Fluconazole 50mg, 100mg, 150mg and 200mg Capsules

PL 32019/0017-20

UKPAR

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PL 32019/0017-20

LAY SUMMARY

The MHRA granted Roger Oakes Limited Marketing Authorisations (licences) for the medicinal products Fluconazole 50mg, 100mg, 150mg and 200mg Capsules (PL 32019/0017-20) on 29th October 2008. These are Prescription-only medicines (POM).

Fluconazole, the active substance in this medicine belongs to the substance group of triazol derivates. It is indicated for the treatment of fungal infections caused by yeast fungi.

No new or unexpected safety concerns arose from these simple applications and it was, therefore, judged that the benefits of taking Fluconazole Capsules outweigh the risks, hence Marketing Authorisations have been granted.
Fluconazole 50mg, 100mg, 150mg and 200mg Capsules

PL 32019/0017-20

SCIENTIFIC DISCUSSION

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INTRODUCTION

The UK granted marketing authorisations for the medicinal products Fluconazole 50mg, 100mg, 150mg and 200mg Capsules (PL 32019/0017-20) to Roger Oakes Limited on 29\textsuperscript{th} October 2008. The products are Prescription-only medicines (POM).

The applications were submitted as simple abridged applications according to Article 10c of Directive 2001/83/EC. The reference products are Fluconazole 50, 100, 150 and 200mg Capsules (PL 11311/0267-70), authorised to Tillomed Laboratories Limited on 24\textsuperscript{th} June 2004.

Fluconazole is used in the treatment of mycoses caused by yeast fungi (Candida and cryptococci), in particular:
- systemic candidiasis including candidaemia, candiduria, disseminated and other invasive, especially in risk patients potentially life-threatening candidal infections, such as infections of peritoneum, lung and urinary tract.
- cryptococcal meningitis. Immunocompromised patients (e.g. with AIDS or after organ transplantation) may also be treated.
- superficial mucosal candidiasis such as
  - recurrent oropharyngeal and oesophageal candidiasis
  - chronic-atrophic oral candidiasis (infection of the oral cavity in patients with dentures, in whom dental hygiene or topical measures are not sufficient)
  - non-invasive bronchopulmonary candidiasis (infection of the mucosa of the upper respiratory tract)
- Fluconazole is also indicated as therapeutic trial to prevent cryptococcal meningitis (relapse prophylaxis) in AIDS patients.
- Preventon of candidiasis in patients with malignancies during chemotherapy or radiotherapy and in immunocompromised patients (e.g. in AIDS or chemotherapy).
- Fungal infections of the skin including dermatomycosis like tinea corporis/cruris/pedis and Pityriasis versicolor identified by direct microscopy and/or positive culture and where systemic therapy should be considered accordingly.
- Acute and recurrent vaginal candidiases which do not respond to local therapy.

Consideration should be given to official guidance on the appropriate use of antifungal agents. Not all indications are applicable for paediatric patients; see details in “4.2 Posology and method of administration”.

Note:
Not all strengths are suitable for each indication. See “4.2 Posology and method of administration”.

No new data was submitted nor was it necessary for these simple applications, as the data is identical to that of the previously granted cross-reference products. As the cross-reference products were granted prior to the introduction of current legislation, no PARs were generated.
PHARMACEUTICAL ASSESSMENT

LICENCE NO: PL 32019/0017-20
PROPRIETARY NAME: Fluconazole 50mg, 100mg 150mg and 200mg Capsules
ACTIVE(S): Fluconazole
COMPANY NAME: Roger Oakes Limited
E.C. ARTICLE: Article 10 (c) of Directive 2001/83/EC
LEGAL STATUS: POM

1. INTRODUCTION
These are simple abridged applications for Fluconazole 50mg, 100mg, 150mg and 200mg Capsules submitted under Article 10(c) of Directive 2001/83/EC. The proposed MA holder is “Roger Oakes Limited, Allstoe House, Church Lane, Greetham, Oakham, LE15 7NF, UK”.

These applications refer to Marketing Authorisations granted to Tillomed Labs (Fluconazole 50, 100, 150 and 200mg Capsules PLs 11311/0267-70). It has been indicated in the application form that the invented names, Fluconazole 50mg, 100mg, 150mg and 200mg Capsules are being applied for, the names are acceptable.

A letter of access has been provided from Tillomed Labs authorising the MHRA to refer to PLs 11311/0267-70 as the reference products for the purpose of these informed consent applications. Signed declarations by Roger Oakes Limited, stating that they have the relevant Quality dossiers for PLs 11311/0267-70 in their possession, have been provided.

Preclinical, pharmaceutical and clinical expert statements have been provided together with CVs showing the experts are appropriately qualified. The experts confirm that the products are identical in composition, manufacture and pharmaceutical characteristics to the respective reference product and that there are no toxicological or clinical issues.

2. MARKETING AUTHORISATION APPLICATION FORMS
2.1 Name(s)
The proposed names of the product are Fluconazole 50mg, 100mg 150mg and 200mg Capsules. The product has been named in line with current requirements.

2.2 Strength, pharmaceutical form, route of administration, container and pack sizes
The products contain fluconazole equivalent to 50, 100, 150 and 200mg Fluconazole respectively. They will be packaged into PVC white, opaque/aluminium blisters and inserted into cartons. The packaging is identical to the blister packaging used for the reference products.

The respective SPCs have indicated that Fluconazole capsules will be packed into blister packs with a pack size of 1, 3, 7, 10, 14, 20, 28, 30, 42, 50 and 100 capsules.

The same pack sizes are stated in the reference products. The proposed shelf life of 3 years is identical to the reference products. The proposed storage condition for the
container closure systems are also consistent with the details registered for the cross-reference products.

2.3 Legal status
The products are Prescription Only Medicines (POM).

2.4 Marketing authorisation holder/Contact Persons/Company
The proposed Marketing Authorisation holder is Roger Oakes Limited, Allstoe House, Church Lane, Greetham, Rutland, LE15 7NF, United Kingdom.

The QP responsible for pharmacovigilance is stated and a CV is included.

2.5 Manufacturers
The proposed manufacturing sites are consistent with that registered for the cross-reference products and evidence of GMP compliance has been provided.

A flow diagram showing the sequence and activities of the different sites involved in the manufacturing process has been provided.

2.6 Qualitative and quantitative composition
The proposed compositions are consistent with the details registered for the cross-reference products.

2.7 Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference products and the maximum batch size is stated.

2.8 Finished product/shelf-life specification
The proposed finished product specifications are in-line with the details registered for the cross-reference products.

2.9 Drug substance specification
The proposed drug substance specification conformed to in house specification for fluconazole and was consistent with that of the reference products.

The manufacturer of the active substance is in-line with the reference products.

2.10 TSE Compliance
TSE declaration has been provided for the excipients lactose and magnesium stearate.

2.11 Bioequivalence / Bioavailability
No bioavailability and bioequivalence data are required to support these informed consent applications as the proposed product is manufactured to the same formula utilising the same process as the cross-referenced products. The finished product manufacturing site is also identical to that used by the reference products.
3. EXPERT REPORTS
The applicant has included detailed expert reports of the applications. Signed declarations and copies of the experts’ CVs are enclosed for the quality, non-clinical and clinical experts. All are considered to have sufficient experience for their responsibilities.

4. PRODUCT NAME & APPEARANCE
See 2.1 for details of the proposed product names. The appearances of the products are identical to the cross-reference products.

5. SUMMARY OF PRODUCT CHARACTERISTICS
The proposed SmPCs are consistent with the details registered for the cross-reference products.

6. PATIENT INFORMATION LEAFLET/BLISTER PIL
The patient information leaflet has been prepared in-line with the details registered for the cross-reference products.

PIL user testing has been submitted and the results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

The proposed artwork complies with the relevant statutory requirements. In-line with current legislation, the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

7. CONCLUSIONS
The data submitted with these applications are acceptable. The grant of marketing authorisations is recommended.
PRECLINICAL ASSESSMENT

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

No new clinical data have been supplied with these applications and none are required for applications of this type.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The data for these applications are consistent with that previously assessed for the cross-reference products and as such have been judged to be satisfactory.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Fluconazole is a well known drug and has been used for many years. These application are identical to previously granted applications for Fluconazole 50mg, 100mg, 150mg and 200mg Capsules (PL 11311/0267-70).

Preclinical, pharmaceutical and clinical expert statements have been provided together with CVs showing the experts are appropriately qualified. The experts confirm that the products are identical in composition, manufacture and pharmaceutical characteristics to the respective reference product and that there are no toxicological or clinical issues.

No new or unexpected safety concerns arise from these applications.

The SPCs, PILs and labelling are satisfactory and consistent with that for the cross-reference products.

RISK-BENEFIT ASSESSMENT
The quality of the products is acceptable and no new preclinical or clinical safety concerns have been identified. The applicant’s products are identical to the cross-reference products. Extensive clinical experience with fluconazole is considered to have demonstrated the therapeutic value of the compound. The risk-benefit is therefore considered to be positive.
# STEPS TAKEN FOR ASSESSMENT

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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 16/01/2008.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA</td>
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<td>considered the applications valid on 18/01/2008.</td>
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<td>3</td>
<td>Following assessment of the applications the MHRA requested further</td>
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<td>information on 01/07/2008 and 03/07/2008.</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information</td>
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<td>The applications were determined on 29/10/2008.</td>
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## STEPS TAKEN AFTER ASSESSMENT

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Fluconazole 50mg, 100mg, 150mg and 200mg Capsules

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Fluconazole 50mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One hard capsule contains 50, 100, 150 and 200 mg fluconazole

For excipients, see 6.1

3 PHARMACEUTICAL FORM
Capsules, hard

50mg:
Upper part: turquoise, lower part: white

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
- Systemic candidiasis including candidaemia, candiduria, disseminated and other invasive, especially in risk patients potentially life-threatening candidal infections, such as infections of peritoneum, lung and urinary tract.
Fluconazole may be used in patients with malignancies, in patients in intensive care units, on cytostatic or immunosuppressive therapy
- Cryptococcal meningitis. Immunocompromised patients (e.g. with AIDS or after organ transplantation) may also be treated.
- Superficial mucosal candidiasis such as
  - Recurrent oropharyngeal and oesophageal candidiasis
  - Chronic-atrophic oral candidiasis (infection of the oral cavity in patients with dentures, in whom dental hygiene or topical measures are not sufficient)
  - Non-invasive bronchopulmonary candidiasis (infection of the mucosa of the upper respiratory tract)
- Fluconazole is also indicated as therapeutic trial to prevent cryptococcal meningitis (relapse prophylaxis) in AIDS patients.
- Prevention of candidiasis in patients with malignancies during chemotherapy or radiotherapy and in immunocompromised patients (e.g. in AIDS or chemotherapy).
- Fungal infections of the skin including dermatomycosis like tinea corporis/cruris/pedis and pityriasis versicolor identified by direct microscopy and/or positive culture and where systemic therapy should be considered accordingly.
- Acute and recurrent vaginal candidiases which do not respond to local therapy.

Consideration should be given to official guidance on the appropriate use of antifungal agents. Not all indications are applicable for paediatric patients; see details in “4.2 Posology and method of administration”.

Note:
Not all strengths are suitable for each indication. See “4.2 Posology and method of administration”.

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4.2 **Posology and method of administration**

The dosage of *Fluconazole* is determined by the type and severity of the infection, by the sensitivity of the causative pathogen(s) as well as by the patient's age, bodyweight and renal function. Depending on the condition, oral or parenteral treatment can be initiated. The duration of treatment depends on the severity and the clinical course of the disease.

Oral pharmaceutical forms and solutions for infusion are available for therapy. Conversion from intravenous to oral administration or vice versa does not require any alteration in the daily dosage.

**Mode of administration**

The hard capsules are to be taken unchewed together with sufficient liquid. They may be taken prior to or with a meal.

**Administration in adults:**

*Fluconazole 50mg/- 100 mg/- 200mg Capsules*

*Systemic candidiasis*

Initiation of therapy usually with 400 mg fluconazole once daily on the first therapeutic day, afterwards continuation of therapy with 200 mg fluconazole once daily. As required, the dose may be increased to 400 mg fluconazole once daily over the entire duration of treatment.

The duration of administration depends on the clinical efficacy while monitoring laboratory values (see point 4.8 "Undesirable effects"). It is recommended to continue therapy until the laboratory studies exclude an identifiable fungal infection still present up to now. Insufficient duration of treatment may lead to a relapse of the infection.

*Cryptococcal meningitis*

- Therapy of cryptococcal meningitis:  
  Initiation of therapy usually with 400 mg fluconazole once daily on the first therapeutic day, afterwards continuation of therapy with 200 mg fluconazole once daily. As required, the dose should be increased to 400 mg fluconazole once daily over the entire duration of treatment.

  The duration of administration is generally 6–8 weeks.

*Fluconazole 50/-100 mg Capsules.*

Candiduria:

50 mg fluconazole once daily. In severe courses of the disease, the dose may be increased to 100 mg fluconazole once daily as required.

The duration of administration is 14–30 days.

*Candidiasis of superficial mucosae*

- Recurrent oropharyngeal candidiasis:  
  50 mg fluconazole once daily. In severe, especially recurrent courses of the disease, the dose may be increased to 100 mg fluconazole once daily as required.

  The duration of administration is 7–14 days. In case of severe immunocompromised patients the duration of therapy may be prolonged.

- Recurrent oesophageal candidiasis:  
  50mg fluconazole once daily. In severe, especially recurrent courses of the disease, the dose may be increased to 100mg fluconazole once daily as required.

  The duration of administration is 14–30 days.

- Chronic-atrophic candidiasis in patients with dentures:  
  50mg fluconazole once daily. In addition, dental hygiene should be carried out as well as locally disinfectant measures taken.

  The duration of administration is 14 days.
• Non-invasive bronchopulmonary candidiasis:
  50mg fluconazole once daily. In severe courses of the disease, the dose may be increased to
  100mg fluconazole once daily as required.

  The duration of administration is 14-30 days.

• Prophylaxis of cryptococcal meningitis:
  After treatment of cryptococcal meningitis is terminated in AIDS patients (see above), a
  therapeutic trial for prevention (relapse prophylaxis) should be carried out with a dose of 100–
  200mg fluconazole once daily while monitoring laboratory values (see also point 4.8
  "Undesirable effects"). Experience to date results from therapeutic periods up to 25 months.

**Fluconazole 50 mg Capsules:**

**Prevention of candidiases**

in patients with malignancies during chemotherapy or radiotherapy and in immunocompromised
patients (e.g. in AIDS or chemotherapy).

1. 50mg fluconazole once daily to prevent candidiasis in immunocompromised patients (see also
   point 4.8 "Undesirable effects").

2. In patients during cytotoxic chemotherapy or radiotherapy if systemic candidiasis is to be
   expected e.g. due to occurring potentiated or prolonged neutropenic phase, administration of
   400mg fluconazole once daily is advisable. Administration of fluconazole should be initiated
   2–3 days prior to the anticipated onset of neutropenia and continued a further 7 days after the
   neutrophile number has increased to more than 1000 cells per mm³.

In patients with malignancies, yeast prophylaxis should be performed during the therapeutic
duration of chemotherapy or radiotherapy.

**Dermal infections:**

Tinea corporis/cruris, Pityriasis versicolor:
50 mg once daily or 150 mg once weekly for 2–4 weeks.

Tinea pedis:
50 mg once daily for up to 6 weeks.

**Fluconazole 50/- 150mg Capsules:**

**Vaginal candidiasis**

As far as not prescribed otherwise, 150mg fluconazole is taken as a single dose.

Fluconazole is predominantly excreted with urine in unchanged form. As it is single dose therapy,
no adjustment according to the degree of renal dysfunction is necessary.

Administration of Fluconazole 150mg Capsules is usually limited to a single dose.

**Administration in elderly patients**

In elderly patients without any evidence of impaired renal function, the usual dose
recommendations should be heeded. If creatinine clearance is below 50 ml/min, the dosage
should be adjusted according to the guidelines for patients with impaired renal function.

**Administration in children in missing therapeutic alternative**

Especially the pharmaceutical forms solution for oral intake and powder/granules for oral
suspension are advisable for oral use in children.

Fluconazole should not be used in children of less than 16 years except in case of no therapeutic
alternative, as efficacy and safety has not been sufficiently shown. The subsequent daily dosages
are recommended for children:

- **Mucous membrane candidiasis:** The recommended dosage of fluconazole is 3mg/kg daily. A
  loading dose of 6mg/kg may be used on the first day to achieve steady state levels more
  rapidly.
- **Systemic candidal/cryptococcal infections**: Recommended dose is 6–12mg/kg daily, depending on the severity of infection.
- **Prevention of candida infections in neutropenic children**: 3–12mg/kg daily depending on the extent and duration of the neutropenia (see adult dosing).

In children with impaired renal function, the dose should be adjusted according to the guidelines for adults (see below), depending on the degree of renal function impairment.

**Patients (adult and paediatric) with impaired renal function**

Fluconazole is predominantly excreted with urine in unchanged form. No adjustments in single dose therapy are required. Patients with impaired renal function (creatinine clearance <50 ml/min) should receive - if several doses of **Fluconazole** are administered - an initial dose between 50 mg/day and 400 mg/day on therapeutic day 1. Afterwards, the dosage intervals or the daily dose for the relevant indication should be adjusted according to creatinine clearance as follows:

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<tr>
<th>Creatinine clearance (ml/min)</th>
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<td>&gt;50</td>
<td>100 %</td>
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<tr>
<td>11–50 (no dialysis)</td>
<td>50 % or 48 hours 100 %</td>
</tr>
<tr>
<td>Regular dialysis</td>
<td>100 % after each dialysis</td>
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</table>

Creatinine clearance is calculated as follows:

**Men:**

bodyweight in kg x (140 - age in years)

72 x serum creatinine (mg/100 ml)

**Women:**

above value x 0.85

**4.3 Contraindications**

Fluconazole should not be used in patients with known hypersensitivity to fluconazole, other azole derivatives or to any of the excipients.

