Supracan (Fluconazole) Capsule 150mg

سُپراکین کیپسول (فلوکونازول) ۱۵۰ ملی گرام

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Capsule contains:
Fluconazole 150mg

DESCRIPTION

Fluconazole is used to prevent and treat a variety of fungal and yeast infections. It belongs to a class of drugs called azole antifungals. It works by stopping the growth of certain types of fungus.

CLINICAL PHARMACOLOGY

Mechanism of action: Fluconazole is a triazole antifungal drug. Its fundamental mechanism of action consists of the inhibition of the fungal cytochrome P-450 mediated by the demethylation of 14-alpha-lanosterol, a fundamental step in the biosynthesis of fungal ergosterol. The accumulation of 14-alpha-methyl sterols is related to the conse-quent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of fluconazole. Fluconazole has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian P-450 enzyme systems.

Pharmacodynamics: Fluconazole has been demonstrated to show fungistatic activity against the majority of strains of the following microorganisms, curing fungal infections. Candida albicans, Candida glabrata (Many strains are intermediately susceptible), Candida parapsilosis, Candida tropicalis, Cryptococcus neoformans. This is achieved through steroidal inhibition in fungal cells, interfering with cell wall synthesis and growth as well as cell adhesion, thereby treating fungal infections and their symptoms.

Pharmacokinetics: Absorption: Fluconazole is well absorbed by the oral route, with plasmatic levels (and systemic bioavaila-bility) greater than 90%, compared to the levels reached after intravenous administration. Oral absorption is not affected by co-administration with food. Peak fasting plasma concentrations are obtained between 0.5 and 1.5 hours postdose. Plasma concentrations are proportional to dose. About 90% of steady state levels are reached within 4 to 5 days after multiple once daily dosing. The administration of a loading dose (on day 1), twice the usual daily dose, raises plasmatic levels to 90% of normal levels.ele s in a state of equilibrium, already on day 2.

Distribution: The apparent volume of distribution approximates total body water. Plasma protein binding is low (11-12%). Fluconazole penetration into all body fluids studied is high. Fluconazole levels in saliva and sputum are similar to plasma levels . In patients with fungal meningitis, the concentration of fluconazole in the cere-brospinal fluid is approximately 80 % of that in plasma. High concentrations of fluconazole, above serum concentrations, are reached in the stratum corneum, in the dermis and epidermis, and in eccrine sweat. Fluconazole accumulates in the stratum corneum. At the 50 mg once daily dose, the fluconazole concentration after 12 days was 73 ? g/g, and 7 days after stopping treatment, it was still 5.8 g/g. At a dose of 150 mg once a week , the concentration of fluconazole in the stratum corneum on day 7 was 23.4 g/g 7 days after the second dose was still 7.1 ? g/g. The con-

centration of fluconazole in the nails after four months of administration of 150 mg once a week was 4.05 g/g in healthy nails and 1.8 g/g in diseased nails ; fluconazole was still measurable in nail samples tak-en 6 months after completion of treatment.

Biotransformation: Fluconazole is poorly metabolized. Of a radioactive dose, only 11% is excreted metabo-lized in the urine. Fluconazole is a mod-erate inhibitor of CYP2C9 and CYP3A4 isoenzymes . Fluconazole is also a potent inhibitor of the CYP2C19 isoenzyme.

Excretion: The plasma elimination half-life of fluconazole is approximately 30 hours. Its elimination is preferentially renal, with 80% of the unchanged dose appearing in the urine. Fluconazole clearance is pro-portional to creati-nine clearance. There is no evidence of circulating metabolites
Preclinical safety dataIn non-clinical studies, effects were observed only at exposures considered excessive compared to human exposures , which is of little relevance to clinical use.

Carcinogenesis: Fluconazole did not show evidence of carcinogenic po-tential in rats and mice treated orally for 24 months with doses of 2.5; 5 or 10 mg/kg/day (approximately 2-7 times the recommended human dose) . Male rats treated with 5 and 10 mg/kg/day had a high incidence of hepatocellular adenomas.

Mutagenesis: Fluconazole, with or without metabolic activation, was nega-tive in the mutagenicity test in 4 strains of Salmonella typhimurium , and in the L5178Y mouse lymphoma assay. Cytogenetic studies in vivo (murine bone marrow cells, after oral administration of fluconazole) and in vitro (human lymphocytes exposed to fluconazole at a dose of 1000 μg/ml) did not show evidence of chromosomal aberrations.
reproductive toxicity Fluconazole did not impair fertility in male or female rats treated orally with daily doses of 5, 10, or 20 mg/kg or parenterally with doses of 5, 25, or 75 mg/kg. There were no fetal effects at the 5 or 10 mg/kg dose ; An increase in fetal anatomical variants (supernumerary ribs, renal pelvic dilatation) and delayed ossification were observed at doses of 25 and 50 mg/kg and at higher doses. At doses between 80 mg/kg and 320 mg/kg, embryolethality in rats was increased and fetal abnormalities including un-dulating ribs, cleft palate, and abnormal craniofacial ossification .

