Fluzan® 50
Fluconazole

FORMS AND PRESENTATION
Fluzan® 50: Tablets; box of 10.

COMPOSITION
Fluzan® 50: Each tablet contains Fluconazole 50mg.
Excipients: Microcrystalline cellulose, dicalcium phosphate anhydrous, croscarmellose sodium, povidone, magnesium stearate, sodium lauryl sulfate.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: Antimycotics for systemic use, triazole derivatives.
ATC code: J02AC01
Mechanism of action
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. Interaction studies with antipyrine indicate that single or multiple doses of fluconazole 50 mg do not affect its metabolism.
Pharmacokinetic properties
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.
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 moderate inhibitor of the isozymes CYP2C9 and CYP3A4. Fluconazole is also a strong inhibitor of the isozyme CYP2C19.
Elimination
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.

INDICATIONS
Fluzan® 50 is indicated in the following fungal infections.
Fluzan® 50 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 or topical treatment are insufficient.
• Vaginal candidiasis, acute or recurrent; when local therapy is not appropriate.
• Candidal balanitis when local therapy is not appropriate.
• Dermatomycosis including tinea pedis, tinea corporis, tinea cruris, tinea versicolor and dermal candida infections when systemic therapy is indicated.
• Tinea unguinium (onychomycosis) when other agents are not considered appropriate.
Fluzan® 50 is indicated in adults for the prophylaxis of:
• Relapse of cryptococcal 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.
• To reduce the incidence of recurrent vaginal candidiasis (4 or more episodes a year).
• Prophylaxis of candidal infections in patients with prolonged neutropenia (such as patients with haematological malignancies receiving chemotherapy or patients receiving Hematopoietic Stem Cell Transplantation.
Fluzan® 50 is indicated in term newborn infants, infants, toddlers, children, and adolescents aged from 0 to 17 years old:
Fluconazole tablet is used for the treatment of mucosal candidiasis (oropharyngeal, oesophageal), invasive candidiasis, cryptococcal meningitis and the prophylaxis of candidal infections in immunocompromised patients. Fluconazole tablet 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 Fluconazole tablet 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, and erythromycin are contraindicated in patients receiving fluconazole.

PRECAUTIONS
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%. Therefore, Fluconazole tablet should not be used for tinea capitis.
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.
Deep endemic mycoses
The evidence for efficacy of fluconazole in the treatment of other forms of endemic mycoses such as paracoccidioidomycosis, lymphocutaneous sporotrichosis and histoplasmosis is limited, which prevents specific dosing recommendations.
Renal system
Fluconazole tablet should be administered with caution to patients with renal dysfunction.
Adrenal insufficiency
Ketoconazole is known to cause adrenal insufficiency, and this could also although rarely seen be applicable to fluconazole. Adrenal insufficiency relating to concomitant treatment with Prednisone.
Hepatobiliary system
Fluconazole tablet should be administered with caution to patients with liver dysfunction.
Fluconazole tablet 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.
Cardiovascular system
Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. Fluconazole causes QT prolongation via the inhibition of Rectifier Potassium Channel current (Ikr). The QT prolongation caused by other medicinal products (such as amiodarone) may be amplified via the inhibition of cytochrome P450 (CYP) 3A4. During post-marketing surveillance, there have been very rare cases of QT prolongation and *torsades de pointes* in patients taking Fluconazole tablet. 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. Patients with hypokalemia and advanced cardiac failure are at an increased risk for the occurrence of life threatening ventricular arrhythmias and *torsades de pointes*.
Fluconazole tablet 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 cytochrome P450 (CYP) 3A4 are contraindicated.
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.
Dermatological reactions
Patients have rarely developed exfoliative cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, during treatment with fluconazole. Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported. 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 if bullous lesions or erythema multiform develop.
Hypersensitivity
In rare cases anaphylaxis has been reported.
Cytochrome P450
Fluconazole is a moderate CYP2C9 and CYP3A4 inhibitor. Fluconazole is also a strong inhibitor of CYP2C19. Fluconazole tablet treated patients who are concomitantly treated with medicinal products with a narrow therapeutic window metabolised through CYP2C9, CYP2C19 and CYP3A4, should be monitored.
Terfenadine
The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored.
Candidiasis
Studies have shown an increasing prevalence of infections with Candida species other than C. albicans. These are often inherently resistant (e.g. C. krusei and C. auris) or show reduced susceptibility to fluconazole (C. glabrata). Such infections may require alternative antifungal therapy secondary to treatment failure. Therefore, prescribers are advised to take into account the prevalence of resistance in various Candida species to fluconazole.
Excipients
Fluzan® 50 contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.
Effects on ability to drive and use machines
No studies have been performed on the effects of Fluconazole tablet on the ability to drive or use machines.
Patients should be warned about the potential for dizziness or seizures while taking Fluconazole tablet and should be advised not to drive or operate machines if any of these symptoms occur.