Fluconazole should not be co-administered with drugs both known to prolong the QT-interval and metabolised by CYP3A4 such as cisapride, astemizole, terfenadine, pimozide and quinidine.

(see also point 4.5 „Interaction with other medicinal products and other forms of interaction“).

**4.4 Special warnings and precautions for use**

Severe hepatic toxicity, including death, has been reported in rare cases, primarily in patients suffering from serious underlying diseases. No obvious relationship between hepatotoxicity and total daily dose of fluconazole, duration of therapy, gender or age of the patient has been observed. Patients who develop abnormal liver test values or significant increases of originally abnormal levels during treatment must be monitored closely. The benefits of the treatment should be evaluated against the risks of developing serious liver damage if therapy is continued in patients whose liver enzyme values rise during fluconazole treatment. In most cases, liver toxicity has been reversible at discontinuation of the treatment.

Some azoles have been associated with QT-interval prolongation. Rare cases of Torsade de Pointes during treatment with fluconazole have been reported. And although the association of fluconazole and QT-prolongation has not been formally established, fluconazole should be used with caution in patients with potentially proarrythmic conditions such as:

- Congenital or documented acquired QT prolongation
- Cardiomyopathy, in particular when heart failure is present
- Sinus bradycardia
- Existing symptomatic arrhythmias
- Concomitant medication not metabolised by CYP3A4 but known to prolong QT interval (see section 4.5 Interactions with other medicinal products and other forms of interaction).

Electrolyte disturbances such as hypokalaemia, hypomagnesaemia and hypocalcaemia should be corrected prior to initiation of fluconazole treatment.
Halofantrine has been shown to prolong QTc at the recommended therapeutic dose and is a substrate of CYP3A4. The concomitant use of fluconazole and halofantrine is not recommended.

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

Anaphylactic reactions have in rare cases been reported (see 4.8 Undesirable effects).

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

The dose of fluconazole must be reduced when creatinine clearance is below 50 ml/min (see 4.2 Posology and method of administration).

In women of child-bearing potential, appropriate contraceptive measures should be considered in case long-term treatment is indicated (see section 4.6. Pregnancy and lactation).

In addition for Fluconazole 200mg Capsules:
Ponceau 4R (E 124) may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

The following combinations are contra-indicated:
Cisapride (CYP3A4 substrate): There have been reports about cardiac cases including torsades de pointes in patients receiving fluconazole concomitantly with cisapride. Concomitant treatment with fluconazole and cisapride is contra-indicated.

Terfenadine (with doses of 400 mg fluconazole or higher; CYP3A4 substrate): Due to occurrence of serious cardiac dysrhythmias secondarily to prolongation of the QTc-interval in patients on treatment with azole products concomitantly with terfenadine, interaction studies have been performed. One study with 200mg fluconazole daily did not show any prolongation of the QTc-interval. Another study with 400 mg and 800mg fluconazole daily showed that fluconazole 400mg or more daily significantly increases the plasma level of terfenadine, if the two medicinal products are taken concomitantly. Concomitant treatment with terfenadine and fluconazole doses of 400mg or more is contra-indicated. At fluconazole doses below 400mg, the patient should be closely monitored.

Astemizole (CYP3A4 substrate): Astemizole overdoses have led to prolonged QT interval and severe ventricular arrhythmia, torsades de pointes and cardiac arrest. Concomitant treatment with fluconazole and astemizole is contra-indicated due to the potential for serious, even fatal, cardiac effects.

Medicinal products affecting the metabolism of fluconazole:
Hydrochlorothiazide: In a pharmacokinetic interaction study with healthy volunteers who concomitantly received fluconazole and multiple doses of hydrochlorothiazide the plasma concentrations of fluconazole increased with 40%. An effect of this size should not give rise to any change of the fluconazole dose in patients, who are concomitantly treated with diuretics, even though the physician should be observant on this relation.

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

Effect of fluconazole on the metabolism of other medicinal products:
Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4. Besides the observed/documentated interactions listed below there is a risk of increased plasma concentrations of other medicinal products metabolised by CYP2C9 or CYP3A4 (e.g. ergot-alkaloids, quinidine) when co-administered with fluconazole. Therefore, care should always be taken when using these combinations and the patients should be carefully monitored. The enzyme-inhibiting effect of fluconazole may persist for 4–5 days after end of fluconazole treatment due to the long fluconazole half-life.

Alfentanil (CYP3A4 substrate): Concomitant intake of fluconazole 400 mg and alfentanil 20 µg/kg intravenously in healthy volunteers increased the alfentanil AUC10 approximately 2-fold and decreased the clearance by 55 %, probably through inhibition of CYP3A4. When using these combinations a dose adjustment may be required.

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

Anticoagulants (CYP2C9 substrate): Concomitant intake of fluconazole during warfarin treatment has been shown to prolong the prothrombin time up to 2-fold. This is likely due to an inhibition of warfarin metabolism via CYP2C9. The prothrombin time must be closely monitored in patients on treatment with coumarin derivatives.

Benzodiazepines (CYP3A4 substrate): Concomitant intake of fluconazole 400 mg and midazolam 7.5 mg orally increased the midazolam AUC and half-life 3.7-fold and 2.2-fold, respectively. Fluconazole 100 mg daily given concurrently with triazolam 0.25 mg orally increased the triazolam AUC and half-life 2.5-fold and 1.8-fold, respectively. Potentiated and prolonged effects of triazolam have been observed at concomitant treatment with fluconazole. If it is necessary to treat patients with a benzodiazepine concomitantly with fluconazole, a reduction of the benzodiazepine dose should be considered, and the patients should be closely monitored.

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

Carbamazepine (CYP3A4 substrate): Due to the CYP3A4-inhibiting effect of fluconazole concomitant treatment with carbamazepine may lead to increased plasma levels of carbamazepine. The literature includes reports that document increased undesirable effects described for carbamazepine e.g. vertigo, unsteady gait and diplopia. For this reason, the carbamazepine plasma concentration should be checked if such symptoms occur and the dose be reduced if necessary.

Celecoxib (CYP2C9 substrate): In a clinical study, concomitant treatment with Fluconazole 200 mg daily and celecoxib 200 mg resulted in an 68 % and 134 % increase in celecoxib Cmax and AUC, respectively. The interaction is believed to be due to inhibition of cytochrome P450 2C9 metabolism of celecoxib. Halving the Celecoxib dose is recommended to patients concurrently treated with fluconazole.

Cyclosporin (CYP 3A4 substrate): Clinically significant interactions with cyclosporin have been shown at fluconazole doses of 200 mg and higher. In a pharmacokinetic study with renal transplant patients receiving fluconazole200 mg daily and cyclosporin 2.7 mg/kg/day, there was a 1.8-fold increase in cyclosporin AUC and a 55 % decrease in clearance. It is recommended to follow the cyclosporin plasma concentrations in patients on treatment with fluconazole.
Didanosine: Coadministration of didanosine and fluconazole appears to be safe and has little effect on didanosine pharmacokinetics or efficacy. However, it is important to monitor fluconazole response. It may be advantageous to stagger fluconazole dosing to a time prior to didanosine administration.

Halofantrin (CYP3A4 substrate): Drugs that inhibit CYP3A4 lead to an inhibition of halofantrine metabolism.

HMG-CoA reductase inhibitors (CYP2C9 or CYP3A4 substrates): The risk of myopathy is increased when fluconazole is administered concurrently with HMG-CoA reductase inhibitors that are metabolised via CYP3A4, such as atorvastatin and simvastatin, or via CYP2C9, such as fluvastatin. Up to 200% individual increases in the area under the curve (AUC) of fluvastatin may occur as a result of the interaction between fluvastatin and fluconazole. Caution is warranted if concurrent administration of fluconazole and HMG-CoA reductase inhibitors is deemed necessary. The combination may require a dose reduction of the HMG-CoA reductase inhibitors. Patients should be monitored for signs and symptoms of myopathy or rhabdomyolysis and creatine kinase (CK) levels. HMG-CoA therapy should be discontinued if CK levels show a marked increase, or if myopathy or rhabdomyolysis is diagnosed or suspected.

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

Oral contraceptives: Two pharmacokinetic studies have been performed with a combined oral contraceptive and multiple dosing of fluconazole. 50 mg fluconazole did not influence any of the hormone concentrations, but 200 mg daily increased AUC of ethinylestradiol and levonorgestrel with 40 and 24%, respectively. Thus, it is hardly likely that multiple dosing of fluconazole at these doses has an influence on the effect of the combined oral contraceptive.

Phenyoctin (CYP2C9 substrate): Intake of fluconazole 200 mg concomitantly with phenoctin 250 mg intravenously increased the phenoctin AUC by 75% and Cmin by 128%. If it is necessary to administer both substances concomitantly, the phenoctin concentration must be controlled, and the phenoctin dose adjusted, in order to avoid toxic concentrations.

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

Rifabutine (CYP3A4 substrate): Reports about interaction with administration of fluconazole concomitantly with rifabutine have appeared, leading to increased serum levels of rifabutine. Uveitis in patients treated concomitantly with fluconazole and rifabutine has been reported. Patients who receive rifabutine and fluconazole concomitantly must be closely followed.

Sulphonyl urea (CYP2C9 substrate): It has been demonstrated that fluconazole prolongs the plasma half-life of concomitantly administered sulphonyl urea (chlorpropamide, glibenclamide, glipizide and tolbutamide) in healthy volunteers. Fluconazole and oral sulphonyl urea derivatives may be used concomitantly to diabetics, but the possibility of development of hypoglycaemia must be kept in mind and blood glucose levels closely monitored.

Tacrolimus and sirolimus (CYP3A4 substrates): Concomitant intake of fluconazole and tacrolimus 0.15 mg/kg b.i.d. increased tacrolimus Cmin 1.4 and 3.1-fold with fluconazole doses of 100 mg and 200 mg, respectively. Renal toxicity has been reported in patients...
concomitantly receiving fluconazole and tacrolimus. Although no interaction studies have been conducted with fluconazole and sirolimus, a similar interaction as with tacrolimus might be expected. Patients who receive tacrolimus or sirolimus and fluconazole concomitantly must be closely monitored for tacrolimus/sirolimus plasma levels and toxicity.

Theophylline: Intake of fluconazole 200 mg for 14 days resulted in 18 % decrease in the mean plasma clearance of theophylline. Patients on treatment with high doses of theophylline or with other reason to be at increased risk of theophylline toxicity should be carefully observed during fluconazole therapy, and the theophylline dose should be adjusted as necessary.

Trimetrexate: Fluconazole may inhibit the metabolism of trimetrexate, leading to increased trimetrexate plasma concentrations. If the combination cannot be avoided, trimetrexate serum levels and toxicity should be closely monitored.

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

Pharmacodynamic interactions
Medicinal products that prolong QT interval: Case reports indicate that fluconazole might have the potential to induce QT prolongation leading to serious cardiac arrhythmia. Patients treated concomitantly with fluconazole and other drugs that prolong QT interval should be carefully monitored, since an additive effect cannot be excluded.

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

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

4.6 Pregnancy and lactation

Pregnancy
Data from several hundred pregnant women treated with standard doses (below 200 mg/day) of fluconazole, administered as a single or repeated dose during the first trimester, do not indicate undesirable effects on the foetus.

There are reports on multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in children whose mothers were treated for 3 months or longer with high doses (400–800 mg/day) of fluconazole for coccidioidal mycosis. The relationship between these effects and fluconazole is unclear.

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

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

Lactation
Fluconazole passes into breast milk to reach concentrations lower than those in plasma. Breast-feeding may be maintained after single use of a standard dose 200 mg fluconazole or less. Breast-feeding is not recommended after repeated use or after high-dose fluconazole.
4.7 Effects on ability to drive and use machines
Fluconazole has no or negligible influence on the ability to drive and use machines.
However when driving vehicles or operating machines it should be taken into account that occasionally dizziness or seizures may occur.

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

Organ systems

**General**
Uncommon
>1/1,000, <1/100
fatigue, malaise, asthenia, fever

**Central and Peripheral Nervous System**
Common >1/100, <1/10
headache

Uncommon
>1/1,000, <1/100
convulsions, dizziness, paresthesia, tremor, vertigo

**Skin and Appendages**
Common >1/100, <1/10
rash

Uncommon
>1/1,000, <1/100
pruritus

Rare
>1/10,000, <1/1,000
exfoliative skin disorder
(Stevens-Johnson syndrome)

**Gastrointestinal**
Common >1/100, <1/10
nausea and vomiting
abdominal pain,
diarrhoea

Uncommon
>1/1,000, <1/100
anorexia, constipation, dyspepsia, flatulence

**Musculoskeletal**
Uncommon >1/1,000, <1/100
myalgia

**Autonomic Nervous System**
Uncommon >1/1,000, <1/100
dry mouth, increased sweating

**Psychiatric**
Uncommon
>1/1,000, <1/100
insomnia, somnolence
Liver and Biliary System
Common
>1/100, <1/10
Clinically significant increase of AST, ALT and alkaline phosphatase

Uncommon
>1/1,000, <1/100
cholestasis, hepatocellular damage, jaundice Clinically significant

Uncommon
>1/1,000, <1/100
increase of total bilirubin,

Rare
>1/10,000, <1/1,000
hepatic necrosis

Special Senses
Uncommon
>1/1,000, <1/100
taste perversion

Hematopoietic and Lymphatic
Uncommon
>1/1,000, <1/100
anaemia

Immunologic

Rare
>1/10,000, <1/1,000
anaphylaxis

Adverse clinical events were reported more frequently in HIV infected patients (21 %) than in non-HIV infected patients (13 %). However, the patterns of adverse events in HIV infected and non-HIV infected patients were similar.

In addition, the following adverse events have occurred under conditions where a causal association is uncertain (e.g. open trials, during post-marketing experience):

Organ systems
Cardiac
Rare
>1/10,000, <1/1,000
ventricular arrhythmia (QT-prolongation, torsade de pointes)

Central and Peripheral Nervous System
Rare
>1/10,000, <1/1,000
seizures

Skin and Appendages
Rare
>1/10,000, <1/1,000
alopecia

Very rare
<1/10,000
exfoliative skin disorder (Stevens-Johnson syndrome and toxic epidermal necrolysis),
erthema exudativum multiforme

Liver and Biliary System
Rare
>1/10,000, <1/1,000
hepatic failure
hepatitis
hepatic necrosis
Immunoologic

Very rare
<1/10,000
anaphylaxis, angioedema, face oedema and pruritus, fixed drug eruption,
urticaria, acute generalised exanthematous pustulosis

Hematopoietic and Lymphatic
Rare
>1/10,000, <1/1,000
leukopenia, including neutropenia and agranulocytosis, thrombocytopenia

Metabolic
Rare
>1/10,000, <1/1,000
Hypercholesterolemia, hypertriglyceridemia, hypokalemia

4.9 Overdose
In case of overdosing the treatment is symptomatic with supporting measures and gastric lavage,
if necessary. Fluconazole is mainly excreted in the urine. Forced volume diuresis will probably
increase the elimination rate. Haemodialysis for 3 hours decreases the plasma levels with approx.
50%.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic Group
Antimycotics for systemic use, triazole derivatives

ATC code: J02AC01

Fluconazole is a triazole derivative with fungistatic effect, which specifically inhibits the
synthesis of the fungi’s ergosterol, which is believed to lead to defects in the cell membrane.
Fluconazole is highly specific for fungal cytochrome P-450 enzymes. Doses of fluconazole
50 mg daily for 28 days have not been shown to influence serum levels of testosterone in men
or the steroid concentration in fertile women.

The spectrum of application includes a number of pathogens including Candida albicans and
non-Candida albicans species, Cryptococcus spp and dermatophytes. Candida krusei is
resistant to fluconazole. Forty percent of Candida glabrata are primarily resistant to
fluconazole. Infections caused by Aspergillus-species should not be treated with fluconazole.

5.2 Pharmacokinetic properties
Absorption: Fluconazole is well absorbed after oral intake. The absolute bioavailability is
above 90 %. The oral absorption is not affected by concomitant food intake. The maximum
fasting plasma concentration is reached 0.5–1.5 hours after dose intake. 90 % of the steady-
state level is reached 4–5 days after dosing once daily.

Plasma concentration is proportional to the dose. After administration of 200 mg of
fluconazole, Cmax is around 4.6 mg/l and plasma concentrations at steady-state after 15 days
are around 10 mg/l. After administration of 400 mg of fluconazole, Cmax is around 9 mg/l and plasma concentrations at steady-state after 15 days are around 18 mg/l.

Intake of a double dose on day 1 results in plasma concentrations of approx. 90 % of steady-state on day 2.

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

The concentration in saliva corresponds to the plasma concentration. In patients with fungal meningitis the concentration of fluconazole in the cerebrospinal fluid is approx. 80 % of the corresponding plasma concentration.

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

Elimination: Fluconazole is mainly renally excreted. Approx. 80 % of the taken dose is excreted in the urine in non-metabolized form. Fluconazole clearance is proportional to the creatinine clearance. Circulating metabolites have not been demonstrated.

The half-life in plasma is approximately 30 hours.

