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Instruction for medical use

FUSYS® DT

Composition:
active substance: fluconazole;
1 tablet contains fluconazole 50 mg;
excipients: lactose monohydrate, microcrystalline cellulose, povidone K30, talc, magnesium stearate, croscarmellose sodium, colloidal anhydrous silica, "American Ice Cream DC 129" flavor*, sodium saccharin.
* "American Ice Cream DC 129" flavor – lactose monohydrate, acacia (gumiarabic) E 414, natural identical flavor.

Pharmaceutical form. Dispersible tablets.
Main physical and chemical properties: white, circular tablets with bevelled edges and breakline on one side and plain on the other with ice cream flavor.

Pharmacotherapeutic group. Antifungal agents for systemic use. Triazole derivatives. ATC Code: J02A C01.

Pharmacological properties.
Pharmacodynamics.
Mechanism of action.
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 cytochrome P450 enzymes than for various mammalian cytochrome P450 enzyme systems.
Fluconazole 50 mg daily given up to 28 days has been shown not to effect testosterone plasma concentrations in males or endogenous steroid concentration in females of child-bearing age. Fluconazole 200 mg to 400 mg daily has no clinically significant effect on endogenous steroid levels or on adrenocorticotropic hormone (ACTH) stimulated response in healthy male volunteers.
Interaction studies with antipyrine indicate that single or multiple doses of fluconazole 50 mg do not affect its metabolism.
Susceptibility *in vitro*.
In vitro, fluconazole displays antifungal activity against clinically common *Candida* species (including *C. albicans*, *C. parapsilosis*, *C. tropicalis*). *C. glabrata* shows reduced susceptibility to fluconazole while *C. krusei* and *C. auris* are resistant to fluconazole. The minimum inhibitory concentrations (MIC) and EUCAST epidemiological cut-off value (ECOFF) of fluconazole for *C. guilliermondii* are higher than for *C. albicans*.

Fluconazole also exhibits activity *in vitro* against *Cryptococcus neoformans* and *Cryptococcus gattii* as well as the endemic moulds *Blastomyces dermatiditis*, *Coccidioides immitis*, *Histoplasma capsulatum* and *Paracoccidioides brasiliensis*.

Pharmacokinetic/pharmacodynamic relationship.

In animal studies, there is a correlation between minimum inhibitory concentration (MIC) values and efficacy against experimental mycoses models due to *Candida* spp. In clinical studies, there is an almost 1:1 linear relationship between the AUC and the dose of fluconazole. There is also a direct though imperfect relationship between the AUC or dose and a successful clinical response of oral candidosis and to a lesser extent candidemia to treatment. Similarly, cure is less likely for infections caused by strains with a higher fluconazole MIC.

Mechanisms of resistance.

Candida spp. have developed a number of resistance mechanisms to azole antifungal agents. Fungal strains which have developed one or more of these resistance mechanisms are known to exhibit high MICs to fluconazole which impacts adversely efficacy *in vivo* and clinically.

In usually susceptible species of *Candida*, the most commonly encountered mechanism of resistance development involves the target enzymes of the azoles, which are responsible for the biosynthesis of ergosterol. Resistance may be caused by mutations, increased production of an enzyme, drug efflux mechanisms, or the development of compensatory pathways.

There have been reports of superinfection with *Candida* species other than *C. albicans*, which often have reduced susceptibility (*C. glabrata*) or resistance to fluconazole (e.g., *C. krusei*, *C. auris*). Such infections may require alternative antifungal therapy. The resistance mechanisms have not been completely elucidated in some intrinsically resistant (*C. krusei*) or emerging (*C. auris*) species of *Candida*.

EUCAST Breakpoints (European Committee on Antimicrobial Susceptibility Testing).

