Flucozole

Name and Strength of Active Ingredient(s):
Flucozole 50 mg
Each capsule contains: Fluconazole 50 mg
Flucozole 100 mg
Each capsule contains: Fluconazole 100 mg
Flucozole 150 mg
Each capsule contains: Fluconazole 150 mg
Flucozole 200 mg
Each capsule contains: Fluconazole 200 mg

Product Description:
Flucozole 50 mg
White granule in blue-white capsule No. 4 with "50" and "Siam" in black ink on the capsule shell.
Flucozole 100 mg
White granule in blue-white capsule No. 2 with "100" and "Siam" in black ink on the capsule shell.
Flucozole 150 mg
White granule in blue-blue capsule shell No. 1 with "150" and "Siam" in black ink on the capsule shell.
Flucozole 200 mg
White granule in violet-white capsule No. 0 with "200" and "Siam" in black ink on the capsule shell.

Pharmacodynamic Properties:
Fluconazole is a triazole antifungal agent. Its primary mode of action is the inhibition of fungal cytochrome P450-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 CYP450 enzymes than for various mammalian CYP450 enzyme systems.

Pharmacokinetic Properties:
The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral route.
Absorption
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.
Biotransformation
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.
Excretion
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:
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.
1. Cryptococcosis, including cryptococcal meningitis and infections of other sites (e.g., pulmonary, cutaneous). Normal hosts and patients with AIDS, organ transplants or other causes of immunosuppression may be treated. Fluconazole can be used as maintenance therapy to prevent relapse of cryptococcal disease in patients with AIDS.
2. Systemic candidiasis, including candidemia, disseminated candidiasis and other forms of invasive candidal infections. These include infections of the peritoneum, endocardium, eye, and pulmonary and urinary tracts. Patients with malignancy, in intensive care units, receiving cytotoxic or immunosuppressive therapy, or with other factors predisposing to candidal infection may be treated.
3. Mucosal candidiasis. These include oropharyngeal, esophageal, non-invasive bronchopulmonary infections, candiduria, mucocutaneous and chronic oral atrophic candidiasis (denture sore mouth). Normal hosts and patients with compromised immune function may be treated. Prevention of relapse of oropharyngeal candidiasis in patients with AIDS.
4. Genital candidiasis. Vaginal candidiasis, acute or recurrent, and prophylaxis to reduce the incidence of recurrent vaginal candidiasis (three or more episodes a year). Candidal balanitis.
5. Prevention of fungal infections in patients with malignancy who are predisposed to such infections as a result of cytotoxic chemotherapy or radiotherapy.
6. Dermatomycosis, including tinea pedis, tinea corporis, tinea cruris, tinea versicolor, and dermal Candida infections.

Dosage and administration:
The daily dose of fluconazole should be based on the nature and severity of the fungal infection. Most cases of vaginal candidiasis respond to single-dose therapy. Therapy for those types of infections requiring multiple-dose treatment 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. Patients with AIDS and cryptococcal meningitis or recurrent oropharyngeal candidiasis usually require maintenance therapy to prevent relapse.
IN THE DOSING INSTRUCTIONS BELOW, THE DAILY DOSE OF FLUCONAZOLE IS THE SAME FOR ORAL (CAPSULES) AND INTRAVENOUS ADMINISTRATION SINCE ORAL ABSORPTION IS RAPID AND ALMOST COMPLETE.
Use in Adults
1. For cryptococcal meningitis and cryptococcal infections at other sites, the usual dose is 400 mg on the first day followed by 200 mg to 400 mg once daily. Duration of treatment for cryptococcal infections will depend on the clinical and mycological response but is usually at least 6 to 8 weeks for cryptococcal meningitis.
   For the prevention of relapse of cryptococcal meningitis in patients with AIDS, after the patient receives a full course of primary therapy, fluconazole may be administered indefinitely at a once daily dose of 200 mg.
2. For candidemia, disseminated candidiasis and other invasive candidal infections, the usual dose is 400 mg on the first day followed by 200 mg once daily. Depending on the clinical response, the dose may be increased to 400 mg once daily. Duration of treatment is based upon the clinical response.
3. For oropharyngeal candidiasis, the usual dose is 50 mg to 100 mg once daily for 7 to 14 days. If necessary, treatment can be continued for longer periods in patients with severely compromised immune function. For atrophic oral candidiasis associated with dentures, the usual dose is 50 mg once daily for 14 days administered concurrently with local antiseptic measures to the denture.
   For other candidal infections of mucosa except genital candidiasis (see below) (e.g., esophagitis, non-invasive bronchopulmonary infections, candiduria, mucocutaneous candidiasis, etc.), the usual effective dose is 50 mg to 100 mg once daily, given for 14 to 30 days.
   For the prevention of relapse of oropharyngeal candidiasis in patients with AIDS, after the patient receives a full course of primary therapy, fluconazole may be administered at a 150 mg once-weekly dose.
4. For the treatment of vaginal candidiasis, fluconazole 150 mg should be administered as a single oral dose.
   To reduce the incidence of recurrent vaginal candidiasis, a 150 mg once-monthly dose may be used. The duration of therapy should be individualized, but ranges from 4 to 12 months. Some patients may require more frequent dosing.
   For Candidal balanitis, fluconazole 150 mg should be administered as a single oral dose.
5. The recommended fluconazole dosage for the prevention of candidiasis is 50 mg to 400 mg once daily, based on the patient's risk for developing fungal infection. For patients at high risk of systemic infection, e.g., patients who are anticipated to have profound or prolonged neutropenia, the recommended daily dose is 400 mg once daily. Fluconazole administration should start several days before the anticipated onset of neutropenia and continue for 7 days after the neutrophil count rises above 1000 cells/mm^3.
6. For dermal infections including tinea pedis, tinea corporis, tinea cruris and Candida infections, the recommended dosage is 150 mg once weekly or 50 mg once daily. Duration of treatment is normally 2 to 4 weeks, but tinea pedis may require treatment for up to 6 weeks.
   For tinea versicolor, the recommended dose is 300 mg once weekly for 2 weeks; a third weekly dose of 300 mg may be needed in some patients, whereas, in some patients, a single dose of 300 mg to 400 mg may be sufficient. An alternate dosing regimen is 50 mg once daily for 2 to 4 weeks.