Children eliminate fluconazole more rapidly than adults do. The half-life in children and adolescents of 5–15 years is between 15.2–17.6 hours.

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate, Gelatin, Maize starch, Magnesium stearate, Sodium lauril sulphate, Colloidal silicon dioxide, Titanium dioxide (E 171) printing ink: Shellac, Black iron oxide (E 172), Propylene glycol Indigo carmine (E 132)

6.2 Incompatibilities
No incompatibilities are known to date.

6.3 Shelf life
The shelf life is 3 years.

6.4 Special precautions for storage
Do not store above 25°C.

6.5 Nature and contents of container
The hard capsules are packed in PVC white, opaque/aluminium blisters and inserted into a carton.

Packages containing
*Fluconazole 50mg Capsules:*
1, 3, 7, 10, 14, 20, 28, 30, 42, 50 and 100 capsules, hard

Not all pack sizes may be marketed.

6.6 Special precautions for disposal
None

7 MARKETING AUTHORIZATION HOLDER
Roger A Oakes Limited,
Allstoe House, Church Lane,
Greetham, Rutland,
LE15 7NF,
United Kingdom.

8 MARKETING AUTHORIZATION NUMBER(S)
*Fluconazole 50mg Capsules*
PL 32019/0017

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
29/10/2008

10 DATE OF REVISION OF THE TEXT
29/10/2008
1 **NAME OF THE MEDICINAL PRODUCT**
Fluconazole 100mg Capsules

2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**
One hard capsule contains 50, 100, 150 and 200 mg fluconazole

For excipients, see 6.1

3 **PHARMACEUTICAL FORM**
Capsules, hard

100mg:
Upper part: blue, lower part: white

4 **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**
- Systemic candidiasis including candidaemia, candiduria, disseminated and other invasive, especially in risk patients potentially life-threatening candidal infections, such as infections of peritoneum, lung and urinary tract.
  - Fluconazole may be used in patients with malignancies, in patients in intensive care units, on cytostatic or immunoospressive therapy
  - Cryptococcal meningitis. Immunocompromised patients (e.g. with AIDS or after organ transplantation) may also be treated.
  - Superficial mucosal candidiasis such as
    - Recurrent oropharyngeal and oesophageal candidiasis
    - Chronic-atrophic oral candidiasis (infection of the oral cavity in patients with dentures, in whom dental hygiene or topical measures are not sufficient)
    - Non-invasive bronchopulmonary candidiasis (infection of the mucosa of the upper respiratory tract)
  - Fluconazole is also indicated as therapeutic trial to prevent cryptococcal meningitis (relapse prophylaxis) in AIDS patients.
  - Prevention of candidiasis in patients with malignancies during chemotherapy or radiotherapy and in immunocompromised patients (e.g. in AIDS or chemotherapy).
  - Fungal infections of the skin including dermatomycosis like tinea corporis/cruris/pedis and pityriasis versicolor identified by direct microscopy and/or positive culture and where systemic therapy should be considered accordingly.
  - Acute and recurrent vaginal candidiasis which do not respond to local therapy.

Consideration should be given to official guidance on the appropriate use of antifungal agents. Not all indications are applicable for paediatric patients; see details in “4.2 Posology and method of administration”.

**Note:**
Not all strengths are suitable for each indication. See “4.2 Posology and method of administration”.


4.2 Posology and method of administration

The dosage of Fluconazole is determined by the type and severity of the infection, by the sensitivity of the causative pathogen(s) as well as by the patient's age, bodyweight and renal function. Depending on the condition, oral or parenteral treatment can be initiated. The duration of treatment depends on the severity and the clinical course of the disease.

Oral pharmaceutical forms and solutions for infusion are available for therapy. Conversion from intravenous to oral administration or vice versa does not require any alteration in the daily dosage.

Mode of administration

The hard capsules are to be taken unchewed together with sufficient liquid. They may be taken prior to or with a meal.

Administration in adults:

Fluconazole 50mg/-100mg/-200mg Capsules

Systemic candidiasis

Initiation of therapy usually with 400mg fluconazole once daily on the first therapeutic day, afterwards continuation of therapy with 200mg fluconazole once daily. As required, the dose may be increased to 400mg fluconazole once daily over the entire duration of treatment.

The duration of administration depends on the clinical efficacy while monitoring laboratory values (see point 4.8 "Undesirable effects"). It is recommended to continue therapy until the laboratory studies exclude an identifiable fungal infection still present up to now. Insufficient duration of treatment may lead to a relapse of the infection.

Cryptococcal meningitis

- Therapy of cryptococcal meningitis:
  Initiation of therapy usually with 400mg fluconazole once daily on the first therapeutic day, afterwards continuation of therapy with 200 mg fluconazole once daily. As required, the dose should be increased to 400mg fluconazole once daily over the entire duration of treatment.

The duration of administration is generally 6–8 weeks.

Fluconazole 50/-100 mg Capsules.

Candiduria:

50mg fluconazole once daily. In severe courses of the disease, the dose may be increased to 100mg fluconazole once daily as required.

The duration of administration is 14–30 days.

Candidiasis of superficial mucosae

- Recurrent oropharyngeal candidiasis:
  50mg fluconazole once daily. In severe, especially recurrent courses of the disease, the dose may be increased to 100 mg fluconazole once daily as required.

The duration of administration is 7–14 days. In case of severe immunocompromised patients the duration of therapy may be prolonged.

- Recurrent oesophageal candidiasis:
  50mg fluconazole once daily. In severe, especially recurrent courses of the disease, the dose may be increased to 100 mg fluconazole once daily as required.

  The duration of administration is 14–30 days.

- Chronic-atrophic candidiasis in patients with dentures:
  50mg fluconazole once daily. In addition, dental hygiene should be carried out as well as locally disinfectant measures taken.

  The duration of administration is 14 days.
- Non-invasive bronchopulmonary candidiasis:
  50mg fluconazole once daily. In severe courses of the disease, the dose may be increased to 100 mg fluconazole once daily as required.

  The duration of administration is 14-30 days.

- Prophylaxis of cryptococcal meningitis:
  After treatment of cryptococcal meningitis is terminated in AIDS patients (see above), a therapeutic trial for prevention (relapse prophylaxis) should be carried out with a dose of 100–200mg fluconazole once daily while monitoring laboratory values (see also point 4.8 "Undesirable effects"). Experience to date results from therapeutic periods up to 25 months.

**Fluconazole 50 mg Capsules:**

**Prevention of candidiases**

- in patients with malignancies during chemotherapy or radiotherapy and in immunocompromised patients (e.g. in AIDS or chemotherapy).
- 50mg fluconazole once daily to prevent candidiasis in immunocompromised patients (see also point 4.8 "Undesirable effects").

- In patients during cytotoxic chemotherapy or radiotherapy if systemic candidiasis is to be expected e.g. due to occurring potentiated or prolonged neutropenic phase, administration of 400mg fluconazole once daily is advisable. Administration of fluconazole should be initiated 2–3 days prior to the anticipated onset of neutropenia and continued a further 7 days after the neutrophile number has increased to more than 1000 cells per mm³.

In patients with malignancies, yeast prophylaxis should be performed during the therapeutic duration of chemotherapy or radiotherapy.

**Dermal infections:**

Tinea corporis/cruris, Pityriasis versicolor:
50 mg once daily or 150 mg once weekly for 2–4 weeks.

Tinea pedis:
50 mg once daily for up to 6 weeks.

**Fluconazole 50/- 150mg Capsules:**

**Vaginal candidiasis**

As far as not prescribed otherwise, 150mg fluconazole is taken as a single dose.

Fluconazole is predominantly excreted with urine in unchanged form. As it is single dose therapy, no adjustment according to the degree of renal dysfunction is necessary.

Administration of **Fluconazole 150mg Capsules** is usually limited to a single dose.

**Administration in elderly patients**

In elderly patients without any evidence of impaired renal function, the usual dose recommendations should be heeded. If creatinine clearance is below 50 ml/min, the dosage should be adjusted according to the guidelines for patients with impaired renal function.

**Administration in children in missing therapeutic alternative**

Especially the pharmaceutical forms solution for oral intake and powder/granules for oral suspension are advisable for oral use in children.

**Fluconazole** should not be used in children of less than 16 years except in case of no therapeutic alternative, as efficacy and safety has not been sufficiently shown. The subsequent daily dosages are recommended for children:
**UKPAR Fluconazole 50, 100, 150 and 200mg Capsules**

- **Mucous membrane candidiasis:** The recommended dosage of fluconazole is 3mg/kg daily. A loading dose of 6mg/kg may be used on the first day to achieve steady state levels more rapidly.
- **Systemic candidal/cryptococcal infections:** Recommended dose is 6–12mg/kg daily, depending on the severity of infection.
- **Prevention of candida infections in neutropenic children:** 3–12 mg/kg daily depending on the extent and duration of the neutopenia (see adult dosing).

In children with impaired renal function, the dose should be adjusted according to the guidelines for adults (see below), depending on the degree of renal function impairment.

**Patients (adult and paediatric) with impaired renal function**

Fluconazole is predominantly excreted with urine in unchanged form. No adjustments in single dose therapy are required. Patients with impaired renal function (creatinine clearance <50 ml/min) should receive - if several doses of Fluconazole are administered - an initial dose between 50 mg/day and 400 mg/day on therapeutic day 1. Afterwards, the dosage intervals or the daily dose for the relevant indication should be adjusted according to creatinine clearance as follows:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Percentage of recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>100 %</td>
</tr>
<tr>
<td>11–50 (no dialysis)</td>
<td>50 % or 48 hours 100 %</td>
</tr>
<tr>
<td>Regular dialysis</td>
<td>100 % after each dialysis</td>
</tr>
</tbody>
</table>

Creatinine clearance is calculated as follows:

Men:

bodyweight in kg x (140 - age in years)

72 x serum creatinine (mg/100 ml)

Women:

above value x 0.85

4.3 **Contraindications**

Fluconazole should not be used in patients with known hypersensitivity to fluconazole, other azole derivatives or to any of the excipients.

Fluconazole should not be co-administered with drugs both known to prolong the QT-interval and metabolised by CYP3A4 such as cisapride, astemizole, terfenadine, pimozide and quinidine.

(see also point 4.5 „Interaction with other medicinal products and other forms of interaction”).

4.4 **Special warnings and precautions for use**

Severe hepatic toxicity, including death, has been reported in rare cases, primarily in patients suffering from serious underlying diseases. No obvious relationship between hepatotoxicity and total daily dose of fluconazole, duration of therapy, gender or age of the patient has been observed. Patients who develop abnormal liver test values or significant increases of originally abnormal levels during treatment must be monitored closely. The benefits of the treatment should be evaluated against the risks of developing serious liver damage if therapy is continued in patients whose liver enzyme values rise during fluconazole treatment. In most cases, liver toxicity has been reversible at discontinuation of the treatment.

Some azoles have been associated with QT-interval prolongation. Rare cases of Torsade de Pointes during treatment with fluconazole have been reported. And although the association of fluconazole and QT-prolongation has not been formally established, fluconazole should be used with caution in patients with potentially proarrhythmic conditions such as:

- Congenital or documented acquired QT prolongation
- Cardiomyopathy, in particular when heart failure is present
- Sinus bradycardia
- Existing symptomatic arrhythmias
Concomitant medication not metabolised by CYP3A4 but known to prolong QT interval (see section 4.5 Interactions with other medicinal products and other forms of interaction).

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

Halofantrine has been shown to prolong QTc at the recommended therapeutic dose and is a substrate of CYP3A4. The concomitant use of fluconazole and halofantrine is not recommended.

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

Anaphylactic reactions have in rare cases been reported (see 4.8 Undesirable effects).

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

The dose of fluconazole must be reduced when creatinine clearance is below 50 ml/min (see 4.2 Posology and method of administration).

In women of child-bearing potential, appropriate contraceptive measures should be considered in case long-term treatment is indicated (see section 4.6. Pregnancy and lactation).

In addition for Fluconazole 200 mg Capsules:
Ponceau 4R (E 124) may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

The following combinations are contra-indicated:
Cisapride (CYP3A4 substrate): There have been reports about cardiac cases including torsades de pointes in patients receiving fluconazole concomitantly with cisapride. Concomitant treatment with fluconazole and cisapride is contra-indicated.

Terfenadine (with doses of 400 mg fluconazole or higher; CYP3A4 substrate): Due to occurrence of serious cardiac dysrhythmias secondarily to prolongation of the QTc-interval in patients on treatment withazole products concomitantly with terfenadine, interaction studies have been performed. One study with 200 mg fluconazole daily did not show any prolongation of the QTc-interval. Another study with 400 mg and 800 mg fluconazole daily showed that fluconazole 400 mg or more daily significantly increases the plasma level of terfenadine, if the two medicinal products are taken concomitantly. Concomitant treatment with terfenadine and fluconazole doses of 400 mg or more is contra-indicated. At fluconazole doses below 400 mg, the patient should be closely monitored.

Astemizole (CYP3A4 substrate): Astemizole overdoses have led to prolonged QT interval and severe ventricular arrhythmia, torsades de pointes and cardiac arrest. Concomitant treatment with fluconazole and astemizole is contra-indicated due to the potential for serious, even fatal, cardiac effects.

Medicinal products affecting the metabolism of fluconazole:
Hydrochlorothiazide: In a pharmacokinetic interaction study with healthy volunteers who concomitantly received fluconazole and multiple doses of hydrochlorothiazide the plasma concentrations of fluconazole increased with 40%. An effect of this size should not give rise to any change of the fluconazole dose in patients, who are concomitantly treated with diuretics, even though the physician should be observant on this relation.
Rifampicin (CYP450 inducer): Concomitant intake of fluconazole and rifampicin resulted in a 25% reduction of AUC and 20% shorter half-life of fluconazole. Increase of dosage should be considered in patients concomitantly receiving rifampicin.

Effect of fluconazole on the metabolism of other medicinal products:
Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4. Besides the observed documented interactions listed below there is a risk of increased plasma concentrations of other medicinal products metabolised by CYP2C9 or CYP3A4 (e.g. ergot-alkaloids, quinidine) when co-administered with fluconazole. Therefore, care should always be taken when using these combinations and the patients should be carefully monitored. The enzyme-inhibiting effect of fluconazole may persist for 4–5 days after end of fluconazole treatment due to the long fluconazole half-life.

Alfentanil (CYP3A4 substrate): Concomitant intake of fluconazole 400mg and alfentanil 20μg/kg intravenously in healthy volunteers increased the alfentanil AUC10 approximately 2-fold and decreased the clearance by 55%, probably through inhibition of CYP3A4. When using these combinations a dose adjustment may be required.

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

Anticoagulants (CYP2C9 substrate): Concomitant intake of fluconazole during warfarin treatment has been shown to prolong the prothrombin time up to 2-fold. This is likely due to an inhibition of warfarin metabolism via CYP2C9. The prothrombin time must be closely monitored in patients on treatment with coumarin derivatives.

Benzodiazepines (CYP3A4 substrate): Concomitant intake of fluconazole 400 mg and midazolam 7.5mg orally increased the midazolam AUC and half-life 3.7-fold and 2.2-fold, respectively. Fluconazole 100mg daily given concurrently with triazolam 0.25mg orally increased the triazolam AUC and half-life 2.5-fold and 1.8-fold, respectively. Potentiated and prolonged effects of triazolam have been observed at concomitant treatment with fluconazole. If it is necessary to treat patients with a benzodiazepine concomitantly with fluconazole, a reduction of the benzodiazepine dose should be considered, and the patients should be closely monitored.

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

Carbamazepine (CYP3A4 substrate): Due to the CYP3A4-inhibiting effect of fluconazole concomitant treatment with carbamazepine may lead to increased plasma levels of carbamazepine. The literature includes reports that document increased undesirable effects described for carbamazepine e.g. vertigo, unsteady gait and diplopia. For this reason, the carbamazepine plasma concentration should be checked if such symptoms occur and the dose be reduced if necessary.

Celecoxib (CYP2C9 substrate): In a clinical study, concomitant treatment with Fluconazole 200 mg daily and celecoxib 200mg resulted in an 68% and 134% increase in celecoxib Cmax and AUC, respectively. The interaction is believed to be due to inhibition of cytochrome P450 2C9 metabolism of celecoxib. Halving the Celecoxib dose is recommended to patients concurrently treated with fluconazole.

Cyclosporin (CYP 3A4 substrate): Clinically significant interactions with cyclosporin have been shown at fluconazole doses of 200mg and higher. In a pharmacokinetic study with renal
transplant patients receiving fluconazole 200mg daily and cyclosporin 2.7mg/kg/day, there was a 1.8-fold increase in cyclosporin AUC and a 55% decrease in clearance. It is recommended to follow the cyclosporin plasma concentrations in patients on treatment with fluconazole.

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

Halofantrin (CYP3A4 substrate): Drugs that inhibit CYP3A4 lead to an inhibition of halofantrine metabolism.

HMG-CoA reductase inhibitors (CYP2C9 or CYP3A4 substrates): The risk of myopathy is increased when fluconazole is administered concurrently with HMG-CoA reductase inhibitors that are metabolised via CYP3A4, such as atorvastatin and simvastatin, or via CYP2C9, such as fluvastatin. Up to 200% individual increases in the area under the curve (AUC) of fluvastatin may occur as a result of the interaction between fluvastatin and fluconazole. Caution is warranted if concurrent administration of fluconazole and HMG-CoA reductase inhibitors is deemed necessary. The combination may require a dose reduction of the HMG-CoA reductase inhibitors. Patients should be monitored for signs and symptoms of myopathy or rhabdomyolysis and creatine kinase (CK) levels. HMG-CoA therapy should be discontinued if CK levels show a marked increase, or if myopathy or rhabdomyolysis is diagnosed or suspected.