Based on analyses of pharmacokinetic/pharmacodynamic (PK/PD) data, susceptibility *in vitro* and clinical response breakpoints has been determined for fluconazole for *Candida* species (EUCAST Fluconazole rationale document (2020) – version 3; European Committee on Antimicrobial Susceptibility Testing, Antifungal Agents, Breakpoint tables for interpretation of MICs, Version 10.0, valid from 04.02.2020). These have been divided into non-species related breakpoints; which have been determined mainly on the basis of pharmacokinetic/pharmacodynamic (PK/PD) data and are independent of MIC distributions of specific species, and species related breakpoints for those species most frequently associated with human infection. These breakpoints are given in the table below.

Antifungal agent	Species-related breakpoints (S≤ / R>) in mg/L						Non-species related breakpoints[a] S≤ / R> in mg/L
	Candida albicans	*Candida dubliniensis*	*Candida glabrata*	*Candida krusei*	*Candida parapsilosis*	*Candida tropicalis*	
Fluconazole	2/4	2/4	0.001*/16	--	2/4	2/4	2/4

S – Susceptible, R – Resistant;

a – non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints;

-- – susceptibility testing not recommended as the species is a poor target for therapy with the medicinal product;

* – the entire *C. glabrata* is in the I category. MICs against *C. glabrata* should be interpreted as resistant when above 16 mg/L. Susceptible category (≤0.001 mg/L) is simply to avoid misclassification of "I" strains as "S" strains. "I" – susceptible, increased exposure: A microorganism is categorized as "susceptible, increased exposure" when there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.

Pharmacokinetics.

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 cerebrospinal fluid (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 metabolized 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.

Pharmacokinetics in renal impairment.

In patients with severe renal insufficiency (glomerular filtration rate (GFR) <20 ml/min), half-life increased from 30 to 98 hours. Consequently, reduction of the fluconazole dose is needed. Fluconazole is removed by hemodialysis and to a lesser extent by peritoneal dialysis. After three hours of hemodialysis session, around 50% of fluconazole is eliminated from blood.

Pharmacokinetics during lactation.

A pharmacokinetic study in ten lactating women, who had temporarily or permanently stopped breast-feeding their infants, evaluated fluconazole concentrations in plasma and breast milk for 48 hours following a single 150 mg dose of fluconazole. Fluconazole was detected in breast milk at an average concentration of approximately 98% of those in maternal plasma. The mean peak breast milk concentration was 2.61 mg/L at 5.2 hours post-dose. The estimated daily infant dose of fluconazole from breast milk (assuming mean milk consumption of 150 ml/kg/day) based on the mean peak milk concentration is 0.39 mg/kg/day, which is approximately 40% of the recommended neonatal dose (<2 weeks of age) or 13% of the recommended infant dose for mucosal candidiasis.

Pharmacokinetics in children.

Pharmacokinetic data were assessed for pediatric patients from 5 studies; 2 single dose studies, 2 multiple dose studies and a study in premature neonates. After administration of 2–8 mg/kg fluconazole to children between the ages of 9 months to 15 years, an AUC of about 38 μg·h/ml was found per 1 mg/kg dose units. The average fluconazole plasma elimination half-life varied between

15 and 18 hours and the distribution volume was approximately 880 ml/kg after multiple doses. A higher fluconazole plasma elimination half-life of approximately 24 hours was found after a single dose. This is comparable with the fluconazole plasma elimination half-life after a single administration of 3 mg/kg i.v. to children of 11 days-11 months old. The distribution volume in this age group was about 950 ml/kg.
Experience with fluconazole in neonates is limited to pharmacokinetic studies in 12 premature newborns of average gestation around 28 weeks. The mean age at first dose was 24 hours (range 9–36 hours) and mean birth weight was 0.9 kg (range 0.75–1.10 kg). A maximum of five 6 mg/kg intravenous infusions of fluconazole were administered every 72 hours. The mean half-life was 74 hours (range 44–185) on day 1 which decreased with time to a mean of 53 (range 30–131) on day 7 and 47 (range 27–68) on day 13. The area under the curve (μg·h/ml) was 271 (range 173–385) on day 1 and increased with a mean of 490 (range 292–734) on day 7 and decreased with a mean of 360 (range 167–566) on day 13. The volume of distribution (ml/kg) was 1183 (range 1070–1470) on day 1 and increased with time to a mean of 1184 (range 510–2130) on day 7 and 1328 (range 1040–1680) on day 13.
Pharmacokinetics in elderly.
A pharmacokinetic study was conducted in 22 subjects, 65 years of age or older receiving a single 50 mg oral dose of fluconazole. Ten of these patients were concomitantly receiving diuretics. The C_{max} was 1.54 μg/ml and occurred at 1.3 hours post-dose. The mean AUC was 76.4 ± 20.3 μg·h/ml, and the mean terminal half-life was 46.2 hours. These pharmacokinetic parameter values are higher than analogous values reported for normal young volunteers. Coadministration of diuretics did not significantly alter AUC or C_{max}. In addition, creatinine clearance (74 ml/min), the percent of medicinal product recovered unchanged in urine (0–24 h, 22%) and the fluconazole renal clearance estimates (0.124 ml/min/kg) for the elderly were generally lower than those of younger volunteers. Thus, the alteration of fluconazole disposition in the elderly appears to be related to reduced renal function characteristics of this group.

