{max}}$ of saquinavir with approximately 50% and 55% respectively, due to inhibition of saquinavir’s hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein. Interaction with saquinavir/ritonavir has not been studied and might be more marked. Dose adjustment of saquinavir may be necessary.

Sulfonylureas: Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulfonylureas (e.g., chlorpropamide, glibenclamide, glipizide, tolbutamide) in healthy volunteers. Frequent monitoring of blood glucose and appropriate reduction of sulfonylurea dose is recommended during coadministration.

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 rate of theophylline.
Patients who are receiving high dose theophylline or who are otherwise at increased risk for theophylline toxicity should be observed for signs of theophylline toxicity while receiving fluconazole. Therapy should be modified if signs of toxicity develop.

Vinca alkaloids: Although not studied, fluconazole may increase the plasma levels of the vinca alkaloids (e.g. vincristine and vinblastine) and lead to neurotoxicity, which is possibly due to an inhibitory effect on CYP3A4.

Vitamin A: Based on a case-report in one patient receiving combination therapy with all-trans-retinoid acid (an acid form of vitamin A) and fluconazole, CNS related undesirable effects have developed in the form of pseudotumour cerebri, which disappeared after discontinuation of fluconazole treatment. This combination may be used but the incidence of CNS related undesirable effects should be borne in mind.

Voriconazole: (CYP2C9 and CYP3A4 inhibitor): Coadministration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 2.5 days) and oral fluconazole (400 mg on day 1, then 200 mg Q24h for 4 days) to 8 healthy male subjects resulted in an increase in $C_{\text{max}}$ and $\text{AUC}_{\text{0-48h}}$ of voriconazole by an average of 57% (90% CI: 20%, 107%) and 79% (90% CI: 40%, 128%), respectively. The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole associated adverse events is recommended if voriconazole is used sequentially after fluconazole.

Zidovudine: Fluconazole increases $C_{\text{max}}$ and AUC of zidovudine by 84% and 74%, respectively, due to an approx. 45% decrease in oral zidovudine clearance. The half life of zidovudine was likewise prolonged by approximately 128% following combination therapy with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions. Dose reduction of zidovudine may be considered.

Azithromycin: An open-label, randomized, three-way crossover study in 18 healthy subjects assessed the effect of a single 1200 mg oral dose of azithromycin on the pharmacokinetics of a single 800 mg oral dose of fluconazole as well as the effects of fluconazole on the pharmacokinetics of azithromycin. There was no significant pharmacokinetic interaction between fluconazole and azithromycin.

Oral contraceptives: Two pharmacokinetic studies with a combined oral contraceptive have been performed using multiple doses of fluconazole. There were no relevant effects on hormone level in the 50 mg fluconazole study, while at 200 mg daily, the AUCs of ethinyl estradiol 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.

### 4.6 Fertility, pregnancy and lactation

**Pregnancy**

Data from several hundred pregnant women treated with standard doses (<200 mg/day) of fluconazole, administered as a single or repeated dose in the first trimester, show no undesirable effects in the foetus. There have been reports of multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in infants whose mothers were treated for at least three or more months with high doses (400-800 mg daily) of fluconazole for coccidioidomycosis. The relationship between fluconazole use and these events is unclear.

Studies in animals have shown reproductive toxicity (see section 5.3).

Fluconazole in standard doses and short-term treatments should not be used in pregnancy unless clearly necessary.

Fluconazole in high dose and/or in prolonged regimens should not be used during pregnancy except for potentially life-threatening infections.
Breast-feeding
Fluconazole passes into breast milk to reach concentrations lower than those in plasma. Breast-feeding may be maintained after a single use of a standard dose 200 mg fluconazole or less. Breast-feeding is not recommended after repeated use or after high dose fluconazole.

Fertility
Fluconazole did not affect the fertility of male or female rats (see section 5.3)

4.7 Effects on ability to drive and use machines

No studies have been performed on the effects of fluconazole on the ability to drive or use machines. Patients should be warned about the potential for dizziness or seizures (see section 4.8) while taking Fluconazole and should be advised not to drive or operate machines if any of these symptoms occur.

4.8 Undesirable effects

The most frequently (>1/10) reported adverse reactions are headache, abdominal pain, diarrhoea, nausea, vomiting, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased and rash.

