Flukas 100mg – Flukas 200mg, injectable solution

Fluconazole

Read all of this leaflet carefully before you start using 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 “Flukas 100mg – Flukas 200mg” is and what it is used for?

PHARMACOLOGICAL PROPERTIES:
Fluconazole is a Triazoles analogue, water soluble for intravenous injection.
Fluconazole acts by inhibiting fungi ergosterol biosynthesis and is highly selective for fungal rather than mammalian sterol synthesis.
The subsequent loss of normal sterols correlates with the accumulation of 14-α-methyl sterols in fungi and may be responsible for the fungistatic activity of fluconazole.
The in-vivo activity of fluconazole appears to be substantially higher than might be expected based on in vitro results.
SUSCEPTIBLE SPECIES ARE:
• Species which are usually sensitive: Candida, especially Candida albicans, and Cryptococcus neoformans.
• Species which are usually resistant: Candida krusei.
In a majority of the studies, fluconazole MIC90 values against C. glabrata were above the susceptible breakpoint (≥ 16μg/ml).
Resistance in Candida glabrata usually includes upregulation of CDR genes resulting in resistance to multiple azoles. For an isolate where the MIC is categorized as intermediate (16 to 32 μg/ml), the highest dose is recommended. For resistant isolates alternative therapy is recommended.
PHARMACOKINETIC :
Oral and intravenous forms are equivalent on a pharmacokinetic basis. After oral administration, fluconazole is well absorbed and its bioavailability is 90%.
Absorption is not affected by food intake.
Peak plasma concentrations (Cmax) in fasted normal volunteers occur between 1 and 2 hours with a terminal plasma elimination half-life of approximately 30 hours (range: 20-50 hours) after oral administration.
In fasted normal volunteers, administration of a single oral 400 mg dose of fluconazole leads to a mean Cmax of 6.72 μg/mL (range: 4.12 to 8.08 μg/mL) and after single oral doses of 50-400 mg, fluconazole plasma concentrations and AUC (area under the plasma concentration-time curve) are dose proportional.
Administration of a single oral 150 mg tablet of fluconazole to ten lactating women resulted in a mean Cmax of 2.61 μg/mL (range: 1.57 to 3.65 μg/mL).
Steady-state concentrations are reached within 5-10 days following oral doses of 50-400 mg given once daily. Administration of a loading dose (on day 1) of twice the usual daily dose results in plasma concentrations close to steady-state by the second day. The apparent volume of distribution of fluconazole approximates that of total body water.
The plasma elimination half-life is approximately 30 hours. The major route of excretion is renal with approximately 80% of the administered dose appears 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 should be reduced in patients with creatinine clearance less than or equal to 50 ml/minute. About 50% of fluconazole is eliminated from 3 hour haemodialysis session.
THERAPEUTIC INDICATIONS:
1- Cryptococcal meningitis:
- Loading treatment: the efficiency of fluconazole was demonstrated, especially in patients affected by AIDS. For the other types of immunodepression (organs transplants, hemopathy) and in immunocompetent patients, in case of severe forms, the use of fluconazole instead of amphotericin B is not well documented. Amphotericin B appears in sterilize CSF more rapidly.
- Fluconazole is also recommended as a maintenance therapy of Cryptococcal meningitis in patients suffering from AIDS. In this case, it should be prescribed indefinitely.
- The efficacy of fluconazole for other pulmonary or cutaneous cryptococcal localizations has not been as clearly established.
2- systemic candidiasis:, including disseminated and deep candidiasis (candidemias, peritonitis), and oesophageal and urinary candidiasis. Candida albicans represents the most found species in clinical studies. The efficiency of fluconazole in the infections due to other species of Candida, is not established, especially those caused by Candida glabrata and Candida krusei (usually resistant species).
3- prevention of infections due to sensitive Candida in adults exposed to severe and prolonged neutropenia during induction and consolidation treatment in patients with acute leukemia and undergoing bone marrow transplantation.

2. Before you use “Flukas 100mg – Flukas 200mg”?

Contraindications:
- Hypersensitivity to fluconazole and/or to other Triazole’ compounds.
- There is no information regarding cross-hypersensitivity between fluconazole and other azole antifungal agents. Caution should be used in prescribing fluconazole to patients with hypersensitivity to other azoles.
- Coadministration of terfenadine is contraindicated in patients receiving fluconazole at multiple doses of 400 mg or higher based upon results of a multiple dose interaction study.
- Coadministration of cisapride is contraindicated in patients receiving fluconazole.

Warnings and precautions of use
Warnings:
- In patients with known hepatic and/or renal impairment and when a severe pathology is associated, the monitoring of the hepatic function is recommended; the discontinuation of fluconazole is to be considered in case of worsening of hepatic tests.
- Fluconazole has been associated with rare cases of serious hepatic toxicity, including fatalities primarily in patients with serious underlying medical conditions. In cases of fluconazole associated hepatotoxicity, no obvious relationship to total daily dose, duration of therapy, sex or age of the patient has been observed. fluconazole hepatotoxicity has usually, but not always, been reversible on discontinuation of therapy.
- The patients should be informed that in case of occurrence of symptoms evoking severe hepatic impairment (important asthenia, anorexia, persisting nausea, vomiting and icterus), they should immediately stop fluconazole and rapidly consult their doctor.
- A special clinical monitoring is to be imposed in patients with already presented a cutaneous reaction following fluconazole or another azoles derivative use. The patients should be informed that in case of occurrence of bullous lesions, they should immediately stop fluconazole and rapidly consult their doctor.
- Anaphylaxis: In rare cases, anaphylaxis has been reported.

