DIFLUCAN®

Fluconazole

1/ TRADE NAME OF THE MEDICINAL PRODUCT

Diflucan 150 mg capsule
Diflucan 50 mg capsule

2/ QUALITATIVE AND QUANTITATIVE COMPOSITION

Active principle:
Fluconazole
50.00 mg and 150.00 mg
Excipients:
List of excipients : Cf. 6.1

3/ PHARMACEUTICAL FORM

capsule

4/ CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Fluconazole 150 mg is indicated in the the treatment of acute or recurrent vaginal and perineal candidiasis.

Fluconazole 50 mg is indicated in the treatment of :

- oropharyngeal candidiasis in patients with compromised immune function, either because of a malignant disease or Acquired Immune Deficiency Syndrome (AIDS)
- atrophic oral candidiasis.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

In adults

- In acute and recurrent vaginal and perineal candidiasis : 150 mg unique dose prescription
- oropharyngeal candidiasis, including those patients with compromised immune function, the usual dose is 50 mg once daily for 7 14 days. If necessary, treatment can be continued for longer periods at the same dosage.
- atrophic oral candidiasis associated with dentures, the usual dose is 50 mg once daily for 14 days administered concurrently with local hygiene.
- Use in elderly

No dosage adjustment limited to creatinine clearance is required in case of 150 mg unique dose treatment.

The prescription will be prudent. Daily dosage will be adjusted according to creatinine clearance. Where there is no evidence of renal impairment, normal dosage recommendations should be adopted. For patients with renal impairment (creatinine clearance ≤ 50 ml/min) in adult should be adjusted as described below.

Patients with renal impairment

Fluconazole is predominantly excreted in urine as unchanged drug.

In case of renal impairment, after a first administration, the daily dosage will be adjusted according to indication and creatinine clearance as follows :

Creatinine clearance (ml/min)	Recommended dose (Usual dosage percentage or dosage intervals)
>50	100 % or 24 H
11 to 50	50 % or 48 H
10 - 20	72 (or 1/3 normal daily dose)
Patients receiving regular dialysis	one dose after every dialysis session

4.3 CONTRA-INDICATIONS

Fluconazole SHOULD NOT BE ADMINISTERED in the following cases:

- hypersensitivity to fluconazole and/or other azole derivatives
- pregnancy and lactation (cf. 4.6 pregnancy and lactation)
- in combination with:
  . cisapride
  . pimozide
  (cf. 4.5 interaction with other medicines and other forms of interaction)

Fluconaole is GENERALLY UNADVISED in association with halofantrine (cf. 4.5 interaction with other medicines and other forms of interaction

4.4 SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

Children : available data are too limited for recommending its use.

In patients with hepatic or renal impairment and in case of a severe pathology associated, a monitoring of hepatic tests is recommended. The administration of fluconazole should be stopped in case of aggravation of previous hepatic tests disorder.

The patients should be informed in case of outbreak of symptoms suggesting a severe hepatic impairment (severe asthenia, anorexia, persisting nausea, vomiting, jaundice) that the fluconazole treatment should be immediately stopped and that he should consult a doctor.

A clinical supervision is needed in patients with a previous cutaneous reaction associated with absorption of fluconazole or another azole derivative. The patient should be informed in case of blisters outbreak that the treatment by fluconazole should be immediately stopped and that he should consult a doctor as soon as possible

Due to the presence of lactose, this medicine is contra-indicated in case of congenital galactosemia, glucose and galactose malabsorption syndrome and lactase deficiency.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Fluconazole is highly specific for fungal cytochrom P450 dependent enzymes.

COMBINATIONS CONTRA-INDICATED :

. ***cisapride*** : increased risk of ventricular arrhythmia troubles notably torsades de pointes.

. ***pimozide*** : increased risk of ventricular arrhythmia troubles notably torsades de pointes.

COMBINATIONS UNADVISABLE :

. ***halofantrine*** : increased risk of ventricular arrythmia, notably torsades de pointe.

If possible, stop the antifungal azole. If the association is unavoidable, an initial QT control and monitored ECG surveillance are required.

COMBINATIONS NEEDING PRECAUTIONS :

. ***Alfentanil*** : increase of respiratory depressing effect of the opiate analgesic by decrease of its hepatic metabolism.

Adapt the dosage of the opiate analgesic in case of a treatment by fluconazole.

