FUNCID

Instructions for the medicinal product

Trade name: Funcid.
International Nonproprietary Name: Fluconazole.
Dosage form: Solution for infusion.
Composition: Each 100 ml contains:
Fluconazole USP 200 mg;
Excipients q.s.
Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives.
ATC Code: J02AC01.
Pharmacological action:
Pharmacodynamics:
Fluconazole is a triazole antifungal agent. Its primary mode of action is the inhibition of fungal cytochrome P-450-mediated 14 alpha-lanosterol demethylation, an essential step in fungal ergosterol biosynthesis. The accumulation of 14 alpha-methyl sterols correlates with the subsequent 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 cytochrome P-450 enzyme systems.
Fluconazole 50 mg daily given up to 28 days has been shown not to effect testosterone plasma concentrations in males or steroid concentration in females of child-bearing age.
Susceptibility in vitro:
In vitro, fluconazole displays antifungal activity against most clinically common Candida species (including C. albicans, C. parapsilosis, C. tropicalis), C. glabrata shows a wide range of susceptibility while C. krusei is resistant to fluconazole.
Fluconazole also exhibits activity in vitro against Cryptococcus neoformans and Cryptococcus gattii as well as the endemic moulds Blastomyces dermatidiitis, Coccidioides immitis, Histoplasma capsulatum and Paracoccidioides brasiliensis.
Pharmacokinetics:
The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral route.
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. 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.
Distribution
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% the corresponding plasma levels.
High skin concentration 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 50 mg once daily, the concentration of fluconazole after 12 days was 73 µg/g and 7 days after cessation of treatment the concentration was still 5.8 µg/g. At the 150 mg once-a-week dose, the concentration of fluconazole in stratum corneum on day 7 was 23.4 µg/g and 7 days after the second dose was still 7.1 µg/g.
Concentration of fluconazole in nails after 4 months of 150 mg once-a-week dosing was 4.05 µg/g in healthy and 1.8 µg/g in diseased nails; and, fluconazole was still measurable in nail samples 6 months after the end of therapy.
Fluconazole is metabolised only to a minor extent. Of a radioactive dose, only 11% is excreted in a changed form in the urine.
Fluconazole is a selective inhibitor of the isozymes CYP2C9 and CYP3A4. Fluconazole is also an inhibitor of the isozyme CYP2C19.
Plasma elimination half-life for fluconazole is approximately 30 hours. The major route of excretion is renal, with approximately 80% of the administered dose appearing in the urine as unchanged medicinal product. 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 vaginal candidiasis, once daily and once weekly dosing for other indications.
Pharmacokinetics in renal impairment:
In patients with severe renal insufficiency, (GFR< 20 ml/min) half life increased from 30 to 98 hours. Consequently, reduction of the dose is needed. Fluconazole is removed by haemodialysis and to a lesser extent by peritoneal dialysis. After three hours of haemodialysis session, around 50% of fluconazole is eliminated from blood.
Indications for use:
Funcid is indicated in the following fungal infections.
Funcid is indicated in adults for the treatment of:
- Cryptococcal meningitis.
- Coccidioidomycosis. Invasive candidiasis.
- Mucosal candidiasis including oropharyngeal, oesophageal candidiasis, candiduria and chronic mucocutaneous candidiasis.
- Chronic oral atrophic candidiasis (denture sore mouth) if dental hygiene topical treatment are insufficient.

Funcid is indicated in adults for the prophylaxis of:
- Relapse of crytopcoccal meningitis in patients with high risk of recurrence.
- Relapse of oropharyngeal or oesophageal candidiasis in patients infected with HIV who are at high risk of experiencing relapse.
- Prophylaxis of candidal infections in patients with prolonged neutropenia (such as patients with haematological malignancies receiving chemotherapy or patients receiving Hematopoietic Stem Cell Transplantation).

Funcid is indicated in term newborn infants, infants, toddlers, children and adolescents aged from 0 to 17 years old:
- Funcid is used for the treatment of mucosal candidiasis (oropharyngeal, oesophageal), invasive candidiasis, cryptococcal meningitis and the prophylaxis of candidal infections in immunocompromised patients. Funcid can be used as maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of reoccurrence.

Therapy may be instituted before the results of the cultures and other laboratory studies are known; however, once these results become available, anti-infective therapy should be adjusted accordingly.
Consideration should be given to official guidance on the appropriate use of antifungals.
Contraindications:
- Hypersensitivity to the active substance to related azole substances, or to any of the excipients.
