

**FLUCONAZOLE 150MG CAPSULES
PL 08137/0120**

UKPAR

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FLUCONAZOLE 150MG CAPSULES
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LAY SUMMARY

On 13th February 2008, the MHRA granted Neolab Limited a Marketing Authorisation (licence) for the medicinal product Fluconazole 150mg Capsules (PL 08137/0120). This is a pharmacy-only medicine (P) for the treatment of infections caused by fungi (including yeasts, such as one called *Candida*).

Fluconazole 150mg Capsules contain the active ingredient fluconazole, which is an antifungal.

This product is considered the same as the original product Diflucan Capsules 150mg (Pfizer Limited) based on the bioequivalence study submitted and no new safety issues arose as a result of this study. No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Fluconazole 150mg Capsules outweigh the risks, hence a Marketing Authorisation has been granted.

FLUCONAZOLE 150MG CAPSULES
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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Fluconazole 150mg Capsules (PL 08137/0120) on 13th February 2008. This is a pharmacy-only medicine (P) for the treatment of vaginal candidiasis, acute or recurrent, and candidal balanitis associated with vaginal candidiasis.

This was submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, claiming essential similarity to the original products Diflucan Capsules 150mg (Pfizer Limited). The reference products have been authorised in the EU since September 1995 and so the 10-year period of data exclusivity has expired.

The product contains the active ingredient fluconazole, one of the triazole class of antifungal agents and a potent selective inhibitor of fungal enzymes involved in the synthesis of ergosterol. This leads to impairment of the correct functioning of the cell membranes, inhibiting growth and other essential actions taking place at the cell surface. High concentrations can be fungicidal.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

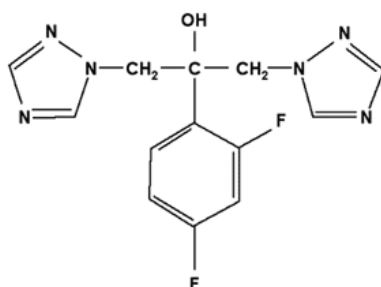
Fluconazole

INN: Fluconazole

Chemical Name: 2-(2,4-difluorophenyl)-1,3-bis-(1H-1,2,4-triazol-1-yl)-2-propanol

CAS No: 86386-73-4

Structure:



Molecular formula: C₁₃H₁₂N₆OF₂

Molecular weight: 306.3

Physical form: A white to almost white crystalline powder

There is no chirality or optical isomerism observed. Three polymorphs of fluconazole have been identified.

Fluconazole is the subject of a European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied by all active substance manufacturers. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the specification. Batch analysis data are provided and comply with the proposed specification.

The active substance is packaged in double polyethylene bags, which are contained in fibreboard drums. Specifications have been provided for all packaging used. All primary packaging complies with current European Directives concerning contact with food.

Based on stability data provided, suitable retest periods have been provided by the active substance manufacturer. Suitable post approval commitments have been given to provide additional stability data as and when it becomes available.

DRUG PRODUCT**Other ingredients**

Other ingredients consist of pharmaceutical excipients, namely lactose, maize starch, colloidal anhydrous silica, talc, sodium lauryl sulphate, capsule shells (composed of gelatin, patent blue [E131] and titanium dioxide [E171]) and printing ink (composed of shellac, propylene glycol and black iron oxide [E172]). Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeial monograph, with the exception of patent blue E131 and the printing ink (which both comply with suitable in-house specifications). Satisfactory certificates of analysis have been provided for all excipients.

With the exception of gelatin and lactose, none of the excipients contain materials of animal or human origin. A satisfactory statement has been provided, stating that lactose is sourced from healthy animals under the same conditions as milk for human consumption. EDQM certificates of suitability have been provided from the supplier of gelatin, showing that it complies with current guidelines concerning the minimising of TSE/BSE transmission.

There were no novel excipients used and no overages stated.

Product Development

Suitable product development data have been provided.

Dissolution and impurity profiles were found to be similar to those for the reference product.

