APPROVED
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Healthcare of Ukraine
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Registration certificate
No. UA/7617/01/03

Instruction for medical use FUSYS®

Composition:
active substance: fluconazole;
1 tablet contains fluconazole 150 mg;
excipients: lactose monohydrate, microcrystalline cellulose, povidone K30, talc, magnesium stearate, starch glycolate sodium (type A), crosscarmellose sodium.

Pharmaceutical form. Tablets.
Main physical and chemical properties: white, circular tablets with bevelled edges and breakline on one side.

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

Pharmacological properties.
Pharmacodynamics.
Mechanism of action.
Fluconazole is an antifungal agent of triazole class, powerful and selective inhibitor of the fungal enzymes, needed for ergosterol synthesis. The primary mechanism of its action is an inhibition of fungal lanosterol 14 alpha-demethylation, mediated by cytochrome P450, which is an essential step in fungal ergosterol biosynthesis. An accumulation of 14 alpha-methyl sterols correlates with the subsequent ergosterol loss by fungal cell membrane and may be responsible for the antifungal activity of fluconazole. Fluconazole is more selective to fungal cytochrome P450 enzymes, than to variety of the mammalian cytochrome P450 enzymes.
The use of fluconazole at a dose of 50 mg per day for 28 days does not affect the testosterone level in the men's blood plasma or the endogenous steroids level in women of reproductive age. Fluconazole at a dose of 200–400 mg per day does not show a clinically significant effect on the endogenous steroid levels or on a response to ACTH stimulation in healthy male volunteers.
The examination of interaction with antipyrine demonstrated that the use of fluconazole 50 mg once or many times has no effect on the antipyrine metabolism.
In vitro sensibility.
Fluconazole *in vitro* demonstrates an antifungal activity against *Candida* species that occur frequently (including *Candida albicans*, *Candida parapsilosis*, *Candida tropicalis*). *Candida glabrata* demonstrates a wide range of susceptibility to fluconazole, whereas *C. krusei* is resistant to it.
Also, fluconazole *in vitro* demonstrates activity against both, *Cryptococcus neoformans* and *Cryptococcus gattii*, and against endemic mold *Blastomices dermatitidis*, *Coccidioides immitis*, *Histoplasma capsulatum*, and *Paracoccidioides brasiliensis*.
Pharmacodynamics – Pharmacokinetics.
According to the results of animal studies, there is a correlation between the minimum inhibitory concentration and efficacy against experimental models of mycoses, caused by *Candida* species. According to the clinical trial results, there is a linear dependence between the AUC and the dose of fluconazole (approximately 1:1). Also, there is a direct, but insufficient connection between the dose and AUC or a positive clinical response to an oral treatment of candidiasis and to a lesser

extent of candidemia. Similarly, the treatment of infections, caused by strains to which fluconazole demonstrates a high minimum inhibitory concentration, is less satisfactory.

The mechanism of resistance.

Microorganisms of *Candida* genus demonstrate the multiple mechanisms of resistance to azole antifungal agents. Fluconazole demonstrates high minimum inhibitory concentration against strains of fungi having one or more mechanisms of resistance that negatively affects the efficiency, both *in vivo* and in clinical practice. It has been reported about cases of *Candida spp*. superinfection, different than *C. albicans* species that are often unsusceptible to fluconazole (e.g. *Candida krusei*). Alternative antifungals should be used to treat such cases.

Pharmacokinetics.

Fluconazole pharmacokinetic properties are similar after intravenous and oral use.

Absorption.

Fluconazole is well absorbed after an oral use, and the drug level in plasma and systemic bioavailability exceed 90% level of fluconazole in plasma, which is achieved by intravenous administration of the drug. Concomitant food intake does not affect the absorption of the drug at oral administration. A peak plasma concentration is reached in 0.5–1.5 hours after the drug administration. The drug concentration in plasma is proportional to the dose. Equilibrium concentration of 90% is achieved on the second day of treatment when on the first day the loading dose was used, which is twice the usual daily dose.

Distribution.

The volume of distribution is approximately equal to the total fluid content in body. Binding to plasma proteins is low (11–12%).

Fluconazole penetrates well into all body fluids studied. The level of fluconazole in saliva and sputum is similar to the drug plasma concentration. The level of fluconazole in saliva and sputum is similar to the drug plasma concentration. In patients with fungal meningitis, fluconazole level in the cerebrospinal fluid is 80% of concentration in blood plasma.