. ***oral anticoagulants*** (described for warfarine) : increase of the oral anticoagulant effect and the hemorragic risk by decreasing of its hepatic catabolism. More frequent monitoring of prothrombin time and observation of the INR ; the oral anticoagulant dosage should be adapted during treatment by the fluconazole and 8 days after its stopping.

. ***ciclosporin, tacrolimus*** : possible increase of the immunodepressant plasmatic concentration (inhibition of its metabolism) and of the creatininemia. Monitor the renal function, dosage of the ciclosporin circulating rate and potential dosage adjustment during the association and after its stopping.

. ***phenytoin*** : phenytoin plasmatic concentrations increase, which may reach toxic values. Mechanism invoked : inhibition of the phenytoin hepatic metabolism. Careful clinical monitoring, phenytoin plasmatic concentrations control and potential adjustment of its dosage during treatment by the fluconazole and after its stopping.

. ***hypoglycaemic sulfonylureas*** : sulfonylureas half-life increase, with the possibility of hypoglycemic episodes. Inform the patient of the hypoglycemic risk, intensify the glycemic self-watching and adapt the sulfonylureas dosage during the treatment by the fluconazole.

. ***rifampicin*** : decrease of the fluconazole plasmatic concentrations and of the efficacy of both anti-infectious drugs (enzymatic induction by the rifampicin and decrease of the intestinal absorption by the azole antifungic). Delay the administrations of both anti-infectious drugs, monitor the azole antifungic plasmatic level and possibly adapt the dosage.

. ***rifabutine*** : risk of increase of the rifabutine side-effects (uveitis) due to the increase of the rifabutine and its active metabolite blood levels.

Regular clinical monitoring.

. ***theophylline (base and salts) and aminophylline*** : increase of the theophyllinemia with risk of overdose (decrease of the clearance of the theophylline). Clinical monitoring and possibly of the theophyllinemia ; if necessary, adapt the theophylline dosage during treatment by fluconazole and after its stopping.

. ***triazolam*** : increase of triazolam plasmatic concentration by decrease of hepatic metabolism with an increase of sedation.

Clinical monitoring and possible adaptation of triazolam dosage during fluconazole treatment.

COMBINATIONS TO BE TAKEN INTO ACCOUNT :

. **Due to the lack of clinical studies**, the association of fluconazole with xanthic bases and INH must be prudent ; a clinical even biological control is then necessary.

. ***with diuretics*** : An increase of plasmatic levels (40%) of the fluconazole has been observed in healthy volunteers, receiving concomitantly hydrochlorothiazide. Although it cannot be excluded, this increase does not necessitate fluconazole dosage adjustment in patients treated by diuretics.

The fluconazole multiple dose interaction studies did not show :

. with a 50 mg daily dosage, any modification of the kinetics of the oral contraceptives in the woman.

. with a 200 to 400 mg daily dosage in healthy male volunteer, any consequence on endogenous steroid levels or on ACTH stimulated cortisol response.

The fluconazole 50 mg daily given up to 28 days has been shown not to affect testosterone plasma concentrations in males or steroid concentrations in females of child-bearing age.

No modification on fluconazole absorption leading to clinical consequences has been observed during interactions studies with food, cimetidin, antiacid agents, total body irradiation for bone marrow transplants.

Although interactions studies between fluconazole and zidovudine and/or pentamidine have not been conducted, these drugs have been simultaneously prescribed in patients suffering for AIDS, without any significant difference in side effects frequency.

Interaction studies with antipyrine indicate that single or multiple doses of fluconazole do not affect its metabolism.

4.6 PREGNANCY AND LACTATION

. **Pregnancy** :

Animal studies do not allow to rule out the possibility of a teratogenic effect and human data are insufficient to determine the risk. Thus the fluconazole prescription is contra-indicated during pregnancy except in patients suffering from severe fungic or potentially lethal infections. In these patients the fluconazole may be administered when considering that the benefit expected is higher than the risk for the fœtus. In woman of child bearing age effective contraceptive methods should be introduced.

. **Lactation** :

Fluconazole concentrations in milk are similar to concentrations in plasma thus the fluconazole is contra-indicated during breast-feeding time.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES : /

Not applicable

4.8 UNDESIRABLE EFFECTS

Gastro intestinal and cutaneous effects are the most commonly observed side effects.

Gastro intestinal side effects : nausea, flatulence, abdominal pain, diarrhea.