The following adverse reactions have been observed and reported during treatment with Fluconazole with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and the lymphatic system disorders</td>
<td>Anaemia</td>
<td>Agranulocytosis, leukopenia, thrombocytopenia, neutropenia</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td>Anaphylaxis</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>Hypercholesterolaemia, hypertriglyceridaemia, hypokalemia</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td>Somnolence, insomnia</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Seizures, paraesthesia, dizziness, taste perversion</td>
<td>Tremor</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
<td>Vertigo</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Torsade de pointes (see section 4.4), QT prolongation (see section 4.4)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain, vomiting, diarrhoea, nausea</td>
<td>Constipation, dyspepsia, flatulence, dry mouth</td>
<td></td>
</tr>
<tr>
<td>Hepato-biliary disorders</td>
<td>Alanine aminotransferase increased (see section 4.4), aspartate aminotransferase</td>
<td>Cholestasis (see section 4.4), jaundice (see section 4.4), bilirubin increased (see section 4.4)</td>
<td>Hepatic failure (see section 4.4), hepatocellular necrosis (see section 4.4), hepatitis (see section 4.4), hepatocellular</td>
</tr>
</tbody>
</table>
System Organ Class | Common | Uncommon | Rare
---|---|---|---
increased (see section 4.4), blood alkaline phosphatase increased (see section 4.4) |  |  | damage (see section 4.4)

Skin and subcutaneous disorders
- Rash (see section 4.4)
- Drug eruption (see section 4.4), urticaria (see section 4.4), pruritus, increased sweating
- Toxic epidermal necrolysis, (see section 4.4), Stevens-Johnson syndrome (see section 4.4), acute generalised exanthematouspustulosis (see section 4.4), dermatitis exfoliative, angioedema, face oedema, alopecia

Musculoskeletal, connective tissue disorders
- Myalgia

General disorders and administration site conditions
- Fatigue, malaise, asthenia, fever

Paediatric population
The pattern and incidence of adverse reactions and laboratory abnormalities recorded during paediatric clinical trials, excluding the genital candidiasis indication, are comparable to those seen in adults.

4.9 Overdose
There have been reports of overdose with Fluconazole and hallucination and paranoid behaviour have been concomitantly reported. In the event of overdose, symptomatic treatment (with supportive measures and gastric lavage if necessary) may be adequate.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC classification
Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives, ATC code: J02AC01.

Mode of action
Fluconazole is a triazole antifungal agent. Its primary mode of action is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of fluconazole. Fluconazole has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.

Fluconazole 50 mg daily given up to 28 days has been shown not to effect testosterone plasma concentrations in males or steroid concentration in females of child-bearing age. Fluconazole 200 mg to 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.

Susceptibility in vitro
In vitro, fluconazole displays antifungal activity against most clinically common Candida species (including C. albicans, C. parapsilosis, C. tropicalis). C. glabrata shows a wide range of susceptibility while C. krusei is resistant to fluconazole.

Fluconazole also exhibits activity in vitro against Cryptococcus neoformans and Cryptococcus gattii as well as the endemic moulds Blastomyces dermatiditis, Coccidioides immitis, Histoplasma capsulatum and Paracoccidioides brasiliensis.

PK/PD relationship
In animal studies, there is a correlation between MIC values and efficacy against experimental mycoses due to Candida spp. In clinical studies, there is an almost 1:1 linear relationship between the AUC and the dose of fluconazole. There is also a direct though imperfect relationship between the AUC or dose and a successful clinical response of oral candidosis and to a lesser extent candidaemia to treatment. Similarly cure is less likely for infections caused by strains with a higher fluconazole MIC.

Mechanism(s) of resistance
Candida spp have developed a number of resistance mechanisms toazole antifungal agents. Fungal strains which have developed one or more of these resistance mechanisms are known to exhibit high minimum inhibitory concentrations (MICs) to fluconazole which impacts adversely efficacy in vivo and clinically.

There have been reports 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.

Breakpoints (according to EUCAST)
Based on analyses of pharmacokinetic/pharmacodynamic (PK/PD) data, susceptibility in vitro and clinical response EUCAST-AFST (European Committee on Antimicrobial susceptibility Testing-subcommittee on Antifungal Susceptibility Testing) has determined breakpoints for fluconazole for Candida species (EUCAST Fluconazole rational document (2007)-version 2). These have been divided into non-species related breakpoints; which have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species, and species related breakpoints for those species most frequently associated with human infection. These breakpoints are given in the table below:

<table>
<thead>
<tr>
<th>Antifungal</th>
<th>Species-related breakpoints (S≤/R&gt;)</th>
<th>Non-species related breakpoints&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Candida albicans</td>
<td>Candida glabrata</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>2/4</td>
<td>-</td>
</tr>
</tbody>
</table>

S=Susceptible, R=Resistant
A = Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints.
-- = Susceptibility testing not recommended as the species is a poor target for therapy with the medicinal product.
IE = There is insufficient evidence that the species in question is a good target for therapy with the medicinal product.

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

**Absorption**
After oral administration fluconazole is well absorbed, and plasma levels (and systemic bioavailability) are over 90% of the levels achieved after intravenous administration. Oral absorption is not affected by concomitant food intake. Peak plasma concentrations in the fasting state occur between 0.5 and 1.5 hours post-dose. 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.