INDICATIONS

Supracan is indicated in adults for the treatment of:

- Cryptococcal meningitis.
- Coccidioidomycosis.
- Invasive yeast infection.
- Mucosal candidiasis including oropharyngeal and oesophageal candidiasis, candiduria and chronic mucocutaneous candidiasis.
- Chronic atrophic oral candidiasis (associated with the use of dental prostheses) when dental hygiene or topical treatment is insufficient.
- Acute or recurrent vaginal candidiasis when local therapy is not appropriate.
- Candida balanitis when local therapy is not appropriate.
- Dermatomycoses, including those caused by Tinea pedis, Tinea corporis, Tinea cruris, Tinea versicolor and Candida skin infections when systemic therapy is indicated.
- Treatment of Tinea unguinum infection (onychomycosis) when the use of other antifun-gal agents is not considered appropriate.

CONTRAINDICATIONS

Hypersensitivity to the active substance, to other related azole compounds or to any of the excipients listed in section. Terfenadine is contraindicated in patients receiving multiple doses of fluconazole 400mg or greater daily, based on the results of a multiple-dose interaction study. Co-administration

of medicinal products known to prolong the QT interval and to be metabolised via cytochrome P450 (CYP) 3A4, such as cisapride, astemi-zole, pimozide, quinidine and erythromycin, is contraindicated in patients receiving fluconazole

INTERACTIONS

Cisapride: Cardiac events including torsade de pointes have been reported in patients co-administered with fluconazole and cisapride. A controlled study revealed that concomitant use of fluconazole 200 mg once daily and cisapride 20 mg 4 times daily resulted in a significant increase in cisapride plasma levels and prolongation of the QTc interval. Co-administration of cisapride is contraindicated in patients receiving fluconazole.

Terfenadine: Interaction studies due to the occurrence of severe cardiac dysrhythmias secondary to QTc interval prolongation have been performed in patients receiving azole antifungals concurrently with terfenadine. A study conducted with fluconazole 200 mg daily did not demonstrate prolongation of the QTc interval. Another study using daily doses of 400 and 800 mg of fluconazole demonstrated that fluconazole at doses of 400 mg daily or higher significantly increases terfenadine plasma levels when terfenadine is administered concomitantly. concomitant. The combined use of fluconazole at doses of 400 mg or higher in conjunction with terfenadine is contraindicated. The patient should be carefully monitored on concomitant administration of terfenadine and fluconazole at doses less than 400 mg daily.

Astemizole: Co-administration of fluconazole with astemizole may decrease the clearance of astemizole. The resulting increase in astemizole plasma concentrations may cause QT prolongation and rarely torsade de pointes. The concomitant administration of fluconazole and astemizole is contraindicated.

Pimozide: Although no in vitro or in vivo studies have been performed, concomitant administration of fluconazole and pimozide may result in inhibition of pimozide metabolism. Increased plasma concentrations of pimozide may cause QT prolongation and rarely torsade de pointes. Concomitant administration of fluconazole and pimozide is contraindicated.

Quinidine: Although not studied in vitro or in vivo, concomitant administration of fluconazole with quinidine may result in inhibition of quinidine metabolism. Quinidine use has been associated with interval prolonga-tion and rare cases of torsade de pointes. Co-administration of fluconazole and quinidine is contraindicated.

Erythromycin: Concomitant use of fluconazole and erythromycin may increase the risk of cardiotoxicity (QT prolongation, torsade de pointes) and consequently sudden cardiac death. Co-administration of fluconazole and erythromycin is contraindicated.

Halofantrine: Fluconazole may increase the plasma concentration of halofantrine due to its inhibitory effect on CYP3A4. Concomitant use of fluconazole and halofantrine has the potential to increase the risk of cardio-toxicity (QT prolongation, torsade de pointes) and consequently sudden cardiac death. This combination should be avoided.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Tinea capitis:
Fluconazole has been studied for the treatment of tinea capitis in children. It has not shown superiority over griseofulvin and the overall success rate was less than 20%. Therefore, Supracan should not be adminis-tered for tinea capitis infection.
Cryptococcosis:

Evidence for the efficacy of fluconazole in the treatment of cryptococcosis elsewhere (eg, pulmonary and cutaneous cryptococcosis) is limited, precluding specific dose recommendations.

