

APPROVED
by the Order of the Ministry of
Health of Ukraine
13.01.2020 No. 48
Marketing Authorization
No. UA/14391/01/01

PACKAGE LEAFLET
for medical use of a medicinal product

FLUCONAZOLE-DARNITSA

Qualitative and quantitative composition:

active substance: fluconazole;

1 ml of solution contains fluconazole 2 mg;

List of excipients: sodium chloride, water for injections.

Pharmaceutical form. Solution for injection.

Main physical and chemical properties: clear colorless liquid.

Pharmacotherapeutic group. Antimycotics for systemic use. Triazole derivatives. ATC code J02A C01.

Pharmacological properties.

Pharmacodynamic properties.

Mechanism of action.

Fluconazole is a triazole antifungal agent, its primary mode of action is the inhibition of fungal enzymes required for ergosterol synthesis. 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 cumulation of 14 alphamethyl 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.

The use of fluconazole at a dose of 50 mg per day for 28 days does not affect the level of testosterone in the blood plasma in men or the level of endogenous steroids in women of reproductive age. Fluconazole at a dose of 200-400 mg per day has no clinically significant effect on the level of endogenous steroids or in response to adrenocorticotrophic hormone (ACTH) stimulation in healthy male volunteers.

Studies of interaction with antipyrine have shown that the use of 50 mg of fluconazole once or repeatedly does not affect the metabolism of antipyrine.

Sensitivity in vitro.

In vitro, fluconazole displays antifungal activity against most clinically common Candida species (including *C. albicans*, *C. parapsilosis*, *C. tropicalis*). *C. glabrata* shows a wide range of susceptibility while *C. krusei* is resistant to fluconazole.

Fluconazole also exhibits activity *in vitro* against *Cryptococcus neoformans* and *Cryptococcus gattii*, as well as against endemic fungi *Blastomices dermatitidis*, *Coccidioides immitis*, *Histoplasma capsulatum* and *Paracoccidioides brasiliensis*.

Pharmacodynamic properties–Pharmacokinetic properties.

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 results of clinical studies, there is a linear relationship between the AUC and the dose of fluconazole (approximately 1:1). There is also a direct but insufficient relationship between AUC or dose and a positive clinical response to treatment for oral candidiasis and, to a lesser extent, – candidiasis. Similar treatment of infections caused by strains for which fluconazole exhibits a high minimum inhibitory concentration is less satisfactory.

Mechanism of resistance.

Microorganisms of the genus *Candida* exhibit multiple mechanisms of resistance to azole antifungal agents. Fluconazole demonstrates a high minimum inhibitory concentration against fungal strains that have one or more resistance mechanisms, which has a negative impact on efficacy *in vivo* and in clinical practice. Cases of superinfection of *Candida spp.*, other than *C. albicans*, have been reported and are often insensitive to fluconazole (e.g. *Candida krusei*). Alternative antifungal agents should be used to treat such cases.

Pharmacokinetic properties.

The pharmacokinetic properties of fluconazole are similar for intravenous and oral administration.

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 level of fluconazole in saliva and sputum is similar to the concentration of the medicinal product in blood plasma. In patients with fungal meningitis, fluconazole levels in the CSF are approximately 80% of the corresponding plasma levels. High skin concentrations of fluconazole, above serum concentrations, are achieved in the stratum corneum, epidermis-dermis and eccrine sweat. Fluconazole accumulates in the stratum corneum. When using a dose of 50 mg once a day, the concentration of fluconazole after 12 days of treatment was 73 µg/g, and after 7 days after completion of treatment, the concentration was still 5.8 µg/g. When using a dose of 150 mg once a week, the concentration of fluconazole on the 7th day of treatment was 23.4 µg/g; 7 days after the next dose, the concentration was still 7.1 µg/g.

The concentration of fluconazole in the nails after 4 months of application of 150 mg once a week was 4.05 µg/g in healthy volunteers and 1.8 µg/g in patients with nail diseases; fluconazole was detected in nail samples 6 months after completion of therapy.

Metabolism.

Fluconazole is slightly metabolized. When a dose labeled with radioactive isotopes is administered, only 11% of fluconazole is excreted in the urine in a modified form. Fluconazole is a selective inhibitor of the isozymes CYP2C9 and CYP3A4, and also an inhibitor of the isozyme CYP2C19.

Excretion.

Plasma elimination half-life for fluconazole is approximately 30 hours. The major route of excretion is renal, with approximately 80% of the administered dose appearing in the urine as unchanged medicinal product. Fluconazole clearance is proportional to creatinine clearance. There is no evidence of circulating metabolites.

The long half-life of the drug from the blood plasma makes it possible to use it once for vaginal candidiasis, as well as to use the drug once a week for other indications.

Renal failure.

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

Children.

Pharmacokinetic data were evaluated in 113 children during 5 studies: two single-use studies, two multiple-use studies and one study in preterm infants.

After administration of 2–8 mg/kg of fluconazole to children from 9 months to 15 years, AUC was about 38 µg × h/ml per 1 mg/kg dose. After repeated administration, the mean plasma half-life of fluconazole varied between 15 and 18 hours; the volume of distribution was 880 ml/kg. A longer half-

life from blood plasma, which was approximately 24 hours, was after a single use of fluconazole. This indicator is comparable with the half-life of fluconazole from blood plasma after a single dose of 3 mg/kg intravenously in children from 11 days to 11 months. The volume of distribution in patients of this age group was about 950 ml/kg.

