

PACKAGE LEAFLET
for medical use of a medicinal product

VERADAR-DARNITSA

Qualitative and quantitative composition:

active substance: verapamil;

1 tablet contains verapamil hydrochloride 80 mg;

excipients: lactose monohydrate, cellulose microcrystalline, corn starch, hypromellose, croscarmellose sodium, anhydrous colloidal silicon dioxide, talc, magnesium stearate, sepifilm 752 white, macrogol 4000.

Pharmaceutical form. Film-coated tablets.

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

Pharmacotherapeutic group. Selective calcium channel blockers with direct cardiac effect. Phenylalkylamine derivatives. Verapamil. ATC code C08D A01.

Pharmacological properties.

Pharmacodynamic properties.

Verapamil 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.

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

The medicinal product Veradar-Darnitsa 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.

Verapamil is rapidly and almost completely absorbed in the small intestine. The degree of absorption is 90-92 %. Peak plasma levels are reached 1 to 2 hours after administration. The elimination half-life ranges from 3 to 7 hours. Binding to plasma proteins is 90 %. Verapamil is almost completely metabolised resulting in formation of various metabolites. Of these metabolites, only norverapamil is pharmacologically active. Verapamil and norverapamil are not removed during hemodialysis.

Verapamil and its metabolites are mainly eliminated renally; only 3–4 % are excreted as unchanged. 50 % of the administered dose is eliminated within 24 hours, 70 % is eliminated within 5 days. Up to 16 % of dose is excreted in the faeces. Recently obtained data indicate that there is no difference in the pharmacokinetics of verapamil between subjects with normal renal function and patients with end-stage renal failure. The elimination half-life is increased in patients with liver cirrhosis due to

low clearance and large volume of distribution.

The average absolute bioavailability in healthy volunteers after a single dose of the drug is 22 %, which is explained by extensive first-pass hepatic metabolism. After repeated administration bioavailability increases by 1.5–2 times.

Clinical particulars.

Therapeutic indications.

- Coronary heart disease, including: stable tension angina; unstable angina (progressive angina, rest angina), vasospastic angina (variant angina, Prinzmetal's angina), post-infarction angina in patients without heart failure, if β -adrenoblockers are not indicated.
- Arrhythmias: paroxysmal supraventricular tachycardia; atrial flutter/fibrillation with rapid atrioventricular conduction [excluding Wolff-Parkinson-White (WPW) syndrome].
- Arterial hypertension.

Contraindications.

- Cardiogenic shock.
- Severe conduction disorders: II and III degree of atrioventricular AV block (except in patients with a functioning artificial pacemaker).
- Sick sinus syndrome (except in patients with a functioning artificial pacemaker).
- Hypersensitivity to verapamil or to any drug components.
- Heart failure with a decreased ejection fraction of less than 35 % and/or pulmonary artery pressure above 20 mm Hg (unless verapamil therapy is ineffective in secondary supraventricular tachycardia), severe bradycardia (less than 50 bpm).
- Acute myocardial infarction complicated by bradycardia, severe hypotension, or left ventricular failure.
- Atrial fibrillation/flutter in the presence of additional pathways [WPW syndrome and LGL-syndrome (Lown-Ganong-Levine syndrome)]. These patients are at risk to develop ventricular tachyarrhythmia including ventricular fibrillation if verapamil is administered.
- Use in combination with ivabradine (see Section "Interactions with other drugs and other types of interactions").
- Verapamil should not be co-administered with intravenous β -adrenoblockers (excepting emergency treatment).
- Concomitant use of grapefruit juice is contraindicated.

Interaction with other medicinal products and other forms of interaction.

In vitro studies of verapamil hydrochloride metabolism have shown that it is metabolized by cytochrome P450 CYP3A4, CYP1A2, CYP2C8, CYP2C9, and CYP2C18. Verapamil is a CYP3A4 and P-glycoprotein (P-gp) enzyme inhibitor. 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.

Concomitant use of verapamil and drugs that are mainly metabolized by CYP3A4 or are a substrate of P-gp may be associated with increased concentrations of these drugs, which may increase or prolong both the therapeutic and adverse effects of the concomitant drug.

Potential interactions associated with the CYP450 enzyme system.

Prazosin: increased C_{max} of prazosin (~40 %) without affecting the elimination half-life. Additive hypotensive effect.

Terazosin: increased AUC (~24 %) and C_{max} (~25 %) of terazosin. Additive hypotensive effect.

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

The combination of verapamil and antiarrhythmic agents can lead to additive cardiovascular effects (for example, AV block, bradycardia, hypotension, heart failure).

Flecainide: minimal effect on plasma clearance of flecainide (< ~ 10 %); does not affect plasma clearance of verapamil (see "Special warnings and precautions for use" section).