Deep endemic mycoses: Evidence for the efficacy of fluconazole in the treatment of other forms of endemic mycoses such as para-coccidioidomycosis, lymphocutaneous sporotrichosis, and histoplasmosis is limited, precluding specific dos-age recommendations.

Renal system: Supracan should be used with caution in patients with renal dysfunction.

Hepatobiliary system: Supracan should be used with caution in patients with hepatic dysfunction. Fluconazole has been associated with rare cases of severe liver toxicity, including death, primarily in pa-tients with serious underlying medical conditions. In cases where hepatotoxicity was associated with flu-conazole, no relationship was observed with the total daily dose, duration of treatment, gender or age of the patient. Fluconazole hepatotoxicity has usually been reversible after discontinuation of treatment.

USE IN SPECIFIC POPULATION

Pregnancy An observational study has indicated an increased risk of spontaneous abortion in women treated with fluconazole during the first trimester. Data from several thousand pregnant women treated with a cumulative dose of ≤150 mg fluconazole, administered in the first trimester, do not show an increase in the overall risk of fetal abnormalities. In a large observational cohort study, oral fluconazole exposure during the first trimester was associated with a small increased risk of musculoskeletal abnormalities, corresponding to approximately 1 additional case per 1000 women treated with cumulative doses ≤450 mg compared with women treated with topical azoles already approximately 4 additional cases per 1000 women treated with cumulative doses greater than 450 mg. The adjusted relative risk was 1.29 (95% CI 1.05 to 1.58) for oral fluconazole 150 mg and 1.98 (95% CI 1.23 to 3.17) for doses greater than 450mg fluconazole. Lactation Fluconazole passes into breast milk reaching concentrations similar to those in plasma Breastfeeding can be maintained after administration of a single 150 mg dose of fluconazole. Breast-feeding is not recommended after multiple dose administration or after a high dose of fluconazole. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Supracan, as well as any possible adverse reactions in the nursing infant due to Supracan or the underlying maternal condition.

ADVERSE REACTIONS

The most frequently reported adverse reactions are : headache, abdominal pain, diarrhoea, nausea, vomit-ing, alanine aminotransferase and aspartate aminotransferase increased, alkaline phosphatase increased in blood and rash.

OVERDOSE

Cases of overdose with fluconazole, as well as concomitant hallucinations and paranoid behavior have been reported.In case of overdose, symptomatic treatment may be appropriate, with maintenance of vital signs and gastric lavage if necessary.Fluconazole is largely eliminated in the urine; therefore, forced diuresis will most likely increase the rate of elimination. A three-hour hemodialysis session decreases plasma levels by approximately 50%.

DOSAGE AND ADMINISTRATION

Posology The dosage should be based on the nature and severity of the fungal infection. Treatment of infections requiring multiple doses should be continued until clinical parameters or laboratory tests indicate that the active fungal infection has subsided. An inadequate treatment period can lead to recurrence of active infection.

Indication		Posology	Treatment Duration
Cryptococcosis	Treatment of cryptococcal meningitis	Loading dose: 400mg on the 1st day Subsequent doses: 200mg to 400mg once daily	It will usually last 6 to 8 weeks. In life-threatening infections, the daily dose may be increased to 800mg per day.
	Maintenance therapy to prevent recurrences of cryptococcosis in patients at high risk of recurrence	200mg once a day	Indefinite at the dose of 200mg per day
Coccidioidomycosis		200mg to 400mg once a day	11 months to 24 months or more depending on the patient. A dose of 800 mg once daily may be considered for some infections and especially for meningeal disease.
Invasive candidiasis		Loading dose: 800 mg on the 1st day Subsequent doses: 400mg once daily	In general, the recommended treatment duration for candidemia is 2 weeks after the first negative blood culture result and resolution of signs and symptoms attributable to candidemia.
Treatment of mucosal candidiasis	Oropharyngeal candidiasis	Loading dose: 200mg to 400 mg on the 1st day Subsequent doses: 100mg to 200mg once daily	7 to 21 days (until oropharyngeal candidiasis is in remission). In patients with severely decreased immune function it can be used for longer periods of time
Treatment of mucosal candidiasis	Oropharyngeal candidiasis	Loading dose: 200mg to 400 mg on the 1st day Subsequent doses: 100mg to 200mg once daily	7 to 21 days (until oropharyngeal candidiasis is in remission). In patients with severely decreased immune function it can be used for longer periods of time
	Esophageal candidiasis	Loading dose: 200mg to 400 mg on the 1st day Subsequent doses: 100mg to 200mg once daily	14 to 30 days (until esophageal candidiasis is in remission). In patients with severely decreased immune function it can be used for longer periods of time
	Candiduria	200 mg to 400 mg once a day	7 to 21 days. In patients with severely decreased immune function it can be used for longer periods of time
	Chronic atrophic candidiasis	50 mg once a day	14 days
	Chronic mucocutaneous candidiasis	50mg to 100mg once a day	Up to 28 days. Depending on the severity of the infection or the compromise of the underlying immune system, it may be used for longer periods of time.
Prophylaxis of relapses of mucosal candidiasis in HIV infected patients who are at high risk of suffering a relapse.	Oropharyngeal candidiasis	100mg to 200mg once a day or 200mg 3 times a week	Indefinite period for patients with chronic immune system suppression
	Esophageal candidiasis	100mg to 200mg once a day or 200mg 3 times a week	Indefinite period for patients with chronic immune system suppression
Genital candidiasis	"Acute vaginal candidiasis	150mg	Single dose

