

PACKAGE LEAFLET
for medical use of a medicinal product

VERADAR-DARNITSA

Qualitative and quantitative composition:

active substance: verapamil;

1 ml of the solution contains 2.5 mg of verapamil hydrochloride;

excipients: sodium chloride, citric acid, monohydrate, sodium hydroxide, acid hydrochloric diluted (1 M), water for injection.

Pharmaceutical form. Solution for injection.

Basic physical and chemical properties: clear colorless liquid.

Pharmacotherapeutic group.

Selective calcium antagonists with direct cardiac effect. ATC code C08D A01.

Pharmacological properties.

Pharmacodynamic properties.

Verapamil, the active substance of the drug, blocks the transmembrane flow of calcium ions into cardiomyocytes and vascular smooth muscle cells. It directly reduces the need for oxygen in the myocardium by affecting the energy-consuming processes of metabolism in myocardial cells and indirectly reduce the afterload.

By blocking the calcium channels of the smooth muscles of the coronary arteries, blood flow to the myocardium increases, even in post-stenotic areas, and the spasm of the coronary arteries is removed. These properties determine the anti-ischemic and antianginal efficacy of the drug in all types of coronary heart disease.

Verapamil exerts antihypertensive effects by decreasing the peripheral vascular resistance without increasing in heart rate as a reflex response. Undesirable changes in the physiological values of blood pressure are not observed.

The drug has a pronounced antiarrhythmic effect, especially in supraventricular arrhythmia. It delays the conduction of the impulse in the atrioventricular node, as a result of which, depending on the type of arrhythmia, the sinus rhythm is restored and/or the frequency of ventricular contractions is normalized.

Pharmacokinetic properties.

Approximately 90 % of verapamil binds to plasma proteins. Due to the extensive metabolism of verapamil, a large number of metabolites is formed. Of these metabolites, only norverapamil is pharmacologically active (approximately 20 % of the hypotensive activity of verapamil). When administered intravenously, the half-life of verapamil is biphasic: early – almost 4 minutes, final – 2 to 5 hours. After intravenous administration the antiarrhythmic effect develops within 1-5 minutes (usually less than 2 minutes), hemodynamic effects – within 3-5 minutes. When administered intravenously, the antiarrhythmic effect lasts approximately 2 hours, hemodynamic – 10 to 20 minutes. In patients with impaired liver function the elimination of verapamil is prolonged. Approximately 70 % of verapamil hydrochloride is eliminated renally as metabolites, only 3-4% of

the drug is eliminated unchanged. Due to this, impaired renal function does not affect the pharmacokinetics of verapamil. Approximately 16 % of verapamil is excreted with feces.

Clinical particulars.

Therapeutic indications.

Paroxysmal supraventricular tachycardia; atrial flutter/fibrillation (except for Wolff-Parkinson-White syndrome [WPW]).

Unstable angina including vasospastic angina, variant angina, Prinzmetal's angina in patients who are contraindicated to use nitrates and/or β -adrenoblockers.

Arterial hypertension; hypertensive crisis.

In pediatric practice – for paroxysmal supraventricular tachycardia.

Contraindications.

- Cardiogenic shock.
- Acute phase of myocardial infarction with complications (bradycardia, hypotension, heart failure).
- Severe conduction disorders: II and III degree of sinoatrial or atrioventricular block, except in patients with a functioning artificial pacemaker.
- Bradycardia with a heart rate less 50 bpm, hypotension with a blood pressure level less 90 mm Hg.
- Sick sinus syndrome, except in patients with a functioning artificial pacemaker.
- Decompensated heart failure.
- Atrial flutter/fibrillation with concomitant Wolff-Parkinson-White syndrome (risk of ventricular tachycardia).
- Hypersensitivity to verapamil or to any other drug components.

It is contraindicated to use intravenously in patients on β -adrenoblockers (excepting emergency treatment).