Clinical characteristics.
Indications.
Fusys® DT is indicated in the following fungal infections in adults (see "Pharmacodynamics" section):
- cryptococcal meningitis (see "Special warnings and precautions for use" section);
- coccidioidomycosis (see "Special warnings and precautions for use" section);
- invasive candidiasis;
- mucosal candidiasis including oropharyngeal, esophageal 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.

Fusys® DT is indicated in adults for the prophylaxis of:
- relapse of cryptococcal meningitis in patients with high risk of recurrence;
- relapse of oropharyngeal or esophageal 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 hematological malignancies receiving chemotherapy or patients receiving Hematopoietic Stem Cell Transplantation (see "Pharmacological properties. Pharmacodynamics" section).

Children.
Fusys® DT is indicated for the treatment of mucosal candidiasis (oropharyngeal, esophageal), invasive candidiasis, cryptococcal meningitis and the prophylaxis of candidal infections in immunocompromised patients. The drug can be used as maintenance therapy to prevent relapse of

cryptococcal meningitis in children with high risk of reoccurrence (see "Special warnings and precautions for use" section).
Tableted form of this drug should be used in the for this category of patients when children are able to safely swallow a tablet, which is usually possible at the age of 5 years.
Therapy with Fusys® DT 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.

Contraindications.
- Hypersensitivity to fluconazole, to related azole substances, or to any of the excipients.
- Coadministration of fluconazole and terfenadine 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 fluconazole and other medicinal products known to prolong the QT interval and which are metabolized via the cytochrome CYP3A4, such as cisapride, astemizole, pimozide quinidine and erythromycin (see "Special warnings and precautions for use" and "Interaction with other medicinal products and other forms of interaction" sections).

Interaction with other medicinal products and other forms of interaction.
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. A controlled study found that concomitant fluconazole 200 mg once daily and cisapride 20 mg four times a day yielded a significant increase in cisapride plasma levels and prolongation of QT interval. Concomitant treatment with fluconazole and cisapride is contraindicated (see "Contraindications" section).
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. One study at a 200 mg daily dose of fluconazole failed to demonstrate a prolongation in QTc interval. Fluconazole taken in doses of 400 mg per day or greater significantly increases plasma levels of terfenadine when taken concomitantly. The combined use of fluconazole at doses of 400 mg or greater with terfenadine is contraindicated (see "Contraindications" section). 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 (see "Contraindications" section).
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 (see "Contraindications" section).
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 (see "Contraindications" section).
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 (see "Contraindications" section).
Concomitant use of fluconazole and 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 (see "Special warnings and precautions for use" section).

Concomitant use of fluconazole and the following other medicinal products 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 fluconazole and the following other medicinal products leads to precautions and dose adjustments.

The effect of other medicinal products on fluconazole.

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.

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.

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 moderate inhibitor of cytochrome P450 (CYP) isoenzymes 2C9 and 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 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 (see "Contraindications" section).