**Distribution**
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% the corresponding plasma levels.

High skin concentration 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 μg/g and 7 days after cessation of treatment the concentration was still 5.8 μg/g. At the 150 mg once-a-week dose, the concentration of fluconazole in stratum corneum on day 7 was 23.4 μg/g and 7 days after the second dose was still 7.1 μg/g.

Concentration of fluconazole in nails after 4 months of 150 mg once-a-week dosing was 4.05 μg/g in healthy and 1.8 μg/g in diseased nails; and, fluconazole was still measurable in nail samples 6 months after the end of therapy.

**Biotransformation**
Fluconazole is metabolised only to a minor extent. Of a radioactive dose, only 11% is excreted in a changed form in the urine. Fluconazole is a selective inhibitor of the isozymes CYP2C9 and CYP3A4 (see section 4.5). Fluconazole is also an inhibitor of the isozyme CYP2C19.

**Excretion**
Plasma elimination half-life for fluconazole is approximately 30 hours. The major route of excretion is renal, with approximately 80% of the administered dose appearing in the urine as unchanged medicinal product. Fluconazole clearance is proportional to creatinine clearance. There is no evidence of circulating metabolites.

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

**Pharmacokinetics in renal impairment**
In patients with severe renal insufficiency, (GFR< 20 ml/min) half life increased from 30 to 98 hours. Consequently, reduction of the dose is needed. Fluconazole is removed by haemodialysis and to a lesser extent by peritoneal dialysis. After three hours of haemodialysis session, around 50% of fluconazole is eliminated from blood.

**Pharmacokinetics in children**
Pharmacokinetic data were assessed for 113 paediatric patients from 5 studies; 2 single-dose studies, 2 multiple-dose studies, and a study in premature neonates. Data from one study were not interpretable due to changes in formulation pathway through the study. Additional data were available from a compassionate use study.

After administration of 2.8 mg/kg fluconazole to children between the ages of 9 months to 15 years, an AUC of about 38 μg h/ml was found per 1 mg/kg dose units. The average
Fluconazole plasma elimination half-life varied between 15 and 18 hours and the distribution volume was approximately 880 ml/kg after multiple doses. A higher fluconazole plasma elimination half-life of approximately 24 hours was found after a single dose. This is comparable with the fluconazole plasma elimination half-life after a single administration of 3 mg/kg i.v. to children of 11 days-11 months old. The distribution volume in this age group was about 950 ml/kg.

Experience with fluconazole in neonates is limited to pharmacokinetic studies in premature newborns. The mean age at first dose was 24 hours (range 9-36 hours) and mean birth weight was 0.9 kg (range 0.75-1.10 kg) for 12 pre-term neonates of average gestation around 28 weeks. Seven patients completed the protocol; a maximum of five 6 mg/kg intravenous infusions of fluconazole were administered every 72 hours. The mean half-life (hours) was 74 (range 44-185) on day 1 which decreased, with time to a mean of 53 (range 30-131) on day 7 and 47 (range 27-68) on day 13. The area under the curve (microgram.h/ml) was 271 (range 173-385) on day 1 and increased with a mean of 490 (range 292-734) on day 7 and decreased with a mean of 360 (range 167-566) on day 13. The volume of distribution (ml/kg) was 1183 (range 1070-1470) on day 1 and increased, with time, to a mean of 1184 (range 510-2130) on day 7 and 1328 (range 1040-1680) on day 13.

Pharmacokinetics in elderly
A pharmacokinetic study was conducted in 22 subjects, 65 years of age or older receiving a single 50 mg oral dose of fluconazole. Ten of these patients were concomitantly receiving diuretics. The C\text{max} was 1.54 μg/ml and occurred at 1.3 hours post-dose. The mean AUC was 76.4 ± 20.3 μg.h/ml, and the mean terminal half-life was 46.2 hours. These pharmacokinetic parameter values are higher than analogous values reported for normal young male volunteers. Coadministration of diuretics did not significantly alter AUC or C\text{max}. In addition, creatinine clearance (74 ml/min), the percent of medicinal product recovered unchanged in urine (0-24 h, 22%) and the fluconazole renal clearance estimates (0.124 ml/min/kg) for the elderly were generally lower than those of younger volunteers. Thus, the alteration of fluconazole disposition in the elderly appears to be related to reduced renal function characteristics of this group.

5.3 Preclinical safety data
Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the human exposure indicating little relevance to clinical use.

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 (approximately 27 times the recommended human dose). Male rats treated with 5 and 10 mg/kg/day had an increased incidence of hepatocellular adenomas.

Reproductive toxicity
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.

There were no foetal effects at 5 or 10 mg/kg; increases in foetal 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 to 320 mg/kg embryolethality in rats was increased and foetal abnormalities included wavy ribs, cleft palate, and abnormal cranio-facial ossification.