The experience of using fluconazole in newborns is limited to pharmacokinetic studies with the participation of 12 preterm infants with a gestational age of approximately 28 weeks. The average child's age at the first dose was 24 hours (range 9 to 36 hours); the average birth weight was 900 g (750 to 1100 g). For 7 patients, the study protocol was followed. A maximum of 5 intravenous injections of fluconazole at a dose of 6 mg/kg were administered every 72 hours. The average elimination half-life was 74 hours (44-185) on the first day, then decreased to 53 hours (30-131) on the 7th day and to 47 (27-68) on the 13th day. The area under the curve ($\mu\text{g} \times \text{h/ml}$) was 271 (173-385) on the first day, increased to 490 (292-734) on the 7th day, then decreased to 360 (167-566) on the 13th day. The volume of distribution (ml/kg) was 1183 (1070-1470) on the first day, increased to 1184 (510-2130) on the 7th day and to 1328 (1040-1680) on the 13th day.

Elderly patients.

Pharmacokinetic studies were carried out in 22 patients (over 65 years of age) who took 50 mg of oral fluconazole. Ten participants used diuretics simultaneously. C_{max} was 1.54 $\mu\text{g/ml}$ and was reached within 1.3 hours after the application of fluconazole. The average AUC was $76.4 \pm 20.3 \mu\text{g} \times \text{h/ml}$. The average half-life is 46.2 hours. These pharmacokinetic parameters are higher compared to those in healthy younger volunteers. The concomitant use of diuretics did not have a significant effect on C_{max} and AUC. Also, creatinine clearance (74 ml/min), the percentage of fluconazole excreted in the urine unchanged (0-24 hours, 22%) and renal clearance of fluconazole (0.124 ml/min/kg) in patients of this age group were lower than similar indicators in younger volunteers. Therefore, changes in pharmacokinetics in elderly patients depend on the parameters of renal function.

Clinical particulars.

Therapeutic indications.

Fluconazole-Darnitsa is indicated for the treatment of fungal infections in adults such as:

- cryptococcal meningitis;
- coccidioidomycosis;
- invasive candidiasis;
- candidiasis of the mucous membranes, including candidiasis of the oropharynx and candidiasis of the esophagus, candiduria, chronic candidiasis of the skin and mucous membranes;
- chronic oral atrophic candidiasis (candidiasis caused by the use of dentures) with ineffective oral hygiene or local therapy.

Fluconazole-Darnitsa is indicated for the prevention of fungal infections in adults such as:

- relapse of cryptococcal meningitis in patients at high risk of its development;
- relapse of oropharyngeal or oesophageal candidiasis in patients infected with HIV at high risk of its development;
- prevention of candidal infections in patients with long-term neutropenia (for example, in patients with malignant blood diseases receiving chemotherapy or in patients with hematopoietic stem cell transplantation).

Fluconazole-Darnitsa is used in children from birth for the treatment of candidiasis of the mucous membranes (oropharyngeal candidiasis, esophageal candidiasis), invasive candidiasis, cryptococcal meningitis, and for the prevention of candidal infections in patients with reduced immunity. The medicinal product can be used as supportive therapy to prevent recurrence of cryptococcal meningitis in children at high risk of developing it.

Therapy with medicinal product can be started before the results of culture and other laboratory studies; after the results are obtained, antibiotic therapy should be adjusted accordingly.

Contraindications.

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

Co-administration with terfenadine is contra-indicated in patients receiving fluconazole at multiple doses of 400 mg per day or higher (based upon results of a multiple dose interaction study). Co-administration 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).

Interaction with other medicinal products and other forms of interaction

Co-administration of fluconazole and the following medicinal products is contraindicated.

Cisapride. Cardiac adverse reactions, including paroxysmal ventricular tachycardia of the pirouette type, have been reported in patients receiving fluconazole and cisapride concomitantly. A controlled study showed that co-administration of 200 mg fluconazole once daily and 20 mg cisapride 4 times daily resulted in a significant increase in cisapride plasma levels and prolongation of the QT interval. Concomitant use of fluconazole and cisapride is contraindicated (see section "Contraindications").

Terfenadine. Due to the development of severe cardiac arrhythmias caused by prolonged QTc interval in patients who use azole antifungal medicinal products simultaneously with terfenadine, interaction studies of these medicinal products have been conducted. In one study, no prolongation of the QTc interval was found when using fluconazole 200 mg per day. Another study using fluconazole at doses of 400 and 800 mg per day demonstrated that the use of fluconazole at doses of 400 mg per day or higher significantly increased plasma levels of terfenadine when these medicinal products were used concomitantly. Concomitant use of fluconazole at doses of 400 mg or higher with terfenadine is contraindicated (see section "Contraindications"). When using fluconazole at doses below 400 mg per day concomitantly with terfenadine, the patient's condition should be carefully monitored.

Astemizole. Co-administration of fluconazole and astemizole can reduce the clearance of astemizole. The resulting increase in the concentration of astemizole in the blood plasma can lead to a prolongation of the QT interval and, in rare cases, to paroxysmal ventricular tachycardia of the "pirouette" type. Concomitant use of fluconazole and astemizole is contraindicated.