Abrocitinib: fluconazole (inhibitor of CYP2C19, 2C9, 3A4) increased exposure of abrocitinib active moiety by 155%. If coadministered with fluconazole, adjust the dose of abrocitinib as instructed in 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-amitriptyline may be measured at initiation of the combination therapy and after one week. Dose of amitriptyline/nortriptyline should be adjusted, if necessary.

Amphotericine 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: 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 anticoagulants or indanedione 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: following oral administration of midazolam, fluconazole resulted in substantial increases in midazolam concentrations and psychomotor effects. Concomitant intake of fluconazole 200 mg and midazolam 7.5 mg orally increased the midazolam AUC and half-life 3.7-fold and 2.2-fold, respectively. Fluconazole 200 mg daily given concurrently with triazolam 0.25 mg orally increased the triazolam AUC and half-life 4.4-fold and 2.3-fold, respectively. 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 dosage, 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 and 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 (200 mg daily) and celecoxib (200 mg) the celecoxib C_{max} 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 and fluconazole interaction was reported. 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 (dose-dependent) when fluconazole is coadministered with HMG-CoA reductase inhibitors metabolized through CYP3A4, such as atorvastatin and simvastatin, or through CYP2C9, such as fluvastatin (decreased hepatic metabolism of the statin). 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. Lower doses of HMG-CoA reductase inhibitors may be necessary as instructed in the statins prescribing information.
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): coadministration 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.
A reduction of the ivacaftor (alone or combined) dose is necessary as instructed in the ivacaftor (alone or combined) prescribing information.
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.
Immunosuppressors (i.e. ciclosporin, everolimus, sirolimus and tacrolimus).
Ciclosporin: fluconazole significantly increases the concentration and AUC of ciclosporin. During concomitant treatment with fluconazole 200 mg daily and ciclosporin (2.7 mg/kg/day) there was a 1.8-fold increase in ciclosporin AUC. 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 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 Il-receptor antagonism which occurs during treatment with losartan. Patients should have their blood pressure monitored continuously.
Lurasidone: moderate inhibitors of CYP3A4 such as fluconazole may increase lurasidone plasma concentrations. If concomitant use cannot be avoided, reduce the dose of lurasidone as instructed in the lurasidone prescribing information.
Methadone: fluconazole may enhance the serum concentration of methadone. Dose adjustment of methadone may be necessary.
Non-steroidal anti-inflammatory drugs (NSAIDs): the C_{max} and AUC of flurbiprofen was increased by 23% and 81%, respectively, when coadministered with fluconazole compared to administration of flurbiprofen alone. Similarly, the C_{max} 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.
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. Concomitant repeated administration of 200 mg fluconazole and 250 mg phenytoin intravenously, caused an increase of the phenytoin AUC_{24} by 75% and C_{min} by 128%. 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 C_{max} 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). Frequent monitoring of blood glucose and appropriate reduction of sulfonylurea dose is recommended during coadministration.
Theophylline: the administration of fluconazole 200 mg for 14 days resulted in an 18% decrease in the mean plasma clearance rate of 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 coadministered 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 coadministered 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 as

instructed in the tolvaptan prescribing information and the patient should be frequently monitored for any adverse reactions associated with tolvaptan.
Vinca alkaloids: 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, CYP2C19 and CYP3A4 inhibitor): coadministration of oral voriconazole (400 mg Q12h for 1 day, then 200 mg Q12h for 2.5 days) and oral fluconazole (400 mg on day 1, then 200 mg Q24h for 4 days) resulted in an increase in C_{max} and AUC_{τ} of voriconazole by an average of 57% (90% CI: 20%, 107%) and 79% (90% CI: 40%, 128%), respectively. 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 C_{max} and AUC of zidovudine by 84% and 74%, respectively, due to an approximately 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: there was no significant pharmacokinetic interaction between single oral dose of azithromycin and fluconazole at 1200 mg and 800 mg dose accordingly.
Oral contraceptives: 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.

Special warnings and precautions for use.
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 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 should be administered with caution to patients with renal dysfunction (see "Posology and method of administration" section).
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, see "The effect of fluconazole on other medicinal products" at "Interaction with other medicinal products and other forms of interaction" section.
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.