The onset of parturition was slightly delayed at 20 mg/kg orally and dystocia and prolongation of parturition were observed in a few dams at 20 mg/kg and 40 mg/kg intravenously. The disturbances in parturition were reflected by a slight increase in the number of still-born pups and decrease of neonatal survival at these dose levels. These effects on parturition 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 (see section 5.1).
1. WHAT FLUCONAZOLE CAPSULES ARE AND WHAT THEY ARE USED FOR

Flucloxacil is a group of medicines called “antifungals.”

The active substance is flucloxacil.

Flucloxacil Capsules are used to treat infections caused by fungi and may also be used to stop you from getting a candidal infection. The most common cause of fungal infections is a yeast called Candida.

2. BEFORE YOU TAKE FLUCONAZOLE CAPSULES

Do not take flucloxacil capsules if you:

- Are allergic (hypersensitive) to flucloxacil in other medicines you have taken or to any of the other ingredients of flucloxacil capsules.
- Are taking isoniazid (used to treat tuberculosis).
- Are taking pyrazinamide (used for treating tuberculosis).
- Are taking amphotericin (an antibiotic for fungal infections).

Tell your doctor if you:

- Have liver or kidney problems.
- Have herpes zoster (shingles).
- Have abnormal levels of potassium, calcium or magnesium in your blood.
- Have suffered from a previous skin reaction (itching, swelling of the skin or difficulty in breathing).
- Are taking antifungal or antiviral drugs.
- Are taking immunosuppressants.

Always check with your doctor before taking fluconazole.

3. HOW TO TAKE FLUCONAZOLE CAPSULES

Always take your medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are unsure.

Swallow the capsules whole with a glass of water. It is best to take your capsules at the same time each day. The usual doses of this medicine for different infections are below.

4. POSSIBLE SIDE EFFECTS

Side effects are uncommon (less than 1 in 100 patients).

Common side effects (1 in 10 to 1 in 100 patients):

- Headache
- Dizziness

Side effects are rare (less than 1 in 1,000 patients):

- Rash
- Abdominal pain
- Diarrhoea
- Blood abnormalities

Side effects are uncommon (less than 1 in 100 patients):

- Nausea
- Vomiting
- Constipation
- Diarrhoea
- Loss of appetite
- Sleep problems

Side effects are rare (less than 1 in 1,000 patients):

- Headache
- Dizziness
- Abdominal pain
- Nausea
- Vomiting
- Constipation
- Diarrhoea
- Loss of appetite
- Sleep problems

5. HOW TO STORE FLUCONAZOLE CAPSULES

- Keep the medicine in the original container.
- Keep the medicine in a cool place.
- Keep the medicine out of the reach of children.
- Do not store the medicine in the bathroom.
- Do not throw the medicine into the toilet or drain.
- Do not use the medicine after the expiry date.

6. FOR FURTHER INFORMATION
<table>
<thead>
<tr>
<th>Condition</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>To treat fungal skin and nail infections</td>
<td>Depending on the site of the infection: 50 mg once daily, 100 mg once weekly for up to 6 weeks for nail infections (infectious ringworm of the nails)</td>
</tr>
<tr>
<td>To stop vomiting from getting an infection caused by Candida if your immune system is weak and not working properly</td>
<td>200 mg to 400 mg once daily while you are at risk of getting an infection</td>
</tr>
<tr>
<td>Adolescents from 12 to 17 years old</td>
<td>Follow the dose prescribed by your doctor (either adults or children's dosage).</td>
</tr>
<tr>
<td>Children to 11 years old</td>
<td>The maximum dose in children is 400 mg daily. The dose will be based on the child's weight in kilograms.</td>
</tr>
<tr>
<td>Use in children 0 to 4 weeks of age</td>
<td>5 mg per kg of body weight (12 mg per kg of body weight might be given on the first day).</td>
</tr>
<tr>
<td>Use in children 0 to 2 weeks of age</td>
<td>6 to 12 mg per kg of body weight.</td>
</tr>
<tr>
<td>Use in children less than 2 weeks old</td>
<td>6 to 12 mg per kg of body weight.</td>
</tr>
<tr>
<td>Use in children 0 to 4 weeks of age</td>
<td>5 mg per kg of body weight (12 mg per kg of body weight might be given on the first day).</td>
</tr>
<tr>
<td>Use in children 0 to 2 weeks of age</td>
<td>6 to 12 mg per kg of body weight.</td>
</tr>
<tr>
<td>Use in children less than 2 weeks old</td>
<td>6 to 12 mg per kg of body weight.</td>
</tr>
</tbody>
</table>

**Other side effects:**
- Additionally, if any of the following side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
- **Common side effects which affect 1 to 10 users in 100 are listed below:**
  - headache
  - stomach discomfort, diarrhea
  - feeling sick, vomiting
- **Uncommon side effects which affect 1 to 10 users in 1,000 are listed below:**
  - constipation, difficult digestion, wind, dry mouth
  - muscle pain
  - skin damage and yellowing of the skin and eyes (jaundice)
  - wheezing, blisters (fixed), itching, increased sweating
  - tenderness, general feeling of being unwell |

**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 Expiry.
- 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 when they are no longer required.
- These measures will help protect the environment.