High fluconazole concentrations in the skin exceeding serum ones are achieved in the stratum corneum, epidermis, dermis, and sweat. Fluconazole accumulates in the stratum corneum.

Biotransformation.

Fluconazole is metabolized slightly. At radiolabeled dose administration, only the 11% of fluconazole is excreted with the urine in a modified form. Fluconazole is a selective inhibitor of CYP2C9 and CYP3A4 isoenzymes and isoenzyme CYP2C19 inhibitor.

Excretion.

Plasma elimination half-life of fluconazole is about 30 hours. The major part of the drug is excreted by the kidneys, whereas 80% of the administered dose is detected in the urine in unchanged form. Fluconazole clearance is proportional to creatinine clearance. Circulating metabolites were not detected.

The long plasma elimination half-life of drug makes the single administration of drug in vaginal candidiasis possible, as well as drug administration for 1 time per week in other indications.

Renal insufficiency.

In patients with severe renal insufficiency (glomerular filtration rate <20 ml/min), the half-life is increased from 30 hours to 98 hours. Therefore, this category of patients needs to reduce the dose of fluconazole. Fluconazole is removed by hemodialysis, and to a lesser extent by intraperitoneal dialysis. A hemodialysis session lasting 3 hours reduces fluconazole levels in plasma by about 50%.

Elderly patients.

Changes in pharmacokinetics of elderly patients obviously depend on the parameters of renal function.

Clinical characteristics.

Indications.

Acute vaginal candidiasis when local therapy is not appropriate.

Candidal balanitis when local therapy is not appropriate.

Contraindications.

Hypersensitivity to fluconazole, to other azole compounds, or to any of the excipients of the drug.

Co-administration of terfenadine and fluconazole is contraindicated in patients receiving fluconazole at multiple doses of 400 mg per day or higher.
Co-administration of fluconazole and other medicinal products that prolong the QT interval and are metabolized via the cytochrome CYP3A4 (such as cisapride, astemizole, pimozide, quinidine and erythromycin). See also "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 fluconazole and the following drugs is contraindicated.
Cisapride: there have been reports of cardiac events, including torsade de pointes in patients who used fluconazole and cisapride at the same time. Concomitant use of fluconazole 200 mg once daily and cisapride 20 mg four times a day resulted in 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, caused by prolongation of the QTc interval in patients receiving azole antifungals in conjunction with terfenadine, interaction studies have been performed. 200 mg daily dose of fluconazole did not 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). In case of co-administration of fluconazole at doses lower than 400 mg per day with terfenadine patients should be carefully monitored.
Astemizole: concomitant administration of fluconazole with astemizole may decrease clearance of astemizole. Resulting increased plasma concentrations of astemizole can lead to QT prolongation and rare occurrences of torsade de pointes. Co-administration of fluconazole and astemizole is contraindicated (see "Contraindications" section).
Pimozide and quinidine: the concomitant use of fluconazole and pimozide or quinidine may result in inhibition of metabolism of pimozide or quinidine. An increase in the concentration of pimozide or quinidine in blood plasma can cause QT interval prolongation and, in rare cases, lead to the development of torsade de pointes. Concomitant use of fluconazole and pimozide or 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, torsade de pointes) and, consequently, sudden heart death. Co-administration of these drugs is contraindicated (see "Contraindications" section).
Concomitant use of fluconazole and the following drugs is not recommended.
Halofantrine: fluconazole can increase halofantrine plasma concentration due to an inhibitory effect on CYP3A4. Concomitant use of these drugs has the potential to increase the risk of cardiotoxicity (prolonged QT interval, torsade de pointes) and consequently, to sudden heart death. The use of these drugs combination should be avoided (see "Special warnings and precautions for use" section).
Concomitant use of fluconazole and the following drugs requires caution.
Amiodarone: concomitant administration of fluconazole and amiodarone may lead to QT interval prolongation. Caution should be exercised when it is necessary to co-administer fluconazole and amiodarone, especially when fluconazole is used in high doses (800 mg).
Concomitant use of fluconazole and the following drugs requires caution and dose adjustment.
The effect of other medicinal products on fluconazole.
Clinically significant effect on the absorption of fluconazole during oral administration was not produced by concurrent food intake, cimetidine, antacids, as well as radiation therapy throughout the body (for bone marrow transplantation).
Rifampicin: concomitant administration of fluconazole and rifampicin resulted in a 25% decrease in the AUC and 20% shorter half-life period of fluconazole. Therefore, in patients receiving rifampicin, increasing in fluconazole dose should be considered.
Hydrochlorothiazide: in pharmacokinetic interaction study, the simultaneous multiple use of hydrochlorothiazide in healthy volunteers receiving fluconazole increased blood fluconazole

concentrations by 40%. Such interaction parameters do not require changes in the dosage regimen of fluconazole for patients receiving diuretics at the same time.