- Coadministration of terfenadine is contraindicated in patients receiving Funcid at multiple doses of 400 mg per day or higher based upon results of a multiple dose interaction study. Coadministration of other medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 such as cisapride, astemizole, pimozide, quinidine, amiodarone and erythromycin are contraindicated in patients receiving fluconazole.

Should be administered *with caution* to patients with renal and liver dysfunction.
Pregnancy and Nursing Mother:
Fluconazole in standard doses and short-term treatments should not be used in pregnancy unless clearly necessary.
Fluconazole in high dose and/or in prolonged regimens should not be used during pregnancy except for potentially life-threatening infections.
Fluconazole passes into breast milk to reach concentrations lower than those in plasma. Breast-feeding may be maintained after a single use of a standard dose 200 mg fluconazole or less. Breast-feeding is not recommended after repeated use or after high dose fluconazole.

Dosage and Direction for use:
Posology
The dose should be based on the nature and severity of the fungal infection. Treatment of infections requiring multiple dosing should be continued until clinical parameters or laboratory tests indicate that active fungal infection has subsided. An inadequate period of treatment may lead to recurrence of active infection.
Adults:
Cryptococcosis:
• *Treatment of cryptococcal meningitis* - Loading dose: 400 mg on Day 1. Subsequent dose: 200 mg to 400 mg daily. Duration of treatment - Usually at least 6 to 8 weeks. In life threatening infections the daily dose can be increased to 800 mg.
• *Maintenance therapy to prevent relapse of cryptococcal meningitis in patients with high risk of recurrence* - 200 mg daily. Duration of treatment - Indefinitely at a daily dose of 200 mg.
Coccidioidomycosis - 200 mg to 400 mg. Duration of treatment - 11 months up to 24 months or longer depending on the patient. 800 mg daily may be considered for some infections and especially for meningeal disease.
Invasive candidiasis - Loading dose: 800 mg on Day 1. Subsequent dose: 400 mg daily. Duration of treatment - In general, the recommended duration of therapy for candidemia is for 2 weeks after first negative blood culture result and resolution of signs and symptoms attributable to candidemia.
Treatment of mucosal candidiasis:
• *Oropharyngeal candidiasis* - Loading dose: 200 mg to 400 mg on Day 1. Subsequent dose: 100 mg to 200 mg daily. Duration of treatment - 7 to 21 days (until oropharyngeal candidiasis is in remission). Longer periods may be used in patients with severely compromised immune function.
• *Oesophageal candidiasis* - Loading dose: 200 mg to 400 mg on Day 1. Subsequent dose: 100 mg to 200 mg daily. Duration of treatment - 14 to 30 days (until oesophageal candidiasis is in remission). Longer periods may be used in patients with severely compromised immune function.
• *Candiduria* - 200 mg to 400 mg daily. Duration of treatment - 7 to 21 days. Longer periods may be used in patients with severely compromised immune function.
• *Chronic atrophic candidiasis* - 50 mg daily. Duration of treatment - 14 days.
• *Chronic mucocutaneous candidiasis* - 50 mg to 100 mg daily. Duration of treatment - Up to 28 days. Longer periods depending on both the severity of infection or underlying immune compromisation and infection.
Prevention of relapse of mucosal candidiasis in patients infected with HIV who are at high risk of experiencing relapse:
• *Oropharyngeal candidiasis* - 100 mg to 200 mg daily or 200 mg 3 times per week. Duration of treatment - An indefinite period for patients with chronic immune suppression.
• *Oesophageal candidiasis* - 100 mg to 200 mg daily or 200 mg 3 times per week. Duration of treatment - An indefinite period for patients with chronic immune suppression.
Prophylaxis of candidal infections - 200 mg to 400 mg. Duration of treatment - Treatment should start several days before the anticipated onset of neutropenia and continue for 7 days after recovery from neutropenia after the neutrophil count rises above 1000 cells per mm3.
Special populations:
Elderly: Dosage should be adjusted based on the renal function.
Renal impairment:
Funcid is predominantly excreted in the urine as unchanged active substance. No adjustments in single dose therapy are necessary. In patients (including paediatric population) with impaired renal function who will receive multiple doses of fluconazole, an initial dose of 50 mg to 400 mg should be given, based on the recommended daily dose for the indication. After this initial loading dose, the daily dose (according to indication) should be based on the following table:
Creatinine clearance (ml/min) >50 - Percent of recommended dose - 100%
Creatinine clearance (ml/min) ≤50 (no dialysis) - Percent of recommended dose - 50%
Creatinine clearance (ml/min) Regular dialysis - Percent of recommended dose - 100% after each dialysis.