In case of acute coronary insufficiency, intravenous administration of the drug should be thoroughly justified (it is necessary to exclude the possibility of myocardial infarction), and the patient's condition should be closely monitored.

Interaction with other medicinal products and other forms of interaction.

Verapamil hydrochloride is metabolized by cytochrome P450 CYP3A4, CYP1A2, CYP2C8, CYP2C9 and CYP2C18. Verapamil is an inhibitor of CYP3A4 enzymes and P-glycoprotein (P-gp). Clinically significant interactions have been reported with inhibitors of CYP3A4 causing elevation of plasma levels of verapamil hydrochloride while inducers of CYP3A4 have caused a lowering of plasma levels of verapamil hydrochloride, therefore, patients should be monitored for drug interactions.

Antiarrhythmic drugs, β -adrenoblockers: synergism in increasing the cardiovascular action (increasing a degree of high-grade atrioventricular block, significant decreasing the heart rate, onset of heart failure, significant decreasing the blood pressure).

Quinidine: reduction of oral clearance of quinidine (~35 %). Hypotension may develop, and pulmonary edema may occur in patients with hypertrophic obstructive cardiomyopathy.

Flecainidine: minimal effect on plasma clearance of flecainidine (< ~10 %); does not affect plasma clearance of verapamil.

Metoprolol: increase of AUC of metoprolol (~32.5 %) and C_{\max} (~41 %) in patients with angina pectoris.

Propranolol: increase of AUC of propranolol (~65 %) and C_{\max} (~94%) in patients with angina pectoris.

Antihypertensive agents, diuretics, vasodilators: potentiation of hypotensive effect.

Prazosin, terazosin: additional hypotensive effect (*prazosin:* increased C_{\max} of prazosin (~40 %) without affecting the half-life; *terazosin:* increased AUC of terazosin (~24 %) and C_{\max} (~25 %)).

Antiviral (HIV) agents: plasma concentrations of verapamil may be increased. Prescribe with caution or it may be necessary to reduce the dose of verapamil.

Carbamazepine: increased carbamazepine levels, increased neurotoxic side effects of carbamazepine – diplopia, headache, ataxia, dizziness. Increased AUC (~46 %) of carbamazepine in patients with refractory partial epilepsy.

Lithium: increased neurotoxicity of lithium.

Antimicrobial agents: clarithromycin, erythromycin, telithromycin: possible increasing the verapamil levels.

Rifampicin: possible decrease of hypotensive effect. Reduction the AUC of verapamil (~97 %), C_{max} (~94 %), bioavailability after oral administration (~92 %).

Colchicine: co-administration with verapamil is not recommended due to increased colchicine exposure.

Inhalation anesthetics: should be administered with caution to prevent excessive inhibition of cardiovascular activity.

Sulfapyrazone: increased oral clearance of verapamil by 3 times, and bioavailability by 60 %. There may be a decrease in the hypotensive effect.

Neuromuscular blockers: possible potentiation of the effect due to verapamil hydrochloride.

Acetylsalicylic acid: increased chance of bleeding.

Ethanol: increased plasma level of ethanol.

HMG-CoA reductase inhibitors: treatment with HMG-CoA reductase inhibitors (simvastatin, atorvastatin, lovastatin) in patients taking verapamil should be started with the lowest possible doses and increased gradually. If a patient on verapamil needs to be prescribed an HMG-CoA reductase inhibitor, reduction the dose of statin should be considered and dosage should be adjusted according to the plasma concentration of cholesterol.

Atorvastatin: may increase the level of atorvastatin. Atorvastatin increases the AUC of verapamil by approximately 42.8 %.

Lovastatin: possible increase of lovastatin level.

Simvastatin: increased AUC of simvastatin by approximately 2.6 times, the C_{max} of simvastatin – by 4.6 times.

Fluvastatin, pravastatin, and rosuvastatin are not metabolized by cytochrome CYP3A4 and do not interact with verapamil.

Digoxin: in healthy people, the C_{max} of digoxin increased by 45-53 %, C_{ss} – by 42 %, AUC – by 52 %.

