

PACKAGE LEAFLET
for medical use of a medicinal product

VAZOKLIN-DARNITSA

Qualitative and quantitative composition:

active substance: atorvastatin;

1 tablet contains atorvastatin calcium related to atorvastatin 10 mg or 20 mg;

excipients: calcium carbonate with povidone, cellulose microcrystalline, lactose monohydrate, sodium lauryl sulfate, crospovidone, magnesium stearate, opadray II 85F white.

Pharmaceutical form. Film-coated tablets.

Basic physical and chemical properties: white to off white, biconvex, round, film-coated tablets.

Pharmacotherapeutic group.

Medications that reduce the level of cholesterol and triglycerides in the blood serum. HMG-CoA reductase inhibitors. ATC code C10A A05.

Pharmacological properties.

Pharmacodynamic properties.

Atorvastatin is a synthetic lipid-lowering drug. Atorvastatin is 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitor. This enzyme catalyzes the conversion of HMG-CoA to mevalonate – an early stage of cholesterol biosynthesis that limits the rate of cholesterol formation.

Atorvastatin is a selective competitive HMG-CoA reductase inhibitor, the enzyme that determines the conversion rate of 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Cholesterol and triglycerides circulate in the bloodstream in a complex with lipoproteins. These complexes are separated by ultracentrifugation into HDL (high-density lipoproteins), IDL (intermediate-density lipoproteins), LDL (low-density lipoproteins) and VLDL (very low-density lipoproteins). Triglycerides (TG) and cholesterol in the liver are incorporated into VLDL and released into the blood plasma for delivery to peripheral tissues. LDL is formed from VLDL and catabolized by interacting with high-affinity LDL receptors. There is evidence that elevated plasma levels of total cholesterol (TCL), LDL cholesterol (LDL-CL), and apolipoprotein B (Apo B) contribute to the development of atherosclerosis in humans and are risk factors for cardiovascular diseases, while elevated HDL cholesterol levels are associated with a reduced risk of cardiovascular disease.

In experimental animal models, atorvastatin reduces plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic LDL receptors on the cell surface to enhance LDL uptake and catabolism; atorvastatin also reduces LDL production and the number of these particles. Atorvastatin reduces LDL cholesterol levels in some patients with homozygous familial hypercholesterolemia, i.e. groups of people who rarely respond to treatment with other lipid-lowering medications.

There is evidence that elevated levels of total cholesterol, LDL cholesterol, and apo B (a membrane complex for LDL cholesterol) provoke the development of atherosclerosis. Similarly, reduced levels of HDL cholesterol (and its transport complex – apo A) are associated with the development of atherosclerosis. Cardiovascular morbidity and mortality are known to vary directly in proportion to total cholesterol and LDL cholesterol levels and inversely in proportion to HDL cholesterol levels.

Atorvastatin reduces total cholesterol, LDL cholesterol, and apo B levels in patients with homozygous and heterozygous familial hypercholesterolemia, non-familial forms of hypercholesterolemia, and mixed dyslipidemia. Atorvastatin also reduces VLDL and TG cholesterol levels, and causes an unstable increase in HDL cholesterol and apolipoprotein A-1. Atorvastatin reduces total cholesterol, LDL cholesterol, VLDL cholesterol, apo B, triglycerides, and non-HDL cholesterol, and increases HDL cholesterol in patients with isolated hypertriglyceridemia. Atorvastatin reduces HDL cholesterol in patients with dysbetalipoproteinemia.

Like LDL, cholesterol-and triglyceride-rich lipoproteins, including VLDL, HDL, and residues, can also contribute to the development of atherosclerosis. Elevated plasma triglyceride levels are often found in the triad with low HDL-C levels and small LDL particles, as well as in combination with non-lipid

metabolic risk factors for coronary heart disease. Total plasma triglyceride levels as such have not been consistently shown to be an independent risk factor for coronary heart disease. In addition, there was no independent effect of increasing HDL or lowering triglyceride levels on the risk of coronary and cardiovascular morbidity and mortality.

Atorvastatin, like some of its metabolites, is pharmacologically active in humans. The main site of atorvastatin's action is liver, which plays a major role in cholesterol synthesis and LDL clearance. The dose of the drug, in contrast to the systemic concentration of the drug, better correlates with a decrease in LDL cholesterol. Individual selection of the drug dose should be carried out depending on the therapeutic response.

Pharmacokinetic properties.

Absorption.

Atorvastatin is rapidly absorbed after oral administration and its maximum plasma concentrations are reached within 1-2 hours. Extent of absorption increases proportionally to the dose of atorvastatin. The absolute bioavailability of atorvastatin (parent drug) is approximately 14 %, and the systemic bioavailability of inhibitory activity against HMG-CoA reductase is approximately 30 %. The low systemic availability of the drug is associated with presystemic clearance in gastrointestinal mucosa and/or presystemic biotransformation in the liver. Although food reduces the rate and degree of drug absorption by approximately 25 % and 9 %, respectively, based on C_{max} and AUC, the reduction in LDL cholesterol is similar regardless of whether the drug is taken with or without food. When atorvastatin was administered in the evening, its plasma concentration was lower (approximately by 30 % for C_{max} and AUC) than when taken in the morning. However, the reduction in LDL cholesterol is similar regardless of the time of drug administration.

Distribution.

Mean volume of distribution of atorvastatin is approximately 381 l. More than 98 % of the drug is bound to plasma proteins. The blood/plasma concentration ratio, which is approximately 0.25, indicates poor penetration of the drug into red blood cells. Based on observations in animals, it is believed that atorvastatin is able to penetrate into breast milk.

Metabolism.