Patients on regular dialysis should receive 100% of the recommended dose after each dialysis; on non-dialysis days, patients should receive a reduced dose according to their creatinine clearance
Hepatic impairment:
Limited data are available in patients with hepatic impairment, therefore fluconazole should be administered with caution to patients with liver dysfunction.
Paediatric population:
A maximum dose of 400 mg daily should not be exceeded in paediatric population.
As with similar infections in adults, the duration of treatment is based on the clinical and mycological response. Funcid is administered as a single daily dose.
For paediatric patients with impaired renal function, see dosing in "Renal impairment". The pharmacokinetics of fluconazole has not been studied in paediatric population with renal insufficiency (for "Term newborn infants" who often exhibit primarily renal immaturity please see below).
Infants, toddlers and children (from 28 days to 11 years old):
Mucosal candidiasis - Initial dose: 6 mg/kg. Subsequent dose: 3 mg/kg daily. Initial dose may be used on the first day to achieve steady state levels more rapidly.
Invasive candidiasis, Cryptococcal meningitis - Dose: 6 to 12 mg/kg daily. Depending on the severity of the disease.
Maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of recurrence - Dose: 6 mg/kg daily. Depending on the severity of the disease.
Prophylaxis of Candida in immunocompromised patients - Dose: 3 to 12 mg/kg daily. Depending on the extent and duration of the induced neutropenia (see Adults posology).
Adolescents (from 12 to 17 years old):
Depending on the weight and pubertal development, the prescriber would need to assess which posology (adults or children) is the most appropriate. Clinical data indicate that children have a higher fluconazole clearance than observed for adults. A dose of 100, 200 and 400 mg in adults corresponds to a 3, 6 and 12 mg/kg dose in children to obtain a comparable systemic exposure.
Term newborn infants (0 to 27 days):
Neonates excrete fluconazole slowly. There are few pharmacokinetic data to support this posology in term newborn infants.
Term newborn infants (0 to 14 days) - The same mg/kg dose as for infants, toddlers and children should be given every 72 hours. A maximum dose of 12 mg/kg every 72 hours should not be exceeded.
Term newborn infants (from 15 to 27 days) - The same mg/kg dose as for infants, toddlers and children should be given every 48 hours. A maximum dose of 12 mg/kg every 48 hours should not be exceeded.
Method of administration:
Funcid may be administered either orally or by intravenous infusion, the route being dependent on the clinical state of the patient. On transferring from the intravenous to the oral route, or vice versa, there is no need to change the daily dose.
Intravenous infusion should be administrated at a rate not exceeding 10 ml/minute. Funcid is formulated in sodium chloride 9 mg/ml (0.9%) solution for infusion, each 200 mg (100 ml bottle) containing 15 mmol each of Na+ and C1-. Because Funcid is available as a dilute sodium chloride solution, in patients requiring sodium or fluid restriction, consideration should be given to the rate of fluid administration.
Side-effects:
Blood and the lymphatic system disorders: Uncommon – Anaemia. Rare - Agranulocytosis, leukopenia, thrombocytopenia, neutropenia.
Immune system disorders: Rare – Anaphylaxis.
Metabolism and nutrition disorders: Uncommon – Decreased appetite. Rare - Hypercholesterolaemia, hypertriglyceridaemia, hypokalemia.
Psychiatric disorders: Uncommon – Somnolence, insomnia.
Nervous system disorders: Common – Headache. Uncommon – Seizures, paraesthesia, dizziness, taste perversion. Rare - Tremor.
Ear and labyrinth disorders: Uncommon – Vertigo.
Cardiac disorders: Rare - Torsade de pointes, QT prolongation.
Gastrointestinal disorders: Common – Abdominal pain, vomiting, diarrhoea, nausea. Uncommon – Constipation dyspepsia, flatulence, dry mouth.
Hepatobiliary disorders: Common – Alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased. Uncommon – Cholestasis, jaundice, bilirubin increased. Rare - Hepatic failure, hepatocellular necrosis, hepatitis, hepatocellular damage.
Skin and subcutaneous tissue disorders: Common – Rash. Uncommon – Drug eruption, urticaria, pruritus, increased sweating. Rare - Toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalised exanthematous-pustulosis, dermatitis exfoliative, angioedema, face oedema, alopecia.