Manufacture

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

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of finished product and the results are satisfactory.

Finished product specification

The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container closure system

The finished product is packaged in blisters composed of aluminium, polyvinylidene chloride and white opaque polyvinylchloride in pack sizes of 1 capsule. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with current EU legislation regarding contact with food.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set with the storage conditions “Do not store above 25 degrees” and “Store in original package”, which are satisfactory.

ADMINISTRATIVE**MAA form**

The MAA form is pharmaceutically satisfactory

Expert report

The pharmaceutical expert report is written by an appropriately qualified person and is satisfactory.

Summary of Product Characteristics (SPC)

The SPC is pharmaceutically satisfactory.

Patient Information Leaflet (PIL)

The PIL is pharmaceutically satisfactory. The marketing authorisation holder has provided a commitment to update the marketing authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 1st July 2008.

CONCLUSIONS

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

The requirements for essential similarity of the proposed and reference products have been met with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.

PRECLINICAL ASSESSMENT

This application is for a product claiming to be generic medicinal product of Diflucan Capsules 150mg (Pfizer Limited), which has been licensed within the EEA for over 10 years.

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

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

Pharmacokinetics – Bioequivalence

An open-label, randomised, two-treatment, two-period, two-sequence, single-dose, crossover study was performed on fasted male volunteers to compare the rate and extent of absorption of Fluconazole 200mg Capsules (Test) versus Diflucan 200mg Capsules (Reference). The study was conducted in accordance with Good Clinical Practice.

Plasma samples were taken pre- and up to 168 hours post dose and pharmacokinetic parameters calculated from these. The main results are presented below:

FLUCONAZOLE (In transformed data)				
	Least Square Mean Values		Ratio T/R	Confidence Interval %
	Test	Reference		
C_{max} (mcg/ml)	6.74	6.15	110%	101-119
AUC_{0-t} (mcg.h/ml)	242.66	238.47	102%	96-108
AUC_{0-∞} (mcg.h/ml)	250.96	249.88	100%	95-106
	Mean			
T_{max} (hours)	2.17	2.46		
T_{1/2} (hours)	32.8	32.5		

Although the mean peak level for the test product was slightly higher than that for the reference product, the AUC values were virtually the same. Likewise the time to peak levels were essentially the same for both products and the calculated half-lives accorded with the values published in the literature. The confidence intervals for C_{max} and AUC_t and AUC_∞ were all within the normal acceptance limits 80–120%.

From these results, bioequivalence is considered to have been shown between Fluconazole 200mg Capsules and Diflucan 200mg Capsules. As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 200mg strength can be extrapolated to the other strength capsules.

EFFICACY

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

SAFETY

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

EXPERT REPORT

The expert report is written by a medically qualified pharmaceutical consultant and is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

This is medically satisfactory and consistent with that for the reference product.

PATIENT INFORMATION LEAFLET (PIL)

This is medically satisfactory and consistent with the proposed SPC.

LABELLING

This is medically satisfactory.

CONCLUSIONS

The applicant appears to have demonstrated bioequivalence. A marketing authorisation should be granted for this product.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT**QUALITY**

The important quality characteristics of Fluconazole 150mg Capsules are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

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

EFFICACY

Bioequivalence has been demonstrated between the applicant's Fluconazole 200mg Capsules and Diflucan 200mg Capsules. As these products meet all the criteria as specified in the Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), the results and conclusions of the bioequivalence study on the 200mg strength can be extrapolated to the other strength capsules.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the reference product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's product and the innovator product are interchangeable. 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.

FLUCONAZOLE 150MG CAPSULES
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STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 17 th March 2003
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 4 th April 2003
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 26 th June 2003, and further information relating to the quality dossiers on 29 th July 2003, 22 nd June 2004 and 13 th January 2006.
4	The applicant responded to the MHRA's requests, providing further information on 28 th July 2003 and 28 th July 2004 for the clinical sections, and again on 6 th November 2003, 28 th July 2004 and 28 th October 2006 for the quality sections.
5	The applications were determined on 10 th December 2007

**FLUCONAZOLE 150MG CAPSULES
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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fluconazole 150 mg Capsule

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 150 mg of the active ingredient fluconazole.