The effect of fluconazole on other medicinal products.

Fluconazole is a potent inhibitor of cytochrome P450 (CYP) isoenzyme 2C9 and a moderate inhibitor of CYP3A4. Fluconazole is also an inhibitor of the isoenzyme CYP2C19. In addition to the observed/documented interactions mentioned below, there is a risk of increased plasma concentration of other compounds, metabolized by CYP2C9 and CYP3A4 when co-administered with fluconazole. Therefore caution should be exercised when using these combinations; and the patients should be carefully monitored. Due to the prolonged half-life of fluconazole, its suppressive action on enzymes persists for 4–5 days (see "Contraindications" section).

Alfentanil: the concomitant administration of fluconazole 400 mg and alfentanil 20 μg/kg intravenously is accompanied by a twofold increase in AUC_{10} (possibly due to CYP3A4 inhibition). This necessitates adjusting the dose of alfentanil.

Amitriptyline, nortriptyline: fluconazole increases the effect of amitriptyline and nortriptyline. 5-nortriptyline and/or S-amitnptyline concentrations should be measured at initiation of the combination therapy and after one week. Dosage of amitriptyline/nortriptyline should be adjusted if necessary.

Amphotericin B: concomitant administration of fluconazole and amphotericin B in infected mice with normal immunity and infected mice with reduced immunity showed the following results: a small additive antifungal effect in *Candida albicans* systemic infection, no interaction *in Cryptococcus neoformans* intracranial infection, and antagonism of the two medicinal products in *Aspergillus fumigatus* systemic infection. The clinical significance of these results is unknown.

Anticoagulants: as with other azole antifungals, bleeding events (bruising, epistaxis, gastrointestinal bleeding, hematuria, and melena) have been reported, along with increases in prothrombin time in patients receiving fluconazole concurrently with warfarin. During concomitant treatment with fluconazole and warfarin a twofold increase in prothrombin time was observed, probably due to the inhibition of warfarin metabolism via CYP2C9. The prothrombin time should be closely monitored in patients using coumarin anticoagulants or indadione at the same time. Correction of anticoagulant dose may be necessary.

Benzodiazepines (short-acting), i.e. midazolam, triazolam: oral administration of midazolam resulted in substantial increases in midazolam concentrations and in enhancing of 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 dose, and the patients should be appropriately monitored.

Carbamazepine: fluconazole inhibits the metabolism of carbamazepine and causes 30% increase in serum carbamazepine. There is a risk of carbamazepine toxicity developing. Dose adjustment of carbamazepine may be necessary depending on its concentration level and action.

Calcium channel blockers: certain calcium channel antagonists (nifedipine, isradipine, amlodipine, and felodipine) are metabolized by CYP3A4. Fluconazole has the potential to increase the systemic exposure of the calcium channel blockers. Careful monitoring is recommended for the development of adverse reactions.

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. At simultaneous administration of celecoxib and fluconazole, 2-fold reduction of the dose of celecoxib may be required.

Cyclophosphamide: concomitant use of cyclophosphamide and fluconazole results in serum bilirubin and serum creatinine increasing. These drugs may be used concomitantly, taking into account the possible risk of increased concentrations of bilirubin and creatinine in serum.

Fentanyl: it was reported about one fatal case of fentanyl intoxication due to possible interaction of fentanyl with fluconazole. Fluconazole delayed the elimination of fentanyl significantly. Elevated

