

**APPROVED**  
**by the Order of the Ministry of**  
**Health of Ukraine**  
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**VARIATIONS APPLIED**  
**By the Order of the Ministry of**  
**Health of Ukraine**  
**06.02.2020 No. 269**

**PACKAGE LEAFLET**  
**for medical use of a medicinal product**

**FLUCONAZOLE-DARNITSA**

***Qualitative and quantitative composition:***

*active substance:* fluconazole;

1 capsule contains 150 mg of fluconazole;

*List of excipients:* potato starch, lactose monohydrate, colloidal anhydrous silica, sodium lauryl sulfate, magnesium stearate, gelatin, titanium dioxide (E 171).

**Pharmaceutical form.** Capsules.

*Main physical and chemical properties:* hard gelatin capsules with a body and white lid. The contents of the capsule are a white or almost white powder.

**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 accumulation of 14 alpha-methyl sterols correlates with the subsequent loss of ergosterol in the fungal cell membrane and may be responsible for the antifungal activity of fluconazole. Fluconazole has been shown to be more selective for fungal cytochrome P-450 enzymes than for various mammalian cytochrome P-450 enzyme systems.

Susceptibility 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 the endemic moulds *Blastomyces dermatitidis*, *Coccidioides immitis*, *Histoplasma capsulatum* and *Paracoccidioides brasiliensis*.

*Pharmacokinetic properties.*

Absorption. After oral administration fluconazole is well absorbed and plasma levels 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 – 1.5 hours post-dose. Plasma concentrations are proportional to dose. The administration of a loading dose (on the day 1),

of twice the usual daily dose, enables plasma levels to approximate to 90 % steady-state levels by day 2.

**Distribution.** The apparent volume of distribution approximates to total body water. Plasma protein binding is low (11-12 %). Fluconazole achieves good penetration in all body fluids studied. The levels of fluconazole in saliva and sputum are similar to plasma levels. In patients with fungal meningitis, fluconazole levels in the CSF are approximately 80 % 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.

**Biotransformation** Fluconazole is metabolised only to a minor extent, of a radioactive dose, only 11 % is excreted in a changed form in the urine. Fluconazole is a selective inhibitor of the isozymes CYP2C9 and CYP3A4, 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 plasma elimination half-life provides the basis for single dose for vaginal candidiasis and once weekly for other indications.

*Pharmacokinetic properties in special categories of patients.*

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

**Use in elderly patients.**

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

## **Clinical particulars.**

### ***Therapeutic indications.***

Acute vaginal candidiasis, *Candidal balanitis* (when local therapy is not appropriate).

### ***Contraindications.***

- Hypersensitivity to the fluconazole, other azole substances or to other components of the medicinal product;
- 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 enzyme CYP3A4 (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, astemizole, pimozide, quinidine, erythromycin:* concomitant use of the above medicinal products and fluconazole may lead to QT prolongation, torsades de pointes and, as a consequence, sudden death. The use of a combination of these medicinal products is contraindicated.

*Terfenadine:* when using fluconazole at a dose of 200 mg per day simultaneously with terfenadine, no prolongation of the QT interval was detected. Concomitant use of fluconazole at a dose of 400 mg per day and with terfenadine significantly increases its level in blood plasma, which can lead to severe cardiac arrhythmias caused by prolongation of the QT interval. With the simultaneous use of fluconazole at a dose below 400 mg per day with terfenadine, careful monitoring of the patient's condition should be carried out. Concomitant use of fluconazole at a dose of 400 mg per day with terfenadine is contraindicated.

*Amiodarone:* concomitant use of fluconazole with amiodarone may lead to inhibition of amiodarone metabolism. An association between amiodarone use and QT prolongation has been observed. Concomitant use of fluconazole and amiodarone is contraindicated.

*Concomitant use of fluconazole and the following 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. 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.*

*The effect of other medicinal products on fluconazole* Interaction studies have shown that concomitant food intake, cimetidine, antacids, or subsequent whole-body radiation for bone marrow transplantation have no clinically significant effect on oral absorption of fluconazole.

*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, co-administration of multiple-dose hydrochlorothiazide to healthy volunteers receiving fluconazole increased plasma concentration of fluconazole by 40 %. An effect of this magnitude should not necessitate a change in the fluconazole dose regimen in subjects receiving concomitant diuretics.