For excipients, see 6.1.

3 PHARMACEUTICAL FORM

Size 1 hard gelatin capsules, blue opaque cap and body: marked with the codes 'FCZ 150' and 'NEO'.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Vaginal candidiasis, acute or recurrent. Candidal balanitis associated with vaginal candidiasis.

4.2 Posology and method of administration

For oral use.

Use in adults

Candidal vaginitis or balanitis: 150 mg single oral dose.

Use in children

Not recommended in children under 16 years.

Use in the elderly

Not recommended in patients aged over 60 years.

Use in patients with impaired renal function

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

Method of administration

Fluconazole capsules should be swallowed whole and may be taken without regard to meals.

4.3 Contraindications

- Patients with known hypersensitivity to fluconazole or to related triazole anti-fungal agents or to any other ingredient in the formulation.
- Patients who are taking cisapride, terfenadine or astemizole (see sections 4.4 and 4.5).
- Patients with congenital or documented acquired QT prolongation.
- Patients who are taking other medicaments that prolong the QT interval such as antiarrhythmics of classes IA and III.
- Patients with electrolyte disturbance, particularly hypokalaemia and hypomagnesaemia.
- Patients with clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency.

4.4 Special warnings and precautions for use

The product is intended for pharmacy availability without prescription and will include a leaflet which will advise the patient:

Do not use this Fluconazole 150 mg Capsule without first asking your pharmacist or doctor if:

- You are under 16 or over 60 years of age.
- You are or have you ever been told that you are allergic to fluconazole or to other drugs of the same type (called triazoles) that are used to treat fungal infections.
- You are allergic to any of the other ingredients in these capsules
- You are taking cisapride, terfenadine or astemizole. Fluconazole must not be taken by people who are taking one of these medicines because there is a risk of a serious rhythm disturbance of the heart.

- You take medicine(s) to control your heart rate or rhythm. These drugs include quinidine, amiodarone, sotalol, disopyramide, but there are many others so check with your doctor or pharmacist before you take fluconazole.
- You have a very slow heart rate or a serious heart rhythm disturbance or heart failure. Also, have you ever been told that you have a long QT interval (a type of heart rhythm disturbance that is found on ECG's).
- You suffer from low levels of potassium or magnesium in your blood.
- You have a serious ongoing illness, such as cancer, or severe problems with your body, liver or kidneys. Fluconazole is particularly likely to cause changes in blood test results in such people.
- You have AIDS. You can still take fluconazole but be aware that people who have AIDS are more likely to develop very severe skin reactions to fluconazole.
- You developed problems with your liver while taking fluconazole previously. If so, you should not take fluconazole to treat vaginal thrush.

Women Only:

- You are pregnant or trying to become pregnant or are breast feeding (see below).
- You have any abnormal or irregular vaginal bleeding or a blood stained discharge.
- You have vulval or vaginal sores, ulcers or blisters.
- You are experiencing lower abdominal pain or burning on passing urine.

Men Only:

- Your sexual partner does not have vaginal thrush.
- You have penile sores, ulcers or blisters.
- You have an abnormal penile discharge (leakage)
- Your penis has started to smell.
- You have pain passing urine.

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

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

In some patients, particularly those with serious underlying diseases such as AIDS and cancer, abnormalities in haematological, hepatic, renal and other biochemical function test results have been observed during multiple-dose treatment with fluconazole but the clinical significance and relationship to treatment is uncertain.

In cases of hepatotoxicity, no obvious relationship to total daily dose of fluconazole, duration of therapy, sex or age of the patient has been observed; the abnormalities have usually been reversible on discontinuation of fluconazole therapy. However, fluconazole should not be given to patients who developed clinical signs or symptoms consistent with liver disease during previous treatment with fluconazole.

Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, during or after treatment with fluconazole. AIDS patients are more prone to the development of severe cutaneous reactions to many medicinal products.

Patients who developed a rash that was considered attributable to fluconazole during previous therapy should not receive fluconazole again, even as single dose therapy.

Lactose intolerance: the 150 mg capsules contain approximately 112 mg of lactose. This amount is not thought likely to cause symptoms in patients with lactose intolerance.

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 (CYP3A4 substrate): Due to the occurrence of serious cardiac dysrhythmias secondary to prolongation of the QTc-interval in patients receiving azole antifungal drugs 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 400mg and 800mg fluconazole daily showed that fluconazole 400mg or more daily significantly increases the plasma level of terfenadine when taken concomitantly. There have been spontaneous case-reports of palpitations, tachycardia, dizziness and chest pain in patients taking concomitant fluconazole and terfenadine. Concomitant treatment with terfenadine and fluconazole is contra-indicated.

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, potentially fatal, cardiac effects.

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 pg/kg intravenously in healthy volunteers increased the alfentanil AUC₁₀ approximately 2-fold and decreased the clearance by 55%, probably through inhibition of CYP3A4. Adjustment of the alfentanil dose 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 may prolong the prothrombin time up to 2-fold. This is likely to be due to an inhibition of warfarin metabolism via CYP2C9. As for other azoles there have been reports of bleeding (bruises, nose bleeding, gastrointestinal bleeding, blood in the urine and faeces) in connection with an increase of prothrombin time in patients concomitantly treated with warfarin. Prothrombin times 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, and also the psychomotor effects. 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 during concomitant treatment with 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.

Celecoxib (CYP2C9 substrate): In a clinical study, concomitant treatment with fluconazole 200 mg daily and celecoxib 200 mg resulted in a 68% and 134% increase in celecoxib C_{max} 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 in patients concurrently treated with fluconazole.

Ciclosporin (CYP3A4 substrate): Clinically significant interactions with ciclosporin 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 ciclosporin 2.7 mg/kg/day, there was an 1.8-fold increase in ciclosporin AUC and a 55% decrease in clearance. However, in another study, multiple dosing with fluconazole 100 mg daily did not influence ciclosporin concentrations in patients after bone marrow transplants. Plasma concentrations of ciclosporin should be monitored during treatment with fluconazole.

Didanosine: Although co-administration of didanosine and fluconazole appears to have little effect on the pharmacokinetics or efficacy of didanosine, the response to fluconazole should be monitored. It may be advantageous to administer fluconazole at some time prior to didanosine.

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 (muscle pain, tenderness or weakness) 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 ethinylestradiol and levonorgestrel by 40 and 24%, respectively. Thus, it is unlikely that multiple dosing of fluconazole at these doses is unlikely to impair the efficacy of combined oral contraceptive pills.

Phenytoin (CYP2C9 substrate): Intake of fluconazole 200 mg concomitantly with phenytoin 250 mg intravenously increased the phenytoin AUC by 75% and C_{min} by 128%. If it is necessary to administer both substances concomitantly, the plasma concentration of phenytoin 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 was likely to have caused an increase in CYP3A4 activity, leading to an increase in the degradation of prednisone. Patients receiving long-term therapy with fluconazole and prednisone should be closely monitored for signs of adrenal insufficiency when fluconazole is withdrawn.

Rifabutin (CYP3A4 substrate): There have been reports that concomitant administration of fluconazole and rifabutin can lead to increased serum levels of rifabutin. Uveitis in patients treated concomitantly with fluconazole and rifabutin has been reported. Patients who receive rifabutin and fluconazole concomitantly must be closely followed.

Sulphonylureas (CYP2C9 substrate): It has been demonstrated that fluconazole prolongs the plasma half-life of concomitantly administered sulphonylurea drugs (chlorpropamide, glibenclamide, glipizide and tolbutamide) in healthy volunteers. Fluconazole and oral sulphonylurea derivatives may be used concomitantly in diabetics, but the possibility of development of hypoglycaemia must be kept in mind.