fentanyl concentration may lead to respiratory depression, so it is necessary to monitor patient's state closely. Dosage adjustment of fentanyl may be necessary.
HMG-CoA reductase inhibitors: the risk of myopathy and rhabdomyolysis increases when fluconazole is co-administered with HMG-CoA reductase inhibitors metabolized through CYP3A4 (atorvastatin and simvastatin), or through CYP2C9 (fluvastatin). If concomitant use of these drugs is necessary, the patient should be observed for symptoms of myopathy and rhabdomyolysis; and creatinine kinase level 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. In case of a significant increasing of creatine kinase, as well as suspicion or detection of myopathy/rhabdomyolysis the use of HMG-CoA reductase inhibitors should be discontinued.
Olaparib: moderate CYP3A4 inhibitors, such as fluconazole, increase the plasma olaparib concentration; simultaneous use is not recommended. If it is not possible to avoid the use of this combination, the dose of olaparib should be reduced to 200 mg twice daily.
Immunosuppresors (i.e. cyclosporin, everolimus, sirolimus and tacrolimus).
Cyclosporin: fluconazole significantly increases the concentration and AUC of cyclosporin. During concomitant treatment with fluconazole 200 mg daily and cyclosporin 2.7 mg/kg/day the 1.8-fold increasing of cyclosporin AUC was observed. These drugs may be used concomitantly provided that dose of cyclosporin is reduced depending on its concentration.
Everolimus: fluconazole may increase serum concentrations of everolimus through CYP3A4 inhibition.
Sirolimus: fluconazole increases plasma concentrations of sirolimus presumably by inhibiting the metabolism of sirolimus via CYP3A4 and P-glycoprotein. These drugs may be used concomitantly if a dose of sirolimus is adjusted depending on the effect/concentration level of the drug.
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 intestine. 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 conversion of losartan to its active metabolite (E-31 74), which causes most of the antagonism to angiotensin II receptors when taking losartan. Continuous monitoring of blood pressure in patients is recommended.
Methadone: fluconazole may enhance the serum concentration of methadone. Dose adjustment of methadone may be necessary in case of concomitant use of methadone and fluconazole.
Non-steroidal anti-inflammatory drugs (NSAID): the C_{max} and AUC of flurbiprofen were increased by 23% and 81%, respectively, when co-administered with fluconazole compared to administration of flurbiprofen alone. Similarly, the C_{max} and AUC of the pharmacologically active isomer [S-(+)-ibuprofen] were increased by 15% and 82%, respectively, when fluconazole was co-administered 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 NSAIDs-related toxicity is recommended. Adjustment of NSAIDs dose may be needed.
Phenytoin: fluconazole inhibits the hepatic metabolism of phenytoin. Concomitant repeated administration of fluconazole 200 mg and phenytoin 250 mg intravenously caused an increase of the phenytoin AUC_{24} by 75% and C_{min} by 128%. With co-administration of these drugs, serum phenytoin concentration levels should be monitored in order to avoid phenytoin toxicity.
Prednisone: it was reported about a case when 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 co-administered. 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 hepatic metabolism by CYP3A4 and inhibition of P-glycoprotein. Fluconazole interaction with saquinavir/ritonavir has not been studied, and therefore they 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 (chlorpropamide, glibenclamide, glipizide, and tolbutamide). Frequent monitoring of blood glucose and appropriate reduction of sulfonylurea dose is recommended during co-administration with fluconazole.
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 receive high dose of theophylline or who are at increased risk for theophylline toxicity for other reasons should be observed for signs of theophylline toxicity while receiving fluconazole. Therapy should be modified if signs of toxicity develop.
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: in one patient receiving combination therapy with all-trans retinoic 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): co-administration of voriconazole orally (400 mg each 12 h for 1 day, then 200 mg each 12 h for 2.5 days) and oral fluconazole (400 mg on day 1, then 200 mg each 24 h for 4 days) resulted in an increase in C_{max} and AUCτ of voriconazole by an average of 57% (90% CI: 20%, 107%) and 79% (90% CI: 40%, 128%), respectively. It is not known whether the reduction of dose and/or frequency of voriconazole or fluconazole can eliminate this effect. 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: with the simultaneous oral administration of azithromycin and fluconazole at doses of 1200 mg and 800 mg, no significant pharmacokinetic interactions were detected.
Oral contraceptives: when fluconazole was administered at a dose of 50 mg, no effect on the level of hormones was observed, whereas when fluconazole was administered at a dose of 200 mg/day, an increase in ethinylestradiol AUC increased by 40%, and for levonorgestrel it was increased by 24%. This suggests that multiple administration of fluconazole at these doses is unlikely to influence the effectiveness of the combined oral contraceptive.
Ivacaftor: concomitant use with ivacaftor, an amplifier of cystic fibrosis transmembrane conductance regulator, increases the exposure of ivacaftor by 3 times, and hydroxymethyl ivacaftor (M1) by 1,9 times. For patients who are also taking moderate CYP3A inhibitors, such as fluconazole and erythromycin, it is recommended to reduce the dose of ivacaftor to 150 mg once daily.