**4. POSSIBLE SIDE EFFECTS**
- Like all medicines, Fluconazole Capsules can cause side effects, although not everybody gets them.
- A few people develop allergic reactions although serious allergic reactions are rare. If you get any of the following symptoms, tell your doctor immediately.
  - sudden itching, difficulty in breathing or tightness in the chest
  - swelling of the eyelids, face or lips
  - feeling ill over the body, redness of the skin or other rashes
- Floconazole Capsules may affect your liver. The signs of liver problems include:
  - tiredness
  - loss of appetite
  - loss of weight
  - yellowing of your skin or the whites of your eyes (jaundice)
  - vomiting
- If any of these happen, stop taking Fluconazole Capsules and tell your doctor immediately.
UKPAR Fluconazole 50mg, 100mg, 150mg & 200mg Capsules

PL 18909/0372-6

Updated PIL for PL 18909/0374-0008:

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 they are the same as you.

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

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

Fluconazole Capsules belong to a group of medicines called "antifungals". The active substance is Fluconazole. Fluconazole Capsules are used to treat infections caused by fungi and may also be used to stop you from getting a candida infection. The most common cause of fungal infections is a yeast called Candida.

Adults

You might be given this medicine by your doctor to treat the following types of fungal infections:

- Candidal meninges - a fungal infection in the brain
- Coccidioidomycosis - a disease of the bronchopulmonary system
- Infections caused by Candida and found in the blood stream, body organs (e.g. heart, lungs) or urinary tract
- Meniscal thrust - infection affecting the lining of the mucous, throat and buccal oronasal area
- Gastrointestinal - infection of the vagina or penis
- Skin infections - e.g. athlete's foot, ringworm, jock itch, nail infection

You might also be given Fluconazole Capsules to:

- stop-candidal meningitis from coming back
- stop-candidal thrust from coming back
- reduce recurrence of vaginal thrust
- stop you from getting an infection caused by Candida if your immune system is weak and not working properly

Children and adolescents (0 to 17 years old)

You might be given this medicine by your doctor to treat the following types of fungal infections:

- Meniscal thrust - infection affecting the lining of the mouth, throat and buccal oronasal area caused by Candida and found in the blood stream, body organs (e.g. heart, lungs) or urinary tract
- Coccidioidomycosis - a fungal infection in the brain

You might also be given Fluconazole Capsules to:

- stop you from getting an infection caused by Candida if your immune system is weak and not working properly
- stop-candidal meningitis from coming back

2. BEFORE YOU TAKE FLUCONAZOLE CAPSULES

Do not take Fluconazole Capsules if you:

- are allergic (hypersensitive) to Fluconazole or to any of the other ingredients of Fluconazole Capsules. The symptoms may include itching, redness of the skin or difficulty in breathing
- are taking astemizole, terfenadine (antihistamine medicines for allergies) or cisapride (used for stomach upsets)
- are taking phenotiazine (used for treating mental illness)
- are taking quinine (used for treating heart arrhythmia)
- are taking erythromycin (an antibiotic for treating infections).

Take special care with Fluconazole Capsules

Tell your doctor if you:

- have liver or kidney problems
- suffer from heart disease, including heart rhythm problems
- have abnormal levels of potassium, calcium or magnesium in your blood
- develop severe skin reactions (itching, swelling of the skin or difficulty in breathing)

Taking other medicines

Tell your doctor immediately if you are taking erythromycin, terfenadine (antihistamine for treating allergies) or cisapride (used for stomach upsets) or paroxetine (used for treating mental illness) or quinine (used for treating heart arrhythmia) or erythromycin (an antibiotic for treating infections) as these should not be taken with Fluconazole Capsules (see section "Do not take Fluconazole Capsules if you..."

There are some medicines that may interact with Fluconazole Capsules. Make sure your doctor knows if you are taking any of the following medicines:

- amphotericin B (antifungals for infections)
- diltiazem (used for angina)
- omeprazole (used for stomach ulcers) or ranitidine (used for stomach ulcers) or cimetidine (used for stomach ulcers)
- methotrexate (used for anti-cancer treatment)
- nevirapine (anti-HIV medication)
- drugs that thin the blood to prevent blood clots (warfarin or similar medicines)
- benzodiazepines (tranquilizers, trazodon or similar medicines) used to help you sleep or for anxiety
- warfarin (anti-coagulant) (used for treating fits)
- methotrexate, bleomycin and anthracyclines (used for treating cancer)
- cyclosporin, everolimus, sirolimus or tacrolimus (to prevent transplant rejection)
- cyclosporin, vinca alkaloids (vincristine, vinblastine or similar medicines) used for treating cancer
- cyclophosphamide, vincristine (vincristine, vinblastine or similar medicines)
- prednisolone (used for treating asthma)
- stitols (analgesics, paracetamol and ibuprofen or similar medicines) used for reducing high cholesterol levels
- methadone (used for pain)
- celecoxib, flurbiprofen, naproxen, ibuprofen, ibuprofen, diclofenac (Non-Steroidal Anti-Inflammatory Drugs [NSAIDs])
- oral contraceptives
- prednisolone
- ciclosporin, also used as A-ZL (used in HIV-infected patients)
- protease inhibitors
- nevirapine
- protease inhibitors (used to control viral infections)
- vitamin A (a nutritional supplement)

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

Taking Fluconazole Capsules with food and drink

You can take your medicine with or without food, is not a total.