Use in Children
As with similar infections in adults, the duration of treatment is based on the clinical and mycological response. The maximum adult daily dosage should not be exceeded in children. Fluconazole is administered as a single dose each day. The recommended dosage of fluconazole for mucosal candidiasis is 3 mg/kg once daily. A loading dose of 6 mg/kg may be used on the first day to achieve steady-state levels more rapidly.
For the treatment of systemic candidiasis and cryptococcal infections, the recommended dosage is 6 to 12 mg/kg once daily, depending on the severity of the disease.
For suppression of relapse of cryptococcal meningitis in children with AIDS, the recommended dose of fluconazole is 6 mg/kg once daily.
For the prevention of fungal infections in immunocompromised patients considered at risk as a consequence of neutropenia following cytotoxic chemotherapy or radiotherapy, the dose should be 3 mg/kg to 12 mg/kg once daily, depending on the extent and duration of the induced neutropenia (see Use in Adults). (For children with impaired renal function, see Use in Renal Impairment).
Use in Children 4 Weeks of Age and Younger
Neonates excrete fluconazole slowly. In the first 2 weeks of life, the same mg/kg dosing as in older children should be used but administered every 72 hours. During week 3 and 4 of life, the same dose should be given every 48 hours.
Use in Elderly
Where there is no evidence of renal impairment, normal dosage recommendations should be adopted. For patients with renal impairment (creatinine clearance < 50 mL/min), the dosage schedule should be adjusted as described below.
Use in Renal Impairment
Fluconazole is predominantly excreted in the urine as unchanged drug. No adjustments in single-dose therapy are necessary. In patients (including children) with impaired renal function who will receive multiple doses of fluconazole, an initial loading dose of 50 mg to 400 mg should be given. After the loading dose, the daily dose (according to indication) should be administered as outlined in Table 1:

Table 1: Daily Dose

Creatinine Clearance (mL/min)	Recommended Dose (%)
> 50	100
≤ 50 (no dialysis)	50
Hemodialysis	100 after each hemodialysis

Patients on hemodialysis 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.
Method of administration
The capsules should be swallowed whole and independent of food intake.
Administration
Fluconazole may be administered either orally (capsules) or by intravenous infusion (solution for 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 route, or vice versa, there is no need to change the daily dosage.
Fluconazole 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 dilute saline solution, in patients requiring sodium or fluid restriction, consideration should be given to the rate of fluid administration.

Route of Administration:
Oral

Contraindications:
Fluconazole should not be used in patients with known hypersensitivity to fluconazole or related azole substances.
Coadministration of terfenadine is contraindicated in patients receiving fluconazole 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 CYP3A4 such as cisapride, astemizole, pimozide, quinidine, and erythromycin are contraindicated in patients receiving fluconazole.