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 CYP3A4. 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 to QT prolongation. 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 should be administered with caution to patients with potentially proarrhythmic conditions. Coadministration of other medicinal products known to prolong the QTc interval and which are metabolized via the cytochrome P450 CYP3A4 are contraindicated (see "Contraindications" and "Interaction with other medicinal products and other forms of interaction" sections).
Halofantrine. Halofantrine is a substrate of CYP3A4 and has been shown to prolong QTc interval at the recommended therapeutic dose. The concomitant use of fluconazole and halofantrine is therefore not recommended (see "Interaction with other medicinal products and other forms of interaction" section).
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 multiforme develop.
Hypersensitivity. In rare cases anaphylaxis has been reported (see "Contraindications" section).
Cytochrome P450. Fluconazole is a moderate CYP2C9 and CYP3A4 inhibitor. Fluconazole is also a strong inhibitor of CYP2C19. Fluconazole treated patients who are concomitantly treated with medicinal products with a narrow therapeutic window metabolised through CYP2C9, CYP2C19 and CYP3A4, should be monitored (see "Interaction with other medicinal products and other forms of interaction" section).
Terfenadine. The coadministration of fluconazole at doses lower than 400 mg per day with terfenadine should be carefully monitored (see "Contraindications" and "Interaction with other medicinal products and other forms of interaction" sections).
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.
This medicinal product contains lactose. Patients with established intolerance to some sugars should consult a doctor before using the medicine.
Each FUSYS® DT tablet contains less than 1 mmol sodium (23 mg), that is to say essentially 'sodium-free'.

P*regnancy and lactation.*
Pregnancy.
An observational study has suggested an increased risk of spontaneous abortion in women treated with fluconazole during the first trimester.
Data from several thousand pregnant women treated with a cumulative dose of ≤150 mg of fluconazole, administered in the first trimester, show no increase in the overall risk of malformations in the fetus. In one large observational cohort study, first trimester exposure to oral fluconazole was associated with a small increased risk of musculoskeletal malformations,

corresponding to approximately 1 additional case per 1000 women treated with cumulative doses ≤450 mg compared with women treated with topical azoles and to approximately 4 additional cases per 1000 women treated with cumulative doses over 450 mg. The adjusted relative risk was 1.29 (95% CI 1.05 to 1.58) for 150 mg oral fluconazole and 1.98 (95% CI 1.23 to 3.17) for doses over 450 mg fluconazole.
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.
Studies in animals have shown reproductive toxicity.
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 (see "Pharmacokinetics" section). 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.
The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for Fusys® DT and any potential adverse effects on the breast-fed child from Fusys® DT or from the underlying maternal condition.
Fertility.
Fluconazole did not affect the fertility of male or female rats.

Effects on ability to drive and use machines.
No studies have been performed on the effects of fluconazole on the ability to drive or use machines.
Patients should be warned about the potential for dizziness or seizures (see "Adverse reactions" section) while taking the drug and should be advised not to drive or operate machines if any of these symptoms occur.

Posology and method of administration.
This medicinal product is intended for oral use. Dosing does not depend on food intake.
The fluconazole 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 is 400 mg on day 1. Maintenance dose – 200 mg to 400 mg once daily. Duration of treatment usually is 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: the recommended dose is 200 mg once daily indefinitely.
Coccidioidomycosis. The recommended dose is 200 mg to 400 mg once daily. Duration of treatment is 11 months up to 24 months or longer depending on the patient. 800 mg once daily may be considered for some infections and especially for meningeal disease.
Invasive candidiasis. Loading dose is 800 mg on day 1. Subsequent dose – 400 mg once daily. 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 (rinse and hold in the mouth for 2 minutes, then swallow): the loading dose is 200 mg to 400 mg on day 1, maintenance dose – 100 mg to 200 mg once daily. Duration of treatment is 7 to 21 days (until oropharyngeal candidiasis is in remission). Longer periods may be used in patients with severely compromised immune function.
- Esophageal candidiasis: loading dose is 200 mg to 400 mg on day 1, maintenance dose – 100 mg to 200 mg once daily. Duration of treatment is 14 to 30 days (until esophageal candidiasis is in remission). Longer periods may be used in patients with severely compromised immune function.
- Candiduria: the recommended dose is 200 mg to 400 mg once daily for 7 to 21 days. Longer periods may be used in patients with severely compromised immune function.
- Chronic atrophic candidiasis: the recommended dose is 50 mg once daily for 14 days.
- Chronic mucocutaneous candidiasis: the recommended dose is 50 mg to 100 mg once daily. Duration of treatment is up to 28 days. Longer periods may be used depending on the severity and type of infection or on immune compromisation.