PREGNANCY AND LACTATION
Pregnancy
An observational study has suggested an increased risk of spontaneous abortion in women treated with fluconazole during the first trimester.
There have been reports of multiple congenital abnormalities (including brachycephalia, ears dysplasia, giant anterior fontanelle, femoral bowing and radio-humeral synostosis) in infants whose mothers were treated for at least three or more months with high doses (400-800 mg daily) of fluconazole for coccidioidomycosis. The relationship between fluconazole use and these events is unclear.
Before becoming pregnant a washout period of approximately 1 week (corresponding to 5-6 half-lives) is recommended after a single-dose or discontinuation of a course of treatment.
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.
Breast-feeding
Fluconazole passes into breast milk to reach concentrations similar to those in plasma. Breast-feeding is not recommended after repeated use or after high dose fluconazole. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for Fluconazole tablets and any potential adverse effects on the breast-fed child from Fluconazole tablets or from the underlying maternal condition.

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 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 of *torsades 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.
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 that should be used with caution:
Amiodarone: Concomitant administration of fluconazole with amiodarone may increase QT prolongation. Therefore, caution should be taken when both drugs are combined, 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: In pharmacokinetic interaction study, co-administration 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.

Rifampicin Concomitant administration of fluconazole and rifampicin resulted in a 25% decrease in the AUC and 20% shorter half-life of fluconazole. In patients receiving concomitant rifampicin, an increase in 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.

The effect of fluconazole on other medicinal products

Fluconazole is a moderate inhibitor of cytochrome P450 (CYP) isoenzymes 2C9 3A4. Fluconazole is also a strong 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 co-administered 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.

Abrocitinib: Fluconazole (inhibitor of CYP2C19, 2C9, 3A4) increased exposure of abrocitinib active moiety by 155%. If co-administered with fluconazole, adjust the dose of abrocitinib as instructed in the abrocitinib prescribing information.

Alfentanil: During concomitant treatment with fluconazole (400 mg) and intravenous alfentanil (20 µg/kg) in healthy volunteers the alfentanil AUC 10 increased 2-fold, probably through inhibition of CYP3A4. Dose adjustment of alfentanil may be necessary.

Amitriptyline, nortriptyline: Fluconazole increases the effect of amitriptyline and nortriptyline. 5- nortriptyline and/or S-amitnptyline 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 medicinal products in systemic infection with Aspergillus fumigatus. The clinical significance of results obtained in these studies is unknown.

Anticoagulants: In post-marketing experience, as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria, and melena) have been reported, in association with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. During concomitant treatment with fluconazole and warfarin the prothrombin time was prolonged up to 2-fold, 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 anticoagulantmay be necessary.

Benzodiazepines (short acting), i.e. midazolam, triazolam: Following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. Potentiated and prolonged effects of triazolam have been observed at concomitant treatment with fluconazole. 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: During concomitant treatment with fluconazole (a dose of 200 mg daily) and celecoxib (200 mg) the celecoxib Cmax and AUC increased by 68% and 134%, respectively. 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: One fatal case of fentanyl intoxication due to possible fentanyl fluconazole interaction was reported. Furthermore, it was shown in healthy volunteers that fluconazole delayed the elimination of fentanyl significantly. 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 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.

Ibrutinib: Moderate inhibitors of CYP3A4 such as fluconazole increase plasma ibrutinib concentrations and may increase risk of toxicity. If the combination cannot be avoided, reduce the dose of ibrutinib to 280 mg once daily for the duration of the inhibitor use and provide close clinical monitoring.

Ivacaftor (alone or combined with drugs in the same therapeutic class): Co-administration with ivacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator, increased ivacaftor exposure by 3-fold and hydroxymethyl-ivacaftor (M1) exposure by 1.9-fold.

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 significantly increases the concentration and AUC of ciclosporin. The combination of fluconazole and ciclosporin may be used by reducing the dose of ciclosporin depending on ciclosporin concentration.