Warning and Precautions:
Hepatobiliary system
Fluconazole should be administered with caution to patients with liver dysfunction. 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 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.
Dermatological reactions
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 drugs. If a rash develops in a patient treated for a superficial fungal infection which is considered attributable to fluconazole, further therapy with this agent should be discontinued. If patients with invasive/systemic fungal infections develop rashes, they should be monitored closely and fluconazole discontinued if bullous lesions or erythema multiforme develop.
Terfenadine
The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored.
Hypersensitivity
In rare cases anaphylaxis has been reported.
Cardiovascular system
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 torsade 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 medications that may have been contributory.
Fluconazole should be administered with caution to patients with these potentially proarrhythmic conditions. Coadministration of other medicinal products known to prolong the QT interval and which are metabolised via the CYP3A4 are contraindicated.
Renal System
Use with caution in patients with renal dysfunction.
Adrenal insufficiency
Ketoconazole is known to cause adrenal insufficiency, and this could also although rarely be seen, applicable to fluconazole.
Tinea capitis
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%.
Cryptococcosis
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.
Halofantrine
Halofantrine has been shown to prolong QTc interval at the recommended therapeutic dose and is a substrate of CYP3A4. The concomitant use of fluconazole and halofantrine is therefore not recommended.
Cytochrome P450
Fluconazole is a moderate CYP2C9 inhibitor and a moderate CYP3A4 inhibitor. Fluconazole is also an inhibitor of the isoenzyme CYP2C19. Fluconazole-treated patients who are concomitantly treated with drugs with a narrow therapeutic window metabolized through CYP2C9, CYP2C19 and CYP3A4 should be monitored.
Excipients
The capsules contain lactose and should not be given to patients with rare hereditary problems of galactose intolerance, the LAPP lactase deficiency or glucose-galactose malabsorption.

Interactions with other Medicaments:
Concomitant use of the following other medicinal products is contraindicated:
Cisapride: There have been reports of cardiac events including torsade 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, 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 torsade de pointes. Coadministration of fluconazole and astemizole is contraindicated.
Pimozide: 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 torsade de pointes. Coadministration of fluconazole and pimozide is contraindicated.
Quinidine: 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 of torsade 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, torsade de pointes) and consequently sudden heart death. Coadministration of fluconazole and erythromycin 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, torsade de pointes) and consequently sudden heart death. This combination should be avoided.