Special warnings and precautions for use.
Dermatophytosis. It is known that in the use of fluconazole for the treatment of dermatophytia in children, the latter does not exceed the effectiveness of griseofulvin, and the overall efficiency is less than 20%. Therefore, fluconazole should not be used to treat dermatophytes.
Cryptococcosis. The evidences for efficacy of fluconazole in the treatment of cryptococcosis of other localizations (e.g. pulmonary and cutaneous cryptococcosis) are limited; therefore there is no dose recommendation for the treatment of such diseases.

Deep endemic mycoses. The evidences for efficacy of fluconazole for the treatment of other forms of endemic mycoses, such as paracoccidioidomycosis, histoplasmosis and cutaneous lymphatic sporotrichosis, are limited; therefore there is no dose recommendation for the treatment of such diseases.

Renal system. The drug should be administered with caution to patients with renal dysfunction (see "Administration and dosage" section).

Insufficiency of the adrenal glands. Ketoconazole is known to cause insufficiency of the adrenal glands, and this may also be related to fluconazole, although it is rare. Adrenal insufficiency associated with simultaneous treatment with prednisone is described in the "The effect of fluconazole on other medicinal products" subsection in the "Interaction with other medicinal products and other forms of interaction" section.

Hepatobiliary system. The drug should be administered with caution to patients with liver dysfunction. Fluconazole administration has been associated with the rare cases of serious hepatic toxicity including fatalities appearance, primarily in patients with serious underlying medical conditions. In cases where the development of hepatotoxicity was associated with the use of fluconazole, its apparent dependence on the total daily dose of the drug, duration of therapy, gender or age of the patient was not noted. Typically, hepatotoxicity caused by fluconazole is reversible, and its manifestations disappear after the termination 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 patients should be informed of suggestive symptoms of serious hepatic effect (significant asthenia, anorexia, persistent nausea, vomiting, and jaundice). Treatment with fluconazole should be immediately discontinued and the patient should consult a doctor.

Cardiovascular system. Some azoles, including fluconazole, have been associated with prolongation of the QT interval on the electrocardiogram. Fluconazole causes prolongation of QT interval by inhibition of ion current through potassium channels of internal straightening (Ikr). Prolongation of the QT interval caused by other drugs (such as amiodarone) may be aggravated by inhibition of the CYP3A4 enzyme of cytochrome P450. Very rare cases of prolongation of QT interval and torsade de pointes were reported when fluconazole was administered. Such reports relate to patients with severe illnesses when combined with many risk factors, such as structural heart disease, electrolyte disturbances, and the simultaneous use of other drugs that affect the QT interval. Patients with hypokalemia and severe heart failure have an increased risk of life-threatening ventricular arrhythmias and torsade de pointes.

Fluconazole should be used with caution in patients at risk for developing arrhythmias. Concomitant use with drugs prolonging the QTc interval and metabolized by the CYP3A4 enzyme of cytochrome P450 is 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 not recommended (see "Interaction with other medicinal products and other forms of interaction" sections).

Caution should be exercised when combination of fluconazole and amiodarone is used (see "Interaction with other medicinal products and other forms of interaction" section).

Dermatological reactions. During treatment with fluconazole, it was rarely reported about the exfoliative cutaneous reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis development. AIDS patients are more prone to the development of severe cutaneous reactions when using many drugs. If patients with interfacial mycotic infection have a rash, which could be caused by fluconazole administration, therapy with this medicinal product should be discontinued. If a person with an invasive/systemic fungal infection has skin rash, the condition should be carefully observed, and in the case of bullous rashes or multiform erythema, the use of fluconazole should be discontinued.

Hypersensitivity. In rare cases anaphylaxis has been reported (see "Contraindications" section).

Cytochrome P450. Fluconazole is a potent CYP2C9 inhibitor and a moderate CYP3A4 inhibitor. Fluconazole is also an inhibitor of CYP2C19. State of patients who are concomitantly treated with medicinal products with a small therapeutic window metabolized through CYP2C9, CYP2C19 and

CYP3A4 should be monitored (see “Interaction with other medicinal products and other forms of interaction” section).
Terfenadine. Careful observation should be made of the patient’s state in case of concomitant use of terfenadine and fluconazole at a dose of less than 400 mg per day (see “Contraindications” and “Interaction with other medicinal products and other forms of interaction” sections).
Excipients.
The drug contains lactose. If the patient has intolerance to some sugars he should consult a doctor before taking this medicine.