Pimozide and quinidine. The combined use of fluconazole and pimozide or quinidine can lead to inhibition of the metabolism of pimozide or quinidine, although there have been no corresponding *in vitro* and *in vivo* studies. An increase in the concentration of pimozide or quinidine in blood plasma can cause prolongation of the QT interval and, in rare cases, lead to the development of paroxysmal ventricular tachycardia of the "pirouette" type. Concomitant use of fluconazole and pimozide or quinidine is contraindicated.

Erythromycin. The simultaneous use of erythromycin and fluconazole can potentially lead to an increased risk of cardiotoxicity (prolongation of the QT interval, paroxysmal ventricular tachycardia of the "pirouette" type) and, as a consequence, to sudden cardiac death. The use of a combination of these medicinal products is contraindicated.

Concomitant use of fluconazole and the following medicinal products is not recommended.

Halofantrine. Fluconazole may increase plasma concentrations of halofantrine by inhibiting CYP3A4. Concomitant use of these medicinal products could potentially lead to the development of cardiotoxicity (QT prolongation, paroxysmal ventricular tachycardia such as "pirouette") and, as a consequence, sudden cardiac death. The use of a combination of these medicinal products should be avoided.

Concomitant use of fluconazole and the following medicinal products requires caution and dose adjustment.

Amiodarone. Concomitant use of fluconazole with amiodarone can lead to prolongation of the QT interval. Fluconazole should be used with caution in conjunction with amiodarone, especially when a high dose of fluconazole (800 mg) is prescribed.

Effect of other medicinal products on fluconazole.

Interaction studies have shown that oral administration of fluconazole concurrently with food intake, cimetidine, antacids, or subsequent whole body irradiation for bone marrow transplantation does not have a clinically significant effect on fluconazole absorption.

Rifampicin. Co-administration of fluconazole and rifampicin reduced the AUC by 25% and reduced the half-life of fluconazole by 20%. Therefore, for patients taking rifampicin, the feasibility of increasing the dose of fluconazole should be considered.

Hydrochlorothiazide. In a pharmacokinetic interaction study, concomitant repeated administration of hydrochlorothiazide to healthy volunteers receiving fluconazole increased fluconazole plasma concentrations by 40 %. Such interaction parameters do not require changes in the dosage regimen of fluconazole for patients receiving concomitant diuretics.

Effect of fluconazole on other medicinal products.

Fluconazole is a potent inhibitor of cytochrome P450 isoenzyme 2C9 (CYP) and a moderate inhibitor of CYP3A4. Fluconazole is also a CYP2C19 inhibitor. In addition to the observed/documented interactions described below, with simultaneous use with fluconazole, there is a risk of increased plasma concentrations of other compounds that are metabolized by CYP2C9 and CYP3A4. Therefore, such combinations of medicinal products should be used with caution; in this case, it is necessary to carefully monitor the condition of the patients. The inhibitory effect of fluconazole on enzymes persists for 4–5 days after its administration due to the long half-life.

Alfentanil. With the simultaneous use of alfentanil at a dose of 20 µg/kg and fluconazole at a dose of 400 mg in healthy volunteers, a twofold increase in AUC₁₀ was observed, possibly due to inhibition of CYP3A4. Dose adjustment of alfentanil may be required.

Amitriptyline, nortriptyline. Fluconazole enhances the action of amitriptyline and nortriptyline. It is recommended to measure the concentration of 5-nortriptyline and/or S-amitriptyline at the beginning of combination therapy and after 1 week. If necessary, the dose of amitriptyline/nortriptyline should be adjusted.

Amphotericin B. The simultaneous use of fluconazole and amphotericin B to infected mice with normal immunity and infected mice with reduced immunity led to the following results: a small additive antifungal effect in systemic infection of *C. albicans*, lack of interaction in intracranial infection of *Cryptococcus neoformans* and antagonism of two medicinal products in systemic infection of *A. fumigatus*. The clinical significance of the results obtained from these studies is unknown.

Anticoagulants. As with the use of other azole antifungal agents, with the simultaneous use of fluconazole and warfarin, cases of bleeding (hematomas, nosebleeds, gastrointestinal bleeding, hematuria and melena) in combination with prolonged prothrombin time have been reported. With the simultaneous use of fluconazole and warfarin, a twofold increase in prothrombin time was observed, probably due to inhibition of the metabolism of warfarin through CYP2C9. Prothrombin time should be carefully monitored in patients concomitantly taking coumarin anticoagulants. Dose adjustment of warfarin may be required.

Short-acting benzodiazepines, (e.g., midazolam, triazolam). The administration of fluconazole after oral administration of midazolam led to a significant increase in the concentration of midazolam and to an increase in psychomotor effects. The simultaneous use of fluconazole at a dose of 200 mg and midazolam at a dose of 7.5 mg orally led to an increase in AUC and half-life by 3.7 and 2.2 times, respectively. The use of fluconazole at a dose of 200 mg per day and 0.25 mg of triazolam orally led to an increase in AUC and half-life by 4.4 and 2.3 times, respectively. With the simultaneous use of fluconazole and triazolam, potentiation and prolongation of the effects of triazolam were observed.

If a patient undergoing treatment with fluconazole should be simultaneously prescribed therapy with benzodiazepines, the dose of the latter should be reduced and proper monitoring of the patient's condition should be established.

Carbamazepine. Fluconazole inhibits the metabolism of carbamazepine and causes an increase in the serum carbamazepine level by 30%. There is a risk of developing manifestations of toxicity from carbamazepine. It may be necessary to adjust the dose of carbamazepine depending on the level of its concentration and the effect of the medicinal product.