Musculoskeletal and connective tissue disorders: Uncommon – Myalgia.
General disorders and administration site conditions: Uncommon – Fatigue, malaise, asthenia, fever.
Overdose:
There have been reports of overdose with fluconazole and hallucinations and paranoid behaviour have been concomitantly reported.
In the event of overdose, symptomatic treatment (with supportive measures and gastric lavage if necessary) may be adequate.
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%.
Drug interactions:
Concomitant use of the following other medicinal products is contraindicated:
Cisapride: There have been reports of cardiac events including torsades de pointes in patients to whom fluconazole and cisapride were coadministered. Concomitant treatment with fluconazole and cisapride is contraindicated.
Terfenadine: Because of the occurrence of serious cardiac dysrhythmias secondary to prolongation of the QTc interval in patients receiving azole antifungals in conjunction with terfenadine, interaction studies have been performed. The combined use of fluconazole at doses of 400 mg or greater with terfenadine is contraindicated. The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored.
Astemizole: Concomitant administration of fluconazole with astemizole may decrease the clearance of astemizole. Resulting increased plasma concentrations of astemizole can lead to QT prolongation and rare occurrences of torsades de pointes.
Coadministration of fluconazole and astemizole is contraindicated.
Pimozide: Although not studied in vitro or in vivo, concomitant administration of fluconazole with pimozide may result in inhibition of pimozide metabolism. Increased pimozide plasma concentrations can lead to QT prolongation and rare occurrences of torsades de pointes. Coadministration 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. Use of quinidine has been associated with QT prolongation and rare occurrences oftorsades de pointes. Coadministration of fluconazole and quinidine is contraindicated.
Erythromycin: Concomitant use of fluconazole and erythromycin has the potential to increase the risk of cardiotoxicity (prolonged QT interval, torsades de pointes) and consequently sudden heart death. Coadministration of fluconazole and erythromycin is contraindicated.
Amiodarone: Concomitant administration of fluconazole with amiodarone may result in inhibition of amiodarone metabolism. Use of amiodarone has been associated with QT prolongation. Coadministration of fluconazole and amiodarone is contraindicated.
Concomitant use of the following other medicinal products cannot be recommended:
Halofantrine: Fluconazole can increase halofantrine plasma concentration due to an inhibitory effect on CYP3A4. Concomitant use of fluconazole and halofantrine has the potential to increase the risk of cardiotoxicity (prolonged QT interval, torsades de pointes) and consequently sudden heart death. This combination should be avoided.
Concomitant use of the following other medicinal products lead to precautions and dose adjustments:
The effect of other medicinal products on fluconazole
Rifampicin: Concomitant administration of fluconazole and rifampicin resulted in a 25% decrease in the AUC and a 20% shorter half-life of fluconazole. In patients receiving concomitant rifampicin, an increase of the fluconazole dose should be considered.
Interaction studies have shown that when oral fluconazole is coadministered with food, cimetidine, antacids or following total body irradiation for bone marrow transplantation, no clinically significant impairment of fluconazole absorption occurs.
Hydrochlorothiazide: In a pharmacokinetic interaction study, coadministration of multiple-dose hydrochlorothiazide to healthy volunteers receiving fluconazole increased plasma concentration of fluconazole by 40%. An effect of this magnitude should not necessitate a change in the fluconazole dose regimen in subjects receiving concomitant diuretics.
The effect of fluconazole on other medicinal products
Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4. Fluconazole is also an inhibitor of the isozyme CYP2C19. In addition to the observed/documented interactions mentioned below, there is a risk of increased plasma concentration of other compounds metabolized by CYP2C9, CYP2C19 and CYP3A4 coadministered with fluconazole. Therefore caution should be exercised when using these combinations and the patients should be carefully monitored. The enzyme inhibiting effect of fluconazole persists 4-5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole.
Alfentanil: Dose adjustment of alfentanil may be necessary.
Amitriptyline, nortriptyline: Fluconazole increases the effect of amitriptyline and nortriptyline. 5-nortriptyline and/or S-amitriptyline may be measured at initiation of the combination therapy and after one week. Dose of amitriptyline/nortriptyline should be adjusted, if necessary.
Anticoagulants: In patients receiving coumarin-type or indanedione anticoagulants concurrently with fluconazole the prothrombin time should be carefully monitored. Dose adjustment of the anticoagulant may be necessary.
Benzodiazepines (short acting), i.e. midazolam, triazolam: If concomitant benzodiazepine therapy is necessary in patients being treated with fluconazole, consideration should be given to decreasing the benzodiazepine dose, and the patients should be appropriately monitored.
