FLUCAND® 2 mg/ml

Parentral solution for infusion

PHARMACOLOGICAL PROPERTIES

Fluconazole is a Triazoles analogue, water soluble for intravenous injection.
Fluconazole acts by inhibiting fungal ergosterol biosynthesis and is highly selective for fungal rather than mammalian sterol synthesis.
The in-vivo activity of Fluconazole appears to be substantially higher than might be expected based on in vitro results.
Susceptible species are:

- Candida especially albicans.
- Cryptococcus neoformanis

Usually resistant species:

- Candida krusei
- Dermatophytes (microsporum, Trichophyten)
- Aspergillus species

PHARMACOKINETICS

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 in the fasting state occur between 0.5 and 1.5 hours post dose.
Plasma concentrations are proportional to the dose:

- Peak plasma concentrations are 4.6 mcg/ml after a single 200 mg dose and 10 mcg/ml at steady state on the fifteenth day after administration of 200 mg/day.
- Peak plasma concentrations are 9 mcg/ml after a single 400 mg dose and 18 mcg/ml at steady state on the fifteenth day after administration of 400 mg/day. Ninety percent of steady state level is reached by day 4 - 5 with once daily multiple dosing. 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 less than or equal to 40 ml/minute.
About 50% of Fluconazole is eliminated from 3 hour haemodialysis session.

INDICATIONS:

** Cryptococcal meningitis:*

In acute treatment, its efficacy has been demonstrated, mainly in patients suffering from AIDS. For other types of immunodepression (organ transplants, hemopathy), in patients previously not immunocompromised and in severe cases, the activity of fluconazole in relation to amphotericine B is not well known. The latter appears in sterilize CSF more rapidly.
Fluconazole is also indicated as a maintenance therapy in cryptcoccal meningitis of patients suffering from AIDS, In such case it must be prescribed indefinitely.
The efficacy of Fluconazole for other pulmonary or cutaneous cryptococcal localizations has not been as clearly established.

** Systemic candidiasis:*

Including disseminated and deep candidiasis, (candidemias, Peritonitis), esophageal & urinary candidiasis. The efficacy in neutropenic patients has not been established in severe types, its efficacy versus Amphoterecin B is not known.

DOSAGE AND ADMINISTRATION

Fluconazole may be administered either orally or by intravenous infusion at a rate not exceeding 10 ml/minute, the route being dependent on the clinical state of the patient.
On transferring from the intravenous to the oral rate or vice versa, there is no need to change the daily dosage. Fluconazole IV is formulated in 0.9 % sodium chloride solution, each 200 mg (100 ml bottle) containing 15 mmol each of Na^+ and Cl^-.
Because fluconazole is available as a saline solution in patients requiring sodium or fluid 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 clinical trials and when administered incompatibilities with other products have not been noted as at this date. However, by way of a precautionary measure, the mixing of fluconazole with any other drug prior to infusion is not recommended.

In adults:

Cryptococcosis:

Acute treatment	400 mg/day (6 to 8 weeks)
Maintenance therapy	200 mg/day
(Lifetime treatment for patients suffering from AIDS)	

Candidiasis:

Esophageal	100 mg/day
Urinary	100 to 200 mg/day
Peritonitis	200 - 400 mg/day
Disseminate candidiasis,	200 - 400 mg/day
Candidemias	200 to 400 mg/day*

The duration of treatment is subject to clinical response.
*For deep and disseminated candidiasis a 400 mg loading dose on day 1 is necessary.

Use in elderly

Caution must be applied to the prescription daily dosage should be adjusted according to creatinine clearance. Where there is no evidence of renal impairment no dosage recommendations in adults should be adopted.
For patients with renal impairment (Creatinine clearance < 40 ml/mm) the dosage schedule should be adjusted as described below.

Patients with renal impairment

Fluconazole is predominantly excreted in the urine as unchanged drug.
Normal doses should be given on day 1 and 2 of treatment and thereafter the dosing intervals should be modified in accordance with creatinine clearances as follows:

Creatinine clearance (ml/mm)	Dosing intervals (hours)
> 40	24 (normal dosage regimen)
21 - 40	48 (or one half of normal dose)
10 - 20	72 (or one third of normal dose)
Patients undergoing regular dialysis	One dose after every dialysis session

CONTRAINDICATIONS

- Hypersensitivity to this drug or to related azole compounds
- Pregnancy

Based on experimental studies in animals a possible teratogenic effect cannot be excluded and presently available data do not allow for precise assessment of the risk in humans.
Consequently the use of fluconazole during pregnancy is contraindicated except in patients with severe or potentially life-threatening fungal infections in whom fluconazole may be used if the anticipated benefit outweighs the possible risk to the fetus. Effective means of contraception must be used by women of child-bearing age.

Lactation

Fluconazole is found in humans breast milk at concentrations similar to Plasma levels, hence its use in nursing mothers is not recommended.