Tacrolimus and sirolimus (CYP3A4 substrates): Concomitant intake of fluconazole and tacrolimus 0.15 mg/kg b.i.d. increased tacrolimus C_{min} 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 (anaemia, leucopenia, thrombocytopenia, hypokalaemia, diarrhoea).

Theophylline: In a placebo controlled interaction study, intake of fluconazole 200 mg for 14 days resulted in an 18% decrease in the mean plasma clearance of theophylline. Patients being treated with high doses of theophylline or with any other reason to be at increased risk of theophylline toxicity should be observed carefully during concomitant treatment with fluconazole and the dose of theophylline must be adjusted as necessary.

Trimetrexate: Medicaments such as fluconazole that inhibit the P450 enzyme system may cause interactions that increase trimetrexate plasma concentrations. If it is not possible to avoid concomitant administration of trimetrexate and fluconazole, trimetrexate serum levels and trimetrexate toxicity (bone marrow suppression, renal and hepatic dysfunction, and gastrointestinal ulceration) must be monitored carefully.

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 glucuronidation. Patients receiving this combination must be monitored for zidovudine related side-effects.

Medicinal products affecting the metabolism and/or excretion 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 by 40%. An effect of this size should not necessitate a change in the fluconazole dose regimen in patients who are concomitantly treated with diuretics, although the prescriber should bear this in mind.

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

Pharmacodynamic interactions

Medicinal products that prolong QT interval: There have been cases reported in which fluconazole might have contributed to QT prolongation leading to serious cardiac arrhythmias. 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.

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**

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

Fluconazole should not be used for the treatment of vaginal candidiasis during pregnancy.

Use during lactation

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

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

Experience with fluconazole indicates that therapy is unlikely to impair a patient's ability to drive or use machinery. However, when driving or operating machines it should be taken into account that occasionally dizziness or seizures may occur.

4.8 **Undesirable effects**

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

Central and Peripheral Nervous System:

Headache.

Dermatological:

Skin rash, accompanied by eosinophilia and pruritis has been reported in about 5% of patients receiving fluconazole.

Gastrointestinal:

Abdominal pain, diarrhoea, flatulence, nausea.

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

Liver/Biliary:

Hepatic toxicity including rare cases of fatalities, elevated alkaline phosphatase, elevated bilirubin, alanine aminotransferase (ALAT) and elevated aspartate aminotransferase (ASAT).

In addition, the following adverse events have occurred during post-marketing:

Allergic reactions:

Anaphylaxis (including angio-oedema, facial oedema and pruritis).

Dermatological:

Alopecia, exfoliative skin disorders including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Central and Peripheral Nervous System:

Dizziness, seizures.

Gastrointestinal:

Dyspepsia, vomiting.

Haematopoietic and Lymphatic:

Leukopenia including neutropenia and agranulocytosis, thrombocytopenia.

Immunological Anaphylaxis:

(including angioedema, face oedema, pruritus).

Liver/Biliary:

Hepatic failure, hepatitis, hepatocellular necrosis, jaundice.

Metabolic/Nutritional:

Hypercholesterolaemia, hypertriglyceridaemia, hypokalaemia.

Other senses:

Taste perversion.

4.9 Overdose

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

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

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

ATC Code: JO2A CO1. The ATC-classification is: Antimycotics for systemic use; triazole derivatives.

Fluconazole belongs to the group of triazole antimycotics, specifically inhibiting fungal ergosterol synthesis.

5.2 Pharmacokinetic properties

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

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

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

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

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

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

Children metabolise fluconazole more rapidly. The half-life in children of 5-15 years is between 15.2 –17.6 hours, about half that of adults.

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, effects consistent with inhibition of oestrogen synthesis in rat. In reproduction toxicity studies in rabbits abortions were recorded. These effects were observed only at exposures in excess of the maximum human exposure.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents: lactose, maize starch, colloidal anhydrous silica, talc, sodium lauryl sulphate.