Carbamazepine: Fluconazole inhibits the metabolism of carbamazepine and an increase in serum carbamazepine of 30% has been observed. There is a risk of developing carbamazepine toxicity. Dose adjustment of carbamazepine may be necessary depending on concentration measurements/effect.
Calcium channel blockers: Certain calcium channel antagonists (nifedipine, isradipine, amlodipine, verapamil and felodipine) are metabolized by CYP3A4. Fluconazole has the potential to increase the systemic exposure of the calcium channel antagonists. Frequent monitoring for adverse events is recommended.
Celecoxib: Half of the celecoxib dose may be necessary when combined with fluconazole.
Cyclophosphamide: Combination therapy with cyclophosphamide and fluconazole results in an increase in serum bilirubin and serum creatinine. The combination may be used while taking increased consideration to the risk of increased serum bilirubin and serum creatinine.
Fentanyl: Elevated fentanyl concentration may lead to respiratory depression. Patients should be monitored closely for the potential risk of respiratory depression. Dosage adjustment of fentanyl may be necessary.
HMG CoA reductase inhibitors: The risk of myopathy and rhabdomyolysis increases when fluconazole is coadministered with HMG-CoA reductase inhibitors metabolised through CYP3A4, such as atorvastatin and simvastatin, or through CYP2C9, such as fluvastatin. If concomitant therapy is necessary, the patient should be observed for symptoms of myopathy and rhabdomyolysis and creatine kinase should be monitored. HMG-CoA reductase inhibitors should be discontinued if a marked increase in creatine kinase is observed or myopathy/rhabdomyolysis is diagnosed or suspected.
Immunosuppresors (i.e. ciclosporin, everolimus, sirolimus and tacrolimus):
Ciclosporin: Fluconazole significantly increases the concentration and AUC of ciclosporin.
Everolimus: Although not studied in vivo or in vitro, fluconazole may increase serum concentrations of everolimus through inhibition of CYP3A4.
Sirolimus: Fluconazole increases plasma concentrations of sirolimus presumably by inhibiting the metabolism of sirolimus via CYP3A4 and P-glycoprotein. This combination may be used with a dose adjustment of sirolimus depending on the effect/concentration measurements.
Tacrolimus: Fluconazole may increase the serum concentrations of orally administered tacrolimus up to 5 times due to inhibition of tacrolimus metabolism through CYP3A4 in the intestines. No significant pharmacokinetic changes have been observed when tacrolimus is given intravenously. Increased tacrolimus levels have been associated with nephrotoxicity. Dose of orally administered tacrolimus should be decreased depending on tacrolimus concentration.
Losartan: Fluconazole inhibits the metabolism of losartan to its active metabolite (E-31 74) which is responsible for most of the angiotensin II-receptor antagonism which occurs during treatment with losartan. Patients should have their blood pressure monitored continuously.
Methadone: Fluconazole may enhance the serum concentration of methadone. Dose adjustment of methadone may be necessary.
Non-steroidal anti-inflammatory drugs: The Cmax and AUC of flurbiprofen was increased by 23% and 81%, respectively, when coadministered with fluconazole compared to administration of flurbiprofen alone. Similarly, the Cmax and AUC of the pharmacologically active isomer [S-(+)-ibuprofen] was increased by 15% and 82%, respectively, when fluconazole was coadministered with racemic ibuprofen (400 mg) compared to administration of racemic ibuprofen alone.
Although not specifically studied, fluconazole has the potential to increase the systemic exposure of other NSAIDs that are metabolized by CYP2C9 (e.g. naproxen, lornoxicam, meloxicam, diclofenac). Frequent monitoring for adverse events and toxicity related to NSAIDs is recommended. Adjustment of dose of NSAIDs may be needed.
Phenytoin: With coadministration, serum phenytoin concentration levels should be monitored in order to avoid phenytoin toxicity.
Prednisone: Patients on long-term treatment with fluconazole and prednisone should be carefully monitored for adrenal cortex insufficiency when fluconazole is discontinued.
Rifabutin: Fluconazole increases serum concentrations of rifabutin, leading to increase in the AUC of rifabutin up to 80%. In combination therapy, symptoms of rifabutin toxicity should be taken into consideration.
Saquinavir: Fluconazole increases the AUC and Cmax of saquinavir with approximately 50% and 55% respectively, due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein. Interaction with saquinavir/ritonavir has not been studied and might be more marked. Dose adjustment of saquinavir may be necessary.