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Concomitant use that should be used with caution:
Amiodarone: Concomitant administration of fluconazole with amiodarone may increase QT prolongation. Caution must be exercised if the concomitant use of fluconazole and amiodarone is necessary, notably with high-dose fluconazole (800 mg).
Concomitant use of the following other medicinal products lead to precautions and dose adjustments:
The effect of other medicinal products on fluconazole
Hydrochlorothiazide: Hydrochlorothiazide increases plasma concentrations of fluconazole. An effect of this size should not give rise to any change of fluconazole dose in patients, who are concomitantly with diuretics.
Rifampicin: Concomitant administration of fluconazole and rifampicin resulted in decrease in the AUC and shorter half-life of fluconazole. In patients receiving concomitant rifampicin, an increase in the fluconazole dose should be considered.
The effect of fluconazole on other medicinal products
Fluconazole is a moderate inhibitor of CYP2C9 and CYP3A4. Fluconazole is also an inhibitor of the isoenzyme CYP2C19. 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 to 5 days after discontinuation of fluconazole treatment due to the long half-life of fluconazole.
Alfentanil: Concomitant treatment with fluconazole and intravenous alfentanil increase the alfentanil AUC_{10}, probably through inhibition of CYP3A4. Dosage 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. Dosage of amitriptyline/nortriptyline should be adjusted, if necessary.
Amphotericin B: Concurrent administration of fluconazole and amphotericin B in infected normal and immunosuppressed mice showed the following results: a small additive antifungal effect in systemic infection with *C. albicans*, no interaction in intracranial infection with *Cryptococcus neoformans*, and antagonism of the two drugs in systemic infection with *Aspergillus fumigatus*. The clinical significance of results obtained in these studies is unknown.
Anticoagulants: Concomitant treatment with fluconazole and warfarin the prothrombin time was prolonged, probably due to an inhibition of the warfarin metabolism through CYP2C9. 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 dosage and the patients should be appropriately monitored.
Carbamazepine: Fluconazole inhibits the metabolism of carbamazepine and an increase in serum carbamazepine. There is a risk of developing carbamazepine toxicity. Dosage 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: During concomitant treatment with fluconazole and celecoxib may increase exposure and toxicity to 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: Concomitant treatment of fluconazole with fentanyl may delay elimination of fentanyl. Elevated fentanyl concentration may lead to respiratory depression. Patient 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 creatinine kinase should be monitored. HMG-CoA reductase inhibitors should be discontinued if a marked increase in creatinine kinase is observed or myopathy/rhabdomyolysis is diagnosed or suspected.
Olaparib: Moderate inhibitors of CYP3A4 such as fluconazole increase olaparib plasma concentrations; concomitant use is not recommended. If the combination cannot be avoided, limit the dose of olaparib to 200 mg twice daily.
Immunosuppresors (i.e., ciclosporin, everolimus, sirolimus and tacrolimus):
Ciclosporin: Fluconazole increases the concentration and AUC of ciclosporin. This combination may be used by reducing the dose of ciclosporin depending on ciclosporin concentration.
Everolimus: 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 dosage adjustment of sirolimus depending on the effect/concentration measurements.
Tacrolimus: Fluconazole may increase the serum concentrations of orally administered tacrolimus due to inhibition of tacrolimus metabolism through CYP3A4 in the intestines. Increased tacrolimus levels have been associated with nephrotoxicity. Dosage of orally administered tacrolimus should be decreased depending on tacrolimus concentration.
Losartan: Fluconazole inhibits the metabolism of losartan to its active metabolite (E-3174) 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. Dosage of adjustment methadone may be necessary.
Non-steroidal anti-inflammatory drugs: 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 dosage of NSAIDs may be needed.
Oral contraceptives: The multiple dose use of fluconazole is unlikely to have an effect on the efficacy of the combined oral contraceptive.
Phenytoin: Fluconazole inhibits the hepatic metabolism of phenytoin. With coadministration, serum phenytoin concentration levels should be monitored in order to avoid phenytoin toxicity.
Prednisone: There was a case report that a liver-transplanted patient treated with prednisone developed acute adrenal cortex insufficiency when a three-month therapy with fluconazole was discontinued. The discontinuation of fluconazole presumably caused an enhanced CYP3A4 activity which led to increased metabolism of 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. There have been reports of uveitis in patients to whom fluconazole and rifabutin were coadministered. In combination therapy, symptoms of rifabutin toxicity should be taken into consideration.
Saquinavir: Fluconazole increases the AUC of saquinavir due to inhibition of saquinavir's hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein. Dosage adjustment of saquinavir may be necessary.
Sulphonylureas: Fluconazole may prolong the serum half-life of concomitantly administered oral sulphonylureas (e.g., chlorpropamide, glibenclamide, glipizide and tolbutamide). Frequent monitoring of blood glucose and appropriate reduction of sulfonylurea dosage is recommended during coadministration.
Theophylline: Patients who are receiving high doses of theophylline or who are otherwise at increased risk for theophylline toxicity should be observed for signs of theophylline toxicity while receiving fluconazole, and the therapy modified appropriately if signs of toxicity develop.
Tofacitinib: Exposure of tofacitinib is increased when tofacitinib is coadministered with medications that result in both moderate inhibition of CYP3A4 and inhibition of CYP2C19 (e.g., fluconazole). Dosage adjustment of tofacitinib may be necessary.
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: Based on a case-report in one patient receiving combination therapy with all-trans-retinoid acid (an acid form of vitamin A) and fluconazole, CNS related undesirable effects have developed in the form of pseudotumour cerebri, which disappeared after discontinuation of fluconazole treatment. This combination may be used but the incidence of CNS related undesirable effects should be borne in mind.
Voriconazole: (CYP2C9 and CYP3A4 inhibitor): Monitoring for voriconazole associated adverse events is recommended if voriconazole is used sequentially after fluconazole.
Zidovudine: Concomitant treatment with fluconazole may increase zidovudine. The half-life of zidovudine was likewise prolonged. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions. Dosage reduction of zidovudine may be considered.
Azithromycin: There was no significant pharmacokinetic interaction between fluconazole and azithromycin.
Ivacaftor: Coadministration with ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, increases ivacaftor exposure and hydroxymethyl-ivacaftor (M1) exposure. 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.