Pregnancy and breast-feeding

Tell your doctor if you are pregnant, trying to become pregnant or breast-feeding. You should not take Fluconazole Capsules while you are pregnant or breast-feeding unless your doctor has told you to.

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

Driving and using machines

When driving vehicles or using machines, it should be taken into account that occasionally dizziness or fits may occur.

Important information about some of the ingredients of Fluconazole Capsules

This medicine contains a small amount of lactose (milk sugar). If you have been told by your doctor that you have an intolerance to milk sugar, please contact your doctor before taking the medicine.

3. HOW TO TAKE FLUCONAZOLE CAPSULES

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

Swallow the capsules whole with a glass of water. It is best to take your capsules at the same time each day.

The usual doses of this medicine for different infections are below.

### Adults

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dose</th>
</tr>
</thead>
</table>
| To treat cryptococcal meningitis | 400 mg on the first day then 200 mg to 400 mg once daily for 6 to 8 weeks or longer if needed. Sometimes doses are increased up to 600 mg.
| To treat candidal meningitis from coming back | 200 mg once daily until you are told to stop. |
| To treat coccidioidomycosis | 200 mg to 400 mg once daily for 11 months for up to 24 months or longer if needed. Sometimes doses are increased up to 600 mg. |
| To treat invasive fungal infections caused by Candida | 800 mg on the first day then 400 mg once daily until you are told to stop. |
| To treat mucosal infections affecting the lining of the mouth, throat and buccal oronasal area | 200 mg to 400 mg on the first day then 100 mg to 200 mg once daily or 200 mg 3 times a week, while you are at risk of getting an infection. |
| To treat genital thrush | 50 mg to 400 mg once daily for 7 to 10 days until you are told to stop. |
| To treat mucosal infections affecting the lining of the mouth, throat and buccal oronasal area | 100 mg to 200 mg once daily, or 200 mg 3 times a week, while you are at risk of getting an infection. |
| To treat genital thrush | 150 mg as a single dose. |
| To reduce recurrence of vaginal thrush | 150 mg every third day for a total of 3 doses (on days 1, 4 and 7) and then once a week for 6 months while you are at risk of getting an infection. |
UKPAR Fluconazole 50mg, 100mg, 150mg & 200mg Capsules

PL 18909/0372-6

Condition | Dose
---|---
To treat fungal skin and nail infections (depending on the site of the infection): 50 mg once daily; 100 mg once weekly; 200 to 400 mg once weekly for 1 to 4 weeks. (Children’s dose may be up to 1.5 times the adult dose.) | For infected skin: 10 mg per kg of body weight every 6 hours (given on the first day). For infected mouth and throat: 10 mg per kg of body weight every 6 hours.

Adolescents from 12 to 17 years old

The maximum dose for children is 400 mg daily.

Children to 11 years old

The dose will be based on the child’s weight in kilograms.

Condition | Dose
---|---
Malabsorption and Thrush infections caused by Candida (if your immune system is weak and not working properly). | 3 mg per kg of body weight (0.6 mg per kg of body weight might be given on the first day).

Oral thrush or infection caused by Candida (if your immune system is weak and not working properly). | 6 mg to 12 mg per kg of body weight.

To stop children from getting an infection caused by Candida (if your immune system is weak and not working properly). | 3 mg to 12 mg per kg of body weight.

Use in children 0 to 4 weeks of age

Use in children 0 to 4 weeks of age:

The same dose as above but given once every 2 days. The maximum dose is 12 mg per kg of body weight every 48 hours.

Use in children less than 2 weeks old:

The same dose as above but given once every 3 days. The maximum dose is 12 mg per kg of body weight every 72 hours.

Doctors sometimes prescribe different doses for you. Always check with your doctor or pharmacist if you are not sure.

Elderly

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

Patients with kidney problems

Your doctor may change your dose depending on your kidney function.

If you take more Fluconazole Capsules than you should

Taking too many capsules at once may make you unwell. Contact your doctor or your nearest hospital casualty department at once. The symptoms of a possible overdose may include sweating, feeling nervous and feeling tired. Symptomatic treatment (with supportive measures and gastric lavage if necessary) may be adequate.