Calcium channel blockers. Some 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. Co-administration of fluconazole (200 mg daily) and celecoxib (200 mg) increased the C_{\max} and AUC of celecoxib by 68% and 134%, respectively. With the simultaneous use of celecoxib and fluconazole, it may be necessary to reduce the dose of celecoxib by half.

Cyclophosphamide. The simultaneous use of cyclophosphamide and fluconazole leads to an increase in the level of bilirubin and creatinine in the blood serum. Medicinal products can be used concomitantly, despite the risk of elevated serum bilirubin and creatinine levels.

Fentanyl. One fatal case of fentanyl intoxication has been reported due to possible interactions between fentanyl and fluconazole. In addition, in a study involving 12 healthy volunteers, it was demonstrated that fluconazole significantly slowed down the elimination of fentanyl. An increase in the concentration of fentanyl can lead to respiratory depression, therefore, the patient's condition should be carefully monitored. Dose adjustment of fentanyl may be required.

HMG-CoA reductase inhibitors. Concomitant use of fluconazole and HMG-CoA reductase inhibitors, which are metabolized by CYP3A4 (atorvastatin and simvastatin), or HMG-CoA reductase inhibitors, which are metabolized by CYP2C9 (fluvastatin), increases the risk of myopathy and rhabdomyolysis. If necessary, the simultaneous use of these medicinal products should carefully monitor the patient for the onset of symptoms of myopathy and rhabdomyolysis and monitor the level of creatine kinase. In the case of a significant increase in the level of creatine kinase, as well as if myopathy/rhabdomyolysis is diagnosed or suspected, the use of HMG-CoA reductase inhibitors should be discontinued.

Olaparib. Moderate CYP3A4 inhibitors such as fluconazole increase plasma concentrations of olaparib; their simultaneous use is not recommended. If this combination cannot be avoided, olaparib should be limited to 200 mg 2 times a day.

Immunosuppressants (e.g., cyclosporine, everolimus, sirolimus and tacrolimus).

Cyclosporin. Fluconazole significantly increases the concentration and AUC of cyclosporine. With the simultaneous use of fluconazole at a dose of 200 mg/day and cyclosporine at a dose of 2.7 mg/kg/day, an increase in the AUC of cyclosporine was observed by 1.8 times. These medicinal products can be used simultaneously, provided that the dose of cyclosporine is reduced depending on its concentration.

Everolimus. Although *in vitro* and *in vivo* studies have not been performed, fluconazole can increase serum everolimus concentration through inhibition of CYP3A4.

Sirolimus. Fluconazole increases the plasma concentration of sirolimus, probably by inhibiting the metabolism of sirolimus by the CYP3A4 enzyme and P-glycoprotein. These medicinal products can be used simultaneously, provided that the dose of sirolimus is adjusted depending on the level of concentration and the effects of the medicinal product.

Tacrolimus. Fluconazole can increase the concentration of tacrolimus in the blood serum up to 5 times with its oral administration due to the inhibition of the metabolism of tacrolimus by the CYP3A4 enzyme in the intestine. With intravenous tacrolimus, no significant changes in pharmacokinetics were observed. Elevated tacrolimus levels are associated with nephrotoxicity. The dose of oral tacrolimus should be reduced depending on the concentration of tacrolimus.

Losartan. Fluconazole inhibits the metabolism of losartan to its active metabolite (E-31 74), which accounts for most of the angiotensin II receptor antagonism with losartan. It is recommended to carry out constant monitoring of blood pressure in patients.

Methadone. Fluconazole can increase the serum methadone concentration. With the simultaneous use of methadone and fluconazole, an adjustment of the methadone dose may be required.

Non-steroidal anti-inflammatory medicinal products (NSAIDs). When co-administered with fluconazole C_{\max} and AUC of flurbiprofen increased by 23 % and 81 %, respectively, compared with the corresponding values when using only flurbiprofen. Similarly, co-administration of fluconazole with racemic ibuprofen (400 mg) increased the C_{\max} and AUC of the pharmacologically active isomer of S - (+) - ibuprofen by 15 % and 82 %, respectively, compared with racemic ibuprofen alone.

Although no specific studies have been conducted, fluconazole has the potential to increase the systemic exposure to other NSAIDs that are metabolized by CYP2C9 (e. g., naproxen, lornoxicam, meloxicam, diclofenac). It is recommended to periodically monitor for undesirable effects and toxicity associated with NSAIDs. Dose adjustment of NSAIDs may be required.

Phenytoin. Fluconazole inhibits the metabolism of phenytoin in the liver. Simultaneous repeated use of 200 mg of fluconazole and 250 mg of phenytoin intravenously leads to an increase in AUC₂₄ of

phenytoin by 75% and C_{min} by 128%. With the simultaneous use of these medicinal products, the concentration of phenytoin in the blood plasma should be monitored to avoid the development of the toxic effect of phenytoin.

Prednisolone. A case has been reported when a patient after liver transplantation while using prednisolone developed acute adrenal cortex insufficiency, which arose after the termination of a three-month course of fluconazole therapy. Discontinuation of fluconazole probably caused an increase in CYP3A4 activity, which led to an acceleration of prednisolone metabolism. Patients who are simultaneously using fluconazole and prednisolone for a long period should be closely monitored in order to prevent the development of adrenal cortex insufficiency after discontinuation of fluconazole.