Precautions of use
- General : Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been rare cases of QT prolongation and torsade de pointes in patients taking fluconazole. Most of these reports involved seriously ill patients with multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities and concomitant medications that may have been contributory. Fluconazole should be administered with caution to patients with these potentially proarrhythmic conditions.
- Pregnancy : There are no adequate and well controlled studies in pregnant women. There have been reports of multiple congenital abnormalities in infants whose mothers were being treated for 3 or more months with high dose (400-800 mg/day) fluconazole therapy for coccidioidomycosis (an unindicated use). The relationship between fluconazole use and these events is unclear. Fluconazole should be used in pregnancy only if the potential benefit justifies the possible risk to the fetus.
- Lactation : Fluconazole is secreted in human milk at concentrations similar to plasma. Therefore, the use of fluconazole in nursing mothers is not recommended.
- Use in pediatrics: The safety profile of fluconazole in children has been studied in 577 children ages 1 day to 17 years who received doses ranging from 1 to 15 mg/kg/day for 1 to 1,616 days.
- Efficacy of fluconazole has not been established in infants less than 6 months of age. A small number of patients (29) ranging in age from 1 day to 6 months have been treated safely with fluconazole.
- Use in geriatrics : Fluconazole is primarily cleared by renal excretion as unchanged drug. Because elderly patients are more likely to have decreased renal function, care should be taken to adjust dose based on creatinine clearance. It may be useful to monitor renal function.

Drugs interactions:
Fluconazole exerts a very specific activity on cytochrome P450 (Derived from fungi) and therefore:
- Not to be used with cicapride and pimozide
- Not to be used with halofantrine and triazoles anti-fungals.
- Use with caution with: warfarin (anticoagulant), sulfonylureas, hydrochlorothiazides, phenytoin, oral contraceptives, rifampicin, cyclosporine, theophyllin, rifabutin, tacrolimus, zidovudine, midazolam and cimetidine.

3. How you use “Flukas 100mg – Flukas 200mg”?

Dosage and mode of administration:
The intravenous infusion of fluconazole should be administered at a maximum rate of approximately 200 mg/hour, given as a continuous infusion. Fluconazole being available in saline solution, in patients needing sodium or water restriction, consideration should be given to the rate of fluid administration.
Fluconazole intravenous infusion is compatible with the following administration fluid:

a. 20% dextrose solution
b. Ringer’s solution
c. Hartmann’s solution
d. Potassium chloride in dextrose solution
e. Sodium bicarbonate
During the administration of Flucanazole until now, there are no known incompatibilities with other products. However, and as a precaution, it is recommended not to mix fluconazole with other products in the same infusion.

Doses in Adults:
• Cryptococcal meningitis: The recommended dosage for treatment of acute cryptococcal meningitis is 400 mg on the first day, followed by 200 mg once daily. A dosage of 400 mg once daily may be used, based on medical judgment of the patient’s response to therapy. The recommended duration of treatment for initial therapy of cryptococcal meningitis is 10-12 weeks after the cerebrospinal fluid becomes culture negative. The recommended dosage of fluconazol for suppression of relapse of cryptococcal meningitis in patients with AIDS is 200 mg once daily.
• Systemic Candida infections: For systemic Candida infections including candidemia, disseminated candidiasis, and pneumonia, optimal therapeutic dosage and duration of therapy have not been established. In open, noncomparative studies of small numbers of patients, doses of up to 400 mg daily have been used.
• Prophylaxis:
In Patients undergoing bone marrow transplantation: the recommended fluconazole injection daily dosage for the prevention of candidiasis in patients undergoing bone marrow transplantation is 400 mg once daily. Patients who are anticipated to have severe granulocytopenia (less than 500 neutrophils per cu mm) should start fluconazol prophylaxis several days before the anticipated onset of neutropenia, and continue for 7 days after the neutrophil count rises above 1000 cells per cu mm.