Atorvastatin is intensively metabolized to ortho- and parahydroxylated derivatives and various beta-oxidation products. In *in vitro* studies of HMG-CoA reductase inhibition by ortho- and parahydroxylated metabolites was equivalent to inhibition by atorvastatin. Approximately 70 % of the circulating inhibitory activity against HMG-CoA reductase is associated with active metabolites. *In vitro* studies indicate the importance of atorvastatin metabolism by cytochrome P450 3A4, which is consistent with increased concentrations of the drug in human blood plasma after concomitant use with erythromycin, a known inhibitor of this isoenzyme.

Excretion.

Atorvastatin and its metabolites are mainly excreted in bile after hepatic and/or extrahepatic metabolism, but this drug does not appear to undergo enterohepatic recirculation. The average elimination half-life of the drug from human blood plasma is approximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase ranges from 20 to 30 hours due to the contribution of active metabolites. After oral administration of the drug, less than 2 % of the dose is excreted in the urine.

Patient populations

Elderly. Plasma concentrations of atorvastatin are higher (approximately 40 % for C_{max} and 30 % for AUC) in healthy elderly patients (aged 65 years and older) than in young adults. There is evidence of a greater degree of LDL reduction with the use of any dose of the drug in elderly patients compared to young people.

Paediatric patients. Pharmacokinetic data for the group of pediatric patients are not available.

Gender. Plasma concentrations of atorvastatin in women differ from those in men (approximately 20 % higher for C_{max} and 10 % lower for AUC). However, there is no clinically significant difference in LDL cholesterol reduction when using the drug in men and women.

Impaired renal function. Kidney diseases have no influence on concentration of atorvastatin in blood plasma or a decrease in LDL-C, and, therefore, dose adjustment of the drug for patients with impaired renal function is not required.

Hemodialysis. Despite the fact that no studies have been conducted in patients with end-stage kidney disease, it is believed that hemodialysis does not significantly increase the clearance of atorvastatin, since the drug intensively binds to plasma proteins.

Hepatic impairment. Plasma concentrations of atorvastatin are markedly elevated in patients with chronic alcoholic liver disease. C_{max} and AUC values are 4 times higher in patients with class A liver disease according to Child-Pugh score. In patients with class B liver disease according to Child-Pugh scale, the values of C_{max} and AUC are increased approximately by 16 times and 11 times, respectively.

Table 1.

Effect of co-administered medicinal products on atorvastatin pharmacokinetics

Co-administered medicinal products and dosage regimen	Atorvastatin		
	Dose (mg)	Change in AUC ^{&}	Change in C_{max} ^{&}
#Ciclosporine 5.2 mg/kg/day, stable dose	10 mg 1 time a day during 28 days	8.7 times	10.7 times
#Tipranavir 500 mg twice a day/ritonavir 200 mg twice a day, 7 days	10 mg 1 time a day	9.4 times	8.6 times
#Telaprevir 750 mg every 8 hours, 10 days	20 mg 1 time a day	7.88 times	10.6 times
#, ‡Saquinavir 400 mg twice a day/ritonavir 400 mg twice a day, 15 days	40 mg 1 time a day for 4 days	3.9 times	4.3 times
#Clarithromycin 500 mg twice a day, 9 days	80 mg 1 time a day during 8 days	4.4 times	5.4 times
#Darunavir 300 mg twice a day/ritonavir 100 mg twice a day, 9 days	10 mg 1 time a day during 4 days	3.4 times	2.25 times
#Itraconazole 200 mg 1 time a day, 4 days	40 mg 1 time a day	3.3 times	20 %
#Fosamprenavir 700 mg twice a day/ritonavir 100 mg twice a day, 14 days	10 mg 1 time a day for 4 days	2.53 times	2.84 times
#Fosamprenavir 1400 mg twice a day, 14 days	10 mg 1 time a day during 4 days	2.3 times	4.04 times
#Nelfinavir 1250 mg 2 times a day, 14 days	10 mg 1 time a day for 28 days	74 %	2.2 times
#Grapefruit juice, 240 ml 1 time a day*	40 mg 1 time a day	37 %	16 %
Diltiazem 240 mg 1 time a day, 28 days	40 mg 1 time a day	51 %	Without changes
Erythromycin 500 mg 4 times a day, 7 days	10 mg 1 time a day	33 %	38 %
Amlodipine 10 mg, single dose	80 mg 1 time a day	15 %	↓ 12 %
Cimetidine 300 mg 4 times a day, 2 weeks	10 mg 1 time a day for 2 weeks	↓ Less than 1%	↓ 11 %
Colestipol 10 mg 2 times a day, 28 weeks	40 mg 1 time a day for 28 days	Not estimated	↓ 26 %**
Maalox TC® 30 ml 1 time a day, 17 days	10 mg 1 time a day for 15 days	↓ 33 %	↓ 34 %
Efavirenz 600 mg 1 time a day, 14 days	10 mg during 3 days	↓ 41 %	↓ 1 %
#Rifampin 600 mg once a day, 7 days (with concomitant administration) [†]	40 mg 1 time a day	30 %	2.7 times
#Rifampin 600 mg 1 time a day, 5 days (in separate doses) [†]	40 mg 1 time a day	↓ 80 %	↓ 40 %
#Gemfibrozil 600 mg twice a day, 7 days	40 mg 1 time a day	35 %	↓ Less than 1 %
#Fenofibrate 160 mg 1 time a day, 7 days	40 mg 1 time a day	3 %	2 %
#Boceprevir 800 mg 3 times a day, 7 days	40 mg 1 time a day	2.30 times	2.66 times

- & The data, indicated as x-fold change, represent a simple correlation between cases of concomitant drug use and the use of atorvastatin alone (i.e., 1-fold = no change). The data, indicated in % change, represent the % difference relative to the indicators when using atorvastatin alone (i.e., 0 % = no change).
- # For information on clinical significance, see the sections "Special warnings and precautions for use" and "Interaction with other medicinal products and other forms of interaction."
- * Greater increases in AUC (up to 2.5 times) and/or C_{max} (up to 71 %) have been reported with excessive consumption of grapefruit juice (750 ml – 1.2 liters per day or more).
- ** A single sample taken 8-16 hours after taking a dose of the drug.
- † Due to the mechanism of double interaction of rifampin, concomitant use of atorvastatin with rifampin is recommended, since it has been shown that delayed use of atorvastatin after rifampin administration is associated with a significant decrease in plasma concentrations of atorvastatin.
- ‡ The dose of the saquinavir + ritonavir combination in this study is not a clinically applicable dose. The increase in exposure to atorvastatin when used in a clinical setting is likely to be higher than that observed in this study. Therefore, the drug should be used with caution at the lowest required dose.