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

Oral contraceptives: Two pharmacokinetic studies have been performed with a combined oral contraceptive and multiple dosing of fluconazole. 50 mg fluconazole did not influence any of the hormone concentrations, but 200mg daily increased AUC of ethinyloestradiol and levonorgestrel with 40 and 24%, respectively. Thus, it is hardly likely that multiple dosing of fluconazole at these doses has an influence on the effect of the combined oral contraceptive.

Phenytoin (CYP2C9 substrate): Intake of fluconazole 200mg concomitantly with phenytoin 250mg intravenously increased the phenytoin AUC by 75% and Cmin by 128%. If it is necessary to administer both substances concomitantly, the phenytoin concentration must be controlled, and the phenytoin dose adjusted, in order to avoid toxic concentrations.

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

Rifabutine (CYP3A4 substrate): Reports about interaction with administration of fluconazole concomitantly with rifabutine have appeared, leading to increased serum levels of rifabutine. Uveitis in patients treated concomitantly with fluconazole and rifabutine has been reported. Patients who receive rifabutine and fluconazole concomitantly must be closely followed.

Sulphonyl urea (CYP2C9 substrate): It has been demonstrated that fluconazole prolongs the plasma half-life of concomitantly administered sulphonyl urea (chlorpropamide, glibenclamide, glipizide and tolbutamide) in healthy volunteers. Fluconazole and oral sulphonyl urea derivatives may be used concomitantly to diabetics, but the possibility of development of hypoglycaemia must be kept in mind and blood glucose levels closely monitored.
Tacrolimus and sirolimus (CYP3A4 substrates): Concomitant intake of fluconazole and tacrolimus 0.15mg/kg b.i.d. increased tacrolimus Cmin 1.4 and 3.1-fold with fluconazole doses of 100mg and 200mg, respectively. Renal toxicity has been reported in patients concomitantly receiving fluconazole and tacrolimus. Although no interaction studies have been conducted with fluconazole and sirolimus, a similar interaction as with tacrolimus might be expected. Patients who receive tacrolimus or sirolimus and fluconazole concomitantly must be closely monitored for tacrolimus/sirolimus plasma levels and toxicity.

Theophylline: Intake of fluconazole 200mg for 14 days resulted in 18% decrease in the mean plasma clearance of theophylline. Patients on treatment with high doses of theophylline or with other reason to be at increased risk of theophylline toxicity should be carefully observed during fluconazole therapy, and the theophylline dose should be adjusted as necessary.

Trimetrexate: Fluconazole may inhibit the metabolism of trimetrexate, leading to increased trimetrexate plasma concentrations. If the combination cannot be avoided, trimetrexate serum levels and toxicity should be closely monitored.

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

Pharmacodynamic interactions
Medicinal products that prolong QT interval: Case reports indicate that fluconazole might have the potential to induce QT prolongation leading to serious cardiac arrhythmia. Patients treated concomitantly with fluconazole and other drugs that prolong QT interval should be carefully monitored, since an additive effect cannot be excluded.

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

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

4.6 Pregnancy and lactation

Pregnancy
Data from several hundred pregnant women treated with standard doses (below 200 mg/day) of fluconazole, administered as a single or repeated dose during the first trimester, do not indicate undesirable effects on the foetus.

There are reports on multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in children whose mothers were treated for 3 months or longer with high doses (400–800 mg/day) of fluconazole for coccidioidal mycosis. The relationship between these effects and fluconazole is unclear.

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

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

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

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

**Organ systems**

**General**
Uncommon
>1/1,000, <1/100
fatigue, malaise, asthenia, fever

**Central and Peripheral Nervous System**
Common >1/100, <1/10
headache

Uncommon
>1/1,000, <1/100
convulsions, dizziness, paresthesia, tremor, vertigo

**Skin and Appendages**
Common >1/100, <1/10
rash

Uncommon
>1/1,000, <1/100
pruritus

Rare
>1/10,000, <1/100
exfoliative skin disorder
(Stevens-Johnson syndrome)

**Gastrointestinal**
Common >1/100, <1/10
nausea and vomiting
abdominal pain,
diarrhoea

Uncommon
>1/1,000, <1/100
anorexia, constipation, dyspepsia, flatulence

**Muscloskeletal**
Uncommon >1/1,000, <1/100
myalgia

**Autonomic Nervous System**
Uncommon >1/1,000, <1/100
dry mouth, increased sweating
Psychiatric
Uncommon
>1/1,000, <1/100
insomnia, somnolence

Liver and Biliary System
Common
>1/100, <1/10
Clinically significant increase of AST, ALT and alkaline phosphatase

Uncommon
>1/1,000, <1/100
cholestasis, hepatocellular damage, jaundice Clinically significant

Uncommon
>1/1,000, <1/100
increase of total bilirubin,

Rare
>1/10,000, <1/1,000
hepatic necrosis

Special Senses
Uncommon
>1/1,000, <1/100
taste perversion

Hematopoietic and Lymphatic
Uncommon
>1/1,000, <1/100
anaemia

Immunologic
Rare
>1/10,000, <1/1,000
anaphylaxis

Adverse clinical events were reported more frequently in HIV infected patients (21 %) than in non-HIV infected patients (13 %). However, the patterns of adverse events in HIV infected and non-HIV infected patients were similar.

In addition, the following adverse events have occurred under conditions where a causal association is uncertain (e.g. open trials, during post-marketing experience):

Organ systems
Cardiac
Rare
>1/10,000, <1/1,000
ventricular arrhythmia (QT-prolongation, torsade de pointes)

Central and Peripheral Nervous System
Rare
>1/10,000, <1/1,000
seizures

Skin and Appendages
Rare
>1/10,000, <1/1,000
alopecia
Very rare
<1/10,000
exfoliative skin disorder (Stevens-Johnson syndrome and toxic epidermal necrolysis),
erthema exudativum multiforme

Liver and Biliary System
Rare
>1/10,000, <1/1,000
hepatic failure
hepatitis
hepatic necrosis

Immunologic
Very rare
<1/10,000
anaphylaxis, angiooedema, face oedema and pruritus, fixed drug eruption,
urticaria, acute generalised exanthematous pustulosis

Hematopoietic and Lymphatic
Rare
>1/10,000, <1/1,000
leukopenia, including neutropenia and agranulocytosis, thrombocytopenia

Metabolic
Rare
>1/10,000, <1/1,000
Hypercholesterolemia, hypertriglyceridemia, hypokalemia

4.9 Overdose
In case of overdosing the treatment is symptomatic with supporting measures and gastric lavage,
if necessary. Fluconazole is mainly excreted in the urine. Forced volume diuresis will probably
increase the elimination rate. Haemodialysis for 3 hours decreases the plasma levels with approx.
50%.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic Group
Antimycotics for systemic use, triazole derivatives

ATC code: J02AC01

Fluconazole is a triazole derivative with fungistatic effect, which specifically inhibits the
synthesis of the fungi’s ergosterol, which is believed to lead to defects in the cell membrane.
Fluconazole is highly specific for fungal cytochrome P-450 enzymes. Doses of fluconazole
50 mg daily for 28 days have not been shown to influence serum levels of testosterone in men
or the steroid concentration in fertile women.

The spectrum of application includes a number of pathogens including Candida albicans and
non-Candida albicans species, Cryptococcus spp and dermatophytes. Candida krusei is
resistant to fluconazole. Forty percent of Candida glabrata are primarily resistant to
fluconazole. Infections caused by Aspergillus-species should not be treated with fluconazole.

5.2 Pharmacokinetic properties
Absorption: Fluconazole is well absorbed after oral intake. The absolute bioavailability is
above 90 %. The oral absorption is not affected by concomitant food intake. The maximum
fasting plasma concentration is reached 0.5–1.5 hours after dose intake. 90 % of the steady-
state level is reached 4–5 days after dosing once daily.
Plasma concentration is proportional to the dose. After administration of 200 mg of fluconazole, Cmax is around 4.6 mg/l and plasma concentrations at steady-state after 15 days are around 10 mg/l. After administration of 400 mg of fluconazole, Cmax is around 9 mg/l and plasma concentrations at steady-state after 15 days are around 18 mg/l.

Intake of a double dose on day 1 results in plasma concentrations of approx. 90 % of steady-state on day 2.

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

The concentration in saliva corresponds to the plasma concentration. In patients with fungal meningitis the concentration of fluconazole in the cerebrospinal fluid is approx. 80 % of the corresponding plasma concentration.

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

Elimination: Fluconazole is mainly renally excreted. Approx. 80 % of the taken dose is excreted in the urine in non-metabolized form. Fluconazole clearance is proportional to the creatinine clearance. Circulating metabolites have not been demonstrated.

The half-life in plasma is approximately 30 hours.

Children eliminate fluconazole more rapidly than adults do. The half-life in children and adolescents of 5–15 years is between 15.2–17.6 hours.

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate,
Gelatin,
Maize starch,
Magnesium stearate,
Sodium lauril sulphate,
Colloidal silicon dioxide,
Titanium dioxide (E 171)
printing ink:
Shellac,
Black iron oxide (E 172),
Propylene glycol
Indigo carmine (E 132)

6.2 Incompatibilities
No incompatibilities are known to date.

6.3 Shelf life
The shelf life is 3 years.
6.4 **Special precautions for storage**
Do not store above 25°C.

6.5 **Nature and contents of container**
The hard capsules are packed in PVC white, opaque/aluminium blisters and inserted into a carton.

Packages containing
*Fluconazole 100 mg Capsules:*
1, 7, 10, 14, 20, 30, 50 and 100 capsules, hard

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
None

7 **MARKETING AUTHORISATION HOLDER**
Roger A Oakes Limited,
Allstoe House, Church Lane,
Greetham, Rutland,
LE15 7NF,
United Kingdom.

8 **MARKETING AUTHORISATION NUMBER(S)**
Fluconazole 100mg Capsules

PL 32019/0018

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
29/10/2008

10 **DATE OF REVISION OF THE TEXT**
29/10/2008
1 NAME OF THE MEDICINAL PRODUCT
Fluconazole 150mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
One hard capsule contains 50, 100, 150 and 200 mg fluconazole

For excipients, see 6.1

3 PHARMACEUTICAL FORM
Capsules, hard

150mg:
Upper part: white, lower part: white

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
- systemic candidiasis including candidaemia, candiduria, disseminated and other invasive, especially in risk patients potentially life-threatening candidal infections, such as infections of peritoneum, lung and urinary tract.
Fluconazole may be used in patients with malignancies, in patients in intensive care units, on cytostatic or immunosuppressive therapy
- cryptococcal meningitis. Immunocompromised patients (e.g. with AIDS or after organ transplantation) may also be treated.
- superficial mucosal candidiasis such as
  · recurrent oropharyngeal and oesophageal candidiasis
  · chronic-atrophic oral candidiasis (infection of the oral cavity in patients with dentures, in whom dental hygiene or topical measures are not sufficient)
  · non-invasive bronchopulmonary candidiasis (infection of the mucosa of the upper respiratory tract)
- Fluconazole is also indicated as therapeutic trial to prevent cryptococcal meningitis (relapse prophylaxis) in AIDS patients.
- Prevention of candidiasis in patients with malignancies during chemotherapy or radiotherapy and in immunocompromised patients (e.g. in AIDS or chemotherapy).
- Fungal infections of the skin including dermatomycosis like tinea corporis/cruris/pedis and Pityriasis versicolor identified by direct microscopy and/or positive culture and where systemic therapy should be considered accordingly.
- Acute and recurrent vaginal candidiases which do not respond to local therapy.

Consideration should be given to official guidance on the appropriate use of antifungal agents. Not all indications are applicable for paediatric patients; see details in “4.2 Posology and method of administration”.

Note:
Not all strengths are suitable for each indication. See “4.2 Posology and method of administration”.
4.2 Posology and method of administration

The dosage of Fluconazole is determined by the type and severity of the infection, by the sensitivity of the causative pathogen(s) as well as by the patient's age, body weight and renal function. Depending on the condition, oral or parenteral treatment can be initiated. The duration of treatment depends on the severity and the clinical course of the disease.

Oral pharmaceutical forms and solutions for infusion are available for therapy. Conversion from intravenous to oral administration or vice versa does not require any alteration in the daily dosage.

Mode of administration

The hard capsules are to be taken unchewed together with sufficient liquid. They may be taken prior to or with a meal.

Administration in adults:

Fluconazole 50 mg/- 100 mg/- 200 mg Capsules

Systemic candidiasis

Initiation of therapy usually with 400 mg fluconazole once daily on the first therapeutic day, afterwards continuation of therapy with 200 mg fluconazole once daily. As required, the dose may be increased to 400 mg fluconazole once daily over the entire duration of treatment.

The duration of administration depends on the clinical efficacy while monitoring laboratory values (see point 4.8 "Undesirable effects"). It is recommended to continue therapy until the laboratory studies exclude an identifiable fungal infection still present up to now. Insufficient duration of treatment may lead to a relapse of the infection.

Cryptococcal meningitis

- Therapy of cryptococcal meningitis:
  - Initiation of therapy usually with 400mg fluconazole once daily on the first therapeutic day, afterwards continuation of therapy with 200mg fluconazole once daily. As required, the dose should be increased to 400mg fluconazole once daily over the entire duration of treatment.

The duration of administration is generally 6–8 weeks.

Fluconazole 50/-100mg Capsules.

Candiduria:

50mg fluconazole once daily. In severe courses of the disease, the dose may be increased to 100mg fluconazole once daily as required.

The duration of administration is 14–30 days.

Candidiasis of superficial mucosae

- Recurrent oropharyngeal candidiasis:
  - 50mg fluconazole once daily. In severe, especially recurrent courses of the disease, the dose may be increased to 100 mg fluconazole once daily as required.

The duration of administration is 7–14 days. In case of severe immunocompromised patients the duration of therapy may be prolonged.

- Recurrent oesophageal candidiasis:
  - 50mg fluconazole once daily. In severe, especially recurrent courses of the disease, the dose may be increased to 100mg fluconazole once daily as required.

The duration of administration is 14–30 days.

- Chronic-atrophic candidiasis in patients with dentures:
  - 50mg fluconazole once daily. In addition, dental hygiene should be carried out as well as locally disinfectant measures taken.

The duration of administration is 14 days.
- Non-invasive bronchopulmonary candidiasis:
  50mg fluconazole once daily. In severe courses of the disease, the dose may be increased to
  100mg fluconazole once daily as required.

  The duration of administration is 14-30 days.

- Prophylaxis of cryptococcal meningitis:
  After treatment of cryptococcal meningitis is terminated in AIDS patients (see above), a
  therapeutic trial for prevention (relapse prophylaxis) should be carried out with a dose of 100–
  200mg fluconazole once daily while monitoring laboratory values (see also point 4.8
  "Undesirable effects"). Experience to date results from therapeutic periods up to 25 months.

Fluconazole 50 mg Capsules:
Prevention of candidiases
in patients with malignancies during chemotherapy or radiotherapy and in immunocompromised
patients (e.g. in AIDS or chemotherapy).
5. 50mg fluconazole once daily to prevent candidiasis in immunocompromised patients (see also
point 4.8 "Undesirable effects").
6. In patients during cytotoxic chemotherapy or radiotherapy if systemic candidiasis is to be
expected e.g. due to occurring potentiated or prolonged neutropenic phase, administration of
400mg fluconazole once daily is advisable. Administration of fluconazole should be initiated
2–3 days prior to the anticipated onset of neutropenia and continued a further 7 days after the
neutrophile number has increased to more than 1000 cells per mm³.

In patients with malignancies, yeast prophylaxis should be performed during the therapeutic
duration of chemotherapy or radiotherapy.

Dermal infections:
Tinea corporis/cruris, Pityriasis versicolor:
50 mg once daily or 150 mg once weekly for 2–4 weeks.

Tinea pedis:
50 mg once daily for up to 6 weeks.

Fluconazole 50/- 150 mg Capsules:
Vaginal candidiasis
As far as not prescribed otherwise, 150 mg fluconazole is taken as a single dose.

Fluconazole is predominantly excreted with urine in unchanged form. As it is single dose therapy,
no adjustment according to the degree of renal dysfunction is necessary.

Administration of Fluconazole 150 mg Capsules is usually limited to a single dose.

Administration in elderly patients
In elderly patients without any evidence of impaired renal function, the usual dose
recommendations should be heeded. If creatinine clearance is below 50 ml/min, the dosage
should be adjusted according to the guidelines for patients with impaired renal function.

Administration in children in missing therapeutic alternative
 Especially the pharmaceutical forms solution for oral intake and powder/granules for oral
suspension are advisable for oral use in children.

Fluconazole should not be used in children of less than 16 years except in case of no therapeutic
alternative, as efficacy and safety has not been sufficiently shown. The subsequent daily dosages
are recommended for children:
- **Mucous membrane candidiasis**: The recommended dosage of fluconazole 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.
- **Systemic candidal/cryptococcal infections**: Recommended dose is 6–12 mg/kg daily, depending on the severity of infection.
- **Prevention of candida infections in neutropenic children**: 3–12 mg/kg daily depending on the extent and duration of the neutropenia (see adult dosing).

In children with impaired renal function, the dose should be adjusted according to the guidelines for adults (see below), depending on the degree of renal function impairment.