Rifabutin. Fluconazole increases the serum concentration of rifabutin, which leads to an increase in the AUC of rifabutin up to 80%. With the simultaneous use of fluconazole and rifabutin, cases of uveitis have been reported. When using such a combination of drugs, the symptoms of the toxic effect of rifabutin should be considered.

Saquinavir. Fluconazole increases the AUC and C_{max} of saquinavir by about 50% and 55%, respectively, through inhibition of saquinavir metabolism in the liver by the CYP3A4 enzyme and through inhibition of P-glycoprotein. Interactions between fluconazole and saquinavir/ritonavir have not been studied and may therefore be more pronounced. Dose adjustment of saquinavir may be necessary.

Sulfonylurea derivatives. With simultaneous use, fluconazole prolongs the half-life of oral sulfonylurea derivatives (chlorpropamide, glibenclamide, glipizide and tolbutamide) when used in healthy volunteers. It is recommended to carry out frequent monitoring of blood sugar and accordingly reduce the dose of sulfonylurea derivatives while using with fluconazole.

Theophylline. In a placebo-controlled study of drug interaction, the use of fluconazole 200 mg for 14 days led to a decrease in the average clearance of theophylline in blood plasma by 18%. Patients who use high doses of theophylline or who have an increased risk of developing toxic manifestations of theophylline for other reasons should be monitored for signs of theophylline toxicity. Therapy should be changed if signs of toxicity appear.

Tofacitinib. The effect of tofacitinib increases with simultaneous use with medicinal products that lead to moderate inhibition of CYP3A4 and powerful inhibition of CYP2C19 (for example, fluconazole). Therefore, it is recommended to reduce the dose of tofacitinib to 5 mg once a day in combination with these medicinal products.

Vinca alkaloids. Although no relevant studies have been carried out, fluconazole, probably through inhibition of CYP3A4, can cause an increase in the concentration of vinca alkaloids in the blood plasma (for example, vincristine and vinblastine), which leads to the development of neurotoxic effects.

Vitamin A. It was reported that in a patient who simultaneously used transretinoic acid (the acid form of vitamin A) and fluconazole, adverse reactions from the central nervous system were observed in the form of a pseudotumour of the brain, which disappeared after discontinuation of fluconazole. Medicinal products can be used simultaneously, but one should be aware of the risk of adverse reactions from the central nervous system.

Voriconazole (inhibitor of CYP2C9 and CYP3A4). Concomitant oral voriconazole (400 mg every 12 hours for 1 day, then 200 mg every 12 hours for 2.5 days) and oral fluconazole (400 mg on the first day, then 200 mg every 24 hours for 4 days) in 8 healthy male volunteers led to an increase in C_{max} and AUC $_{\tau}$ of voriconazole on average to 57% (90% CI: 20%, 107%) and 79% (90% CI: 40%, 128%), respectively. It is not known whether reducing the dose and/or frequency of voriconazole or fluconazole will reverse this effect. When using voriconazole after fluconazole, observations should be made regarding the development of side effects associated with voriconazole.

Zidovudine. Fluconazole increases the C_{max} and AUC of zidovudine by 84% and 74%, respectively, due to a decrease in zidovudine clearance of approximately 45% when administered orally. The half-life of zidovudine was also prolonged by about 128% after the combination of fluconazole and zidovudine. Patients using such a combination of medicinal products should be monitored for the development of adverse reactions associated with the use of zidovudine. Consideration may be given to lowering the dose of zidovudine.

Azithromycin. In an open, randomized, tripartite crossover study, in which 18 healthy volunteers took part, the effect of azithromycin and fluconazole on the pharmacokinetics of each other was assessed when they were simultaneously administered orally at a single dose of 1200 and 800 mg, respectively. No significant pharmacokinetic interactions were found between them.

Oral contraceptives. Two multiple pharmacokinetic studies of fluconazole and combined oral contraceptives were performed. When using fluconazole at a dose of 50 mg, there was no effect on the level of hormones, while when using fluconazole at a dose of 200 mg per day, there was an increase in the AUC of ethinylestradiol by 40% and levonorgestrel by 24%. This indicates that repeated use of fluconazole at the indicated doses is unlikely to affect the effectiveness of the combined oral contraceptive.

Ivacaftor. Simultaneous use with ivacaftor, an amplifier of cystic fibrosis transmembrane conductance regulator, increases the exposure of ivacaftor by 3 times, and hydroxymethylivacaftor (M1) - 1.9 times. For patients who are simultaneously using moderate CYP3A inhibitors, such as fluconazole and erythromycin, it is recommended to reduce the dose of ivacaftor to 150 mg 1 time per day.

Special warnings and precautions for use.

Dermatophytosis. According to the results of a study of fluconazole for the treatment of dermatophytosis in children, fluconazole is not superior to griseofulvin in terms of effectiveness and the overall effectiveness rate is less than 20%. Therefore, the drug should not be used to treat dermatophytosis.

Cryptococcosis. There is insufficient evidence of the efficacy of fluconazole for the treatment of cryptococcosis at other sites (e. g., pulmonary cryptococcosis and skin cryptococcosis); therefore, there are no recommendations regarding the dose regimen for the treatment of such diseases.