WARNING

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

Drug Interactions

Fluconazole is highly specific for fungal cytochrom P450 dependant enzymes.

Combinations Requiring Precautions:

Oral anticoagulants (described with warfarin):
Increase of the oral anticoagulant effect and of hemorrhagic risk through diminished hepatic catabolism; more frequent monitoring of prothrombin time: the oral anticoagulant dosage should be adjusted during treatment by fluconazole for 8 days.

Sulfonylureas:

Increase of sulfonylureas half-life, with the possibility of hypoglycemic episodes; patient should be informed of hypoglycemic risk; urine glucose self-monitoring should be intensified and sulfonylureas dosage be adjusted during treatment by fluconazole.

Rifampicin:

Decrease of fluconazole plasma level and of the efficacy of both anti-infections drugs by enzymatic induction (due to Refampicin) and diminished intestinal absorption (due to fluconazole). Decrease of the fluconazole AUC is 23% in case of combination with Rifampicin. Dosing intervals for administration of both anti-infections drugs should be extended.
Fluconazole plasma level should be monitored and the dosage should be adjusted, if needed.

Phenytoin:

Phenytoin plasma level increase and may reach toxic values.
Through inhibition of the phenytoin hepatic metabolism: careful clinical monitoring of phenytoin plasma levels measurements and if needed adjustment of dosage during treatment by fluconazole and after discontinuation.

Cyclosporin:

Possible increase of the cyclosporin circulating level (cyclosporin catabolism inhibition). Monitoring of renal function, serum cyclosporin level and if needed dosage adjustment during combination treatment and after discontinuation.

Theophylline:

Possible inscrease of serum theophylline level through dismissed plasma clearance of theophylline. Clinical monitoring and if needed monitoring of serum theophylline level is recommended.

Combinations To Be Taken Into Account:

Due to the lack of clinical studies, the combination of fluconazole with xanthic basis and INH calls for caution. In such case, clinical examinations or indeed biological tests are required.

Diuretics:

An increase of plasma level (40%) of fluconazole was noted in healthy volunteers, concomitantly receiving hydrochlorothiazide. Although the eventuality cannot be excluded, this increase does not necessitate fluconazole dosage adjustment in patients treated with diuretics.
Fluconazole multiple dose interaction studies did not show:

- Any modification of the kinetics of the oral contraceptives in women with a 50 mg daily dosage.
- Any consequences on endogenous steroid levels or on ACTH stimulated cortisol response with a 200 to 400 mg daily dosage in healthy male volunteers.

A fluconazole 50 mg daily dosage 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 or fluconazole absorption leading to clinical consequences was reported during interaction studies with food, cimetidine, antacid agents, or total body irradiation for bone marrow transplants.
Although interaction studies between fluconazole and zidovudine and/or pentamidine have not been conducted.
These drugs have been simultaneously prescribed in patients suffering from AIDS, without any significant differences in side effect incidence.
Interaction studies with antipyrine indicate that single or multiple doses of Fluconazole do not affect its metabolism.

SIDE EFFECTS

After gastrointestinal symptoms, the second most commonly observed side effect was rash. Gastro-intestinal disorders include nausea, abdominal pain, diarrhea and flatulence.
In some patients, particularly those with serious underlying diseases such as AIDS and cancer, abnormalities of hepatic function, of cholestatic, or cytolytic type, isolated or combined most often moderate.
Abnormalities of renal and haematological function have been observed during treatment with fluconazole and comparative agents, but the clinical significance and relationship to treatment as at this date is most often unclear.
Patients who develop abnormal liver function tests should be monitored for the development of more severe hepatic injury.
Although serious hepatic reactions have been rare, if clinical signs and symptoms or laboratory values consistent with lever disease develop may be attributable to fluconazole, treatment should be discontinued.
Patients with AIDS are more prone to the development of severe cutaneous reactions to many drugs.
A small number of AIDS patients have developed such reactions, while receiving fluconazole concomitantly with other agents known to be associated with severe exfoliation.
If a rash is considered attributable to fluconazole, the treatment should be discontinued.

OVERDOSAGE

In the event of overdosage, a symptomatic treatment 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%.

STORAGE

Store between 15-25°C. Protect from freezing.

PRESENTATIONS

Vials:

Flucand 200 mg/ 100 ml:	Fluconazole 2 mg/ ml
Flucand 100 mg/ 50 ml:	Fluconazole 2 mg/ ml
Flucand 50 mg/ 25 ml:	Fluconazole 2 mg/ ml

Infusion bags:

Flucand 400 mg/ 200 ml:	Fluconazole 2 mg/ ml
Flucand 200 mg/ 100 ml:	Fluconazole 2 mg/ ml

Excipients: Water for injection, Sodium chloride

THIS IS A MEDICAMENT

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous.
- Follow the doctor's prescription strictly, 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 medicament out of the reach of children

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HIKMA Pharmaceuticals, Amman-Jordan