Digitoxin: reduction of digitoxin clearance (~27 %) and extrarenal clearance (~29 %).

Cimetidine: increased AUC of R-verapamil (~25 %) and S-verapamil (~40 %) with a corresponding decrease in clearance of R- and S-verapamil.

Antidiabetic drugs (glyburide): increased C_{max} of glyburide by approximately 28 %, AUC – by 26 %.

Theophylline: reduction of oral and systemic clearance by approximately 20 %, in smokers – by 11 %.

Imipramine: increase of AUC (~15 %) without affecting the active metabolite desipramine.

Doxorubicin: concomitant administration of doxorubicin and verapamil (orally) increases the AUC (~89 %) and C_{max} of doxorubicin in blood plasma (~61 %) in patients with small cell lung cancer. In patients with a progressive tumor, no significant changes in the pharmacokinetics of doxorubicin are observed with simultaneous intravenous verapamil administration.

Phenobarbital: increases the oral clearance of verapamil by 5 times.

Buspirone: increased the AUC and C_{max} by 3-4 times.

Midazolam: increased the AUC by 3 times and the C_{max} by 2 times.

Almotriptan: increased the AUC by 20 %, C_{max} – by 24 %.

Cyclosporine: increased the AUC, C_{max} , C_{ss} – by approximately 45 %.

Everolimus, sirolimus, tacrolimus: possible increase of the level of these drugs.

Grapefruit juice: increased the AUC of R-verapamil (~49 %) and S-verapamil (~37 %), increase of C_{max} of R- (~75 %) and S-verapamil (~51 %) without changes in half-life and renal clearance.

St. John's wort: decreased the AUC of R-verapamil (~78 %) and S-verapamil (~80 %) with a corresponding decrease in C_{max} .

Special warnings and precautions for use.

When prescribing verapamil and determining its dose, special attention should be paid to patients with the following conditions:

Arterial hypotension.

Intravenous administration of verapamil hydrochloride often leads to a decrease in blood pressure below the initial values, which is usually transient and asymptomatic, but can manifest as dizziness.

Severe bradycardia, asystole.

Verapamil hydrochloride affects the atrioventricular and sinoatrial nodes and very rarely may provoke the atrioventricular block II or III degree, bradycardia and very rarely asystole. This can occur in patients with sick sinus syndrome, which is more common in elderly patients.

In patients without sick sinus syndrome, asystole is usually short (a few seconds or less) with a spontaneous return to atrioventricular node or normal sinus rhythm. If this event persists, appropriate therapy should be initiated immediately.

Heart block.

Verapamil hydrochloride prolongs the period of conduction through the atrioventricular node. The development of II-III degree atrioventricular block or 1-, 2 - or 3-bundle block requires further dose reduction or discontinuation of verapamil therapy and appropriate treatment, if necessary.

Heart failure.

In the case of mild heart failure it should be controlled with cardiac glycosides and diuretics before administration of verapamil hydrochloride. Patients with moderate to severe heart failure may experience acute worsening of heart failure.

Cardiac glycosides.

Since cardiac glycosides and verapamil hydrochloride prolong AV conduction, patients should be monitored for AV block and bradycardia.

Disopyramide.

Disopyramide should not be administered within 48 hours before or 24 hours after verapamil administration.

During the use of the drug, grapefruit containing food and beverages should be avoided. Grapefruit may increase the plasma level of verapamil hydrochloride.

At the beginning of therapy, Veradar-Darnitsa solution for injection should be used only in a hospital where it is possible to carry out resuscitation measures. Patients receiving intravenous verapamil should be controlled by electrocardiographical and hemodynamic monitoring.

Fertility, pregnancy and lactation.

The drug should not be administered in the first and second trimesters of pregnancy. Administration in the third trimester of pregnancy – only if absolutely necessary, when the benefit exceeds the risk for mother and child. Verapamil passes through the placenta and is detected in the umbilical cord blood.