Allergic and cutaneous effects : rash, severe cutaneous blister reactions (Steven Johnson syndrom, Lyell syndrom, specially during AIDS), anaphylactic reactions.

Some cases of alopecia have been observed, generally reversible.

General effects : headache possibly linked to the product.

Hepatic effects : increase of hepatic transaminases reversible when the treatment is stopped, severe hepatic dysfunction possibly linked to fluconazole high serum levels (see special warnings and special precautions for use), sometimes of lethal development, have been exceptionnaly reported.

Haematologic effects : leucopenias (neutropenia, agranulocytosis), thrombopenia.

4.9 OVERDOSE

In case of overdosage, a symptomatic treatment is given with supportive measures and gastric lavage if necessary.

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

5/ PHARMACOLOGICAL PROPERTIES

ANTIFUNGAL FOR SYSTEMIC USE, ATC code : J02AC01 (Antiinfection drug)

5.1 PHARMACODYNAMIC PROPERTIES

Fluconazole is a bistriazole antifungal agent which may be used by oral route.

Fluconazole acts by inhibiting fungal ergosterol biosynthesis and is more selective for fungal rather than mammalian sterol synthesis.

The in vivo activity of fluconazole seems higher than in vitro results.

Usually susceptible species :

- *Candida especially albicans,*
- *Cryptococcus neoformans*

Usually resistant species :

- *Candida krusei*
- Dermatophytes (microsporum, trichophyton)
- *Aspergillus sp.*

5.2 PHARMACOKINETIC PROPERTIES

After oral administration, fluconazole is well absorbed, and its bioavailability is 90 %. Absorption is not affected by food intake. Peak plasma concentrations in the fasting state occur between 0.5 and 1.5 hours post dose:

1.02 mg/l after a 50 mg unique dose

2.37 mg/l at steady state at day 4 5 days after repeated doses at 50 mg/day.

The salivary concentrations are nearly the same as the plasma ones. Plasma concentrations are proportional to dose.

The apparent volume of distribution approximates to total body water (0.6 0.7 l/kg). Plasma protein binding is low (12 %).

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The plasma elimination half life is approximately 30 hours.

The major route of excretion is renal with approximately 80 % of the administered dose appearing in the urine as unchanged drug.

Fluconazole is poorly metabolized (11 % of the administered dose appears in the urine as metabolites) and it does not seem necessary to modify the dose in case of hepatopathy.

Fluconazole clearance is proportional to creatinine clearance, consequently, the daily dose will be reduced in patients with creatinine clearance inferior or equal to 50 ml/minute.

After 3 hours of haemodialysis session, around 50 % of the fluconazole is eliminated from blood.

5.3 PRECLINICAL SAFETY DATA :

Not applicable

6/ PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

lactose, maize starch, sodium lauryl sulfate, magnesium stearate,.anhydrous colloidal silicium dioxide

Capsule shell composition : gelatin, titanium dioxide , yellow iron oxide, indigotin, sodium metabisulfite

6.2 INCOMPATIBILITIES :

Not applicable

6.3 SHELF LIFE

As indicated on the outer carton

6.4 SPECIAL PRECAUTIONS FOR STORAGE : Store at a temperature not > 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

50 mg capsules: 7 capsules in blister packs PVC/ Aluminium.

150 mg capsules : 1 capsules in blister packs PVC/ Aluminium.

Other dosage forms:

200 mg capsules: blister containing 7 capsules

2mg /ml in vials of 50 and 100 ml(glass bottle – type I)

6.6 INSTRUCTION FOR USE / HANDLING :

Not applicable

12/11/2001

MANUFACTURED BY:
Pfizer PGM, France

Ceci est un médicament

- Un médicament est un produit, mais pas comme les autres.
- Un médicament est un produit qui agit sur votre santé et sa consommation non conforme aux prescriptions vous expose à un danger.
- Respectez rigoureusement l'ordonnance de votre médecin et le mode d'emploi qu'il vous prescrit.
- Suivez le conseil de votre pharmacien.
- Votre médecin et votre pharmacien connaissent le médicament, ses indications et ses contre-indications.
- N'arrêtez pas de votre propre initiative le traitement durant la période prescrite.
- Ne reprenez pas, n'en augmentez pas les doses sans consulter votre médecin.

Ne laissez jamais les médicaments à la portée des enfants.