**Patients (adult and paediatric) with impaired renal function**

Fluconazole is predominantly excreted with urine in unchanged form. No adjustments in single dose therapy are required. Patients with impaired renal function (creatinine clearance <50 ml/min) should receive - if several doses of Fluconazole are administered - an initial dose between 50 mg/day and 400 mg/day on therapeutic day 1. Afterwards, the dosage intervals or the daily dose for the relevant indication should be adjusted according to creatinine clearance as follows:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Percentage of recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>100 %</td>
</tr>
<tr>
<td>11–50 (no dialysis)</td>
<td>50 % or 48 hours 100 %</td>
</tr>
<tr>
<td>Regular dialysis</td>
<td>100 % after each dialysis</td>
</tr>
</tbody>
</table>

Creatinine clearance is calculated as follows:

**Men:**

\[
\text{bodyweight in kg} \times (140 - \text{age in years})
\]

\[
72 \times \text{serum creatinine (mg/100 ml)}
\]

**Women:**

above value \times 0.85

### 4.3 Contraindications

Fluconazole should not be used in patients with known hypersensitivity to fluconazole, other azole derivatives or to any of the excipients.

Fluconazole should not be co-administered with drugs both known to prolong the QT-interval and metabolised by CYP3A4 such as cisapride, astemizole, terfenadine, pimozide and quinidine.

(see also point 4.5 „Interaction with other medicinal products and other forms of interaction”).

### 4.4 Special warnings and precautions for use

Severe hepatic toxicity, including death, has been reported in rare cases, primarily in patients suffering from serious underlying diseases. No obvious relationship between hepatotoxicity and total daily dose of fluconazole, duration of therapy, gender or age of the patient has been observed. Patients who develop abnormal liver test values or significant increases of originally abnormal levels during treatment must be monitored closely. The benefits of the treatment should be evaluated against the risks of developing serious liver damage if therapy is continued in patients whose liver enzyme values rise during fluconazole treatment. In most cases, liver toxicity has been reversible at discontinuation of the treatment.

Some azoles have been associated with QT-interval prolongation. Rare cases of Torsade de Pointes during treatment with fluconazole have been reported. And although the association of fluconazole and QT-prolongation has not been formally established, fluconazole should be used with caution in patients with potentially proarrhythmic conditions such as:

- Congenital or documented acquired QT prolongation
- Cardiomyopathy, in particular when heart failure is present
- Sinus bradycardia
- Existing symptomatic arrhythmias
Concomitant medication not metabolised by CYP3A4 but known to prolong QT interval (see section 4.5 Interactions with other medicinal products and other forms of interaction).

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

Halofantrine has been shown to prolong QTc at the recommended therapeutic dose and is a substrate of CYP3A4. The concomitant use of fluconazole and halofantrine is not recommended.

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

Anaphylactic reactions have in rare cases been reported (see 4.8 Undesirable effects).

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

The dose of fluconazole must be reduced when creatinine clearance is below 50 ml/min (see 4.2 Posology and method of administration).

In women of child-bearing potential, appropriate contraceptive measures should be considered in case long-term treatment is indicated (see section 4.6. Pregnancy and lactation).

In addition for Fluconazole 200 mg Capsules:
Ponceau 4R (E 124) may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

The following combinations are contra-indicated:

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

Terfenadine (with doses of 400 mg fluconazole or higher; CYP3A4 substrate): Due to occurrence of serious cardiac dysrhythmias secondarily to prolongation of the QTc-interval in patients on treatment withazole products concomitantly with terfenadine, interaction studies have been performed. One study with 200 mg fluconazole daily did not show any prolongation of the QTc-interval. Another study with 400 mg and 800 mg fluconazole daily showed that fluconazole 400 mg or more daily significantly increases the plasma level of terfenadine, if the two medicinal products are taken concomitantly. Concomitant treatment with terfenadine and fluconazole doses of 400 mg or more is contra-indicated. At fluconazole doses below 400 mg, the patient should be closely monitored.

Astemizole (CYP3A4 substrate): Astemizole overdoses have led to prolonged QT interval and severe ventricular arrhythmia, torsades de pointes and cardiac arrest. Concomitant treatment with fluconazole and astemizole is contra-indicated due to the potential for serious, even fatal, cardiac effects.

Medicinal products affecting the metabolism of fluconazole:
Hydrochlorothiazide: In a pharmacokinetic interaction study with healthy volunteers who concomitantly received fluconazole and multiple doses of hydrochlorothiazide the plasma concentrations of fluconazole increased with 40%. An effect of this size should not give rise to any change of the fluconazole dose in patients, who are concomitantly treated with diuretics, even though the physician should be observant on this relation.
Rifampicin (CYP450 inducer): Concomitant intake of fluconazole and rifampicin resulted in a 25 % reduction of AUC and 20 % shorter half-life of fluconazole. Increase of dosage should be considered in patients concomitantly receiving rifampicin.

Effect of fluconazole on the metabolism of other medicinal products:
Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4. Besides the observed/documented interactions listed below there is a risk of increased plasma concentrations of other medicinal products metabolised by CYP2C9 or CYP3A4 (e.g. ergot-alkaloids, quinidine) when co-administered with fluconazole. Therefore, care should always be taken when using these combinations and the patients should be carefully monitored. The enzyme-inhibiting effect of fluconazole may persist for 4–5 days after end of fluconazole treatment due to the long fluconazole half-life.

Alfentanil (CYP3A4 substrate): Concomitant intake of fluconazole 400 mg and alfentanil 20 µg/kg intravenously in healthy volunteers increased the alfentanil AUC10 approximately 2-fold and decreased the clearance by 55 %, probably through inhibition of CYP3A4. When using these combinations a dose adjustment may be required.

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

Anticoagulants (CYP2C9 substrate): Concomitant intake of fluconazole during warfarin treatment has been shown to prolong the prothrombin time up to 2-fold. This is likely due to an inhibition of warfarin metabolism via CYP2C9. The prothrombine time must be closely monitored in patients on treatment with coumarin derivatives.

Benzodiazepines (CYP3A4 substrate): Concomitant intake of fluconazole 400 mg and midazolam 7.5 mg orally increased the midazolam AUC and half-life 3.7-fold and 2.2-fold, respectively. Fluconazole 100 mg daily given concurrently with triazolam 0.25 mg orally increased the triazolam AUC and half-life 2.5-fold and 1.8-fold, respectively. Potentiated and prolonged effects of triazolam have been observed at concomitant treatment with fluconazole. If it is necessary to treat patients with a benzodiazepine concomitantly with fluconazole, a reduction of the benzodiazepine dose should be considered, and the patients should be closely monitored.

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

Carbamazepine (CYP3A4 substrate): Due to the CYP3A4-inhibiting effect of fluconazole concomitant treatment with carbamazepine may lead to increased plasma levels of carbamazepine. The literature includes reports that document increased undesirable effects described for carbamazepine e. g. vertigo, unsteady gait and diplopia. For this reason, the carbamazepine plasma concentration should be checked if such symptoms occur and the dose be reduced if necessary.

Celecoxib (CYP2C9 substrate): In a clinical study, concomitant treatment with Fluconazole 200 mg daily and celecoxib 200 mg resulted in an 68 % and 134 % increase in celecoxib Cmax and AUC, respectively. The interaction is believed to be due to inhibition of cytochrome P450 2C9 metabolism of celecoxib. Halving the Celecoxib dose is recommended to patients concurrently treated with fluconazole.

Cyclosporin (CYP 3A4 substrate): Clinically significant interactions with cyclosporin have been shown at fluconazole doses of 200 mg and higher. In a pharmacokinetic study with renal
transplant patients receiving fluconazole 200 mg daily and cyclosporin 2.7 mg/kg/day, there was a 1.8-fold increase in cyclosporin AUC and a 55% decrease in clearance. It is recommended to follow the cyclosporin plasma concentrations in patients on treatment with fluconazole.

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

Halofantrin (CYP3A4 substrate): Drugs that inhibit CYP3A4 lead to an inhibition of halofantrine metabolism.

HMG-CoA reductase inhibitors (CYP2C9 or CYP3A4 substrates): The risk of myopathy is increased when fluconazole is administered concurrently with HMG-CoA reductase inhibitors that are metabolised via CYP3A4, such as atorvastatin and simvastatin, or via CYP2C9, such as fluvastatin. Up to 200% individual increases in the area under the curve (AUC) of fluvastatin may occur as a result of the interaction between fluvastatin and fluconazole. Caution is warranted if concurrent administration of fluconazole and HMG-CoA reductase inhibitors is deemed necessary. The combination may require a dose reduction of the HMG-CoA reductase inhibitors. Patients should be monitored for signs and symptoms of myopathy or rhabdomyolysis and creatine kinase (CK) levels. HMG-CoA therapy should be discontinued if CK levels show a marked increase, or if myopathy or rhabdomyolysis is diagnosed or suspected.

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

Oral contraceptives: Two pharmacokinetic studies have been performed with a combined oral contraceptive and multiple dosing of fluconazole. 50 mg fluconazole did not influence any of the hormone concentrations, but 200 mg daily increased AUC of ethinyloestradiol and levonorgestrel with 40 and 24%, respectively. Thus, it is hardly likely that multiple dosing of fluconazole at these doses has an influence on the effect of the combined oral contraceptive.

Phenytoin (CYP2C9 substrate): Intake of fluconazole 200 mg concomitantly with phenytoin 250 mg intravenously increased the phenytoin AUC by 75% and Cmin by 128%. If it is necessary to administer both substances concomitantly, the phenytoin concentration must be controlled, and the phenytoin dose adjusted, in order to avoid toxic concentrations.

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

Rifabutine (CYP3A4 substrate): Reports about interaction with administration of fluconazole concomitantly with rifabutin have appeared, leading to increased serum levels of rifabutin. Uveitis in patients treated concomitantly with fluconazole and rifabutin has been reported. Patients who receive rifabutine and fluconazole concomitantly must be closely followed.

Sulphonyl urea (CYP2C9 substrate): It has been demonstrated that fluconazole prolongs the plasma half-life of concomitantly administered sulphonyl urea (chlorpropamide, glibenclamide, glipizide and tolbutamide) in healthy volunteers. Fluconazole and oral sulphonyl urea derivatives may be used concomitantly to diabetics, but the possibility of
development of hypoglycaemia must be kept in mind and blood glucose levels closely monitored.

Tacrolimus and sirolimus (CYP3A4 substrates): Concomitant intake of fluconazole and tacrolimus 0.15 mg/kg b.i.d. increased tacrolimus Cmin 1.4 and 3.1-fold with fluconazole doses of 100 mg and 200 mg, respectively. Renal toxicity has been reported in patients concomitantly receiving fluconazole and tacrolimus. Although no interaction studies have been conducted with fluconazole and sirolimus, a similar interaction as with tacrolimus might be expected. Patients who receive tacrolimus or sirolimus and fluconazole concomitantly must be closely monitored for tacrolimus/sirolimus plasma levels and toxicity.

Theophylline: Intake of fluconazole 200 mg for 14 days resulted in 18% decrease in the mean plasma clearance of theophylline. Patients on treatment with high doses of theophylline or with other reason to be at increased risk of theophylline toxicity should be carefully observed during fluconazole therapy, and the theophylline dose should be adjusted as necessary.

Trimetrexate: Fluconazole may inhibit the metabolism of trimetrexate, leading to increased trimetrexate plasma concentrations. If the combination cannot be avoided, trimetrexate serum levels and toxicity should be closely monitored.

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

**Pharmacodynamic interactions**

Medicinal products that prolong QT interval: Case reports indicate that fluconazole might have the potential to induce QT prolongation leading to serious cardiac arrhythmia. Patients treated concomitantly with fluconazole and other drugs that prolong QT interval should be carefully monitored, since an additive effect cannot be excluded.

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

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

### 4.6 Pregnancy and lactation

**Pregnancy**

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

There are reports on multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in children whose mothers were treated for 3 months or longer with high doses (400–800 mg/day) of fluconazole for coccidioidal mycosis. The relationship between these effects and fluconazole is unclear.

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

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

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

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

Organ systems

General
Uncommon
>1/1,000, <1/100
fatigue, malaise, asthenia, fever

Central and Peripheral Nervous System
Common >1/100, <1/10
headache

Uncommon
>1/1,000, <1/100
convulsions, dizziness, paresthesia, tremor, vertigo

Skin and Appendages
Common >1/100, <1/10kin
rash

Uncommon
>1/1,000, <1/100
pruritus

Rare
>1/10,000, <1/1,000
exfoliative skin disorder
(Stevens-Johnson syndrome)

Gastrointestinal
Common >1/100, <1/10
nausea and vomiting
abdominal pain, diarrhoea

Uncommon
>1/1,000, <1/100
anorexia, constipation, dyspepsia, flatulence

Musculoskeletal
Uncommon >1/1,000, <1/100
myalgia

Autonomic Nervous System
Uncommon >1/1,000, <1/100
dry mouth, increased sweating
**Psychiatric**
Uncommon
>1/1,000, <1/100
insomnia, somnolence

**Liver and Biliary System**
Common
>1/100, <1/10
Clinically significant increase of AST, ALT and alkaline phosphatase

Uncommon
>1/1,000, <1/100
cholestasis, hepatocellular damage, jaundice Clinically significant

Uncommon
>1/1,000, <1/100
increase of total bilirubin,

Rare
>1/10,000, <1/1,000
hepatic necrosis

**Special Senses**
Uncommon
>1/1,000, <1/100
taste perversion

**Hematopoietic and Lymphatic**
Uncommon
>1/1,000, <1/100
anaemia

Immunologic
Rare
>1/10,000, <1/1,000
anaphylaxis

Adverse clinical events were reported more frequently in HIV infected patients (21 %) than in non-HIV infected patients (13 %). However, the patterns of adverse events in HIV infected and non-HIV infected patients were similar.

In addition, the following adverse events have occurred under conditions where a causal association is uncertain (e.g. open trials, during post-marketing experience):

**Organ systems**

**Cardiac**
Rare
>1/10,000, <1/1,000
ventricular arrhythmia (QT-prolongation, torsade de pointes)

**Central and Peripheral Nervous System**
Rare
>1/10,000, <1/1,000
seizures

**Skin and Appendages**
Rare
>1/10,000, <1/1,000
alopecia

Very rare
<1/10,000
exfoliative skin disorder (Stevens-Johnson syndrome and toxic epidermal necrolysis),
erythema exudativum multiforme

Liver and Biliary System
Rare
>1/10,000, <1/1,000
hepatic failure
hepatitis
hepatic necrosis

Immunologic

Very rare
<1/10,000
anaphylaxis, angioedema, face oedema and pruritus, fixed drug eruption,
urticaria, acute generalised exanthematous pustulosis

Hematopoietic and Lymphatic
Rare
>1/10,000, <1/1,000
leukopenia, including neutropenia and agranulocytosis, thrombocytopenia

Metabolic
Rare
>1/10,000, <1/1,000
Hypercholesterolemia, hypertriglyceridemia, hypokalemia

4.9 Overdose
In case of overdosing the treatment is symptomatic with supporting measures and gastric lavage, if necessary. Fluconazole is mainly excreted in the urine. Forced volume diuresis will probably increase the elimination rate. Haemodialysis for 3 hours decreases the plasma levels with approx. 50%.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic Group
Antimycotics for systemic use, triazole derivatives

ATC code: J02AC01

Fluconazole is a triazole derivative with fungistatic effect, which specifically inhibits the synthesis of the fungi’s ergosterol, which is believed to lead to defects in the cell membrane. Fluconazole is highly specific for fungal cytochrome P-450 enzymes. Doses of fluconazole 50 mg daily for 28 days have not been shown to influence serum levels of testosterone in men or the steroid concentration in fertile women.

The spectrum of application includes a number of pathogens including Candida albicans and non-Candida albicans species, Cryptococcus spp and dermatophytes. Candida krusei is resistant to fluconazole. Forty percent of Candida glabrata are primarily resistant to fluconazole. Infections caused by Aspergillus-species should not be treated with fluconazole.

5.2 Pharmacokinetic properties
Absorption: Fluconazole is well absorbed after oral intake. The absolute bioavailability is above 90 %. The oral absorption is not affected by concomitant food intake. The maximum fasting plasma concentration is reached 0.5–1.5 hours after dose intake. 90 % of the steady-state level is reached 4–5 days after dosing once daily.
Plasma concentration is proportional to the dose. After administration of 200 mg of fluconazole, Cmax is around 4.6 mg/l and plasma concentrations at steady-state after 15 days are around 10 mg/l. After administration of 400 mg of fluconazole, Cmax is around 9 mg/l and plasma concentrations at steady-state after 15 days are around 18 mg/l.

Intake of a double dose on day 1 results in plasma concentrations of approx. 90 % of steady-state on day 2.

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

The concentration in saliva corresponds to the plasma concentration. In patients with fungal meningitis the concentration of fluconazole in the cerebrospinal fluid is approx. 80 % of the corresponding plasma concentration.

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

Elimination: Fluconazole is mainly renally excreted. Approx. 80 % of the taken dose is excreted in the urine in non-metabolized form. Fluconazole clearance is proportional to the creatinine clearance. Circulating metabolites have not been demonstrated.

The half-life in plasma is approximately 30 hours.

Children eliminate fluconazole more rapidly than adults do. The half-life in children and adolescents of 5–15 years is between 15.2–17.6 hours.

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

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

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Lactose monohydrate,
Gelatin,
Maize starch,
Magnesium stearate,
Sodium lauril sulphate,
Colloidal silicon dioxide,
Titanium dioxide (E 171)
printing ink:
Shellac,
Black iron oxide (E 172),
Propylene glycol

6.2 Incompatibilities
No incompatibilities are known to date.

6.3 Shelf life
The shelf life is 3 years.
6.4 **Special precautions for storage**
Do not store above 25°C.

6.5 **Nature and contents of container**
The hard capsules are packed in PVC white, opaque/aluminium blisters and inserted into a carton.