Pregnancy and lactation.
Pregnancy.
The observational study showed an increased risk of spontaneous abortion in women receiving fluconazole during the first trimester.
Numerous innate pathologies were reported in newborns (including brachycephalia, dysplasia of the external ear, excessive enlargement of the anterior fontanel, hip distortion, humero-ulnar synosteosis) whose mothers received high doses of fluconazole (400–800 mg/day) for at least three months or more for treatment of coccidiosis. The relationship between the use of fluconazole and these cases has not been determined.
Animal studies have shown reproductive toxicity.
Normal doses of fluconazole and short-term courses of fluconazole treatment during pregnancy, with the exception of emergency, should not be used.
Do not use high doses of fluconazole and/or long-term treatment with fluconazole during pregnancy, except for the treatment of potentially life-threatening infections.
Lactation.
Fluconazole penetrates into breast milk and reaches concentrations close to concentrations in plasma (see “Pharmacological properties” section). Breastfeeding can be continued after single administration of fluconazole at a dose of 150 mg.
Breastfeeding is not recommended with repeated use of fluconazole or with the use of high doses of fluconazole.
The decision to use the drug during breastfeeding should be taken with a view to the benefits of breastfeeding for the health and development of the child, the clinical need to prescribe fluconazole to the mother and any potential adverse effects on the child associated with fluconazole coming from mother’s milk, or state of her health.
Fertility.
Animal studies indicate that fluconazole did not affect fertility in males and females of rats.

Effects on ability to drive and use machines.
Fluconazole effects on the ability to drive vehicles or to work with other mechanisms have not been conducted.
Patients should be informed of the possibility of dizziness or seizures when using the drug. In the development of such symptoms, it is not recommended to drive a car or work with other mechanisms.

Administration and dosage.
The drug is for oral use. Drug use does not depend on food intake.
Adults.
Use a single 150 mg dose of the drug.
Elderly patients.
In the absence of signs of renal dysfunction, the usual adult dose should be used for treatment of this category of patients.
Renal dysfunction.
Fluconazole is excreted mainly in the urine, unchanged. When using a single dose of fluconazole, dosage adjustment is not required for this category of patients.
Hepatic dysfunction.

Fluconazole should be used with caution in patients with hepatic dysfunction since information on the use of fluconazole in this category of patients is insufficient.

Children.
Efficacy and safety of drug use for treatment of genital candidiasis in children have not been established, despite of extensive data on use of fluconazole in children. If there is absolute necessity of using the drug in adolescents (aged from 12 to 17 years), usual adult doses should be used.

Overdose.
Symptoms: hallucinations and paranoid behavior.
Treatment: symptomatic (including gastric lavage and supportive therapy). Fluconazole is excreted mainly in the urine, therefore, a forced diuresis may accelerate the drug elimination. A three-hour hemodialysis session decreases plasma levels by approximately 50%.

Adverse effects.
Blood and the lymphatic system disorders: anaemia, agranulocytosis, leukopenia, neutropenia, thrombocytopenia.
Disorders of the immune system: anaphylaxis.
Metabolic and nutritional disorders: decreased appetite, hypertriglyceridemia, hypercholesterolemia, hypokalemia.
Psychiatric disorders: insomnia, somnolence.
Disorders of the nervous system: headache, seizures, dizziness, paresthesia, taste disorder, tremor.
Disorders of hearing and vestibular system: vertigo.
Disorders of the heart: torsade de pointes, QT interval prolongation.
Disorders of the gastrointestinal tract: abdominal pain, diarrhea, nausea, vomiting, constipation, dyspepsia, flatulence, dry mouth.
Hepatobiliary disorders: increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, cholestasis, jaundice, increase in bilirubin level, liver failure, hepatocellular necrosis, hepatitis, hepatocellular damage.
Disorders of the skin and subcutaneous tissue: rash, itching, drug-induced dermatitis (including fixed drug-induced dermatitis), urticaria, increased sweating, toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, exfoliative dermatitis, angioedema, face edema, alopecia.
Disorders of the musculoskeletal system and connective tissue: myalgia.
General disorders and administration site reactions: increased fatigue, lack of energy, asthenia, fever.
Children.
Frequency and nature of adverse reactions and deviations from the norm of the results of laboratory tests in children, except for genital candidiasis, are comparable to those in adults.

Shelf-life. 3 years.

Storage conditions.
Keep it out of reach of children, at temperature below 25ºC.

Package.
1 tablet is in a blister; each blister is in a carton box.

Conditions of supply.
Without 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.

Date of last revision.