Table 2.

Effect of atorvastatin on the pharmacokinetics of concomitant medications

Atorvastatin	Concomitantly used drug and dosage regimen		
	Medicinal product/dose (mg)	Change in AUC	Change in C _{max}
80 mg 1 time a day during 15 days	Antipyrine, 600 mg 1 time a day	3 %	↓ 11 %
80 mg 1 time a day during 14 days	#Digoxin 0.25 mg 1 time a day, 20 days	15 %	20 %
40 mg 1 time a day during 22 days	Oral contraceptives 1 time a day, 2 months – norethisterone 1 mg – ethinylestradiol 35 µg	8 % 19 %	3 % 30 %
10 mg a day	Tipranavir 500 mg twice a day /ritonavir 200 mg twice a day, 7 days	Without changes	Without changes
10 mg 1 time a day during 4 days	Fosamprenavir 1400 mg twice a day, 14 days	↓ 27%	↓ 18%
10 mg 1 time a day during 4 days	Fosamprenavir 700 mg twice a day /ritonavir 100 mg twice a day, 14 days	Without changes	Without changes

For information on clinical significance, see the sections "Special warnings and precautions for use" and "Interaction with other medicinal products and other forms of interaction."

Clinical particulars.

Therapeutic indications.

Prevention of cardiovascular diseases

For adult patients without clinically significant coronary heart disease, but with several risk factors for coronary heart disease, such as age, smoking, hypertension, low HDL, or a family history of early coronary heart disease, atorvastatin is indicated for:

- reducing the risk of myocardial infarction;
- reducing the risk of stroke;
- reducing the risk of revascularization procedures and angina pectoris.

In patients with type II diabetes mellitus and without clinically significant coronary heart disease, but with several risk factors for developing coronary heart disease, such as retinopathy, albuminuria, smoking, or arterial hypertension, the drug is indicated for:

- reducing the risk of myocardial infarction;

- reducing the risk of stroke.
- In patients with clinically expressed coronary heart disease, the drug is indicated for:
- reducing the risk of non-lethal myocardial infarction;
- reducing the risk of fatal and non-fatal stroke;
- reducing the risk of revascularization procedures;
- reducing the risk of hospitalization due to congestive heart failure;
- reducing the risk of angina pectoris.

Hyperlipidemia

- As an adjunct to diet to reduce elevated levels of total cholesterol, LDL cholesterol, apolipoprotein B and triglycerides, as well as to increase HDL cholesterol in patients with primary hypercholesterolemia (heterozygous familial and non-familial) and mixed dyslipidemia (types IIa and IIb according to Fredrickson classification).
- As an adjunct to diet for the treatment of patients with elevated serum triglyceride levels (type IV according to the Fredrickson classification).
- In the treatment of patients with primary dysbetalipoproteinemia (type III according to the Fredrickson classification), in cases where diet is not effective enough.
- To reduce total cholesterol and LDL cholesterol in patients with homozygous familial hypercholesterolemia, supplement of other lipid-lowering treatments (e.g. LDL apheresis), or if such treatments are not available.
- As a dietary supplement to reduce the levels of total cholesterol, LDL cholesterol and apolipoprotein B in boys and girls after the onset of menstruation, aged 10 to 17 years with heterozygous familial hypercholesterolemia, if after appropriate diet therapy, the test results are as follows:

a) LDL cholesterol is ≥ 190 mg/dL or

b) LDL cholesterol is ≥ 160 mg/dL and:

- family history of early cardiovascular diseases or
- two or more other risk factors for heart disease are present

in pediatric patient.

Contraindications.

- Active liver disease, which may include a persistent increase in the level of hepatic transaminases of unknown etiology.
- Hypersensitivity to any of the components of this drug.

Interaction with other medicinal products and other forms of interaction.

The risk of myopathy during statin treatment increases with concomitant use of fibric acid derivatives, lipid-modifying doses of niacin, ciclosporine, or potent CYP 3A4 inhibitors (for example, clarithromycin, HIV protease inhibitors, and itraconazole).

Potent CYP 3A4 inhibitors. Atorvastatin is metabolized by cytochrome P450 3A4. Concomitant use of the drug with potent CYP 3A4 inhibitors may lead to increased plasma concentrations of atorvastatin. The degree of interaction and amplification of the action depend on the variability of effect on CYP 3A4. Concomitant use with potent CYP 3A4 inhibitors (e.g. ciclosporine, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors, including ritonavir, lopinavir, atazanavir, indinavir, darunavir) should be avoided, if possible. If co-administration of these drugs with atorvastatin cannot be avoided, lowering of the initial and maximum doses of atorvastatin should be considered. Close clinical monitoring of the patient's condition is also recommended.

Moderate CYP 3A4 inhibitors (e.g. erythromycin, diltiazem, verapamil, and fluconazole) may increase the plasma concentrations of atorvastatin. Concomitant use of erythromycin and statins is accompanied by an increased risk of myopathy. Drug interaction studies to assess the effect of amiodarone or verapamil on atorvastatin have not been conducted. Amiodarone and verapamil are known to inhibit CYP 3A4 activity, and therefore concomitant administration of these drugs with atorvastatin may lead to increased atorvastatin exposure. Therefore, when atorvastatin and these moderate CYP 3A4 inhibitors are co-administered, lowering of the maximum doses of atorvastatin should be considered. Clinical

monitoring of the patient's condition is also recommended. After starting treatment with an inhibitor or after adjusting its dose, it is recommended to conduct clinical monitoring of the patient's condition.