Packages containing
*Fluconazole 150 mg Capsules:*
1 and 2 capsules, hard

Not all pack sizes may be marketed.

6.6 **Special precautions for disposal**
None

7 **MARKETING AUTHORISATION HOLDER**
Roger Oakes Limited,
Allstoe House, Church Lane,
Greetham, Rutland,
LE15 7NF,
United Kingdom.

8 **MARKETING AUTHORISATION NUMBER(S)**
Fluconazole 150mg Capsules

PL 32019/0019

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
29/10/2008

10 **DATE OF REVISION OF THE TEXT**
29/10/2008
1 **NAME OF THE MEDICINAL PRODUCT**
Fluconazole 200mg Capsules

2 **QUALITATIVE AND QUANTITATIVE COMPOSITION**
One hard capsule contains 50, 100, 150 and 200 mg fluconazole

For excipients, see 6.1

3 **PHARMACEUTICAL FORM**
Capsules, hard

200mg:
Upper part: purple, lower part: white

4 **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**
- Systemic candidiasis including candidaemia, candiduria, disseminated and other invasive, especially in risk patients potentially life-threatening candidal infections, such as infections of peritoneum, lung and urinary tract.
- Fluconazole may be used in patients with malignancies, in patients in intensive care units, on cytostatic or immunosuppressive therapy
- Cryptococcal meningitis. Immunocompromised patients (e.g. with AIDS or after organ transplantation) may also be treated.
- Superficial mucosal candidiasis such as
  - Recurrent oropharyngeal and oesophageal candidiasis
  - Chronic-atrophic oral candidiasis (infection of the oral cavity in patients with dentures, in whom dental hygiene or topical measures are not sufficient)
  - Non-invasive bronchopulmonary candidiasis (infection of the mucosa of the upper respiratory tract)
- Fluconazole is also indicated as therapeutic trial to prevent cryptococcal meningitis (relapse prophylaxis) in AIDS patients.
- Prevention of candidiasis in patients with malignancies during chemotherapy or radiotherapy and in immunocompromised patients (e.g. in AIDS or chemotherapy).
- Fungal infections of the skin including dermatomycosis like tinea corporis/cruris/pedis and Pityriasis versicolor identified by direct microscopy and/or positive culture and where systemic therapy should be considered accordingly.
- Acute and recurrent vaginal candidiases which do not respond to local therapy.

Consideration should be given to official guidance on the appropriate use of antifungal agents. Not all indications are applicable for paediatric patients; see details in “4.2 Posology and method of administration”.

**Note:**
Not all strengths are suitable for each indication. See “4.2 Posology and method of administration”.

4.2 **Posology and method of administration**
The dosage of Fluconazole is determined by the type and severity of the infection, by the sensitivity of the causative pathogen(s) as well as by the patient's age, bodyweight and renal function. Depending on the condition, oral or parenteral treatment can be initiated. The duration of treatment depends on the severity and the clinical course of the disease.

Oral pharmaceutical forms and solutions for infusion are available for therapy. Conversion from intravenous to oral administration or vice versa does not require any alteration in the daily dosage.

**Mode of administration**
The hard capsules are to be taken unchewed together with sufficient liquid. They may be taken prior to or with a meal.
**Administration in adults:**

*Fluconazole 50 mg/- 100 mg/- 200 mg Capsules*

**Systemic candidiasis**

Initiation of therapy usually with 400 mg fluconazole once daily on the first therapeutic day, afterwards continuation of therapy with 200 mg fluconazole once daily. As required, the dose may be increased to 400 mg fluconazole once daily over the entire duration of treatment.

The duration of administration depends on the clinical efficacy while monitoring laboratory values (see point 4.8 "Undesirable effects"). It is recommended to continue therapy until the laboratory studies exclude an identifiable fungal infection still present up to now. Insufficient duration of treatment may lead to a relapse of the infection.

**Cryptococcal meningitis**

- Therapy of cryptococcal meningitis:
  - Initiation of therapy usually with 400 mg fluconazole once daily on the first therapeutic day, afterwards continuation of therapy with 200 mg fluconazole once daily. As required, the dose should be increased to 400 mg fluconazole once daily over the entire duration of treatment.

The duration of administration is generally 6–8 weeks.

*Fluconazole 50/-100 mg Capsules.*

**Candiduria:**

50 mg fluconazole once daily. In severe courses of the disease, the dose may be increased to 100 mg fluconazole once daily as required.

The duration of administration is 14–30 days.

**Candidiasis of superficial mucosae**

- Recurrent oropharyngeal candidiasis:
  - 50 mg fluconazole once daily. In severe, especially recurrent courses of the disease, the dose may be increased to 100 mg fluconazole once daily as required.

The duration of administration is 7–14 days. In case of severe immunocompromised patients the duration of therapy may be prolonged.

- Recurrent oesophageal candidiasis:
  - 50 mg fluconazole once daily. In severe, especially recurrent courses of the disease, the dose may be increased to 100 mg fluconazole once daily as required.

The duration of administration is 14–30 days.

- Chronic-atrophic candidiasis in patients with dentures:
  - 50 mg fluconazole once daily. In addition, dental hygiene should be carried out as well as locally disinfectant measures taken.

The duration of administration is 14 days.

- Non-invasive bronchopulmonary candidiasis:
  - 50 mg fluconazole once daily. In severe courses of the disease, the dose may be increased to 100 mg fluconazole once daily as required.

The duration of administration is 14–30 days.

- Prophylaxis of cryptococcal meningitis:
  - After treatment of cryptococcal meningitis is terminated in AIDS patients (see above), a therapeutic trial for prevention (relapse prophylaxis) should be carried out with a dose of 100–200 mg fluconazole once daily while monitoring laboratory values (see also point 4.8 "Undesirable effects"). Experience to date results from therapeutic periods up to 25 months.
Fluconazole 50mg Capsules:  
**Prevention of candidiasis**  
in patients with malignancies during chemotherapy or radiotherapy and in immunocompromised patients (e.g. in AIDS or chemotherapy).

7. 50mg fluconazole once daily to prevent candidiasis in immunocompromised patients (see also point 4.8 "Undesirable effects").

8. In patients during cytotoxic chemotherapy or radiotherapy if systemic candidiasis is to be expected e.g. due to occurring potentiated or prolonged neutropenic phase, administration of 400mg fluconazole once daily is advisable. Administration of fluconazole should be initiated 2–3 days prior to the anticipated onset of neutropenia and continued a further 7 days after the neutrophile number has increased to more than 1000 cells per mm³.

In patients with malignancies, yeast prophylaxis should be performed during the therapeutic duration of chemotherapy or radiotherapy.

**Dermal infections:**
Tinea corporis/cruris, Pityriasis versicolor:
50mg once daily or 150mg once weekly for 2–4 weeks.

Tinea pedis:
50mg once daily for up to 6 weeks.

**Fluconazole 50/- 150mg Capsules:**
**Vaginal candidiasis**
As far as not prescribed otherwise, 150mg fluconazole is taken as a single dose.

Fluconazole is predominantly excreted with urine in unchanged form. As it is single dose therapy, no adjustment according to the degree of renal dysfunction is necessary.

**Administration of Fluconazole 150mg Capsules** is usually limited to a single dose.

**Administration in elderly patients**
In elderly patients without any evidence of impaired renal function, the usual dose recommendations should be heeded. If creatinine clearance is below 50 ml/min, the dosage should be adjusted according to the guidelines for patients with impaired renal function.

**Administration in children in missing therapeutic alternative**
Especially the pharmaceutical forms solution for oral intake and powder/granules for oral suspension are advisable for oral use in children.

**Fluconazole** should not be used in children of less than 16 years except in case of no therapeutic alternative, as efficacy and safety has not been sufficiently shown. The subsequent daily dosages are recommended for children:

- **Mucous membrane candidiasis:** The recommended dosage of fluconazole is 3mg/kg daily. A loading dose of 6 mg/kg may be used on the first day to achieve steady state levels more rapidly.
- **Systemic candidal/cryptococcal infections:** Recommended dose is 6–12mg/kg daily, depending on the severity of infection.
- **Prevention of candida infections in neutropenic children:** 3–12mg/kg daily depending on the extent and duration of the neutopenia (see adult dosing).

In children with impaired renal function, the dose should be adjusted according to the guidelines for adults (see below), depending on the degree of renal function impairment.

**Patients (adult and paediatric) with impaired renal function**
Fluconazole is predominantly excreted with urine in unchanged form. No adjustments in single dose therapy are required. Patients with impaired renal function (creatinine clearance <50ml/min) should receive - if several doses of Fluconazole are administered - an initial dose between
50mg/day and 400mg/day on therapeutic day 1. Afterwards, the dosage intervals or the daily dose for the relevant indication should be adjusted according to creatinine clearance as follows:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Percentage of recommended dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50</td>
<td>100 %</td>
</tr>
<tr>
<td>11–50 (no dialysis)</td>
<td>50 % or 48 hours 100 %</td>
</tr>
<tr>
<td>Regular dialysis</td>
<td>100 % after each dialysis</td>
</tr>
</tbody>
</table>

Creatinine clearance is calculated as follows:

**Men:**

\[
\text{bodyweight in kg} \times (140 - \text{age in years}) \div 72 \times \text{serum creatinine (mg/100 ml)}
\]

**Women:**

above value \times 0.85

4.3 **Contraindications**

Fluconazole should not be used in patients with known hypersensitivity to fluconazole, otherazole derivatives or to any of the excipients.

Fluconazole should not be co-administered with drugs both known to prolong the QT-interval and metabolised by CYP3A4 such as cisapride, astemizole, terfenadine, pimozide and quinidine.

(see also point 4.5 „Interaction with other medicinal products and other forms of interaction“).

4.4 **Special warnings and precautions for use**

Severe hepatic toxicity, including death, has been reported in rare cases, primarily in patients suffering from serious underlying diseases. No obvious relationship between hepatotoxicity and total daily dose of fluconazole, duration of therapy, gender or age of the patient has been observed. Patients who develop abnormal liver test values or significant increases of originally abnormal levels during treatment must be monitored closely. The benefits of the treatment should be evaluated against the risks of developing serious liver damage if therapy is continued in patients whose liver enzyme values rise during fluconazole treatment. In most cases, liver toxicity has been reversible at discontinuation of the treatment.

Some azoles have been associated with QT-interval prolongation. Rare cases of Torsade de Pointes during treatment with fluconazole have been reported. And although the association of fluconazole and QT-prolongation has not been formally established, fluconazole should be used with caution in patients with potentially proarrythmic conditions such as:

- Congenital or documented acquired QT prolongation
- Cardiomyopathy, in particular when heart failure is present
- Sinus bradycardia
- Existing symptomatic arrhythmias
- Concomitant medication not metabolised by CYP3A4 but known to prolong QT interval (see section 4.5 Interactions with other medicinal products and other forms of interaction).

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

Halofantrine has been shown to prolong QTc at the recommended therapeutic dose and is a substrate of CYP3A4. The concomitant use of fluconazole and halofantrine is not recommended.

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

Anaphylactic reactions have in rare cases been reported (see 4.8 Undesirable effects).

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

The dose of fluconazole must be reduced when creatinine clearance is below 50 ml/min (see 4.2 Posology and method of administration).

In women of child-bearing potential, appropriate contraceptive measures should be considered in case long-term treatment is indicated (see section 4.6. Pregnancy and lactation).

In addition for Fluconazole 200 mg Capsules:
Ponceau 4R (E 124) may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

The following combinations are contra-indicated:
Cisapride (CYP3A4 substrate): There have been reports about cardiac cases including torsades de pointes in patients receiving fluconazole concomitantly with cisapride. Concomitant treatment with fluconazole and cisapride is contra-indicated.

Terfenadine (with doses of 400 mg fluconazole or higher; CYP3A4 substrate): Due to occurrence of serious cardiac dysrhythmias secondarily to prolongation of the QTc-interval in patients on treatment with azole products concomitantly with terfenadine, interaction studies have been performed. One study with 200 mg fluconazole daily did not show any prolongation of the QTc-interval. Another study with 400 mg and 800 mg fluconazole daily showed that fluconazole 400 mg or more daily significantly increases the plasma level of terfenadine, if the two medicinal products are taken concomitantly. Concomitant treatment with terfenadine and fluconazole doses of 400 mg or more is contra-indicated. At fluconazole doses below 400 mg, the patient should be closely monitored.

Astemizole (CYP3A4 substrate): Astemizole overdoses have led to prolonged QT interval and severe ventricular arrhythmia, torsades de pointes and cardiac arrest. Concomitant treatment with fluconazole and astemizole is contra-indicated due to the potential for serious, even fatal, cardiac effects.

Medicinal products affecting the metabolism of fluconazole:
Hydrochlorothiazide: In a pharmacokinetic interaction study with healthy volunteers who concomitantly received fluconazole and multiple doses of hydrochlorothiazide the plasma concentrations of fluconazole increased with 40 %. An effect of this size should not give rise to any change of the fluconazole dose in patients, who are concomitantly treated with diuretics, even though the physician should be observant on this relation.

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

Effect of fluconazole on the metabolism of other medicinal products:
Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4. Besides the observed/documented interactions listed below there is a risk of increased plasma concentrations of other medicinal products metabolised by CYP2C9 or CYP3A4 (e.g. ergot-alkaloids, quinidine) when co-administered with fluconazole. Therefore, care should always be taken when using these combinations and the patients should be carefully monitored. The enzyme-inhibiting effect of fluconazole may persist for 4–5 days after end of fluconazole treatment due to the long fluconazole half-life.

Alfentanil (CYP3A4 substrate): Concomitant intake of fluconazole 400 mg and alfentanil 20 µg/kg intravenously in healthy volunteers increased the alfentanil AUC10 approximately 2-fold and decreased the clearance by 55 %, probably through inhibition of CYP3A4. When using these combinations a dose adjustment may be required.
Amitriptyline: Several case reports have described the development of increased amitriptyline concentrations and signs of tricyclic toxicity when amitriptyline was used in combination with fluconazole. Coadministration of fluconazole with nortriptyline, the active metabolite of amitriptyline, has been reported to result in increased nortriptyline levels. Due to the risk of amitriptyline toxicity, consideration should be given to monitoring amitriptyline levels and making dose adjustments as may be necessary.

Anticoagulants (CYP2C9 substrate): Concomitant intake of fluconazole during warfarin treatment has been shown to prolong the prothrombin time up to 2-fold. This is likely due to an inhibition of warfarin metabolism via CYP2C9. The prothrombine time must be closely monitored in patients on treatment with coumarin derivatives.

Benzodiazepines (CYP3A4 substrate): Concomitant intake of fluconazole 400 mg and midazolam 7.5 mg orally increased the midazolam AUC and half-life 3.7- fold and 2.2-fold, respectively. Fluconazole 100 mg daily given concurrently with triazolam 0.25 mg orally increased the triazolam AUC and half-life 2.5-fold and 1.8-fold, respectively. Potentiated and prolonged effects of triazolam have been observed at concomitant treatment with fluconazole. If it is necessary to treat patients with a benzodiazepine concomitantly with fluconazole, a reduction of the benzodiazepine dose should be considered, and the patients should be closely monitored.

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

Carbamazepine (CYP3A4 substrate): Due to the CYP3A4-inhibiting effect of fluconazole concomitant treatment with carbamazepine may lead to increased plasma levels of carbamazepine. The literature includes reports that document increased undesirable effects described for carbamazepine e. g. vertigo, unsteady gait and diplopia. For this reason, the carbamazepine plasma concentration should be checked if such symptoms occur and the dose be reduced if necessary.

Celecoxib (CYP2C9 substrate): In a clinical study, concomitant treatment with Fluconazole 200 mg daily and celecoxib 200 mg resulted in an 68 % and 134 % increase in celecoxib Cmax and AUC, respectively. The interaction is believed to be due to inhibition of cytochrome P450 2C9 metabolism of celecoxib. Halving the Celecoxib dose is recommended to patients concurrently treated with fluconazole.

Cyclosporin (CYP 3A4 substrate): Clinically significant interactions with cyclosporin have been shown at fluconazole doses of 200 mg and higher. In a pharmacokinetic study with renal transplant patients receiving fluconazole200 mg daily and cyclosporin 2.7 mg/kg/day, there was a 1.8-fold increase in cyclosporin AUC and a 55 % decrease in clearance. It is recommended to follow the cyclosporin plasma concentrations in patients on treatment with fluconazole.

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

Halofantrin (CYP3A4 substrate): Drugs that inhibit CYP3A4 lead to an inhibition of halofantrine metabolism.

HMG-CoA reductase inhibitors (CYP2C9 or CYP3A4 substrates): The risk of myopathy is increased when fluconazole is administered concurrently with HMG-CoA reductase inhibitors that are metabolised via CYP3A4, such as atorvastatin and simvastatin, or via CYP2C9, such as fluvastatin. Up to 200 % individual increases in the area under the curve (AUC) of
Fluconazole 50, 100, 150 and 200 mg Capsules

Fluconazole may occur as a result of the interaction between fluvalastatin and fluconazole. Caution is warranted if concurrent administration of fluconazole and HMG-CoA reductase inhibitors is deemed necessary. The combination may require a dose reduction of the HMG-CoA reductase inhibitors. Patients should be monitored for signs and symptoms of myopathy or rhabdomyolysis and creatine kinase (CK) levels. HMG-CoA therapy should be discontinued if CK levels show a marked increase, or if myopathy or rhabdomyolysis is diagnosed or suspected.