Deep endemic mycoses. There is insufficient evidence of the efficacy of fluconazole for the treatment of other forms of endemic mycoses, such as paracoccidioidomycosis, histoplasmosis, and lymphatic cutaneous sporotrichosis; therefore, there are no recommendations on the dosage regimen for the treatment of such diseases.

Renal system. For patients with impaired renal function, the drug should be used with caution (see section "Posology and method of administration").

Adrenal insufficiency. Ketoconazole is known to cause adrenal insufficiency and can also cause fluconazole deficiency, although this is rare. Adrenal insufficiency associated with simultaneous treatment with prednisolone, described in the section "Interaction with other medicinal products and other forms of interaction". Influence of fluconazole on other medicinal products.

Hepatobiliary system. Patients with impaired liver function should use the drug with caution. The use of fluconazole has been associated with the occurrence of rare cases of severe hepatotoxicity, including deaths, mainly in patients with severe underlying diseases. In cases where the development of hepatotoxicity was associated with the use of fluconazole, there was no clear dependence on the total daily dose of the drug, the duration of therapy, gender or age of the patient. Usually, hepatotoxicity caused by fluconazole is reversible, and its manifestations disappear after stopping therapy.

Patients who have abnormal liver function tests when using fluconazole should be closely monitored for more severe liver damage.

Patients should be informed about symptoms that may indicate a serious effect on the liver (severe asthenia, anorexia, persistent nausea, vomiting and jaundice). In this case, the use of fluconazole should be stopped immediately and a doctor should be consulted.

Cardiovascular system. Some azoles, including fluconazole, are associated with prolongation of the QT interval on the electrocardiogram. Fluconazole prolongs the QT interval by inhibiting the rectifying potassium channel (I_{Kr}). Prolongation of the QT interval due to the action of other medicinal products (for example, amiodarone) can be enhanced by inhibition of the CYP3A4 enzyme of cytochrome P450. Reported very rare cases of prolongation of the QT interval and paroxysmal ventricular tachycardia type "pirouette" with the use of the medicinal product. Such messages concerned patients with severe diseases with a combination of many risk factors, such as structural heart disease, electrolyte disturbances and the simultaneous use of other medicinal products that affect the QT interval. Patients

with hypokalemia and progressive heart failure have an increased risk of life-threatening ventricular arrhythmias and paroxysmal ventricular tachycardia of the "pirouette" type.

The medicinal product should be used with caution in patients at risk of developing arrhythmias. Simultaneous use with medicinal products that prolong the QTc interval and are metabolized by the CYP3A4 enzyme of cytochrome P450 is contraindicated.

Halofantrine. Halofantrine is a substrate of the CYP3A4 enzyme and prolongs the QTc interval when used in recommended therapeutic doses. The concomitant use of halofantrine and fluconazole is not recommended.

Dermatological reactions. With the use of fluconazole, the development of such exfoliative skin reactions as Stevens-Johnson syndrome and toxic epidermal necrolysis have rarely been reported. Patients with AIDS are more likely to develop severe skin reactions with many drugs. If a patient with a superficial fungal infection develops rashes, which can be associated with the use of fluconazole, further use of the drug should be discontinued. If a patient with an invasive/systemic fungal infection develops a skin rash, his condition should be carefully monitored, and if bullous rash or polymorphic erythema develops, the use of fluconazole should be discontinued.

Hypersensitivity. In rare cases, anaphylactic reactions have been reported.

Cytochrome P450. Fluconazole is a potent inhibitor of the CYP2C9 enzyme and a moderate inhibitor of the CYP3A4 enzyme. Fluconazole is also an inhibitor of the enzyme CYP2C19. The condition of patients taking fluconazole and medicinal products with a narrow therapeutic window that are metabolized with the participation of CYP2C9, CYP2C19 and CYP3A4 should be monitored.

Terfenadine. The patient's condition should be closely monitored when terfenadine and fluconazole are co-administered at a dose of less than 400 mg per day.

Important information about excipients. The medicinal product contains 0.9% sodium chloride solution. Each 200 mg (100 ml bottle) contains 15 mmol of sodium ions (0.145 mmol of sodium in 1 ml) and chlorine, which should be taken into account when prescribing to patients who need to limit sodium and liquid intake.

Fertility, pregnancy and lactation.

Pregnancy.

According to an observational study, there is an increased risk of spontaneous abortion in women who received fluconazole during the first trimester of pregnancy. Numerous congenital abnormalities have been reported in neonates (including bradyphrenia, pinna dysplasia, excessive enlargement of the anterior fontanelle, hip curvature, brachial synostosis) whose mothers received high doses of fluconazole (400-800 mg/day) for at least three months or more for the treatment of coccidioidosis. The relationship between the use of fluconazole and these cases has not been determined.

Animal studies have demonstrated reproductive toxicity.

Do not use the usual doses of fluconazole and short courses of treatment with fluconazole during pregnancy, unless absolutely necessary.

Do not use high doses of fluconazole and/or long courses of treatment with fluconazole during pregnancy, except for the treatment of life-threatening infections.

Breastfeeding period.

Fluconazole passes into breast milk and reaches a lower concentration than in blood plasma. Breastfeeding can be continued after a single dose of fluconazole of 200 mg or less.

Breastfeeding is not recommended if fluconazole is used repeatedly or in high doses.

The developmental and health benefits of breastfeeding should be assessed, as well as the mother's clinical need for the drug and any potential side effects of the drug or underlying maternal illness for the breastfeeding infant.