Pregnancy & Lactation:
Use During Pregnancy
There have been reports of spontaneous abortion and congenital abnormalities in infants whose mothers were treated with 150 mg of fluconazole as a single or repeated dose in the first trimester.
Use in pregnancy should be avoided except in patients with severe or potentially life-threatening fungal infections in whom Flucozole may be used if the anticipated benefit outweighs the possible risk to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking the drug, the patient should be informed of the potential hazard to the fetus.
Effective contraceptive measures should be considered in women of childbearing potential and should continue throughout the treatment period and for approximately 1 week (5 to 6 half-lives) after the final dose.
There have been reports of multiple congenital abnormalities in infants whose mothers were treated with high-dose (400 mg/day to 800 mg/day) fluconazole therapy for coccidioidomycosis (an unapproved indication). The relationship between fluconazole use and these events is unclear. Adverse fetal effects have been seen in animals only at high-dose levels associated with maternal toxicity. There were no fetal effects at 5mg/kg or 10 mg/kg; increases in fetal anatomical variants (supernumerary ribs, renal pelvis dilation) and delays in ossification were observed at 25 mg/kg and 50 mg/kg and higher doses. At doses ranging from 80 mg/kg (approximately 20-60 times the recommended human dose) to 320 mg/kg, embryolethality in rats were increased and fetal abnormalities included wavy ribs, cleft palate and abnormal craniofacial ossification.
Case reports describe a distinctive and a rare pattern of birth defects among infants whose mothers received high dose (400-800 mg/day) fluconazole during most or all of the first trimester of pregnancy. The features seen in these infants include brachycephaly, abnormal facies, abnormal calvarial development, cleft palate, femoral bowing, thin ribs and long bones, arthrogryposis, and congenital heart disease.
Use During Lactation
Fluconazole is found in human breast milk at concentrations similar to plasma. Breast-feeding may be maintained after a single dose of 150 mg fluconazole. Breast-feeding is not recommended after repeated use or after high-dose fluconazole.

Undesirable effects:
The most frequently reported adverse reactions are headache, abdominal pain, diarrhoea, nausea, vomiting, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased and rash.
The following adverse reactions have been observed and reported during treatment with fluconazole:

System Order Class	Frequency	Undesirable effects
Blood and the lymphatic system disorders	Rare	Agranulocytosis, leukopenia, neutropenia, thrombocytopenia
	Uncommon	Anaemia
Immune system disorders	Rare	Anaphylaxis
Metabolism and nutrition disorders	Uncommon	Decreased appetite
	Rare	Hypertriglyceridaemia, hypercholesterolaemia, hypokalaemia
Psychiatric disorders	Uncommon	Insomnia, somnolence
Nervous system disorders	Common	Headache
	Uncommon	Seizures, dizziness, paraesthesia, taste perversion
	Rare	Tremor
Ear and labyrinth disorders	Uncommon	Vertigo
Cardiac disorders	Rare	Torsade de pointes, QT prolongation
Gastrointestinal disorders	Common	Abdominal pain, diarrhoea, nausea, vomiting
	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	Pruritus, urticaria, increased sweating, drug eruption*
	Rare	Toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalised exanthematouspustulosis, dermatitis exfoliative, angioedema, face oedema, alopecia
	Not known	Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal, connective tissue and bone disorders	Uncommon	Myalgia
General disorders and administration site conditions	Uncommon	Fatigue, malaise, asthenia, fever

* including Fixed Drug Eruption

Paediatric Population
The pattern and incidence of adverse reactions and laboratory abnormalities recorded during paediatric clinical trials, excluding the genital candidiasis indication are comparable to those seen in adults.

Overdose and Treatment:
There have been reports of overdosage with fluconazole. Hallucination and paranoid behaviour have been concomitantly reported.
In the event of overdosage, supportive measures and symptomatic treatment, with gastric lavage if necessary, may be adequate.
As 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%.

Effects on Ability to Drive and Use Machine:
When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or seizures may occur.

Shelf Life: Refer to unit box for shelf-life.

Storage Condition: Store below 30°C.

Dosage Form and Packaging Available:
FLUCOZOLE Capsules 50 mg - Box of 100 capsules
FLUCOZOLE Capsules 150 mg - Box of 1 capsule
FLUCOZOLE Capsules 100 mg, 200 mg - Box of 50 capsules

Date of Revision of PI:
Date of revision: 02/02/2024

Manufacturer:
SIAM BHEASACH CO., LTD.
123 Soi Chokechairuammitr, Vibhavadi-Rangsit Road, Chomphon, Chatuchak, Bangkok 10900 and 9 Soi Chokechairuammitr 3, Vibhavadi-Rangsit Road, Dindang, Dindang, Bangkok 10400, Thailand.

Product Registration Holder, Importer:
SPG PHARMA (MALAYSIA) SDN. BHD.
Suite 1701, Block A, Damansara Intan e-Business Park,
No 1, Jalan SS20/27, 47400 Petaling Jaya, Selangor Darul Ehsan, Malaysia.

FLU-50-100-150-200-02-L-ENG-MY-A0006

Font: PLS Text Pro,size 8

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