Grapefruit juice. Grapefruit contains one or more components that inhibit CYP 3A4 and may increase the plasma concentrations of atorvastatin, especially with excessive consumption of grapefruit juice (more than 1.2 liters per day).

Clarithromycin. The AUC value of atorvastatin was significantly increased with concomitant use of the drug at dose of 80 mg and clarithromycin (500 mg twice daily) compared to the use of atorvastatin alone. Therefore, at atorvastatin doses exceeding 20 mg, clinical monitoring of these patients is recommended.

Combination of protease inhibitors. The AUC value of atorvastatin was significantly increased when used concomitantly with several combinations of HIV protease inhibitors, as well as with the hepatitis C virus protease inhibitor telaprevir compared to use of the drug alone. Therefore, concomitant use with atorvastatin should be avoided in patients taking the HIV protease inhibitor tipranavir + ritonavir or the hepatitis C virus protease inhibitor telaprevir. The drug should be used with caution in patients taking the HIV protease inhibitor lopinavir + ritonavir, and used at the lowest required dose. For patients taking HIV protease inhibitors saquinavir + ritonavir, darunavir + ritonavir, fosamprenavir or fosamprenavir + ritonavir, the dose of the drug should not exceed 20 mg and should be used with caution. When used in patients taking the HIV protease inhibitor nelfinavir or the hepatitis C virus protease inhibitor boceprevir, the dose of atorvastatin should not exceed 40 mg, and careful clinical monitoring of patients is recommended.

Itraconazole. The AUC value of atorvastatin was significantly increased with concomitant use of atorvastatin at dose of 40 mg and itraconazole at a dose of 200 mg. Therefore, patients taking itraconazole should be careful if the dose of atorvastatin exceeds 20 mg.

Ciclosporin. Atorvastatin and its metabolites are substrates of the OATP1B1 transporter. OATP1B1 inhibitors (e.g. ciclosporine) may increase the bioavailability of atorvastatin. The AUC value of atorvastatin was significantly increased with concomitant use of atorvastatin at a dose of 10 mg and ciclosporine at a dose of 5.2 mg/kg/day compared to atorvastatin alone. Concomitant use of atorvastatin and ciclosporine should be avoided.

Medical recommendations for the use of interacting drugs are summarized in Table 3.

Table 3.

Drug interactions associated with an increased risk of myopathy/rhabdomyolysis.

Interacting medicinal products.	Medical recommendations for use
Ciclosporine, HIV protease inhibitors (tipranavir + ritonavir), hepatitis C virus protease inhibitor (telaprevir)	Avoid using atorvastatin
HIV protease inhibitor (lopinavir + ritonavir)	Use with caution and at the lowest required dose
Clarithromycin, itraconazole, HIV protease inhibitors (saquinavir + ritonavir*, darunavir + ritonavir, fosamprenavir, fosamprenavir + ritonavir)	Do not exceed the daily dose of 20 mg of atorvastatin
HIV protease inhibitor (nelfinavir) Hepatitis C virus protease inhibitor (boceprevir)	Do not exceed the daily dose of 40 mg of atorvastatin

*Use with caution and at the lowest required dose.

Gemfibrozil. Due to the increased risk of myopathy/rhabdomyolysis, concomitant use of HMG-CoA reductase inhibitors with gemfibrozil should be avoided.

Other fibrates. Since it is known that the risk of myopathy development during treatment with HMG-CoA reductase inhibitors increases with concomitant administration of other fibrates, atorvastatin should be used with caution when combined with other fibrates.

Niacin. The risk of skeletal muscle side effects may be increased when using the drug in combination with niacin, and therefore, under such conditions, the possibility to reduce the dose of atorvastatin should be considered.

Rifampin or other cytochrome P450 3A4 inducers. Concomitant use of the drug with cytochrome P450 3A4 inducers (for example, efavirenz, rifampin) may lead to an unstable decrease in the plasma concentration of atorvastatin. Due to the dual interaction mechanism of rifampin, concomitant use of atorvastatin with rifampin is recommended, since it has been shown that delayed use of atorvastatin after rifampin administration is associated with a significant reduction in plasma concentrations of atorvastatin.

Diltiazem hydrochloride. Concomitant administration of atorvastatin (40 mg) and diltiazem (240 mg) is accompanied by an increase in the concentration of atorvastatin in blood plasma.

Cimetidine. As a result of the conducted studies, no signs of interaction between atorvastatin and cimetidine were found.

Antacids. Concomitant oral administration of atorvastatin and suspension of antacids containing magnesium and aluminum hydroxide is accompanied by decrease in the plasma concentration of atorvastatin by approximately 35 %. At the same time, the lipid-lowering effect of atorvastatin is unchanged.

Colestipol. The concentration of atorvastatin in blood plasma was lower (by about 25 %) with concomitant administration of atorvastatin and colestipol. At the same time, the lipid-lowering effect of the combination of atorvastatin and colestipol was exceeding the effect of using each of these drugs separately.

Azithromycin. Concomitant administration of atorvastatin (10 mg 1 time per day) and azithromycin (500 mg 1 time per day) was not accompanied by changes in the plasma concentration of atorvastatin.

Inhibitors of transporter protein Inhibitors of transporter protein (for example, ciclosporine) may increase the level of systemic exposure to atorvastatin. The effect of inhibition of storage and transport proteins on the concentration of atorvastatin in liver cells is unknown. If concomitant administration of these drugs cannot be avoided, it is recommended to reduce the dose and conduct clinical monitoring of atorvastatin effectiveness.