Doses in children:
Experience with flucanazol in neonates is limited to pharmacokinetic studies in premature newborns. Based on the prolonged half-life seen in premature newborns (gestational age 26 to 29 weeks), these children, in the first two weeks of life, should receive the same dosage (mg/kg) as in older children, but administered every 72 hours. After the first two weeks, these children should be dosed once daily. No information regarding flucanazol pharmacokinetics in full-term newborns is available.
• Systemic Candida infections: For the treatment of candidemia and disseminated Candida infections, daily doses of 6-12 mg/kg/day have been used in an open, noncomparative study of a small number of childen.
• Cryptococcal meningitis: For the treatment of acute cryptococcal meningitis, the recommended dosage is 12 mg/kg on the first day, followed by 6 mg/kg once daily. A dosage of 12 mg/kg once daily may be used, based on medical judgment of the patient’s response to therapy. The recommended duration of treatment for initial therapy of cryptococcal meningitis is 10-12 weeks after the cerebrospinal fluid becomes culture negative. For suppression of relapse of cryptococcal meningitis in children with AIDS, the recommended dose of flucanazol is 6 mg/kg once daily.
Dose equivalency table:
The following dose equivalency scheme should generally provide equivalent exposure in paediatric and adult patients:

Pediatric Patients	Adults
3 mg/kg	100 mg
6 mg/kg	200 mg
12 mg/kg*	400 mg

* Some older children may have clearances similar to that of adults. Absolute doses exceeding 600 mg/day are not recommended.

Doses in renal failure:
Fluconazole is cleared primarily by renal excretion as unchanged drug. There is no need to adjust single dose therapy because of impaired renal function. In patients with impaired renal function who will receive multiple doses of flucanazol, an initial loading dose of 50 to 400 mg should be given. After the loading dose, the daily dose (according to indication) should be based on the following table:

Creatinine Clearance (ml/min)	Percent of Recommended Dose
> 50	100%
≤ 50 (no dialysis)	50%
Regular dialysis	100% after each dialysis

These are suggested dose adjustments based on pharmacokinetics following administration of multiple doses. Further adjustment may be needed depending upon clinical condition.

Doses in Elderly:
The prescription should be done with caution. The dosage will be adjusted according to creatinin clearance.
If the renal function is normal, the usual recommended adult dosage will be adopted.

Over dose
In the event of overdosage, a symptomatic treatment with supportive measures and gastric lavage is indicated only 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%.

4. Possible side effects:

Like all drugs, flukas is susceptible to induce undesirable effects: gastro-intestinal and cutaneous effects are the most frequently reported effects.
- gastro-intestinal effects : nausea, vomiting, flatulence, abdominal pains and diarrhea.
- Cutaneous and allergic : rashes, severe cutaneous reactions such as bullous toxidermia (Stevens - Johnson syndrome, Lyell syndrome, particularly in case of AIDS), anaphylactic reactions.
- Some cases of alopecia, generally reversible, were reported.
- General effects : headaches which could be related to the product.
- Hepatic effects : increase in hepatic transaminases, usually reversible after treatment discontinuation; some cases of severe hepatic impairment were exceptionally reported, eventually associated with increased serum levels of fluconazole, and, sometimes, with a fatal issue,
- Hematologic effects : leukopenia (neutropenia, agranulocytosis), thrombocytopenia.
- Cardiac : QT prolongation, torsade de pointes
- Central Nervous System : Seizures ,dizziness
- Metabolic: hypercholesterolemia , hypertriglyceridemia, hypokalemia.

5. How to store “Flukas 100mg – Flukas 200mg”?

Store the product in a temperature not exceeding 30°C.

6. Further information

a. What “Flukas 100mg – Flukas 200mg” contains:
1- FLUKAS 200:
The active substance is :
Fluconazole: 200 mg
The other ingredients are:
Hydrochloride acid or sodium hydroxide for pH adjustment
Sodium chloride: 900 mg
W.F.I: q.s 100 ml
2- FLUKAS 100:
The active substance is:
Fluconazole: 100 mg
The other ingredients are:
Hydrochloride acid or sodium hydroxide for pH adjustment
Sodium chloride: 450 mg
W.F.I: q.s. 50 ml

b. What “Flukas 100mg – Flukas 200mg” looks like and contents of the pack:
Flukas 100 mg is presented in injectable solutions form for intravenous infusion, box of 1 vial of 50 ml.
Flukas 200 mg is presented in injectable solutions form for intravenous infusion, box of 1 vial of 100 ml.

c. Marketing autorisation holder and manufacturer :
LES LABORATOIRES MEDIS- S.A.
Route de Tunis - KM 7 - BP 206 - 8000 Nabeul - Tunisie
Tel : (216) 72 23 50 06
Fax: (216) 72 23 51 06
E-mail: medis@planet.com.tn
For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:
Salehiya Trading Establishment
(Medical equipment & pharmaceuticals)
P.O.Box: 991, Riyadh 11421- Kingdom of Saudi Arabia
Tel: 00 966 1 46 46 955
Fax: 00 966 1 46 34 362

d. This leaflet was last approved in “July /2011”; version number “ 00”

e. To report any side effect(s):

SAUDI ARABIA
- National Pharmacovigilance Center (NPC)
- Fax: +966-1-210-7398
- E-mail: npc.drug@sfda.gov.sa
- Website: www.sfda.gov.sa/npc

THIS IS A MEDICAMENT

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow Strictly the doctor’s prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of reach of children

LES LABORATOIRES MEDIS- S.A.
Route de Tunis - KM 7 - BP 206 - 8000 Nabeul - Tunisie
Tel : (216) 72 23 50 06 - Fax: (216) 72 23 51 06

MédiS

N000106
V00