Fertility.

Fluconazole did not affect the fertility of male and female rats.

Effects on ability to drive and use machines

No studies on the effects of medicinal product on the ability to drive and use machines have been performed.

Patients should be informed about the possibility of dizziness or seizures developing when using the medicinal product. With the development of such symptoms, it is not recommended to drive vehicles or work with other mechanisms.

Posology and method of administration.

The dose of fluconazole depends on the type and severity of the fungal infection.

If it is necessary to use the drug multiple times, the treatment of infections should be continued until the clinical and laboratory manifestations of the activity of the fungal infection disappear. Insufficient duration of treatment can lead to the resumption of an active infectious process.

The medicinal product is administered intravenously by infusion. There is no need to change the daily dose of the drug when changing the route of its administration from oral to intravenous and vice versa. The infusion solution should be administered at a rate not exceeding 10 ml/min.

Compatibility of the medicinal product.

The medicinal product is compatible with such solutions as:

- 5% and 20% glucose solution;
- Ringer's solution;
- Hartmann's solution;
- solution of potassium chloride in glucose;
- 4.2% and 5% sodium bicarbonate solution;
- 3.5% solution of aminosine;
- 0.9% sodium chloride solution;
- dialaflex (6.36% solution for intraperitoneal dialysis).

Fluconazole can be administered to the infusion system along with one of the above solutions. Although cases of non-specific incompatibility of the drug with other medicinal products have not been described, it is not recommended to mix fluconazole with other medicinal products before infusion.

The infusion solution is intended for single use only. Dilution should be carried out under aseptic conditions. The solution must be checked for foreign particles and discoloration. The solution should be used only when it is transparent and free of foreign particles. Unused drug residues must be destroyed.

Adults.

Cryptococcosis.

- Treatment of cryptococcal meningitis: the recommended loading dose is 400 mg on the first day, the maintenance dose is 200-400 mg/day. The duration of treatment is usually at least 6-8 weeks. For life-threatening infections, the daily dose can be increased to 800 mg.

- - Supportive therapy to prevent recurrence of cryptococcal meningitis in patients at high risk of developing it: the recommended dose of the drug is 200 mg/day for an unlimited time.

Coccidioidomycosis. The recommended dose is 200-400 mg/day. The duration of treatment is 11-24 months or longer, depending on the patient's condition. For the treatment of some forms of infection, especially for the treatment of meningitis, a dose of 800 mg/day may be appropriate.

Invasive candidiasis. The loading dose is 800 mg on the first day, the maintenance dose is 400 mg/day. Usually, the recommended duration of treatment for candidemia is 2 weeks after the first negative blood culture results and the disappearance of the signs and symptoms of candidemia.

Mucosal candidiasis.

- Oropharyngeal candidiasis: the recommended loading dose is 200-400 mg on the first day, the maintenance dose is 100-200 mg/day. The duration of treatment is 7–21 days (until remission is achieved), but may be increased for patients with severe immunodeficiency.

- Esophageal candidiasis: the recommended loading dose is 200-400 mg on the first day, the maintenance dose is 100-200 mg/day. The duration of treatment is 14-30 days (until remission is achieved), but may be increased for patients with severe immunodeficiency.

- Candidiasis: The recommended dose is 200-400 mg/day during 7-21 days. For patients with severe immunodeficiency, the duration of treatment can be increased.

- Chronic atrophic candidiasis: the recommended dose is 50 mg/day during 14 days.

- Chronic candidiasis of the skin and mucous membranes: the recommended dose is 50-100 mg/day. The duration of treatment is up to 28 days, but it can be increased depending on the severity and type of infection or decreased immunity.

Prevention of recurrence of mucosal candidiasis in HIV patients at high risk of its development.

- Oropharyngeal candidiasis, esophageal candidiasis: the recommended dose is 100-200 mg/day or 200 mg 3 times a week. The duration of treatment is unlimited for immunosuppressed patients.

Prevention of candidal infections in patients with prolonged neutropenia. The recommended dose is 200-400 mg. Treatment should begin several days before the expected development of neutropenia and continue for 7 days after the increase in the neutrophil count over 1000/mm³.

Use in elderly patients

The dose must be selected depending on the state of renal function (see below).

Patients with renal impairment.

Fluconazole is excreted from the body mainly in the urine unchanged. With a single use, there is no need to adjust the dose. Patients (including children) with impaired renal function, if multiple use of the drug is required on the first day of treatment, should be given an initial dose of 50-400 mg, depending on the indication. After that, the daily dose (depending on the indications) should be calculated in accordance with the table:

Creatinine clearance (ml/min)	Percentage of the recommended dose
> 50	100 %
≤ 50 (without dialysis)	50 %
Continuous dialysis	100% after each dialysis

Patients on continuous dialysis should receive 100% of the recommended dose after each dialysis. On the day that dialysis is not performed, the patient should receive a dose adjusted for creatinine clearance.

Patients with impaired liver function.

Fluconazole should be used with caution in patients with impaired liver function, since there is insufficient information on the use of fluconazole in this category of patients.

Children.

The maximum daily dose should not exceed 400 mg.

As with similar infections in adults, the duration of treatment depends on the clinical and mycological response. Fluconazole should be used once a day.