Sulfonylureas: Frequent monitoring of blood glucose and appropriate reduction of sulfonylurea dose is recommended during coadministration.
Theophylline: Patients who are receiving high dose theophylline or who are otherwise at increased risk for theophylline toxicity should be observed for signs of theophylline toxicity while receiving fluconazole. Therapy should be modified if signs of toxicity develop.
Vinca alkaloids: Although not studied, fluconazole may increase the plasma levels of the vinca alkaloids (e.g. vincristine and vinblastine) and lead to neurotoxicity, which is possibly due to an inhibitory effect on CYP3A4.
Vitamin A: This combination may be used but the incidence of CNS related undesirable effects should be borne in mind.
Voriconazole: Monitoring for voriconazole associated adverse events is recommended if voriconazole is used sequentially after fluconazole.
Zidovudine: Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions. Dose reduction of zidovudine may be considered.
Azithromycin: There was no significant pharmacokinetic interaction between fluconazole and azithromycin.
Oral contraceptives: Two pharmacokinetic studies with a combined oral contraceptive have been performed using multiple doses of fluconazole. There were no relevant effects on hormone level in the 50 mg fluconazole study, while at 200 mg daily, the AUCs of ethinyl estradiol and levonorgestrel were increased 40% and 24%, respectively. Thus, multiple dose use of fluconazole at these doses is unlikely to have an effect on the efficacy of the combined oral contraceptive.
Ivacaftor: A reduction of the ivacaftor dose to 150 mg once daily is recommended for patients taking concomitant moderate CYP3A inhibitors, such as fluconazole and erythromycin.
Cautions:
Fluconazole has been studied for treatment of tinea capitis in children. It was shown not to be superior to griseofulvin and the overall success rate was less than 20%. Therefore, Funcid should not be used for tinea capitis.
The evidence for efficacy of fluconazole in the treatment of cryptococcosis of other sites (e.g. pulmonary and cutaneous cryptococcosis) is limited, which prevents dosing recommendations.
The evidence for efficacy of fluconazole in the treatment of other forms of endemic mycoses such asparacoccidioidomycosis, lymphocutaneous sporotrichosis and histoplasmosis is limited, which prevents specific dosing recommendations.
Ketoconazole is known to cause adrenal insufficiency, and this could also although rarely seen be applicable to fluconazole.
Funcid 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 patient has been observed. Fluconazole hepatotoxicity has usually been reversible on discontinuation of therapy.
Patients who develop abnormal liver function tests during fluconazole therapy must be monitored closely for the development of more serious hepatic injury.
The patient should be informed of suggestive symptoms of serious hepatic effect (important asthenia, anorexia, persistent nausea, vomiting and jaundice). Treatment of fluconazole should be immediately discontinued and the patient should consult a physician.
Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. During post-marketing surveillance, there have been very rare cases of QT prolongation and torsades de pointes in patients taking fluconazole. These reports included seriously ill patients with multiple confounding risk factors, such as structural heart disease, electrolyte abnormalities and concomitant treatment that may have been contributory.
Funcid should be administered with caution to patients with these potentially proarrhythmic conditions.
Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, during treatment with fluconazole. AIDS patients are more prone to the development of severe cutaneous reactions to many medicinal products. If a rash, which is considered attributable to fluconazole, develops in a patient treated for a superficial fungal infection, further therapy with this medicinal product should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and fluconazole discontinued ifbullous lesions or erythema multiforme develop.
Fluconazole is a potent CYP2C9 inhibitor and a moderate CYP3A4 inhibitor. Fluconazole is also an inhibitor of CYP2C19. Funcid treated patients who are concomitantly treated with medicinal products with a narrow therapeutic window metabolised through CYP2C9, CYP2C19 and CYP3A4, should be monitored.
This medicinal product contains 0.154 mmol sodium per ml. To be taken into consideration by patients on a controlled sodium diet.
Effects on ability to drive and use machines:
No studies have been performed on the effects of Funcid on the ability to drive or use machines.
Patients should be warned about the potential for dizziness or seizures while taking Funcid and should be advised not to drive or operate machines if any of these symptoms occur.
Presentation:
1X1, 100 ml FFS Plastic bottle in a monocarton, with instruction for use.
Storage:
Keep in dry place protected from light at a temperature below 30°C. Keep out of reach of children.
Shelf life:
Labeled. Do not use after expiry date.
Distribution Condition:
Prescription only medicine (POM).