*Effect of fluconazole on other medicinal products.*

*Medicinal products metabolized by CYP2C9 and CYP3A4:* Fluconazole is a potent inhibitor of CYP2C9 and a moderate inhibitor of CYP3A4. Fluconazole is also an inhibitor of the isozyme CYP2C19. With simultaneous use with fluconazole, there is a risk of an increase in the blood plasma concentrations of other compounds that are metabolized by CYP2C9 and CYP3A4, including *vinca alkaloids, alfentanil, calcium channel blockers, everolimus, sirolimus* (also by inhibition of P-glycoprotein), *tacrolimus, nonsteroidal drugs which are metabolized by CYP2C9* (for example, *naproxen, lornoxicam, meloxicam, diclofenac, flurbiprofen*), *saquinavir* (also by inhibition of P-glycoprotein). *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. An increase in the concentration of vinca alkaloids in the blood plasma (for example, vincristine and vinblastine) leads to the development of neurotoxic effects. Elevated tacrolimus levels are associated with nephrotoxicity. The use of such combinations of medicinal products should be used with caution, while careful monitoring of the patient's condition should be carried out. The inhibitory effect of fluconazole on enzymes persists for 4–5 days after its administration due to the long half-life. Interactions between fluconazole and the saquinavir/ritonavir combination have not been studied and may therefore be more pronounced.

*HMG-CoA reductase inhibitors:* the simultaneous 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. With the simultaneous use of medicinal products, it is recommended to carefully monitor the patient's condition regarding the onset of symptoms of myopathy and rhabdomyolysis and control the level of creatine kinase in the blood plasma. In the case of a significant increase in the level of creatine kinase, as well as when myopathy/rhabdomyolysis is diagnosed or suspected, the use of HMG-CoA reductase inhibitors should be discontinued.

*Voriconazole, zidovudine, carbamazepine, methadone, rifabutin, celecoxib, cyclosporine, phenytoin (intravenous):* the simultaneous use of fluconazole and the above medicinal products increases  $C_{max}$  (for phenytoin  $C_{min}$ ) and AUC of the latter; medicinal products can be used simultaneously, provided that the dose of the above medicinal products is adjusted depending on the concentration in the blood plasma. 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. With the simultaneous use of fluconazole and rifabutin, cases of uveitis have been reported. Symptoms of rifabutin toxicity should be considered. Serum concentrations of phenytoin should be monitored to avoid the development of toxic effects of phenytoin.

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

*Azithromycin*: in an open-label, randomized, tripartite crossover study involving 18 healthy volunteers, 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 mg and 800 mg, respectively. No significant pharmacokinetic interactions were found between them.

*Alfentanil*: during the simultaneous use of alfentanil at a dose of 20 µg/kg and fluconazole at a dose of 400 mg to healthy volunteers, a twofold increase in AUC<sub>10</sub> was observed, possibly due to inhibition of CYP3A4. Alfentanil dose adjustment may be required.

*Amitriptyline/nortriptyline*: fluconazole enhances the action of amitriptyline/nortriptyline. With the simultaneous use of medicinal products, it is recommended to monitor the concentration of 5-nortriptyline and/or S-amitriptyline at the beginning of combination therapy, after 1 week and, if necessary, adjust their dose.

*Amphotericin B*: in preclinical studies, the simultaneous use of fluconazole and amphotericin B in infected mice with normal immunity and infected mice with reduced immunity led to 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 two medicinal products systemic infection *A. Fumigatus*; the clinical significance of these findings is unknown.

*Anticoagulants*: As with the use of other azole antifungal agents, with the simultaneous use of fluconazole and warfarin, cases of bleeding (hematomas, epistaxis, 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. With the simultaneous use of medicinal products, it is recommended to carefully monitor the prothrombin time and, if necessary, adjust the dose of warfarin.

*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. With the simultaneous use of medicinal products, careful monitoring of the patient's condition and a decrease in the dose of benzodiazepines is recommended. 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/day and 0.25 mg of triazolam orally led to an increase in AUC and half-life of triazolam 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.

*Vitamin A*: it was reported that in a patient who simultaneously used transretinoic acid (an acid form of vitamin A) and fluconazole, adverse reactions from the central nervous system (CNS) were observed in the form of pseudotumour of the brain, which disappeared after discontinuation of fluconazole. Medicines can be used simultaneously, taking into account the risk of adverse reactions from the central nervous system.

*Losartan*: fluconazole inhibits the metabolism of losartan to its active metabolite (E-3174), which accounts for most of the antagonism to angiotensin II receptors when losartan is used. It is recommended to monitor blood pressure in patients.

*Oral contraceptives*: conducted 2 pharmacokinetic studies of repeated use of fluconazole and combined oral contraceptive. 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.

*Prednisone:* a case was reported when a patient after liver transplantation, while using prednisone, 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 prednisone metabolism. It is recommended to monitor the condition of patients in order to prevent the development of adrenal cortex insufficiency after discontinuation of fluconazole.