Theophylline: reduction of oral and systemic clearance by approximately 20 %, in smokers – by 11 %. Elevated serum theophylline levels can lead to increased side effects.

Carbamazepine: increase of carbamazepine AUC (~46 %) in patients with refractory partial epilepsy; increase of carbamazepine levels may cause carbamazepine side effects such as diplopia, headache, ataxia, or dizziness.

Phenytoin: decrease in the concentration of verapamil in blood plasma.

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

Dantrolene: concomitant use of verapamil with intravenous dantrolene may cause hypotension, myocardial depression, and hyperkalemia, so this combination should be avoided.

Glyburide: increase of C_{\max} of glyburide by approximately 28 %, AUC – by 26 %.

Colchicine: an increase in the AUC (approximately by 2 times) and C_{\max} (approximately by 1.3 times) of colchicine. It is recommended to reduce the dose of colchicine (see the instructions for medical use of colchicine).

Colchicine is a substrate for both CYP3A and the leakage transporter, P-glycoprotein (P-gp). Verapamil is known to inhibit CYP3A and P-gp. When verapamil and colchicine are administered together, inhibition of P-gp and/or CYP3A by verapamil may increase the effect of colchicine, so combined use is not recommended.

Clarithromycin, erythromycin, telithromycin: verapamil levels may be increased.

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

Doxorubicin: concomitant administration of doxorubicin and verapamil (orally) increases the AUC (~104 %) and C_{\max} (~61 %) of doxorubicin in blood plasma in patients with small cell lung cancer. In patients with a progressive tumor, no significant changes in the pharmacokinetics of doxorubicin are observed when co-administrated with intravenous verapamil.

Phenobarbital: increase of oral clearance of verapamil by 5 times.

Buspirone: increased AUC and C_{\max} of buspirone by 3.4 times.

Midazolam: increased AUC of midazolam by 3 times and increased C_{\max} by 2 times.

Verapamil may increase plasma concentrations of β -blockers, which may lead to additive cardiovascular effects (for example, AV block, bradycardia, hypotension, heart failure).

Intravenous β -blockers should not be used in patients treated with verapamil.

Metoprolol: increase of AUC of metoprolol (~32.5 %) and C_{\max} (~41 %) in patients with angina pectoris (see Section "Special warnings and precautions for use").

Propranolol: increase of AUC of propranolol (~65 %) and C_{\max} (~94 %) in patients with angina pectoris (see Section "Special warnings and precautions for use").

Digoxin: healthy volunteers showed an increase in C_{\max} of digoxin (~44 %), C_{12h} (~53 %), C_{ss} (~44 %), AUC (~50 %), so caution should be exercised regarding digitalis toxicity. It is recommended to reduce the dose of digoxin (see Section "Special warnings and precautions for use").

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

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

Cyclosporine: increase of AUC, C_{\max} , C_{ss} of cyclosporine by approximately 45 %.

Everolimus: increase of AUC of everolimus (approximately by 3.5 times) and C_{\max} (approximately by 2.3 times). Increase in C_{trough} of verapamil (approximately by 2.3 times). Accurate determination of concentration and dose of everolimus may be necessary.

Sirolimus: increase of AUC (approximately by 2.2 times) of sirolimus, increase of AUC (approximately by 1.5 times) of S-verapamil. Determination of concentrations and adjustment of the dose of sirolimus may be necessary.

Tacrolimus: possible increased plasma level of this drug.

Hypolipidemic agents (HMG-CoA-reductase inhibitors (statins)): treatment with HMG-CoA-reductase inhibitors (simvastatin, atorvastatin, lovastatin) in patients taking verapamil should begin with the lowest possible doses with gradual increase. If a patient who is already taking verapamil needs to be prescribed an HMG-CoA reductase inhibitor, the need of statin dose reduction should be considered and the dosage should be adjusted according to the concentration of cholesterol in

blood plasma.

Verapamil may increase plasma concentrations of atorvastatin, lovastatin, and simvastatin.

Atorvastatin: may increase the level of atorvastatin. Atorvastatin increases the AUC of verapamil by approximately 43%. Although there are no direct clinical *in vivo* data, verapamil has a strong potential to significantly affect the pharmacokinetics of atorvastatin, as well as simvastatin or lovastatin. Caution should be exercised in concomitant use of atorvastatin and verapamil.

Lovastatin: may increase the level of lovastatin. Increase of AUC (~63 %) and C_{\max} (~32 %) of verapamil.

Simvastatin: increase of 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 are less likely to interact with verapamil.

Almotriptan: increase of AUC by 20%, C_{\max} – by 24%.

Sulfinpyrazone: increase of oral clearance of verapamil by 3 times, decrease of bioavailability – by 60 %. There may be a decrease in the hypotensive effect.