Ezetimibe. The use of ezetimibe as monotherapy is associated with muscle related events, including rhabdomyolysis. Thus, with concomitant use of ezetimibe and atorvastatin, the risk of development of these events is increasing. Appropriate clinical monitoring of the condition of such patients is recommended.

Fusidic acid. Interaction studies with atorvastatin and fusidic acid have not been conducted. After the drug entered the market, as in the case of other statins, muscle related events (including rhabdomyolysis) were observed with concomitant administration of atorvastatin and fusidic acid. The mechanism of this interaction remains unknown. Patients need close monitoring, as temporary suspension of atorvastatin treatment may be required.

Digoxin. With concomitant use of multiple doses of atorvastatin and digoxin, steady-state concentrations of digoxin in blood plasma increase by approximately 20 %. Patients taking digoxin should be properly monitored.

Oral contraceptives. Concomitant use of atorvastatin with oral contraceptives increased the AUC values for norethisterone and ethinylestradiol. These increases should be taken into account when choosing an oral contraceptive for a woman taking atorvastatin.

Warfarin. Atorvastatin did not have a clinically significant effect on prothrombin time when used in patients undergoing long-term warfarin treatment.

Colchicine. Cases of myopathy, including rhabdomyolysis, have been reported during concomitant use of atorvastatin with colchicine, therefore the caution should be exercised when prescribing atorvastatin with colchicine.

Other medications. It is known that concomitant use of atorvastatin and antihypertensive drugs and its use during estrogen replacement therapy is not accompanied by clinically significant side effects.

Studies of interaction with other drugs have not been conducted.

Special warnings and precautions for use.

Skeletal muscles

Rare cases of rhabdomyolysis with acute renal failure due to myoglobinuria were reported during administration of atorvastatin and other drugs of this class. A history of impaired renal function may be a risk factor for rhabdomyolysis. Such patients need more careful monitoring to detect skeletal muscle disorders.

Atorvastatin, like other statin medications, sometimes causes myopathy, which is defined as muscle pain or muscle weakness in combination with an increase in creatine phosphokinase (CPK) values more than 10 times higher than the upper limit of normal. Concomitant use of higher doses of atorvastatin with certain medications, such as ciclosporine and potent CYP 3A4 inhibitors (e.g. clarithromycin, itraconazole, and HIV protease inhibitors) increases the risk of myopathy/rhabdomyolysis.

There are also rare reports of cases of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy associated with statin use. IMNM is characterized by the following signs: weakness of the proximal muscles and elevated serum creatine kinase levels, which persist despite discontinuation of statin treatment; muscle biopsy reveals necrotizing myopathy without significant inflammation; when using immunosuppressants, a positive trend is observed.

The possibility of myopathy development should be considered in any patient with diffuse myalgia, muscle soreness or weakness, and/or a significant increase in CPK. Patients should be advised to immediately report cases of muscle pain, soreness, or muscle weakness of unknown etiology, especially if this is accompanied by a feeling of malaise or fever, or if signs and symptoms of muscle disease persist after atorvastatin discontinuation. Treatment with the drug should be discontinued in case of a significant increase in CPK levels, diagnosis or suspicion of myopathy.

The risk of myopathy during treatment with drugs of this class increases with concomitant use of ciclosporine, fibric acid derivatives, erythromycin, clarithromycin, hepatitis C virus protease inhibitor telaprevir, combinations of HIV protease inhibitors, including saquinavir + ritonavir, lopinavir + ritonavir, tipranavir + ritonavir, darunavir + ritonavir, fosamprenavir and fosamprenavir + ritonavir as well as niacin or antimycotics of the azole group. Physicians considering combination therapy of atorvastatin and fibric acid derivatives, erythromycin, clarithromycin, saquinavir + ritonavir, lopinavir + ritonavir, darunavir + ritonavir, fosamprenavir, fosamprenavir + ritonavir, azole antimycotics or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks, as well as carefully monitor the condition of patients with respect to any signs or symptoms of muscle pain, soreness, or weakness, especially during the initial months of therapy and during any of the dose titration periods in the direction of increasing any of the drugs. Consideration should be given to the possibility of using low initial and maintenance doses of atorvastatin when taken concomitantly with the above-mentioned drugs (see the section "Interaction with other medicinal products and other forms of interaction"). In such situations, periodic determination of CPK may be considered, but there is no guarantee that such monitoring will help prevent cases of severe myopathy.

Cases of myopathy, including rhabdomyolysis, have been reported during concomitant use of atorvastatin with colchicine, so atorvastatin with colchicine should be prescribed to patients with caution.

Atorvastatin therapy should be temporarily or completely discontinued in any patient with an acute, serious condition that indicates the development of myopathy, or in the presence of a risk factor for renal failure due to rhabdomyolysis (for example, severe acute infection, hypotension, surgery, trauma, severe metabolic, endocrine and electrolytic disorders, as well as uncontrolled seizures).

Impaired liver function

Statins, like some other lipid-lowering therapeutic agents, have been shown to be associated with abnormal biochemical parameters of liver function. Atorvastatin administration is sometimes associated with a persistent increase (more than 3 times higher than the upper limit of the normal range, which occurred 2 times or more) in serum transaminase levels.

It is known about the development of jaundice when taking atorvastatin and increase in liver function tests (LFT), which are not associated with jaundice or other clinical signs and symptoms. After reducing the dose, interrupting the use of the drug or stopping its use, transaminase levels return to pre-treatment levels or approximately these levels without residual events.

Before starting therapy with atorvastatin, it is recommended to obtain the results of liver enzyme tests and repeat the tests, if clinically necessary. Cases of fatal and non-fatal hepatic insufficiency are also reported in patients taking statins, including atorvastatin. In case of serious liver damage with clinical

symptoms and/or hyperbilirubinemia or jaundice, treatment with atorvastatin should be discontinued immediately. If an alternative etiology is not determined, do not re-start treatment with the drug. Atorvastatin should be used with caution in patients who consume significant amounts of alcohol and/or have a history of liver disease. The drug is contraindicated in cases of active liver disease or persistent increased hepatic transaminase levels of unknown etiology.