*Sulfonylurea derivatives:* with simultaneous use of fluconazole prolonged the half-life of oral sulfonylurea derivatives (chlorpropamide, glibenclamide, glipizide and tolbutamide) in healthy volunteers. It is recommended to monitor glucose levels and, if necessary, adjust the dose of fluconazole.

*Theophylline:* in a study of medicinal product 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 %. For patients using high doses of theophylline, or those who have an increased risk of developing toxic manifestations of theophylline for other reasons, it is recommended to monitor for signs of the development of toxic effects of theophylline. If signs of toxicity appear, the medicinal product should be canceled.

*Fentanyl:* reported one fatal case of fentanyl intoxication due to the interaction of fentanyl and fluconazole. Studies have shown that fluconazole significantly slowed down the elimination of fentanyl. An increase in fentanyl concentration can lead to respiratory depression. With the simultaneous use of drugs, it is recommended to carefully monitor the patient's condition and, if necessary, adjust the dose of fentanyl.

*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, given the risk of increased serum bilirubin and creatinine concentrations.

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

*Non-steroidal anti-inflammatory drugs (NSAIDs):* with simultaneous use with fluconazole,  $C_{max}$  and AUC of flurbiprofen increased by 23 % and 81 %, respectively, compared with the corresponding indicators when using flurbiprofen alone. Similarly, with the simultaneous use of fluconazole with racemic ibuprofen (400 mg), the  $C_{max}$  and AUC of the pharmacologically active isomer S - (+) - ibuprofen increased by 15 % and 82 %, respectively, compared with such indicators when using only racemic ibuprofen.

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

*Ivacaftor:* concomitant use with ivacaftor, an amplifier of cystic fibrosis transmembrane conductance regulator, increases the exposure of ivacaftor by 3 times, and hydroxymethylivacaftor (M1) by 1.9 times. For patients who are concomitantly using mild CYP3A inhibitors such as fluconazole and erythromycin, it is recommended to reduce the dose of ivacaftor to 150 mg once a day.

### ***Special warnings and precautions for use.***

Insufficient duration of treatment can lead to the restoration of an active infectious process.

*Use in deep endemic mycoses, cryptococcosis, dermatophytes.* There is insufficient evidence of the efficacy of fluconazole for the treatment of cryptococcosis and other forms of endemic mycoses, such as paracoccidioidomycosis, histoplasmosis, and cutaneous lymphatic sporotrichosis; therefore, there are no recommendations on the dosage regimen for the treatment of such diseases. According to the results of a study of fluconazole for the treatment of dermatophytosis in children, fluconazole does not exceed griseofulvin in effectiveness, therefore fluconazole should not be used for the treatment of dermatophytosis.

*Effects on the urinary system.* The medicinal product should be used with caution in patients with impaired renal function (see section "Posology and method of administration").

*Adrenal insufficiency.* Ketoconazole is known to cause adrenal insufficiency, and this can also affect fluconazole, although it is rarely observed. Adrenal insufficiency associated with concomitant prednisone treatment is described in the subsection "Effects of fluconazole on other medicinal products" above.

*Effects on the hepatobiliary system.* 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. It is recommended to carefully monitor the condition of patients in whom abnormal liver function tests are observed when using fluconazole to detect symptoms of more severe liver damage.

The medicinal product should be used with caution in patients with impaired liver function. 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.

*Effects on cardiovascular system.* Some azoles, including fluconazole, are associated with QT prolongation on the electrocardiogram. Very rare cases of lengthening of the QT interval and paroxysmal ventricular tachycardia of the "pirouette" type have been reported with fluconazole. Such messages concerned patients with severe diseases with a combination of many risk factors, such as structural heart disease, electrolyte metabolism disorders and the simultaneous use of other medicinal products that affect the QT interval.

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

*Effects on the cytochrome P450 system.* Fluconazole is a potent inhibitor of the enzyme CYP2C9 and a moderate inhibitor of the enzyme CYP3A4. Fluconazole is also an inhibitor of the enzyme CYP2C19.

Patients should be closely monitored while concomitant use of fluconazole and medicinal products with a narrow therapeutic window, which are metabolized with the participation of CYP2C9, CYP2C19 and CYP3A4.

*Dermatological reactions.* With the use of fluconazole, the development of such exfoliative skin reactions as malignant exudative erythema (Stevens-Johnson syndrome) and toxic epidermal necrolysis (Lyell's syndrome) were rarely reported. AIDS patients are more likely to develop severe skin reactions with many medications. Patients with AIDS are more likely to develop severe skin reactions with many medicinal products.