If you forget to take Fluconazole Capsules

Do not take a double dose to make up for a forgotten dose. If you forget to take it, do not take it, then tear up your empty dose. (If you are not sure when to take your next dose, do not take the dose that you missed). If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Fluconazole Capsules can cause side effects, although not everybody gets them. A few people develop allergic reactions although serious allergic reactions are rare. If you get any of the following symptoms, tell your doctor immediately:

- Swollen breathing or tightness in the chest
- Swelling of the face, lips or eyes
- A rash all over the body reddening of the skin or red or pink spots
- Fluconazole Capsules may affect your liver: The signs of liver problems include:
  - Nausea
  - Loss of appetite
  - Fatigue
- If any of these happen, stop taking Fluconazole Capsules and tell your doctor immediately.

Other side effects:

Additionally, if any of the following side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist:

- Common side effects which affect 1 to 10 users in 1,000 are listed below:
  - Headache
  - Stomach discomfort, diarrhoea
  - Feeling sick, vomiting
  - Redness in red blood cells which can cause skin pain and cause weakness (anaemia)
  - Nausea
  - Feeling tired
  - Increased blood pressure
  - Constipation, difficulty in digestion
  - Increased liver function

- Uncommon side effects which affect 1 to 10 users in 1,000 are listed below:
  - Decreased appetite
  - Increased thirst
  - Abnormal electrocardiogram (ECG)
  - Change in heart rate or rhythm
  - Low blood pressure

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

5. HOW TO STORE FLUCONAZOLE CAPSULES

Keep out of reach of children and animals.

Do not use after the expiry date stated on the pack 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 sulphate, silicic acid (anhydrous), magnesium stearate, trinitroxide [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

Aesma Generics Limited, Unit 2, Eastern Way, Stevenage, Hertfordshire, SG1 4SZ, UK

This leaflet was last revised on: 07/2012.
UKPAR Fluconazole 50mg, 100mg, 150mg & 200mg Capsules

Updated PIL for PL 18909/0376-0008:

PACKAGE LEAFLET INFORMATION FOR THE USER
Fluconazole 150mg Capsules
(Fluconazole)

Read all of this leaflet carefully because it contains important information for you.
- 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 onto 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 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
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
Fluconazole Capsules belong to a group of medicines called "antifungals". The active substance is fluconazole.
Fluconazole Capsules are used in adults to treat infections caused by fungi. The most common cause of fungal infections is a yeast called Candida.

You might be given this medicine by your doctor to treat genital thrush, infection of the vagina or penis.

2. BEFORE YOU TAKE FLUCONAZOLE CAPSULES
Do not take Fluconazole Capsules if you
- are allergic (hypersensitive) to fluconazole, to other medicines you have taken to treat fungal infections or to any of the other ingredients of Fluconazole Capsules. The symptoms may include itching, reddening of the skin or difficulty in breathing.
- are taking azithromycin, terbinafine (antibiotics for fungi) or griseofulvin (used for skin infections).
- are taking cisapride (used for stomach upsets) or perindopril (used for treating mental illness).
- are taking quinidine (used for treating heart arrhythmias).
- are taking erythromycin (an antibiotic for treating infections).

Take special care with Fluconazole Capsules

Talk to your doctor if you
- have liver or kidney problems.
- suffer from heart disease, including heart rhythm problems.
- have abnormal levels of potassium, calcium or magnesium in your blood.
- develop severe skin reactions (itching, reddening of the skin or difficulty in breathing).

Children

Although this medicine is for adults it can be used in adolescents (from 12 to 17 years old) if treatment is essential and no suitable alternative exists, and should be taken in the same way as for adults.

Taking other medicines

Tell your doctor immediately if you are taking azithromycin, terbinafine (an antibiotic for treating fungal infections) or cisapride (used for stomach upsets) or perindopril (used for treating mental illness) or quinidine (used for treating heart arrhythmias) or erythromycin (an antibiotic for treating infections) as these should not be taken with Fluconazole Capsules (see section: “Do not take Fluconazole Capsules if you”).

There are some medicines that may interact with Fluconazole Capsules:

Make sure your doctor knows if you are taking any of the following medicines:
- iron preparations or multivitamins (for infections).
- anti-fungal, antibiotic (used as antifungal) or antiviral (used as antifungal).
- amphotericin B, voriconazole (antifungal).
- medicines that thin the blood to prevent blood clots (warfarin or similar medicines).
- benzodiazepines (midazolam, lorazepam or similar medicines) used to help you sleep or for anxiety.
- carbamazepine, phenytoin (used for treating fits), nevirapine, indinavir, lopinavir and ritonavir (to prevent transplant rejection).
- cyclosporin, tacrolimus, ciclosporin or tacrolimus (to prevent transplant rejection).
- isoniazid (used for treating tuberculosis).
- statins (to lower cholesterol levels).
- methotrexate (used for pain).
- colchicine, flurbiprofen, naproxen, ibuprofen, fenofibrate, methylprednisolone, diclofenac (Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)).
- oral contraceptives.
- probiotics (stool).
- zidovudine, also known as AZT, zalcitabine (used in HIV-infected patients).
- medicines for diabetes such as clopidogrel, glimepiride, pioglitazone or tolbutamide.
- statins (to lower cholesterol levels).
- vitamin A (nutritional supplement).