Endocrine function

An increase in HbA1c and fasting serum glucose levels has been reported with the use of HMG-CoA-reductase inhibitors, including atorvastatin.

Statins interfere with cholesterol synthesis and can theoretically decrease the secretion of adrenal and/or gonadal steroids. It is known that atorvastatin does not reduce the basal concentration of cortisol in plasma and does not damage the adrenal reserve. The effect of statins on fertilization ability of sperm has not been studied. It is unknown how the drug affects, and if affects, the "sex glands-pituitary-hypothalamus" system in women of premenopausal period. Caution should be exercised in concomitant use of a statin drug with medications that may reduce the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine.

Use in patients with recent cases of stroke or transient ischemic attack

Studies of atorvastatin effect on prevention of stroke by acute reducing cholesterol levels have shown a higher incidence of hemorrhagic stroke in patients treated with atorvastatin at dose 80 mg compared to the placebo group.

There are no known differences in treatment response between older and younger patients. Since older age (over 65 years) is a predisposing factor for myopathy, caution should be exercised when prescribing atorvastatin to the elderly.

Hepatic impairment

The drug is contraindicated in patients with active liver disease, including a persistent increase in the level of hepatic transaminases of unknown etiology.

Prior to treatment

Atorvastatin should be used with caution in patients with a tendency to rhabdomyolysis development. Before the beginning of statin treatment in patients prone to rhabdomyolysis, the level of CK should be determined when:

- impaired renal function;
- thyroid gland hypofunction;
- hereditary disorders of the muscular system in family or personal history;
- previous cases of toxic effects of statins or fibrates on muscles;
- previous liver diseases and/or consumption of large amounts of alcohol.

In elderly patients (over 70 years of age), the need for these measures should be evaluated taking into account the presence of other predisposing factors to the development of rhabdomyolysis.

An increase the plasma levels of the drug is possible, in particular, in the case of interactions and use in special patient populations, including patients with hereditary diseases.

In such cases, it is recommended to assess the ratio of risks and possible benefits of treatment and conduct clinical monitoring of the patient's condition. If the CK level is significantly elevated before the beginning of the treatment (exceeds the ULN by more than 5 times), treatment should not be started.

Measurement of creatine kinase levels

Creatine kinase levels should not be determined after intense physical activity or in the presence of any possible alternative causes of increased CK levels, as this may make it difficult to interpret the results. If at baseline there is a significant increase in CK (exceeding the ULN by more than 5 times), levels should be remeasured within 5-7 days to confirm the result.

During treatment

Patients should be aware of the need to immediately report about development of muscle pain, cramps, or weakness, especially when accompanied by malaise or fever.

If these symptoms occur during treatment with atorvastatin, the level of CK should be measured. If the CK level is significantly elevated (exceeds the ULN by more than 5 times), treatment should be discontinued.

Discontinuation of treatment should also be considered if the increase in CK does not reach five times the ULN, but muscle symptoms are severe and cause daily discomfort.

After the symptoms disappear and the CK level normalizes, the possibility of resuming treatment with atorvastatin or starting treatment with an alternative statin may be considered, provided that the minimum possible dose of the drug is used and the patient's condition is carefully monitored.

Atorvastatin treatment should be discontinued if there is a clinically significant increase in the CK level (exceeding the ULN by more than 10 times) or if rhabdomyolysis is diagnosed (or the development of rhabdomyolysis is suspected).

Concomitant use with other medications

The risk of rhabdomyolysis development increases with the simultaneous use of atorvastatin with certain medications that may increase the plasma concentration of atorvastatin. Examples of such drugs are potent CYP 3A4 or transport protein inhibitors: ciclosporine, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors, including ritonavir, lopinavir, atazanavir, indinavir, darunavir. When used concomitantly with gemfibrozil and other fibric acid derivatives, erythromycin, niacin and ezetimibe, the risk of myopathies also increases. If possible, other medications (not interacting with atorvastatin) should be used instead of the above-mentioned drugs.

If concomitant treatment with atorvastatin and above-mentioned drugs is necessary, the benefits and risks of such treatment should be carefully weighed. If patients are taking medications that increase the plasma concentration of atorvastatin, it is recommended to reduce the dose of atorvastatin to the minimum. In addition, when administering a potent CYP 3A4 inhibitors, a lower initial dose of atorvastatin should be considered. Proper clinical monitoring of the condition of these patients is also recommended.

Concomitant prescription of atorvastatin and fusidic acid is not recommended, therefore temporary discontinuing of atorvastatin may be considered during treatment with fusidic acid.

Interstitial lung disease

Cases of interstitial lung disease have been reported during treatment with certain statins (especially during long-term treatment). Symptoms of this disease include shortness of breath, non-productive cough, and a general deterioration in health (fatigue, weight loss, and fever). If interstitial lung disease is suspected, statin treatment should be discontinued.

Fillers

The drug contains lactose. This medication should not be taken in patients with rare hereditary diseases associated with galactose intolerance, Lapp lactase deficiency, or impaired glucose-galactose malabsorption. Therapy with lipid-modifying drugs should be one of the components of complex therapy in patients with a significantly increased risk of the development of atherosclerotic vascular diseases due to hypercholesterolemia. Drug therapy is recommended as a supplement to the diet when the result of following a diet that restricts the intake of saturated fat and cholesterol, as well as from the use of other non-drug measures, was insufficient. Patients with coronary heart disease or several risk factors for developing coronary heart disease can start taking the drug at the same time as following a diet.

Restrictions for use

Atorvastatin has not been studied under conditions where the main deviation from the norm on the part of lipoproteins is an increase in the level of chylomicrons (types I and V according to the Fredrickson classification).

Fertility, pregnancy and lactation.