Biologically active substance is excreted in human breast milk. Limited human data from oral administration has shown that the infant relative dose of verapamil is low (0.1-1 % of the mother's oral dose) and that verapamil use may be compatible with breastfeeding. Due to the potential for serious adverse reactions in nursing infants, verapamil should only be used during lactation if it is essential for the welfare of the mother.

Effects on ability to drive and use machines.

Due to the possibility of an individual reaction to the drug, the ability to react may be changed and impaired performing other work that requires increased attention, the speed of mental and motor reactions.

Posology and method of administration.

Intravenous administration should be done by slow injection (at least 2 minutes) under the supervision of medical personnel, under ECG and blood pressure monitoring. Patients receiving verapamil intravenously as an initial treatment for unstable angina should be transferred to oral verapamil as soon as possible.

Recommended doses for adults and adolescents with body weight greater than 50 kg:

the initial dose is 5 mg of verapamil hydrochloride (which corresponds to 2 ml of Veradar-Darnitsa, solution for injection); inject another 5 mg after 5-10 minutes, if necessary. If necessary, further drop infusion of 5-10 mg of Veradar-Darnitsa, diluted in 0.9 % sodium chloride solution, during 1 hour is possible; another solution for dilution may be 5 % glucose solution with pH <6.5. The

average daily dose for intravenous administration should not exceed 100 mg of verapamil hydrochloride.

In patients with impaired liver function, the bioavailability of verapamil increases significantly. In such cases, the dose should be determined with caution.

Recommended doses for children.

In case of tachycardia associated with heart failure, digitalization should be performed before intravenous administration.

Age	Dose
0-1 year	Treatment should be prescribed only according to vital indications, if there is no alternative treatment. Rarely, severe hemodynamic disorders were observed after intravenous administration in newborns and infants, some of them were fatal.
Newborns	0.75-1 mg of verapamil hydrochloride, which corresponds to 0.3-0.4 ml of Veradar-Darnitsa, solution for injection.
Infants	0.75-2 mg of verapamil hydrochloride, which corresponds to 0.3-0.8 ml of Veradar-Darnitsa, solution for injection.
1-5 years	2-3 mg of verapamil hydrochloride, which corresponds to 0.8-1.2 ml of Veradar-Darnitsa, solution for injection.
6-14 years	2-5 mg of verapamil hydrochloride, which corresponds to 1-2 ml of Veradar-Darnitsa, solution for injection.

Administration of the drug should be discontinued immediately after the onset of the effect.

Children.

Controlled studies of verapamil hydrochloride in children have not been conducted.

Caution should be exercised when prescribing verapamil hydrochloride, solution for injection, to children.

Overdose.

Symptoms of verapamil poisoning due to overdose depend on the amount of medication administered, the time when detoxification measures were taken, and the age of patient.

The following symptoms prevail: significant decrease in blood pressure, cardiac arrhythmias (bradycardia, marginal rhythms with AV dissociation and high-degree AV block), which can cause shock and cardiac arrest, dizziness up to a comatose state, stupor, hyperglycemia, hypokalemia, metabolic acidosis, hypoxia, cardiogenic shock with pulmonary oedema, impaired kidney function and convulsions.

Therapeutic measures should include eliminating the substance from the body and restoring the stability of the cardiovascular system.

General measures: gastric lavage is recommended even if more than 12 hours have passed since the drug administration and the motility of the digestive tract is not determined (no intestinal noises). General resuscitation measures include indirect heart massage, artificial respiration, defibrillation, and cardiac pacing. Hemodialysis is not indicated. Hemofiltration and, possibly, plasmapheresis may be useful (calcium antagonists bind well to plasma proteins).

Special measures: elimination of cardiodepressive effects, hypotension and bradycardia. The specific antidote is calcium: intravenously inject 10-20 ml of 10 % solution of calcium gluconate (2.25-4.5 mmol). If necessary, the administration can be repeated or an additional drop infusion can be performed (for example, 5 mmol/h).