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

Oral contraceptives: Two pharmacokinetic studies have been performed with a combined oral contraceptive and multiple dosing of fluconazole. 50 mg fluconazole did not influence any of the hormone concentrations, but 200 mg daily increased AUC of ethinyloestradiol and levonorgestrel with 40 and 24 %, respectively. Thus, it is hardly likely that multiple dosing of fluconazole at these doses has an influence on the effect of the combined oral contraceptive.

Phenytoin (CYP2C9 substrate): Intake of fluconazole 200 mg concomitantly with phenytoin 250 mg intravenously increased the phenytoin AUC by 75 % and Cmin by 128 %. If it is necessary to administer both substances concomitantly, the phenytoin concentration must be controlled, and the phenytoin dose adjusted, in order to avoid toxic concentrations.

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

Rifabutine (CYP3A4 substrate): Reports about interaction with administration of fluconazole concomitantly with rifabutine have appeared, leading to increased serum levels of rifabutine. Uveitis in patients treated concomitantly with fluconazole and rifabutine has been reported. Patients who receive rifabutine and fluconazole concomitantly must be closely followed.

Sulphonyl urea (CYP2C9 substrate): It has been demonstrated that fluconazole prolongs the plasma half-life of concomitantly administered sulphonyl urea (chlorpropamide, glibenclamide, glipizide and tolbutamide) in healthy volunteers. Fluconazole and oral sulphonyl urea derivatives may be used concomitantly to diabetics, but the possibility of development of hypoglycaemia must be kept in mind and blood glucose levels closely monitored.

Tacrolimus and sirolimus (CYP3A4 substrates): Concomitant intake of fluconazole and tacrolimus 0.15 mg/kg b. i. d. increased tacrolimus Cmin 1.4 and 3.1-fold with fluconazole doses of 100 mg and 200 mg, respectively. Renal toxicity has been reported in patients concomitantly receiving fluconazole and tacrolimus. Although no interaction studies have been conducted with fluconazole and sirolimus, a similar interaction as with tacrolimus might be expected. Patients who receive tacrolimus or sirolimus and fluconazole concomitantly must be closely monitored for tacrolimus/sirolimus plasma levels and toxicity.

Theophylline: Intake of fluconazole 200 mg for 14 days resulted in 18 % decrease in the mean plasma clearance of theophylline. Patients on treatment with high doses of theophylline or with other reason to be at increased risk of theophylline toxicity should be carefully observed during fluconazole therapy, and the theophylline dose should be adjusted as necessary.
Trimetrexate: Fluconazole may inhibit the metabolism of trimetrexate, leading to increased trimetrexate plasma concentrations. If the combination cannot be avoided, trimetrexate serum levels and toxicity should be closely monitored.

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

Pharmacodynamic interactions
Medicinal products that prolong QT interval: Case reports indicate that fluconazole might have the potential to induce QT prolongation leading to serious cardiac arrhythmia. Patients treated concomitantly with fluconazole and other drugs that prolong QT interval should be carefully monitored, since an additive effect cannot be excluded.

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

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

4.6 Pregnancy and lactation

Pregnancy
Data from several hundred pregnant women treated with standard doses (below 200 mg/day) of fluconazole, administered as a single or repeated dose during the first trimester, do not indicate undesirable effects on the foetus.

There are reports on multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in children whose mothers were treated for 3 months or longer with high doses (400–800 mg/day) of fluconazole for coccidioidal mycosis. The relationship between these effects and fluconazole is unclear.

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

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

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

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

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

Organ systems
General
Uncommon
>1/1,000, <1/100
fatigue, malaise, asthenia, fever

Central and Peripheral Nervous System
Common >1/100, <1/10
headache

Uncommon
>1/1,000, <1/100
convulsions, dizziness, paresthesia, tremor, vertigo

Skin and Appendages
Common >1/100, <1/10
rash

Uncommon
>1/1,000, <1/100
pruritus

Rare
>1/10,000, <1/1,000
exfoliative skin disorder
(Stevens-Johnson syndrome)

Gastrointestinal
Common >1/100, <1/10
nausea and vomiting
abdominal pain, diarrhoea

Uncommon
>1/1,000, <1/100
anorexia, constipation, dyspepsia, flatulence

Musculoskeletal
Uncommon >1/1,000, <1/100
myalgia

Autonomic Nervous System
Uncommon >1/1,000, <1/100
dry mouth, increased sweating

Psychiatric
Uncommon
>1/1,000, <1/100
insomnia, somnolence

Liver and Biliary System
Common
>1/100, <1/10
 Clinically significant increase of AST, ALT and alkaline phosphatase

Uncommon
>1/1,000, <1/100
cholestasis, hepatocellular damage, jaundice Clinically significant
Uncommon
>1/1,000, <1/100
increase of total bilirubin,

Rare
>1/10,000, <1/1,000
hepatic necrosis

**Special Senses**
Uncommon
>1/1,000, <1/100
taste perversion

**Hematopoietic and Lymphatic**
Uncommon
>1/1,000, <1/100
anaemia

Immunologic

Rare
>1/10,000, <1/1,000
anaphylaxis

Adverse clinical events were reported more frequently in HIV infected patients (21 %) than in non-HIV infected patients (13 %). However, the patterns of adverse events in HIV infected and non-HIV infected patients were similar.

In addition, the following adverse events have occurred under conditions where a causal association is uncertain (e.g. open trials, during post-marketing experience):

**Organ systems**

**Cardiac**
Rare
>1/10,000, <1/1,000
ventricular arrhythmia (QT-prolongation, torsade de pointes)

**Central and Peripheral Nervous System**
Rare
>1/10,000, <1/1,000
seizures

**Skin and Appendages**
Rare
>1/10,000, <1/1,000
alopecia

Very rare
<1/10,000
exfoliative skin disorder (Stevens-Johnson syndrome and toxic epidermal necrolysis), erythema exudativum multiforme

**Liver and Biliary System**
Rare
>1/10,000, <1/1,000
hepatic failure
hepatitis
hepatic necrosis

Immunologic

Very rare
<1/10,000
anaphylaxis, angioedema, face oedema and pruritus, fixed drug eruption, urticaria, acute generalised exanthematous pustulosis

**Hematopoietic and Lymphatic**
Rare
>1/10,000, <1/1,000
leukopenia, including neutropenia and agranulocytosis, thrombocytopenia

**Metabolic**
Rare
>1/10,000, <1/1,000
Hypercholesterolemia, hypertriglyceridemia, hypokalemia

**4.9 Overdose**
In case of overdosing the treatment is symptomatic with supporting measures and gastric lavage, if necessary. Fluconazole is mainly excreted in the urine. Forced volume diuresis will probably increase the elimination rate. Haemodialysis for 3 hours decreases the plasma levels with approx. 50 %.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**
Pharmacotheerapeutic Group
Antimycotics for systemic use, triazole derivatives

ATC code: J02AC01

Fluconazole is a triazole derivative with fungistatic effect, which specifically inhibits the synthesis of the fungi’s ergosterol, which is believed to lead to defects in the cell membrane. Fluconazole is highly specific for fungal cytochrome P-450 enzymes. Doses of fluconazole 50 mg daily for 28 days have not been shown to influence serum levels of testosterone in men or the steroid concentration in fertile women.

The spectrum of application includes a number of pathogens including *Candida albicans* and non-*Candida albicans* species, *Cryptococcus* spp and dermatophytes. *Candida krusei* is resistant to fluconazole. Forty percent of *Candida glabrata* are primarily resistant to fluconazole. Infections caused by Aspergillus-species should not be treated with fluconazole.

**5.2 Pharmacokinetic properties**
Absorption: Fluconazole is well absorbed after oral intake. The absolute bioavailability is above 90 %. The oral absorption is not affected by concomitant food intake. The maximum fasting plasma concentration is reached 0.5–1.5 hours after dose intake. 90 % of the steady-state level is reached 4–5 days after dosing once daily.

Plasma concentration is proportional to the dose. After administration of 200 mg of fluconazole, Cmax is around 4.6 mg/l and plasma concentrations at steady-state after 15 days are around 10 mg/l. After administration of 400 mg of fluconazole, Cmax is around 9 mg/l and plasma concentrations at steady-state after 15 days are around 18 mg/l.

Intake of a double dose on day 1 results in plasma concentrations of approx. 90 % of steady-state on day 2.

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

The concentration in saliva corresponds to the plasma concentration. In patients with fungal meningitis the concentration of fluconazole in the cerebrospinal fluid is approx. 80 % of the corresponding plasma concentration.
In stratum corneum, epidermis-dermis and in exocrine sweat higher concentrations of fluconazole are reached compared to those in serum. Fluconazole is accumulated in stratum corneum. At a dose of 150 mg once weekly the concentration of fluconazole in stratum corneum was after 2 doses 23.4 μg/g and 7 days after the second dosing it was still 7.1 μg/g.

Elimination: Fluconazole is mainly renally excreted. Approx. 80 % of the taken dose is excreted in the urine in non-metabolized form. Fluconazole clearance is proportional to the creatinine clearance. Circulating metabolites have not been demonstrated.

The half-life in plasma is approximately 30 hours.

Children eliminate fluconazole more rapidly than adults do. The half-life in children and adolescents of 5–15 years is between 15.2–17.6 hours.

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose monohydrate,
Gelatin,
Maize starch,
Magnesium stearate,
Sodium lauril sulphate,
Colloidal silicon dioxide,
Titanium dioxide (E 171)

printing ink:
Shellac,
Black iron oxide (E 172),
Propylene glycol
Indigo carmine (E 132)
Ponceau 4R (E 124)

6.2 Incompatibilities
No incompatibilities are known to date.

6.3 Shelf life
The shelf life is 3 years.

6.4 Special precautions for storage
Do not store above 25 °C.

6.5 Nature and contents of container
The hard capsules are packed in PVC white, opaque/aluminium blisters and inserted into a carton.

Packages containing
Fluconazole 200 mg Capsules:
7, 10, 14, 20, 30, 50 and 100 capsules, hard

Not all pack sizes may be marketed.
6.6 Special precautions for disposal
None

7 MARKETING AUTHORISATION HOLDER
Roger A Oakes Limited,
Allstoe House, Church Lane,
Greetham, Rutland,
LE15 7NF, United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)
Fluconazole 200 mg Capsules
PL 32019/0020

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
29/10/2008

10 DATE OF REVISION OF THE TEXT
29/10/2008
Read all of this leaflet carefully before you start taking this medicine.

• Keep this leaflet. You may need to read it again.
• If you have any further questions, ask your doctor or pharmacist.
• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
• If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. What Fluconazole 50, 100, 150, 200 mg is and what it is used for
2. Before you take Fluconazole 50, 100, 150, 200 mg
3. How to take Fluconazole 50, 100, 150, 200 mg
4. Possible side effects
5. How to store Fluconazole 50, 100, 150, 200 mg
6. Further information

What Fluconazole 50, 100, 150, 200 mg is and what it is used for

Fluconazole 50, 100, 150, 200 mg is used in:

Fungal infections caused by yeast fungi. In particular:
• Fungal infections caused by yeast fungi of the genus Candida affecting internal organs including:
  - fungal detection in blood
  - Candida pathogens in the urine
  - Candida spread in one or more organs
  - other candidal infections penetrating the body
  - potentially life-threatening especially in risk patients, such as infections of the peritoneum, lung and urinary tract.
• Fluconazole 50, 100, 150, 200 mg can be taken by patients with cancer diseases, patients in intensive care units or as treatment to artificially suppress the immune system.

Infection of the meninges by the yeast fungus Cryptococcus neoformans. Immunocompromised patients (e.g. with AIDS or after organ transplantation) may also be treated. Fluconazole 50, 100, 150, 200 mg is also indicated as a treatment attempt to prevent cryptococcal meningitis in AIDS patients.

Fungal infections of superficial mucosa caused by Candida pathogens such as:
• recurrent affecting mouth, pharynx and gutt
  - chronic infections of the oral cavity in patients with dentures in whom dental hygiene or topical measures are insufficient
  - infections of the upper respiratory tract mucosa without lung involvement.

Prophylaxis of candidiasis in patients with malignancies during chemotherapy or radiotherapy and in immunocompromised patients (e.g. in AIDS)

Microscopically confirmed fungal infections of the skin including fungal diseases of the body, of the lower legs, athlete's foot and Phlyctenis versicolor and/or positive cultures and in cases where systemic treatment should be considered.

Acute and recurrent vaginal fungal infections caused by the yeast fungus Candida which do not respond to local treatment.

Fluconazole, the active substance in this medicine belongs to the substance group of triazol derivatives.

Pregnancy and breast-feeding

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

Pregnancy
If a treatment over one week is indicated, pregnancy should be avoided in women of childbearing potential by means of appropriate contraceptive measures.
Fluconazole doses of up to 4 capsules daily, and a therapy lasting up to one week should only be used during pregnancy if absolutely necessary. Fluconazole doses higher than 4 capsules daily, or a treatment longer than one week may only be in life-threatening cases.

Breast-feeding
Fluconazole passes into mother's milk and reaches concentrations lower than those in blood.
Breast-feeding can be continued after single use of a standard dose of 4 capsules, "50 mg of fluconazole or less. Breast-feeding is advised against after repeated use or more than 4 capsules daily".

Fluconazole 100 mg Capsules:

Pregnancy
If a treatment over one week is indicated, pregnancy should be avoided in women of childbearing potential by means of appropriate contraceptive measures.
Fluconazole doses of up to 2 capsules daily, and a therapy lasting up to one week should only be used during pregnancy if absolutely necessary. Fluconazole doses higher than 2 capsules daily, or a treatment longer than one week may only be in life-threatening cases.

Breast-feeding
Fluconazole passes into mother's milk and reaches concentrations lower than those in blood.
Breast-feeding can be continued after single use of a standard dose of 2 capsules, "100 mg of fluconazole or less. Breast-feeding is advised against after repeated use or more than 2 capsules daily".

Fluconazole 150 mg Capsules:

Pregnancy
If a treatment over one week is indicated, pregnancy should be avoided in women of childbearing potential by means of appropriate contraceptive measures.
Fluconazole doses of up to 200 mg*, and a therapy lasting up to one week should only be used during pregnancy if absolutely necessary. Fluconazole doses higher than 200 mg* or a treatment longer than one week may only be in life-threatening cases.
Do not take Fluconazole 50, 100, 150, 200 mg
- If you are allergic (hypersensitive) to fluconazole, to azoles or to any of the other ingredients of Fluconazole 50, 100, 150, 200 mg.
- Concomitantly with medicines which lead to deviations of heart rhythm and are also metabolised via the enzyme system CYP3A4, such as cisapride, astemizole, terfenadine, pimozone and quinidine. See also “Take special care with Fluconazole 50, 100, 150, 200 mg” and “Taking other medicines”.

Take special care with Fluconazole 50, 100, 150, 200 mg
- If your liver values deteriorate during fluconazole treatment, your doctor should monitor you carefully and discontinue the therapy as soon as signs indicating liver damage occur. The alterations are usually reversible.
- Fluconazole should be used with caution if you are concomitantly receiving medicines that influence heart rhythm and if you are prone to arrhythmias. Electrolyte disorders such as lowered potassium, magnesium or calcium level should be corrected prior to fluconazole treatment.
- Concomitant use with the active substance halofantrine is not recommended. See also “Taking other medicines”.
- If you develop a kind of skin peeling or skin rash disorder during fluconazole treatment, the therapy with Fluconazole 50, 100, 150, 200 mg should discontinued or carefully monitored by the doctor.
- If your kidney function is severely impaired, the dose must be reduced accordingly. See also 3. “How to take Fluconazole 50, 100, 150, 200 mg”.

Children
Due to limited knowledge, Fluconazole 50, 100, 150, 200 mg should only be used in children under 16 years of age if no other alternative treatment is available.

Elderly patients, over 65 years
The dosage should be adjusted in patients with impaired kidney function, according to chapter 3.

Taking Fluconazole 50, 100, 150, 200 mg with other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.
It is important to inform your doctor if you are taking the following medicines:
- Terfenadine, a medicine for allergy treatment; astemizole, a medicine for allergy treatment; cisapride, a medicine used in intestinal disorders.
Concomitant use of fluconazole with any of these medicines can lead to increased blood levels resulting in the risk of severe cardiac arrhythmias. Due to the serious risk of cardiac arrhythmias and possibly fatal cardiac arrest, astemizole and cisapride must not be used concomitantly with fluconazole. Terfenadine and fluconazole doses of 400 mg or more must also not be administered concomitantly. For fluconazole doses below 400 mg your doctor should monitor you closely.

Breast-feeding
Fluconazole passes into mother's milk and reaches concentrations lower than those in blood. Breast-feeding can be continued after single use of a standard dose of 200 mg of fluconazole or less. Breast-feeding is advised against after repeated use or more than 200 mg* fluconazole daily.

Fluconazole 200 mg Capsules:

Pregnancy
If a treatment over one week is indicated, pregnancy should be avoided in women of child bearing potential by means of appropriate contraceptive measures. Fluconazole doses of up to 1 capsule daily*, and a therapy lasting up to one week should only be used during pregnancy if absolutely necessary. Fluconazole doses higher than 1 capsule daily*, or a treatment longer than one week may only be in life-threatening cases.

Breast-feeding
Fluconazole passes into mother's milk and reaches concentrations lower than those in blood. Breast-feeding can be continued after single use of a standard dose of 1 capsule, 200 mg of fluconazole or less. Breast-feeding is advised against after repeated use or more than 1 capsule, daily*.