Prevention of relapse of mucosal candidiasis in patients infected with HIV who are at high risk of experiencing relapse.
- Oropharyngeal candidiasis, esophageal candidiasis: the recommended dose is 100 mg to 200 mg once daily or 200 mg 3 times per week. Duration of treatment may be indefinite for patients with chronic immune suppression.

Prophylaxis of candidal infections in patients with prolonged neutropenia. The recommended dose is 200 mg to 400 mg once daily. 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 mm^3.

Genital candidiasis.
- Acute vaginal candidiasis, candidal balanitis: the recommended dose is 150 mg, single dose.
- Treatment and prophylaxis of recurrent vaginal candidiasis (4 or more episodes a year): the recommended dose is 150 mg every third day for a total of 3 doses (day 1, 4, and 7) followed by 150 mg once weekly maintenance dose for 6 months.

Dermatomycosis.
- Tinea pedis, tinea corporis, tinea cruris, candida skin infections: the recommended dose is 150 mg once weekly or 50 mg once daily. Duration of treatment is 2 to 4 weeks, tinea pedis may require treatment for up to 6 weeks.
- Tinea versicolor: the recommended dose is 300 mg to 400 mg once weekly 1 to 3 weeks or 50 mg once daily 2 to 4 weeks.
- Tinea unguium (onychomycosis): the recommended dose is 150 mg once weekly. Treatment should be continued until infected nail is replaced (uninfected nail grows in). Regrowth of fingernails and toenails normally requires 3 to 6 months and 6 to 12 months, respectively. However, growth rates may vary widely in individuals, and by age. After successful treatment of long-term chronic infections, nails occasionally remain disfigured.

Special populations.

Elderly.

Dosage should be adjusted based on the renal function (see below).

Renal impairment.

Fluconazole is predominantly excreted in the urine as unchanged active substance. No adjustments in single dose therapy are necessary. In patients (including pediatric population) with impaired renal function who need to receive multiple doses of fluconazole on day 1, 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.

Table 1

Creatinine clearance (ml/min)	**Percent of recommended dose**
>50	100%
≤50 (no hemodialysis)	50%
Hemodialysis	100% after each hemodialysis

Patients on regular hemodialysis should receive 100% of the recommended dose after each hemodialysis; 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 (see "Special warnings and precautions for use" and "Adverse reactions" sections).

Pediatric population.

A maximum dose of 400 mg daily should not be exceeded in pediatric population.

As with similar infections in adults, the duration of treatment is based on the clinical and mycological response. Fluconazole is administered as a single daily dose.

For pediatric patients with impaired renal function, see dosing above. The pharmacokinetics of fluconazole has not been studied in pediatric population with renal insufficiency.

Pediatric population (from 12 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 once-daily dose in children to obtain a comparable systemic exposure.

Efficacy and safety for genital candidiasis indication in pediatric population has not been established. Current available safety data for other pediatric indications are described in "Adverse reactions" section. If treatment is imperative in adolescents (from 12 to 17 years old), the posology should be the same as adults posology.

Pediatric population (from 5 to 11 years old).

Mucosal candidiasis: initial dose is 6 mg/kg; maintenance dose – 3 mg/kg once daily. Initial dose may be used on the first day to achieve steady state levels more rapidly.