Pregnancy.

Atorvastatin is contraindicated in pregnant women and women who may become pregnant. Statins can harm the fetus when used in pregnant women. Atorvastatin can only be used in women of reproductive age if it is very unlikely that such patients will become pregnant and they have been informed about potential risk factors. If woman becomes pregnant during treatment with the drug, it should be immediately discontinued and the patient should be re-consulted regarding potential risk factors for the fetus and the lack of known clinical benefit from continuing to take the drug during pregnancy.

During normal pregnancy, serum cholesterol and triglyceride levels are increased. Taking lipid-lowering medications during pregnancy will not have a beneficial effect, since cholesterol and its derivatives are necessary for the normal fetus development. Atherosclerosis is chronic process, and, therefore, a break

in taking lipid-lowering medications during pregnancy should not have a significant impact on the results of long-term treatment of primary hypercholesterolemia.

Lactation.

It is not known whether atorvastatin penetrates into breast milk, but it is known that a small amount of another drug of this class penetrates into breast milk. Since statins can potentially cause serious adverse reactions in breastfed infants, women, needed to be treated with this medication, should not breastfeed.

Effects on ability to drive and use machines.

It has very little effect on the ability to drive and use machines.

Posology and method of administration.

Hyperlipidemia (heterozygous familial and non-familial) and mixed dyslipidemia (type IIa and IIb according to the Fredrickson classification)

The recommended starting dose of atorvastatin is 10 or 20 mg once a day. For patients who need a significant reduction in LDL cholesterol (by more than 45 %), therapy can be started with a dosage of 40 mg once a day. The dose range of the drug is from 10 to 80 mg once a day. The drug can be taken as single dose at any time and regardless of food intake. Initial and maintenance doses of atorvastatin should be selected individually depending on the purpose of treatment and response. After starting treatment and/or after titration of the dose, lipid levels should be analyzed each 2 to 4 weeks and the dose should be adjusted accordingly.

Heterozygous familial hypercholesterolemia in children (aged 10-17 years)

The recommended starting dose of the drug is 10 mg/day; the maximum recommended dose is 20 mg/day. Doses of the drug should be selected individually in accordance with the recommended treatment goal. Dose adjustments should be made at intervals of 4 weeks or more.

Homozygous familial hypercholesterolemia

The dose of atorvastatin for patients with homozygous familial hypercholesterolemia is 10 to 80 mg per day. Atorvastatin should be used as an adjunct to other lipid-lowering treatments (such as LDL apheresis), or when lipid-lowering treatments are not available.

Concomitant lipid-lowering therapy

Atorvastatin can be used with bile acid sequestrants. The combination of HMG-CoA reductase inhibitors (statins) and fibrates should generally be used with caution (see sections "Special warnings and precautions for use", "Interactions with other medicinal products and other types of interactions").

Dosage for patients with impaired renal function

Kidney diseases do not affect either plasma concentrations, nor LDL cholesterol reduction when using the drug; therefore, dose adjustment of the drug for patients with impaired renal function is not necessary.

Dosage for patients taking ciclosporine, clarithromycin, itraconazole or certain protease inhibitors

Treatment with the drug should be avoided in patients taking ciclosporine or HIV protease inhibitors (tipranavir + ritonavir), or hepatitis C virus protease inhibitor (telaprevir). Atorvastatin should be used with caution in patients with HIV, taking lopinavir + ritonavir, and should be used at the lowest required dose. In patients taking clarithromycin, itraconazole, or HIV patients taking saquinavir + ritonavir, darunavir + ritonavir, fosamprenavir, or fosamprenavir + ritonavir in combination, the therapeutic dose of the drug should be limited to 20 mg and appropriate clinical examinations are recommended to ensure the use of the lowest required dose of atorvastatin. In patients, taking the HIV protease inhibitor nelfinavir or the hepatitis C virus protease inhibitor boceprevir, treatment with atorvastatin should be limited to a dose of 40 mg, and appropriate clinical examinations are recommended to ensure the use of the lowest required dose of the drug.

Children.

The safety and efficacy of the drug in patients aged 10-17 years with heterozygous familial hypercholesterolemia was studied in adolescent boys and girls after the onset of menstruation. Patients treated with atorvastatin at the dose up to 20 mg had a generally similar adverse reaction profile to patients treated with placebo. Infectious diseases were the adverse events that were most often observed in both groups, regardless of the causal assessment. There was no significant effect of the drug on the

growth or puberty of boys or on the duration of the menstrual cycle in girls. The effect of atorvastatin in prepubescent patients or under 10 years of age has not been studied.

Overdose.

There is no specific treatment for atorvastatin overdose. In case of overdose, the patient should be treated symptomatically and, if necessary, supportive measures should be taken. Due to the high degree of binding of the drug to plasma proteins, a significant increase in drug clearance by hemodialysis should not be expected.

Undesirable effects.

Clinical adverse reactions that occurred in 2 % or more of patients treated with any dose of atorvastatin, and with a frequency higher than placebo, regardless of causal relationship (% of patients).