Driving and using machines
This medicine has no or negligible influence on the ability to drive and use machines. However dizziness or seizures may occur. See chapter 4.

Important information about some of the ingredients of Fluconazole 50, 100, 150, 200 mg
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Fluconazole 200 mg Capsules:
The colouring agent ponceau 4R may cause allergic reactions.

Always take Fluconazole 50, 100, 150, 200 mg exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Method of administration
Always take the capsules, hard unchewed with a glass of water at the same time daily independent of meals. Switching from intravenous to oral administration or vice versa does not require any alteration in the daily dose. Both forms are available. The treatment can be initiated oral or via infusion. The dosage and duration of treatment depends on the type and severity of the infection as well as on your age, bodyweight and kidney function. The following information applies where your doctor has not prescribed Fluconazole 50, 100, 150, 200 mg in another dosage regime. Please follow these directions for use, otherwise it will not have the desired effects.

Fungal infections caused by yeast fungi of the genus Candida affecting internal organs
First day: 8 capsules, once daily*
Follow up treatment: 4 capsules, once daily*.
If required, the dose may be increased to 8 capsules.
The effect of the following medicines may be influenced by concomitant fluconazole use:

- Alfentanil, an anaesthetic
- Amitriptyline, a medicine for depression treatment
- Amphotericin B, a medicine against fungal infections
- Anticoagulants of the coumarin type such as phenprocoumon and warfarin
- Benzodiazepines such as midazolam and triazolam
- Calcium channel blockers such as nilidine, isradipine, nicardipine, amiodipine and felodipine
- Carbamazepine, a medicine for epilepsy treatment
- Celecoxib, an anti-inflammatory medicine
- Cyclosporin, a medicine to suppress the defence system
- Didanosine, a medicine for HIV treatment
- Halofantrine, a medicine for malaria treatment
- Medicines to lower elevated cholesterol levels such as atorvastatin, simvastatin and fluvastatin. Concomitant use can increase the risk of alterations in skeletal muscles.
- Losartan, a medicine for the treatment of high blood pressure
- Oral contraceptives
- Phenyleptin, a medicine for epilepsy treatment
- Prednisone, a cortisol
- Pimozide, a medicine for psychoses treatment, and quinidine, a medicine for cardiac arrhythmias treatment. Fluconazole is an inhibitor of the enzymes CYP-2C9 and -3A4. In addition to the interactions described later, when taking fluconazole concomitantly the blood levels may be increased by other medicines metabolised by these enzymes (e.g. also ergotalkaloids). This combination should therefore be used with caution, and patients should be carefully monitored until 4–5 days after therapy ends.
- Rifabutin, a medicine for tuberculosis treatment
- Sugar lowering agents of the sulphonylurea type such as chlorpropamide, glibenclamide, glipizide and tolbutamide
- Tacrolimus and sirolimus, medicines to suppress the defence system
- Theophylline, a medicine for asthma treatment
- Trimetrexate, an anticancer medicine
- Zidovudine, a medicine HIV treatment

Various medicines for the treatment of excessive acid content in the stomach or radiotherapy do not significantly influence the uptake of fluconazole from the gastrointestinal tract.

Taking Fluconazole 50, 100, 150, 200 mg with food and drink?

No significant influence is known.

Once daily. Your doctor may decide the duration or administration. It is recommended that treatment is continued until the laboratory tests exclude the fungal infection.

- Infection of the meninges caused by yeast fungus Cryptococcus neoformans

Treatment of meningitis:
- First day: 8 capsules, once daily*
- Follow up treatment: 4 capsules, once daily*.
- Dosage should be increased to 8 capsules, once daily* for the entire duration of treatment, as required.
- Therapy duration: generally 6–8 weeks.

Prophylaxis of meningitis:
- After cryptococcal meningitis treatment is terminated in AIDS patients as a therapeutic prevention method. This should be carried out with a dose of 2–4 capsules, once daily* while laboratory values are monitored.

- Candida pathogens in urine
  1 capsule, once daily.
  In severe cases, the dose may be increased to 2 capsules, once daily*.
  Therapy duration: 14–30 days.

- Fungal infections of superficial mucosa
  Recurrent fungal infections in mouth and pharynx: 1 capsule, once daily.
  In severe cases, especially in cases of recurrence, the dose may be increased to 2 capsules, once daily*.
  Therapy duration: 7–14 days.
  In case of severely suppressed immune system, the duration of treatment may be prolonged.

- Recurrent infection of the gut: 1 capsule, once daily.
  In severe cases, especially in cases of recurrence, the dose may be increased to 2 capsules, once daily*.
  Therapy duration: 14–30 days.

- Chronic-infections in patients with dentures: 1 capsule, once daily.
  In addition, dental hygiene should be ensured and local disinfectant measures carried out.
  Therapy duration: 14 days.

- Mucosa infection of the upper respiratory tract without lung involvement: 1 capsule, once daily.
  In severe cases of the disorder, the dose may be increased to 2 capsules, once daily*.
  Therapy duration: 14–30 days.
Prophylaxis of candidiasis:
In patients with malignancies during chemotherapy or radiotherapy and in patients with a suppressed immune system (e.g. in AIDS or chemotherapy).
1. 1 capsule, once daily to prevent candidiasis in patients with a suppressed immune system.
2. In patients during chemotherapy or radiotherapy if systemic candidiasis is to be expected e.g. due to severe or prolonged reduction in the number of neutrophil white blood cells, administration of 8 capsules, once daily* is advisable. Administration of fluconazole should be initiated 2-3 days prior to the anticipated onset of this cell reduction and continued a further 7 days after the neutrophils number has increased to more than 1000 cells per µl.

- Fungal infections of the skin:
  - Fungal infections of the body and lower legs, 
Pityriasis versicolor:
    1 capsule, once daily or 3 capsules, once weekly*. 
    Therapy duration: 2-4 weeks.
  - Athlete’s foot infection:
    1 capsule, once daily.
    Therapy duration: up to 6 weeks.
  - Vaginal fungal infections
    3 capsules*, are taken as a single dose.

Fluconazole 100 mg Capsules:
- Fungal infections caused by yeast fungi of the genus Candida, affecting internal organs:
  First day: 4 capsules, once daily* 
  Follow up treatment: 2 capsules, once daily*.
  If required, the dose may be increased to 4 capsules, once daily*.
  Your doctor will decide the duration of administration. It is recommended that treatment is continued until the laboratory tests exclude the fungal infection.

- Infection of the meninges caused by yeast fungus Cryptococcus neoformans
  Treatment of meningitis:
  First day: 4 capsules, once daily*
  Follow up treatment: 2 capsules, once daily*.
  Dosage should be increased to 4 capsules, once daily* for the entire duration of treatment, as required.
  Therapy duration: generally 6-8 weeks.

- Prophylaxis of meningitis:
  After cryptococcal meningitis treatment is terminated in AIDS patients as a therapeutic prevention method. This should be carried out with a dose of 1-2 capsules, once daily* while laboratory values are monitored.

- Candida pathogens in urine
  50 mg fluconazole once daily*.
  In severe cases, the dose may be increased to 1 capsule, Fluconazole 100 mg once daily*.
  Therapy duration: 14-30 days.

- Fungal infections of superficial mucosae
  Recurrent fungal infections in mouth and pharynx:
  50 mg fluconazole once daily*.
  In severe cases, especially in cases of recurrence, the dose may be increased to 1 capsule, Fluconazole 100 mg once daily*.
  Therapy duration: 7-14 days.
  In case of severely suppressed immune system, the duration of treatment may be prolonged.

  Recurrent infection of the gutt: 
  50 mg fluconazole once daily*.
  In severe cases, especially in cases of recurrence, the dose may be increased to 1 capsule, Fluconazole 100 mg once daily*.
  Therapy duration: 14-30 days.

- Chronic-infections in patients with dentures:
  50 mg fluconazole once daily*.
  In addition, dental hygiene should be ensured and local disinfectant measures carried out.
  Therapy duration: 14 days.

- Mucosal infection of the upper respiratory tract without lung involvement:
  50 mg fluconazole once daily*.
  In severe cases of the disorder, the dose may be increased to 1 capsule, Fluconazole 100 mg once daily*.
  Therapy duration: 14-20 days.

The evaluation of side effects is generally based on the following frequency classification:
Side effects can be:
- common more than 1 in 100 patients, but less than 1 in 10 patients
- uncommon more than 1 in 1000 patients, but less than 1 in 100 patients
- rare more than 1 in 10,000 patients, but less than 1 in 1000 patients
- very rare less than 1 in 10,000 patients

Blood and the lymphatic system disorders
Uncommon:
- anaemia
Rare:
- blood count alterations such as reduction in number of white blood cells and blood platelets

Imune system disorders
Rare:
- severe generalised allergic reactions
Very rare:
- skin swelling
- facial swelling
- toxic skin rash caused by medicines
- nettle rash
- pustules

Metabolism and nutrition disorders
Rare:
- increased level of cholesterol in blood
- increased level of triglycerides in blood
- reduced level of potassium in blood

Psychiatric disorders
Uncommon:
- insomnia
- sleeplessness

Nervous system disorders
Common:
- headache
Unc uncommon:
- seizures
- drowsiness
- sensation of creeping
- trembling
- dizziness
- dry mouth
- increased sweating
- changed taste perception

Cardiac disorders
Rare:
- arrhythmia

Gastrointestinal disorders
Common:
- nausea
- vomiting
- abdominal pain
- diarrhoea
Unc uncommon:
- loss of appetite
- constipation
- indigestion
- flatulence

Hepato-biliary disorders
Common:
- increase in certain liver values
Unc uncommon:
- congestion of bile liquid
- liver cell damage
- jaundice
- increase in total bilirubin
Rare:
- liver cell destruction
- liver failure
- inflammation of the liver

Skin and subcutaneous tissue disorders
Common:
- skin rash
Unc uncommon:
- itching
Rare:
- severe skin disorders with peeling
- hair loss
very rare:
- different forms of skin reddening
Fluconazole 150 mg Capsules:

- **Vaginal fungal infections**
  - 1 capsule, is taken as a single dose.
  - Use of Fluconazole 150 mg is usually restricted to one single dose.

Fluconazole 200 mg Capsules:

- **Fungal infections** caused by yeast fungi of the genus Candida affecting internal organs
  - First day: 2 capsules, once daily
  - Follow up treatment: 1 capsule, once daily.
  - If required, the dose may be increased to 2 capsules, once daily. Your doctor will decide the duration of administration. It is recommended that treatment is continued until the laboratory tests exclude the fungal infection.

- **Infection of the meninges** caused by yeast fungus Cryptococcus neoformans

**Treatment of meningitis**:
- First day: 2 capsules, once daily
- Follow up treatment: 1 capsule, once daily
- Dose should be increased to 2 capsules, once daily for the entire duration of treatment, as required.
- Therapy duration: generally 6–8 weeks.

Use in elderly patients

The usual dose is recommended in elderly patients with no evidence of impaired kidney function. If creatinine clearance is below 50 ml/min, the dose should be adjusted according to the guidelines for patients with impaired kidney function.

Fluconazole 50, 100, 200 mg Capsules:

Use in children if there is no therapeutic alternative

For oral use in children a solution and powder/liquid preparations are available and recommended.

Fluconazole 50, 100, 200 mg should not be used in children under 16 years of age unless no therapeutic alternative is available, as efficacy and safety have not been sufficiently demonstrated. The following doses per kg body weight are recommended for children:

- **Mucosal candidiasis**:
  - First day: 6 mg fluconazole per kg once daily.
  - Follow up treatment: 3 mg fluconazole per kg daily.

- **Systemic candidial and cryptococcal infections**:
  - Recommended dose: 6–12 mg fluconazole per kg daily, depending on the severity of the infection.

- **Prophylaxis** of candidal infections in children with a reduced number of white blood cells:
  - Recommended dose: 3–12 mg fluconazole per kg daily, depending on the extent and duration of neutropenia (see dose in adults).

In children with impaired kidney function, the dose should be adjusted according to the guidelines for adults (see below), depending on the degree of kidney function impairment.

Adults and children with impaired kidney function

Dosage adjustment is not required for single dose administration.

If several doses of fluconazole are administered – patients with impaired kidney function should receive an initial dose of 1–8 capsules, once on the first day. Thereafter, your doctor should adjust the dosage for the relevant indication according to your creatinine clearance.

**Fluconazole 100, 150, 200 mg Capsules**:

Dosage adjustment is not required for single dose administration.

If several doses of fluconazole are administered – patients with impaired kidney function should receive an initial dose of 50–400 mg fluconazole once on the first day. Thereafter, your doctor should adjust the dosage for the relevant indication according to your creatinine clearance. Please consult your doctor or pharmacist if you have the impression that the effect of Fluconazole 50, 100, 150, 200 mg Capsules may be reduced.

**Musculoskeletal disorders**

Uncommon:
- muscle pains

**General disorders**

Uncommon:
- exhaustion
- malaise
- weakness
- fever

Side effects were observed more commonly in HIV-infected patients (21 %) than in non-HIV-infected patients (13 %). However, the type of side effects was comparable in both patient groups.

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

**HOW TO STORE FLUCONAZOLE 50, 100, 150, 200 MG**

Keep out of the reach and sight of children.

Do not use Fluconazole 50, 100, 150, 200 mg after the expiry date which is stated on the carton and the blister. The expiry date refers to the last day of that month.

Do not store above 25 °C. Keep container always in the outer carton.

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

**FURTHER INFORMATION**

What Fluconazole 50, 100, 150, 200 mg contains

- The active substance is Fluconazole.
- Each capsule, hard contains 50, 100, 150, 200 mg fluconazole.
- The other ingredients are lactose monohydrate, gelatin, maize starch, magnesium stearate, sodium lauril sulphate, colloidal silicon dioxide, titanium dioxide (E 171).

In addition for Fluconazole 50, 100, 200 mg Capsules: indigo carmine (E 132)

In addition for Fluconazole 200 mg Capsules: ponceau 4R (E 124)

printing ink: shellac, black iron oxide (E 172), propylene glycol.

What Fluconazole 50, 100, 150, 200 mg looks like and contents of the pack

Fluconazole 50 mg capsules, hard are turquoise on the upper part and white on the lower part.

The capsules, hard are packed in PVC white, opaques/aluminium blisters and inserted into a carton.

Packages containing 1, 3, 7, 10, 14, 20, 28, 30, 42, 50 and 100 capsules.

Fluconazole 100 mg Capsules:

Fluconazole 100 mg capsules, are blue on the upper part and white on the lower part.

The capsules, hard are packed in PVC white, opaques/aluminium blisters and inserted into a carton.

Packages containing 1, 7, 10, 14, 20, 30, 50 and 100 capsules.

Fluconazole 150 mg Capsules:

Fluconazole 150 mg capsules, are white on the upper part and blue on the lower part.

The capsules, hard are packed in PVC white, opaques/aluminium blisters and inserted into a carton.

Packages containing 1 and 2 capsules.
mg is too strong or too weak.

If you take more Fluconazole 50, 100, 150, 200 mg than you should
In every case, consult your doctor, so that he can decide on any measures required.

If you forget to take Fluconazole 50, 100, 150, 200 mg
If you have taken insufficient Fluconazole 50, 100, 150, 200 mg, you can take the forgotten dose on the same day without problems. Do not take a double dose to compensate a forgotten dose.

If you stop taking Fluconazole 50, 100, 150, 200 mg
In order to avoid persistence or recurrence of fungal infections, you should take Fluconazole 50, 100, 150, 200 mg regularly and at the dose and for the duration prescribed by your doctor.

* For this dosage schedule capsules with another strength are available.

4 POSSIBLE SIDE EFFECTS

Like all medicines, Fluconazole 50, 100, 150, 200 mg can cause side effects, although not everybody gets them.

Serious life-threatening effects:
If you develop a serious allergic reaction to this medicine, immediately stop taking this and immediately tell your doctor or go to the casualty department at your nearest hospital because you may need urgent medical attention.

Fluconazole 200 mg Capsules:
Fluconazole 200 mg capsules, are purple on the upper part and white on the lower part.
The capsules, hard are packed in PVC white, opaque/aluminium blisters and inserted into a carton.
Packages containing 7, 10, 14, 20, 30, 50 and 100 capsules.
Not all pack sizes may be marketed.

Marketing Authorisation Holder
Roger Oakes Limited,
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Greetham, Rutland,
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United Kingdom

Manufacturer
Salutas Pharma GmbH
Otto-von-Guericke-Allee 1
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Germany

Product Licence Numbers:
Fluconazole 50mg Capsules: PL 32019/0017
Fluconazole 100mg Capsules: PL 32019/0018
Fluconazole 150mg Capsules: PL 32019/0019
Fluconazole 200mg Capsules: PL 32019/0020

This leaflet was last approved in 05/2007.
 Fluconazole 50mg Capsules

Each hard capsule contains 50mg fluconazole

Use as directed by your doctor.

For further information, read the enclosed leaflet.

Do not store above 25°C.

For oral use only.

Also contains lactose.

Keep out of the reach and sight of children.

POM

Attach dispensing label here

Product licence holder:
Roger A Oakes Limited,
Allstoe House, Church Lane,
Greetham, Rutland,
LE15 7NF, United Kingdom
UKPAR Fluconazole 50, 100, 150 and 200mg Capsules

Fluconazole 150mg Capsules
Each hard capsule contains 150mg fluconazole

Use as directed by your doctor.
For further information, read the enclosed leaflet.
Do not store above 25°C.
For oral use only.
Also contains lactose.
Keep out of the reach and sight of children.

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