Capsule shells: gelatin, patent blue (E131), titanium dioxide (E171).

Printing ink: shellac, propylene glycol and black iron oxide (E172).

6.2 Incompatibilities

None.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Blister strip composed of: 25 micron Aluminium foil with 250 micron white opaque PVC film coated with 60 gsm PVdC.

Pack containing 1 capsule.

6.6 Special precautions for disposal

No special precautions are required.

7 MARKETING AUTHORISATION HOLDER

Neolab Limited
57 High Street
Odiham
Hants
RG29 1LF

8 MARKETING AUTHORISATION NUMBER(S)

PL 08137/0120

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13/02/2008

10 DATE OF REVISION OF THE TEXT

13/02/2008



PATIENT INFORMATION LEAFLET Fluconazole 150 mg Capsule

What you should know about your Fluconazole 150 mg Capsule

This leaflet provides a summary of the information available on your medicine. Keep this leaflet. You may need to read it again. If you have any questions or are not sure about anything, ask your pharmacist.

What is in your medicine?

The sky blue capsule contains 150 mg fluconazole. It has 'FCZ 150' and 'NEO' printed on it. Other ingredients: Lactose, maize starch, colloidal anhydrous silica, talc, sodium lauryl sulphate and gelatin (capsule shells only). The colouring agents included in the capsule shells are Patent blue (E131) and titanium dioxide (E171). The ink used to print 'FCZ 150' and 'NEO' contains black iron oxide (E172), shellac and propylene glycol.

Fluconazole 150 mg Capsules come in a pack containing 1 capsule.

The Product Licence Holder and manufacturer responsible for batch release is Neolab Limited Ltd, 57 High Street, Odiham, Hants, RG29 1LF.

Uses

The active substance fluconazole is one of a group of medicines called anti-fungals which are used to treat infections caused by fungi (including yeasts such as one called *Candida*).

Single fluconazole 150mg capsules may be bought from your pharmacist (chemist) for the treatment of vaginal thrush in women and thrush infections of the skin around the tip of the penis in men (including under the foreskin in uncircumcised men). These infections are due to a yeast that is called *Candida*. The medical names for these conditions are vaginal candidiasis in women and candidal balanitis in men. The single 150mg dose treatment is suitable only for treating these specific infections in men and women. It is not enough to treat other infections caused by fungi (yeasts and moulds).

You should take a Fluconazole 150mg Capsule only if you are sure that you have a thrush infection in the vagina or on the penis. Remember that other infections can cause similar symptoms to thrush and that you could have more than one type of infection at the same time. If you are in any doubt that you have thrush or think you could have another infection at the same time, you should see your doctor before you take fluconazole.

Thrush infections can be passed between sexual partners during intercourse. If you are going to take a Fluconazole 150mg Capsule to treat your infection, you should ask your partner if he/she also has symptoms of thrush. If so, you should both take the treatment at the same time otherwise the untreated partner can continue to cause infections in the other partner. If one partner does not have any symptoms of thrush, it is still possible that they have *Candida* in the vagina or on the penis so they might still cause repeated infections in the other partner if not treated.

Before taking your medicine

Do not use this Fluconazole 150 mg Capsule without first asking your pharmacist or doctor if:

- You are under 16 or over 60 years of age.
- You are or have ever been told that you are allergic to fluconazole or to other drugs of the same type (called triazoles) that are used to treat fungal infections.
- You are allergic to any of the other ingredients in these capsules. Although the capsules contain lactose, the amount is not thought likely to cause symptoms in people with lactose intolerance.
- You are taking the medicines terfenadine or astemizole (antihistamines for the relief of allergies such as hay fever) or cisapride (used for certain digestive problems). Fluconazole must not be taken by people who are taking one of these medicines because there is a risk of a serious rhythm disturbance of the heart.
- You take medicine(s) to control your heart rate or rhythm. These include quinidine, amiodarone, sotalol, disopyramide, but there are many others so check with your doctor or pharmacist before you take fluconazole.
- You have a very slow heart rate, a serious heart rhythm disturbance or heart failure. Also, have you ever been told that you have a long QT interval (a type of heart rhythm disturbance that is found on ECG's)?
- You suffer from low levels of potassium or magnesium in your blood.
- You have a serious ongoing illness, such as cancer, or severe problems with your body, liver or kidneys. Fluconazole is particularly likely to cause changes in blood test results in such people.
- You have AIDS. You can still take fluconazole but be aware that people who have AIDS are more likely to develop very severe skin reactions to fluconazole.
- You developed problems with your liver while taking fluconazole previously. If so, you should not take fluconazole to treat vaginal thrush.

Women Only:

- You are pregnant or trying to become pregnant or are breast feeding (see below).
- You have any abnormal or irregular vaginal bleeding or a blood stained discharge.
- You have vulval or vaginal sores, ulcers or blisters.
- You are experiencing lower abdominal pain or burning on passing urine.

Men Only:

- Your sexual partner does not have vaginal thrush.
- You have penile sores, ulcers or blisters.
- You have an abnormal penile discharge (leakage).
- Your penis has started to smelt.
- You have pain passing urine.

If any of the above points apply to you now, applied to you in the past, or if you are unsure about anything, please ask your pharmacist before you take fluconazole. It may also be necessary to check with your doctor.

Pregnancy and breastfeeding

Pregnant women should not take fluconazole for treating vaginal thrush because it may harm the growth of the unborn baby. Pregnant women are given fluconazole only if they have a very serious fungal infection that must be treated immediately.

Fluconazole enters breast milk so women who are breastfeeding should not take fluconazole to treat vaginal thrush.

Driving or using machines

Occasionally dizziness or fits can occur in people taking fluconazole so care should be taken when driving or operating machinery.

Please read the back of this leaflet.

Taking other medicines

Even though you will take only one 150mg dose of fluconazole to treat vaginal thrush or candidal balanitis, it is still possible that the following effects could occur. Please inform your pharmacist if you are taking, or have recently taken, any other medicines, even those not prescribed but have been obtained without a prescription, before you take fluconazole.

- Care is needed if you are taking the following medicines that can affect the blood levels of fluconazole:
 - A diuretic (water tablet) called hydrochlorothiazide (often used to treat high blood pressure) because the blood levels of fluconazole are higher than usual when these two medicines are taken together. The higher blood level of fluconazole means that there is an increased risk of side effects.
 - Certain antibiotics called rifampicin or rifabutin. These medicines can cause the blood level of fluconazole to fall so that it may not work. Also, the blood levels of rifabutin can rise, causing an increased risk of inflammation of the lining of the eye due to the rifabutin.

Fluconazole can increase the blood levels of many other medicines. This sometimes causes them to have a greater effect than usual, which can cause problems, and can increase the risk of side effects. Your doctor may need to adjust the dose of these medicines while you are taking fluconazole. For some medicines, your doctor may need to measure the blood levels in order to adjust the dose correctly. Care is needed if you are taking:

- Medicines called ergot alkaloids for migraine.
- Medicines of the family called HMG-CoA reductase inhibitors, such as atorvastatin or fluvastatin, that are used to lower blood cholesterol levels. In particular, there is an increased risk of side effects that affect the muscles such as muscle weakness, with a risk also to the normal working of the kidneys.
- Medicine(s) to control your heart rate or rhythm. These include quinidine, amiodarone, sotalol and disopyramide.
- Medicines called coumarins that prevent the blood from clotting normally (anticoagulants), such as warfarin.
- Phenytoin for epilepsy.
- Calm medicines (tranquillisers) called benzodiazepines, such as triazolam.
- Medicines called calcium channel antagonists (including nifedipine, isradipine, nicardipine, amlodipine, and felodipine) used to control your angina and/or high blood pressure.
- Medicines to control diabetes such as chlorpropamide, glibenclamide, glipizide and tolbutamide. In particular, fluconazole can increase the risk of having a very low blood sugar level due to these medicines.
- Losartan to control your high blood pressure because it may not work so well while you are taking fluconazole.
- Didanosine or zidovudine (AZT), which are medicines used in the treatment of AIDS. Fluconazole can increase the blood levels of zidovudine while didanosine can affect the blood levels of fluconazole.
- Trimetrexate for the treatment of a type of pneumonia called pneumocystis.
- Cyclosporin, tacrolimus or sirolimus, which are used mainly after transplants to prevent rejection of the new organ.
- Prednisone (a steroid). When fluconazole treatment is stopped, you may need to take more prednisone than before, at least for a while.
- Amitriptyline or nortriptyline (anti-depressants).
- Celecoxib (a non-steroidal anti-inflammatory medicine used to treat arthritis).
- Theophylline to control your asthma or treat bronchitis.
- Alfentanil, which is used to relieve pain during surgical operations. If you going to have an anaesthetic, make sure your anaesthetist knows that you are taking fluconazole because the medicine may affect the result.

If you have a blood/urine/liver function test you should tell your doctor that you are taking fluconazole because the medicine may affect the result.

Taking your medicine

This capsule is for oral use. The complete course of treatment for vaginal thrush or candidal balanitis is one capsule. Take the capsule with a sufficient quantity of liquid – one glass of water. Do not chew the capsule. It can be taken before, with or after food.

The dose for treating thrush in the vagina or on the penis is ONE 150mg capsule ONLY.

If this single dose does not clear up your thrush, or if your thrush comes back very quickly, DO NOT repeat this dose. You should visit your doctor and ask for advice about the right treatment for you. Remember that fluconazole can only treat thrush in the vagina or on the penis. It cannot treat other infections of the genitals. If you still have any sort of symptoms one or two days after you have taken fluconazole, you should visit your doctor in case you have another type of infection.

What to do if you take an overdose?

You need to take only one capsule. If you take many capsules at once contact your doctor immediately or go to the nearest hospital casualty department.

Possible side effects

Like all medicines, Fluconazole Capsules can have side effects which can be seen even with a single dose of 150mg.

The side effects that have been reported with fluconazole include:

- Allergic reactions to fluconazole which can sometimes cause severe sudden reactions with a drop of blood pressure and unconsciousness, swelling of the face and neck or of other body parts, and rashes that involve blistering and peeling of the skin that may affect the eyes, mouth and genitals. If you have any other of these symptoms, you should contact a doctor or the nearest hospital urgently.
 - Less serious allergic reactions include skin rashes, sometimes with itching and also with an increase in a type of white blood cells called eosinophils, are common. If you have any of these symptoms, you should contact your doctor immediately.
 - Headache, dizziness and fits.
 - Stomach pain, indigestion, diarrhoea, wind, feeling and being sick.
 - In some patients, particularly those with serious conditions such as AIDS or cancer, there may be changes in blood tests that monitor the liver, kidneys and numbers of blood cells.
 - Inflammation and damage to the liver, sometimes with jaundice (yellow skin), that may rarely be fatal.
 - Hair loss.
 - Low numbers of white blood cells (leading to an increase in risk of infections) or platelets (leading to easy bruising and bleeding for longer than usual) in the blood.
 - Increases in cholesterol and other fats in the bloodstream, decreases in blood potassium levels.
 - Changes in taste.
- If you notice any side effects not mentioned in this leaflet, please tell your pharmacist or doctor.

Storing your medicine

Do not take this medicine after the expiry date shown on the carton and blister strip. Store in the original package to protect from moisture. Do not store above 25°C. If you notice that the capsule is broken or has an odd colour, take it back to your pharmacist or doctor.

Keep all medicines out of the sight and reach of children. Your medicine can harm them.

This leaflet only applies to Fluconazole 150 mg Capsules.

This leaflet was prepared in June 2004.



LABELLING