Adverse reaction*	Any N=8755	dose 10 mg N=3908	20 mg N=188	40 mg N=604	80 mg N=4055	Placebo N=7311
Nasopharyngitis	8.3	12.9	5.3	7	4.2	8.2
Arthralgia	6.9	8.9	11.7	10.6	4.3	6.5
Diarrhea	6.8	7.3	6.4	14.1	5.2	6.3
Pain in the extremities	6	8.5	3.7	9.3	3.1	5.9
Urinary tract infection	5.7	6.9	6.4	8	4.1	5.6
Dyspepsia	4.7	5.9	3.2	6	3.3	4.3
Nausea	4	3.7	3.7	7.1	3.8	3.5
Musculoskeletal pain	3.8	5.2	3.2	5.1	2.3	3.6
Muscle cramps	3.6	4.6	4.8	5.1	2.4	3
Myalgia	3.5	3.6	5.9	8.4	2.7	3.1
Insomnia	3	2.8	1.1	5.3	2.8	2.9
Pharyngolaryngeal pain	2.3	3.9	1.6	2.8	0.7	2.1
* Adverse reaction >2 % at any dose greater than placebo						

Other adverse reactions, reported during studies, include:

general disorders: malaise, pyrexia;

gastrointestinal disorders: gastrointestinal discomfort, belching, flatulence, hepatitis, cholestasis;

musculoskeletal disorders: musculoskeletal pain, increased muscle fatigue, neck pain, joint swelling, tendinopathy (sometimes complicated by tendon rupture);

metabolic and nutritional disorders: increased transaminases, deviations from the norm of liver function tests, increased levels of alkaline phosphatase in the blood, increased creatine phosphokinase activity, hyperglycemia;

nervous system disorders: nightmares;

respiratory system disorders: nosebleeds;

skin and subcutaneous tissue disorders: urticaria;

eye disorders: blurred vision, visual impairment;

ear and labyrinth disorders: tinnitus;

renal and urinary disorders: leukocyturia;

reproductive system and breast disorders: gynecomastia.

The frequency of adverse reactions was determined as following: common (>1/100, <1/10); uncommon (>1/1000, <1/100); rare (>1/10000, <1/1000); very rare (<1/10000).

Nervous system disorders: common: headache; *uncommon:* dizziness, paresthesia, hypesthesia, dysgeusia, amnesia; *rare:* peripheral neuropathies.

Gastrointestinal disorders: common: constipation; *uncommon:* pancreatitis, vomiting.

Musculoskeletal and connective tissue disorders: common: joint pain, back pain; *rare:* myopathy, myositis, rhabdomyolysis.

General disorders: uncommon: asthenia, chest pain, peripheral edema, fatigue.

Metabolic and nutritional disorders: uncommon: hypoglycemia, weight gain, anorexia.

Hepatobiliary disorders: very rare: liver failure.

Skin and connective tissue disorders: rare: skin rash, pruritus, alopecia; rare: angioedema, bullous dermatitis (including erythema multiforme), Stevens-Johnson syndrome and toxic epidermal necrolysis.

Respiratory, thoracic and mediastinal disorders: common: sore throat and larynx.

Blood and lymphatic system disorders: rare: thrombocytopenia.

Immune system disorders: common: allergic reactions; very rare: anaphylaxis.

Eye disorders: uncommon: blurred vision.

Changes in the results of laboratory tests: common: abnormality of the results of liver function tests, increased blood creatine phosphokinase; uncommon: positive test for white blood cells in the urine.

As with other HMG CoA-reductase inhibitors, increased serum transaminase activity was observed in patients taking atorvastatin. These changes were usually mild, temporary, and did not require intervention or treatment. A clinically significant increase in serum transaminase activity (exceeding the upper limit of normal by more than 3 times) was observed in 0.8 % of patients taking atorvastatin. This increase was dose-dependent and was reversible in all patients.

In 2.5 % of patients taking atorvastatin, an increase in serum creatine kinase activity was observed, which was more than 3 times higher than the upper limit of normal. This coincides with observations during the use of other HMG-CoA-reductase inhibitors in clinical trials. 0.4 % of patients treated with atorvastatin had levels that exceeded the upper limit of normal by more than 10 times.

Adverse reactions that occurred during the research: urinary tract infection, diabetes mellitus, stroke.

Experience of post-marketing use of atorvastatin.

During post-marketing administration of atorvastatin, the following adverse reactions were detected. Since these reactions are reported on a voluntary basis from a population of unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship with the drug use.

Adverse reactions associated with atorvastatin treatment, regardless of causal assessment, include: anaphylaxis, angioedema, bullous rash (including exudative erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), rhabdomyolysis, myositis, increased fatigue, tendon rupture, fatal and non-fatal liver failure, dizziness, depression, peripheral neuropathy, and pancreatitis.

There have been rare reports of cases of immunologically mediated necrotizing myopathy associated with statin use (see Section "Special warnings and precautions for use").

There have been rare post-marketing reports of cognitive impairment (e.g. memory loss, unconsciousness, amnesia, memory impairment, confusion) associated with statins. These cognitive impairments have been reported with all statins. Reports generally did not fall into the category of serious adverse reactions and these manifestations were reversible after statin discontinuation, with varying times before the onset of the symptom (from 1 day to several years) and the disappearance of the symptom (median duration 3 weeks).

The following adverse events have been described during the use of certain statins: sexual dysfunction; exceptional cases of interstitial lung disease especially with long-term treatment.

During post-marketing observations, the following adverse reactions were reported.

Blood and lymphatic system disorders: thrombocytopenia.

Immune system disorders: allergic reactions, anaphylaxis (including anaphylactic shock).

Metabolism and nutritional disorders: weight increased.

Nervous system disorders: headache, hypoesthesia, dysgeusia.

Gastrointestinal disorders: abdominal pain.

Ear and labyrinth disorders: tinnitus.

Skin and subcutaneous tissue disorders: urticaria.

Musculoskeletal and connective tissue disorders: arthralgia, back pain.

General disorders: chest pain, peripheral oedema, malaise, fatigue.

Changes in the results of laboratory tests: increased activity of alanine aminotransferase, increased activity of blood creatine phosphokinase.

Children (aged 10-17 years)

During the study, in boys and girls age at menarche, the safety and tolerability profile of atorvastatin at dose of 10 mg to 20 mg per day was generally similar to that of placebo (see the sections "Posology and method of administration", "Children").

Shelf life. 2 years.

Special precautions for storage.

Store in the original package at temperature not above 25 °C.

Keep out of reach of children

Nature and contents of container.

10 tablets in a blister; 3 blisters in a pack; 14 tablets in a blister; 2 blisters in a pack.

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.

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