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

Taking Fluconazole Capsules with food and drink

You can take your medicine with or without a meal.

Pregnancy and breast-feeding

Tell your doctor if you are pregnant, trying to become pregnant or breast-feeding. You should not take Fluconazole Capsules while you are pregnant or breast-feeding unless your doctor has told you to.

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

Driving and using machines

When driving vehicles or using machines, it should be taken into account that occasionally dizziness or fits may occur.
Important information about some of the ingredients of Fluconazole Capsules
This medicine contains a small amount of lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, please contact your doctor before taking this medicine.

3 HOW TO TAKE FLUCONAZOLE CAPSULES
Always take your medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
Swallow the capsules whole with a glass of water.
Adults
150 mg as a single dose.
Doctors sometimes prescribe different doses to these. Always take your medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.
Elderly
The usual adult dose should be given.
Patients with kidney problems
The usual adult dose should be given.
How quickly will the treatment start to work?
Vaginal Thrush
Your condition should start to clear up within a few days - some women notice an improvement in one day
If your condition does not clear up within a few days you should go back to your doctor.
Penis Thrush infection
Your condition should start to clear up within a few days but it may take up to a week
If your condition has not cleared up after one week, you should go back to your doctor.
If you take more Fluconazole Capsules than you should
Taking too many capsules at once may make you unwell. Contact your doctor or your nearest hospital casualty department at once. The symptoms of a possible overdose may include hearing loss, feeling ill and thinking things that are not real (hallucination and paranoid behaviour). Symptomatic treatment (with supportive measures and gastric lavage if necessary) may be adequate.
If you forget to take Fluconazole Capsules
Do not take a double dose to make up for a forgotten dose. If you forget to take a dose, take it as soon as you remember. If it is almost time for your next dose, do not take the dose that you missed.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4 POSSIBLE SIDE EFFECTS
Like all medicines, Fluconazole Capsules can cause side effects, although not everybody gets them.
A few people develop allergic reactions although serious allergic reactions are rare.
If you get any of the following symptoms, tell your doctor immediately:
- sudden wheezing, difficulty in breathing or tightness in the chest
- swelling of the face, neck, lips, tongue or throat
- itching all over the body or redness of the skin or itchy red spots
- skin rash
- severe skin reactions such as a rash that causes blistering (this can affect the mouth and tongue). Fluconazole Capsules may affect your liver. The signs of liver problems include:
- tiredness
- loss of appetite
- vomiting
- yellowing of your skin or the whites of your eyes (jaundice).
If any of these happen, stop taking Fluconazole Capsules and tell your doctor immediately.
Other side effects:
Additionally, if any of the following side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist:
Common side effects which affect 1 to 10 users in 1,000 are listed below:
- headache
- stomach discomfort, diarrhea, feeling sick, vomiting
- increases in blood tests of liver function
- rash

Uncommon side effects which affect 1 to 10 users in 1,000 are listed below:
- reduction in red blood cells which can make skin pale and cause weakness or breathlessness
- decreased appetite
- inability to sleep, feeling dizzy
- itchy, dry skin, sensation of opening, tingling, pricking or numbness, changes in sense of taste
- constipation, difficult digestion, wind, dry mouth
- muscle pain
- liver damage and yellowing of the skin and eyes (jaundice)
- weight, blisters, burning, itching, increased sweating
- tiredness, general feeling of being unwell, fever
Rare side effects which affect 1 to 10 users in 10,000 are listed below:
- lower than normal white blood cells that help defend against infections and blood cells that help to stop bleeding
- red or purple discolouration of the skin which may be caused by low platelet count, other blood cell changes
- low blood potassium
- blood chemistry changes (high blood levels of cholesterol, fats)
- shaking
- abnormal electrocardiogram (ECG). This is a change in heart rate or rhythm
- liver failure
- allergic reactions (sometimes severe), including widespread blisters, rash and skin peeling, severe skin reactions, swelling of the lips or face
- hair loss.
If any of this side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5 HOW TO STORE FLUCONAZOLE CAPSULES
Keep out of the reach and sight of children.
Do not 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 waste water 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.
- The other ingredients are lactose monohydrate, maize starch, sodium lauryl sulphate, silica (colloidal anhydrous), magnesium stearate, titanium dioxide (E171), potassium hydroxide (E330) and gelatin.
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 50mg of the active ingredient Fluconazole.
Marketing Authorisation Holder and Manufacturer
Arrow Generics Limited, Unit 2, Eastman Way, Silvanoage, S33 4SL, UK
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