The dosage of the medicinal product in children with impaired renal function is given above. The pharmacokinetics of fluconazole have not been investigated in children with renal insufficiency (see below for information on use in newborns, who often have primary renal immaturity).

Children from 12 years of age.

Depending on body weight and puberty, the doctor should evaluate which dose (for adults or for children) is optimal for the patient. Clinical data indicate that fluconazole clearance is higher in children compared to adults. The use of doses of 100, 200 and 400 mg for adults and doses of 3, 6 and 12 mg/kg for children leads to the achievement of comparable systemic exposure.

Children from 28 days to 11 years old.

Mucosal candidiasis: the initial dose is 6 mg/kg/day; the maintenance dose is 3 mg/kg/day. The initial dose can be used on the first day in order to more quickly reach the equilibrium concentration.

Invasive candidiasis, cryptococcal meningitis: the dose of the drug is 6-12 mg/kg/day, depending on the severity of the disease.

Supportive therapy to prevent the recurrence of cryptococcal meningitis in children at high risk of developing it: the dose of the drug is 6 mg/kg/day, depending on the severity of the disease.

Prevention of candidiasis in immunocompromised patients: the dose of the drug is 3–12 mg/kg/day, depending on the severity and duration of induced neutropenia (see doses for adults).

Children from birth to 27 days of age.

In newborns, fluconazole is excreted slowly from the body. The pharmacokinetic data on which the doses for full-term infants are based below are given in the section "Pharmacokinetic properties".

- Full-term newborns aged 0 to 14 days: Doses similar to those above for children 28 days to 11 years old should be used every 72 hours. Do not exceed the maximum dose of 12 mg/kg every 72 hours.

- Full-term newborns aged 15 to 27 days: Doses similar to those above for children 28 days to 11 years old should be used every 48 hours. The maximum dose of 12 mg/kg every 48 hours should not be exceeded.

Children. The medicinal product can be used in children from birth.

Overdose.

Fluconazole overdose has been reported; simultaneously reported hallucinations and paranoid behavior.

In case of overdose, symptomatic supportive therapy should be carried out and, if necessary, gastric lavage should be performed.

Fluconazole is largely excreted in the urine; forced diuresis can accelerate drug elimination. After three hours of haemodialysis session, around 50% of fluconazole is eliminated from blood.

Undesirable effects.

The most commonly reported ($> 1/10$) undesirable effects were: headache, abdominal pain, diarrhea, nausea, vomiting, rash, elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline blood phosphatase.

Adverse events have been ranked under headings of frequency using the following convention: Very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1000$, $< 1/100$); rare ($\geq 1/10000$, $< 1/1000$); very rare ($< 1/10000$), frequency unknown (cannot be estimated from the available data).

Ear and labyrinth disorders:

Uncommon: vertigo.

Gastrointestinal disorders:

Common: abdominal pain, nausea, diarrhoea, vomiting.

Uncommon: constipation, dyspepsia, flatulence, dry mouth.

Hepatobiliary disorders:

Common: increased levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase.

Uncommon: cholestasis, jaundice, increase of bilirubin level.

Rare: liver failure, hepatocellular necrosis, hepatitis, hepatocellular lesion.

Metabolism and nutrition disorders:

Uncommon: decreased appetite.

Rare: hypercholesterolemia, hypertriglyceridemia, hypokalemia.

Nervous system disorders:

Common: headache.

Uncommon: convulsions, paresthesia, dizziness, taste disturbance.

Rare: tremor.

Psychiatric disorders:

Uncommon: insomnia, drowsiness.

Cardiac disorders:

Rare: paroxysmal ventricular tachycardia type "pirouette", prolongation of the QT interval.

Blood and lymphatic system disorders:

Uncommon: anemia.

Rare: agranulocytosis, leukopenia, thrombocytopenia, neutropenia.

Immune system disorders:

Rare: anaphylaxis.

Skin and subcutaneous tissue disorders:

Common: rash.

Uncommon: drug dermatitis (including fixed drug dermatitis), urticaria, pruritus, sweating.

Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis, exfoliative dermatitis, angioneurotic edema, facial edema, anaphylactic shock, alopecia.

Unknown: drug reaction with eosinophilia and systemic manifestations (DRESS).

Musculoskeletal and connective tissue disorders:

Uncommon: myalgia.

General disorders and administration site conditions:

Uncommon: increased fatigue, malaise, asthenia, fever.

Children. The frequency and nature of undesirable effects and abnormalities in laboratory tests in children were comparable to those in adults.

Reporting of suspected adverse reactions.

Reporting suspected adverse reactions after registration of the medicinal product is an important procedure. This allows for continued monitoring of the benefit/risk ratio for the respective medicinal product. Healthcare providers should be informed of any suspected adverse reactions through the national alert system.

Shelf life 3 years.

Special precautions for storage.

Store in the original package at a temperature below 25°C. Do not freeze.

Keep out of the reach of children.

Incompatibilities.

There are no peculiarities regarding the incompatibility of the medicinal product. Do not mix the medicinal product with other medicinal product in the same container, except those listed in this section “Posology and method of administration”.

Nature and contents of container.

100 ml in a vial; 1 vial in a pack; 100 ml in vials.

Category of release. Prescription only medicine.

Manufacturer PrJSC “Pharmaceutical firm “Darnitsa”.

The manufacturer's location and address of the place of business.

13, Boryspilska Street, Kyiv, 02093, Ukraine.

Date of the last revision.