Invasive candidiasis, cryptococcal meningitis: dose is 6 to 12 mg/kg once daily depending on the severity of the disease.

Maintenance therapy to prevent relapse of cryptococcal meningitis in children with high risk of recurrence: dose is 6 mg/kg once daily depending on the severity of the disease.

Prophylaxis of candidiasis in immunocompromised patients: dose is 3 to 12 mg/kg once daily depending on the extent and duration of the induced neutropenia (see adults posology).

Pediatric population.

The drug should be used by children aged 5 and over.

Overdose.

Symptoms: hallucinations and paranoid behavior.

Treatment: symptomatic (including gastric lavage and supportive measures).

Fluconazole is largely excreted in the urine; forced volume diuresis would probably increase the elimination rate. A three-hour hemodialysis session decreases plasma levels by approximately 50%.

Adverse reactions.

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in association with fluconazole treatment (see "Special warnings and precautions for use" section).

The most frequently (≥1/100 to <1/10) reported adverse reactions are headache, abdominal pain, diarrhea, nausea, vomiting, alanine aminotransferase increased (ALT), aspartate aminotransferase (AST) increased, blood alkaline phosphatase increased and rash.

The following classification is used to assess the frequency of adverse reactions: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Blood and the lymphatic system disorders.

Uncommon: anemia.

Rare: agranulocytosis, leukopenia, neutropenia, thrombocytopenia.

Immune system disorders.

Rare: anaphylaxis.
Metabolism and nutrition disorders.
Uncommon: decreased appetite.
Rare: hypertriglyceridemia, hypercholesterolemia, hypokalemia.
Psychiatric disorders.
Uncommon: insomnia, somnolence.
Nervous system disorders.
Common: headache.
Uncommon: seizures, dizziness, paresthesia, taste perversion.
Rare: tremor.
Ear and labyrinth disorders.
Uncommon: vertigo.
Cardiac disorders.
Rare: torsade de pointes, QT interval prolongation (see "Special warnings and precautions for use" section).
Gastrointestinal disorders.
Common: abdominal pain, diarrhea, nausea, vomiting.
Uncommon: constipation, dyspepsia, flatulence, dry mouth.
Hepatobiliary disorders.
Common: increased ALT, AST, alkaline phosphatase (see "Special warnings and precautions for use" section).
Uncommon: cholestasis, jaundice, bilirubin increased (see "Special warnings and precautions for use" section).
Rare: liver failure, hepatocellular necrosis, hepatitis, hepatocellular damage (see "Special warnings and precautions for use" section).
Skin and subcutaneous tissue disorders.
Common: rash (see "Special warnings and precautions for use" section).
Uncommon: itching, drug eruption (including fixed drug eruption), urticaria, increased sweating (see "Special warnings and precautions for use" section).
Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalised exanthematous-pustulosis, exfoliative dermatitis, angioedema, face edema, alopecia (see "Special warnings and precautions for use" section).
Not known: drug reaction with eosinophilia and systemic symptoms (DRESS).
Musculoskeletal and connective tissue disorders.
Uncommon: myalgia.
General disorders and administration site conditions.
Uncommon: increased fatigue, malaise, asthenia, fever.
Children.
The incidence and pattern of adverse reactions and laboratory abnormalities recorded during pediatric clinical trials, excluding the genital candidiasis indication, are comparable to those seen in adults.
Reporting of suspected adverse reactions.
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Medical and pharmaceutical workers, as well as patients or their legal representatives are asked to report any suspected adverse reactions and lack of effectiveness of the medicinal product through the Pharmacovigilance Automated Information System at: https://aisf.dec.gov.ua.

Shelf-life. 4 years.

Storage conditions.
Store at a temperature not more than 25°C.
Keep out of reach of children.

Package.

4 tablets in a strip or blister; each strip or blister in a carton box.

Conditions of supply.
By prescription.

Manufacturer.
KUSUM HEALTHCARE PVT. LTD.

Location of manufacturer and its address of business activity.
SP-289 (A), RIICO Industrial area, Chopanki, Bhiwadi, Dist. Alwar (Rajasthan), India.

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