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: 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, leading to increase in the AUC of rifabutin up to 80%. 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 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: Fluconazole has been shown to prolong the serum half-life of concomitantly administered oral sulfonylureas (e.g., chlorpropamide, glibenclamide, glipizide, tolbutamide) in healthy volunteers. 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.

Tofacitinib: Exposure of tofacitinib is increased when tofacitinib is co-administered with medications that result in both moderate inhibition of CYP3A4 and strong inhibition of CYP2C19 (e.g., fluconazole). Therefore, it is recommended to reduce tofacitinib dose to 5 mg once daily when it is combined with these drugs.

Tolvaptan: Exposure to tolvaptan is significantly increased (200% in AUC; 80% in C_{max}) when tolvaptan, a CYP3A4 substrate, is co-administered with fluconazole, a moderate CYP3A4 inhibitor, with risk of significant increase in adverse reactions particularly significant diuresis, dehydration and acute renal failure. In case of concomitant use, the tolvaptan dose should be reduced and the patient should be frequently monitored for any adverse reactions associated with tolvaptan.

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): The reduced dose and/or frequency of voriconazole and fluconazole that would eliminate this effect have not been established. Monitoring for voriconazole associated adverse events is recommended if voriconazole is used sequentially after fluconazole.

Zidovudine: Fluconazole increases Cmax and AUC of zidovudine by 84% and 74%, respectively, due to an approx. 45% decrease in oral zidovudine clearance. The half-life of zidovudine was likewise prolonged by approximately 128% following combination therapy with fluconazole. Patients receiving this combination should be monitored for the development of zidovudine-related adverse reactions. Dose reduction of zidovudine may be considered.

Azithromycin: An open-label, randomized, three-way crossover study in 18 healthy subjects assessed the effect of a single 1200 mg oral dose of azithromycin on the pharmacokinetics of a single 800 mg oral dose of fluconazole as well as the effects of fluconazole on the pharmacokinetics of 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.

ADVERSE EFFECTS

Adverse effects are listed below by system organ class and frequency. Frequencies are defined as: very common (> 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000); not known (cannot be estimated).

Blood and the lymphatic system disorders: anaemia (uncommon); agranulocytosis, leukopenia, neutropenia, thrombocytopenia (rare).

Immune system disorders: anaphylaxis (rare).

Metabolism and nutrition disorders: decreased appetite (uncommon); hypertriglyceredaemia, hypercholesterolaemia, hypokalaemia (rare).

Psychiatric disorders: insomnia, somnolence (uncommon).

Nervous system disorders: headache (common); seizures, dizziness, paraesthesia, taste perversion (uncommon); tremor (rare).

Ear and labyrinth disorders: vertigo (uncommon).

Cardiac disorders: Torsade de pointes, QT prolongation (rare).

Gastrointestinal disorders: abdominal pain, diarrhea, nausea, vomiting (common); constipation dyspepsia, flatulence, dry mouth (uncommon).

Hepatobiliary disorders: alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased (common); cholestatis, jaundice, bilirubin increased (uncommon); hepatic failure, hepatocellular necrosis, hepatitis, hepatocellular damage (rare).

Skin and subcutaneous tissue disorders: rash (common); pruritus, urticaria, increased sweating, drug eruption (uncommon); toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalised exanthematouspustulosis, dermatitis exfoliative, angioedema, face oedema, alopecia (rare); drug reaction with eosinophilia (DRESS) (not known).

Musculoskeletal and connective tissue disorders: myalgia (uncommon).

General and administration site conditions: fatigue, malaise, asthenia, fever (uncommon).

DOSAGE AND ADMINISTRATION

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.

Paediatric population: a maximum dose of 400 mg daily should not be exceeded in paediatric population.

Adults: Chronic altrophic candidiasis (50mg once daily for 14 days); Chronic mucocutaneous candidiasis (50mg to 100mg once daily up to 28 days).

Elderly: Dosage should be adjusted based on the renal function.

Hepatic impairment: Limited data are available in patients with hepatic impairment, therefore fluconazole should be administered with caution to patients with liver dysfunction.

Method of administration

Fluzan®50 may be administered orally.

The tablets should be swallowed whole and independent of food intake.

OVERDOSAGE

There have been reports of overdose with Fluconazole tablet and hallucination 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%.

STORAGE CONDITIONS

Store below 30°C.

Keep in original pack in intact conditions.

Date of revision: September 2023.

Marketing Authorization Holder and Manufacturer

Benta S.A.L

Dbayeh - Lebanon

BPI