Additional measures: in grade II and III AV block, sinus bradycardia, cardiac arrest, use atropine, isoprenaline, orciprenaline or cardiac pacing. In case of hypotension due to cardiogenic shock and arterial vasodilation, should be used dopamine (up to 25 µg/kg per minute), dobutamine (up to 15 µg/kg per minute) or norepinephrine. Serum concentration of calcium should correspond to the upper limit of normal or be slightly higher than normal. Due to vasodilation, a replacement liquid (Ringer's solution or 0.9 % sodium chloride solution) is administered at the early stages.

Verapamil is not removed during hemodialysis.

Undesirable effects.

Ear and labyrinth disorders: vertigo, tinnitus.

Respiratory, thoracic and mediastinal disorders: bronchoconstriction.

Gastrointestinal disorders: nausea, vomiting, feeling full (stomach), constipation, pain, abdominal discomfort, intestinal obstruction, gum hyperplasia (gingivitis and bleeding).

Hepatobiliary disorders: allergic hepatitis with a reversible increase in liver enzymes is possible.

Metabolism and nutrition disorders: reduced glucose tolerance.

Nervous system disorders: dizziness, headache, fainting, anxiety, lethargy, fatigue, asthenia, somnolence, depression, extrapyramidal disorders (ataxia, mask-like face, shuffling gait, rigidity of hands or legs, tremor of the hands and fingers, difficult swallowing), convulsions, Parkinson's syndrome, choreoathetosis, dystonic syndrome, paresthesia, tremor.

Cardiovascular system disorders: I, II or III degree AV block, bradycardia (less than 50 bpm), asystole, collapse, pronounced decrease in blood pressure, development or increase in heart failure, tachycardia; angina pectoris, up to the development of myocardial infarction (especially in patients with coronary artery stenosis), arrhythmia (including ventricular fibrillation and flutter), hot flashes, peripheral oedema.

Immune system disorders: hypersensitivity.

Skin and subcutaneous tissue disorders: angioedema, Stevens-Johnson syndrome, erythema multiforme, maculopapular rash, alopecia, erythromelalgia, urticaria, pruritus, hemorrhages in the skin or mucous membranes (purpura), photodermatitis, hyperhidrosis were observed.

Musculoskeletal and connective tissue disorders: myalgia, arthralgia, muscle weakness, exacerbation of myasthenia gravis, Lambert-Eaton syndrome, Duchenne progressive muscular dystrophy.

Reproductive system and mammary gland disorders: erectile dysfunction, gynecomastia, increased prolactin levels, galactorrhea.

General disorders: increased fatigue.

Laboratory tests: increased levels of liver enzymes and alkaline phosphatase, prolactin in the blood serum.

Others: weight gain, agranulocytosis, transient vision loss on the background of maximum concentration of the drug in blood plasma, pulmonary oedema, asymptomatic thrombocytopenia.

Paralysis (tetraparesis) associated with the combined use of verapamil and colchicine has been reported. This may be due to the penetration of colchicine across the blood-brain barrier due to verapamil inhibition of CYP3A4 and P-gp. Combined use of colchicine and verapamil is not recommended.

In patients with a pacemaker, an increase in the Pacing-Sensing (step-sensory) threshold due to the use of verapamil hydrochloride is not excluded.

Shelf life: 3 years.

Special precautions for storage.

Store in the original package at temperature not above 25 °C. Keep out of reach of children. Do not freeze.

Incompatibilities.

Co-administration of verapamil hydrochloride solution with albumin, amphotericin B, hydralazine hydrochloride, trimethoprim, and sulfamethoxazole should be avoided. In order to maintain stability, this drug is not recommended to be diluted with solutions containing sodium lactate. Verapamil hydrochloride will precipitate in any solution with a pH above 6.0.

Packaging.

2 ml in an ampoule; 5 ampoules in a blister; 2 blisters in a pack; 10 ampoules in a blister; 1 blister 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.

Date of last revision.

21.11.2017