If rashes appear that can be associated with the use of fluconazole, the medicinal product should be discontinued in patients with superficial fungal infection. If rashes appear that can be associated with the use of fluconazole, careful monitoring of the condition of patients with invasive/systemic fungal infection should be carried out, and in case of development of bullous rashes or polymorphic erythema, the medicinal product should be discontinued.

*Hypersensitivity reactions.* When using fluconazole, in rare cases, the development of anaphylactic reactions has been reported.

The medicinal product contains lactose; therefore, patients with rare hereditary forms of galactose intolerance, lactase deficiency or glucose-galactose malabsorption syndrome should not use the medicinal product.

*Fertility, pregnancy and lactation.*

The data obtained with a single or repeated use of fluconazole in usual doses (<200 mg/day) to several hundred pregnant women during the first trimester of pregnancy did not demonstrate any adverse effects on the fetus. Numerous congenital abnormalities have been reported in newborns (including brachyphrenia, auricular dysplasia, excessive enlargement of the anterior fontanelle, curvature of the hip, brachial synostosis) when pregnant women use high doses of fluconazole (400-800 mg/day) for

at least 3 months for treatment 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.

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 with repeated use of fluconazole or with high doses of fluconazole.

#### *Effects on ability to drive and use machines.*

Studies of the effect of fluconazole on the ability to drive vehicles or operate other mechanisms have not been conducted. Patients should be informed of the possibility of dizziness or seizures while taking the medicinal product. With the development of such symptoms, it is not recommended to drive vehicles or other mechanisms.

#### ***Posology and method of administration.***

The medicinal product should be used in a dose of 150 mg once. Swallow the capsules whole with or without food.

##### Use in elderly patients.

In the absence of signs of impaired renal function for the treatment of this category of patients, the medicinal product should be used at the usual dose for adults.

##### *Patients with renal impairment*

With a single use of fluconazole in patients with mild and moderate renal insufficiency, dose adjustment is not required.

##### *Patients with hepatic impairment*

The medicinal product should be used with caution, as there is insufficient information on the use of fluconazole in this category of patients.

#### *Children.*

The efficacy and safety of the medicinal product for the treatment of genital candidiasis in children has not been established, despite the comprehensive data on the use of fluconazole in children. If there is an urgent need for the use of the medicinal product in adolescents (aged 12 to 17 years), the usual adult doses should be used.

#### ***Overdose.***

Overdose of fluconazole and the development of hallucinations and paranoid behavior have been reported.

*Treatment:* symptomatic supportive therapy and, if necessary, gastric lavage. Fluconazole is largely excreted in the urine, so forced diuresis can accelerate medicinal product elimination. After three hours of haemodialysis session, around 50 % of fluconazole is eliminated from blood.

#### ***Undesirable effects.***

The most common ( $> 1/10$ ) reported adverse reactions are: 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 ( $\geq 1/100$  and  $<1/10$ ), uncommon ( $\geq 1/1000$  and  $<1/100$ ), rare ( $\geq 1/10000$  and  $<1/1000$ ), very rare ( $<1/10,000$ ), frequency unknown (cannot be estimated from the available data).

##### *Ear and labyrinth disorders:*

Uncommon: vertigo.

##### *Gastrointestinal disorders:*

Common: abdominal pain, diarrhea, nausea, vomiting.

Uncommon: constipation, dyspepsia, flatulence, dry mouth.

*Hepatobiliary disorders:*

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

Uncommon: cholestasis, jaundice, increased plasma bilirubin.

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

*Metabolism and nutrition disorders:*

Rare: hypertriglyceridemia, hypercholesterolemia, hypokalemia.

Uncommon: decreased appetite.

*Nervous system disorders:*

Common: headache.

Uncommon: convulsions, dizziness, paresthesia, 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, neutropenia, thrombocytopenia.

*Immune system disorders:*

Rare: anaphylaxis.

*Skin and subcutaneous tissue disorders:*

hypersensitivity reactions, including:

Common: rash.

Uncommon: itching, hyperemia, drug-induced dermatitis, urticaria, increased sweating.

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

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

*Musculoskeletal and connective tissue disorders:*

Uncommon: myalgia.

*General disorders:*

Uncommon: increased fatigue, malaise, asthenia, fever.

*Children.*

The frequency and nature of adverse reactions and abnormalities in laboratory tests in children were comparable to those in adults.

***Shelf life.*** 3 years.

**Special precautions for storage.**

Store in the original package at a temperature below 25°C.

Keep out of the reach of children.

**Nature and contents of container.**

1 capsule in a blister strip; 1 blister strip in a package.

**Category of release.**

Without a prescription.

**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.**

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