	Candida balanitis		
Genital candidiasis	Treatment and prophylaxis of recurrent vaginal candidiasis (more than 4 episodes per year)	150 mg every three days for a total of 3 doses (day 1, 4 and 7) followed by 150 mg once a week as a maintenance dose	6 month maintenance dose
Dermatomycosis	Tinea pedis, Tinea corporis,Tinea cruris, Candida infections	150 mg once a week or 50 mg once a day	2 to 4 weeks. In case of infection by Tinea pedis may require treatment for up to 6 weeks
	Tinea versicolor	"300mg to 400mg once a week 50 mg once a day "	"1 to 3 weeks 2 to 4 weeks"
	tinea unguium (onychomycosis)	150 mg once a week	Treatment should be continued until the infected nail is replaced (uninfected nail grows). Overgrowth of fingernails or toenails may require 3 to 6 months and 6 to 12 months respectively. However, the speed of growth can vary widely in individuals and depending on age. After successful long term treatment for chronic infections, nails can sometimes become disfigured.
Prophylaxis of Candida infections in patients with prolonged neutropenia		200mg to 400mg once a day	Treatment should begin several days before the anticipated onset of neutropenia and last for up to 7 days following recovery from neutropenia after the neutrophil count rises above 1,000 cells/mm3

Pediatric population: In the pediatric population, a maximum dose of 400 mg daily should not be exceeded.

As for similar infections in adults, the duration of treatment is based on the clinical and mycological re-sponse of the patient. Supracan is administered as a single daily dose. Pediatric patients with renal insufficiency, see dosage in " Patients with renal insufficiency ". The pharma-cokinetics of fluconazole in the pediatric renally impaired population have not been studied (see in-for-mation below on term neonates who often have renal immaturity).

Indication	Posology	Recommendations
Mucosal candidiasis	Initial dose: 6mg/kg Next doses: 3mg/kg once a day	The initial dose can be used on the first day to reach steady state levels more quickly
"Invasive candidiasis Cryptococcal meningitis"	Dose: 6 to 12 mg/kg once a day	Depending on the severity of the disease
Maintenance therapy to prevent recurrences of cryptococcal meningitis in children at high risk of recurrences	Dose: 6 mg/kg once a day	
Prophylaxis of Candida infec-tions in immunocompromised patients	Dose: 3 to 12 mg/kg once a day	Depending on the extent and du-ration of induced neutropenia

Adolescents (12 to 17 years old): Depending on weight and pubertal de-velopment, the prescriber may need to confirm which is the most appropri-ate dosage (adults or children). Clinical data indicate that children have a higher clearance of flu-conazole than that observed in adults. Doses of 100, 200, and 400 mg in adults correspond to doses of 3, 6, and 12 mg/kg in chil-

dren to obtain comparable systemic exposure. Safety and efficacy have not been established for the indication genital candidiasis in the pediatric popu-la-tion. Available safety data for other pediatric indications are described in section 4.8. If treatment for geni-tal candidiasis is imperative in adolescents (12 to 17 years), the same dosage as in adults will be estab-lished.

Term neonates (0 to 27 days): Neonates excrete fluconazole slowly. There are few pharmacokinetic data to support the dosing in term neonates

Age Group	Posology	Recommendations
Term neonates (0 to 14 days)	The same dose as for infants and children should be administered every 72 hours.	A maximum dose of 12mg/kg every 72 hours should not be exceeded
Term neonates (15 to 27 days)	The same dose as for infants and children should be adminis-tered every 48 hours	A maximum dose of 12 mg/kg every 48 hours should not be exceeded.

INSTRUCTIONS
Store below 30°C.

PRESENTATION
Supracan is available in pack size of 1's in a carton.

ہدایات: خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
۳۰ ڈگری سینٹی گریڈ سے کم پر رکھیں۔ گرمی، روشنی اور نمی سے محفوظ رکھیں۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخہ پر فروخت کریں۔

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