Dabigatran: verapamil in immediate release tablet form increases the C_{\max} (up to 180 %) and AUC (up to 150 %) of dabigatran. No significant interaction was observed when verapamil was administered 2 hours after dabigatran etexylate (an increase in C_{\max} by about 10% and AUC by about 20 %). The risk of bleeding increases, so careful clinical monitoring is recommended, especially if bleeding occurs in presence of mild to moderate renal impairment. When used concomitantly with oral verapamil, it may be necessary to reduce the dose of dabigatran (see the dosage instructions for dabigatran).

Other direct oral anticoagulants (DOAC): increase of the absorption of DOAC, as they are P-gp substrates. Also, a decrease in the DOAC excretion, which are metabolized by CYP3A4, can lead to an increase in the systemic bioavailability of DOAC.

According to some reports, the risk of bleeding increases, especially in patients with additional risk factors. It may be necessary to reduce the DOAC dose when used with oral verapamil (see the instructions for medical use regarding the DOAC dosage).

Ivabradine: concomitant use with ivabradine is contraindicated due to the additional effect of reducing the heart rate of verapamil (see section "Contraindications").

Grapefruit juice: increase of AUC of R-verapamil (~49 %) and S-verapamil (~37 %), increase of C_{\max} of R-verapamil (~75 %) and S-verapamil (~51 %) without the change of the half-life and renal clearance. Avoid using grapefruit juice with verapamil.

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

Other interactions.

Antiviral (HIV) agents: due to ability of certain antiviral agents, such as ritonavir, to inhibit metabolism, the plasma concentrations of verapamil may increase. Prescribe with caution. It may be necessary to reduce the dose of verapamil.

Lithium: increased lithium neurotoxicity has been reported with concomitant administration of verapamil hydrochloride and lithium without or with elevated plasma lithium levels. However, in patients who chronically received the same dose of lithium orally, the addition of verapamil hydrochloride resulted in a decrease in plasma lithium levels. Patients receiving both medications should be closely monitored.

Neuromuscular blockers: clinical data and animal studies suggest that verapamil hydrochloride may enhance the activity of neuromuscular blockers (curare-like and depolarizing). It may be necessary to reduce the dose of verapamil hydrochloride and/or the dose of neuromuscular blocker when they are used concomitantly.

Acetylsalicylic acid: increased possibility of bleeding.

Ethanol (alcohol): increases the level of ethanol in the blood plasma and slows down its elimination. Therefore, the effect of alcohol can be increased.

Antihypertensive agents, diuretics, vasodilators: increased hypotensive effect due to possible additive action.

Special warnings and precautions for use.

Acute myocardial infarction.

The drug should be used with caution in patients with acute myocardial infarction complicated by bradycardia, severe hypotension or left ventricular dysfunction.

Cardiac block/grade I AV block/bradycardia/asystole.

Verapamil hydrochloride affects the atrioventricular and sinoatrial nodes and prolongs the time of atrioventricular conduction. Use with caution due to the fact that the development of grade II or III AV block (which is a contraindication) or single-bundle, or double-bundle or three-bundle block of the His bundle requires discontinuation of subsequent doses of verapamil hydrochloride and the appointment of appropriate therapy, if necessary.

Verapamil hydrochloride affects the atrioventricular and sinoatrial nodes and very rarely can provoke the occurrence of grade II or III AV block, bradycardia and very rarely – asystole. Most likely that such symptoms will occur in patients with sick sinus syndrome (sinoatrial node disease), which is more common in elderly patients.

In patients without sick sinus syndrome, asystole is usually short-term (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 (see Section "Adverse reactions").

The action of verapamil and β -adrenoblockers or other medications on heart conduction and contraction may be enhanced, so caution should be exercised when using them concomitantly. This is especially true for any intravenous medication.

Antiarrhythmic agents, β - β -adrenoblockers.

Reciprocal increase in cardiovascular action (increase of the degree of high-grade AV block, significant decrease in heart rate, occurrence of heart failure, significant decrease in blood pressure). Asymptomatic bradycardia (36 bpm) with a wandering atrial pacemaker was observed in patients who received concomitant therapy with eye drops with timolol (β -adrenoblocker) during treatment with verapamil hydrochloride.

Digoxin.

When verapamil is co-administered with digoxin, the dose of digoxin should be reduced (see the section "Interactions with other medicinal products and other types of interactions").

Heart failure.

Verapamil may affect left ventricular contractility. The effect is small and usually not significant. However, existing heart failure may worsen or progress. Therefore, before starting treatment with verapamil, it is necessary to compensate for heart failure in patients with an ejection fraction greater than 35 % (for example, digitalis preparations) and adequately monitor the entire treatment period.

HMG-CoA-reductase inhibitors (statins).

See section "Interaction with other medicinal products and other forms of interaction."

Neuromuscular transmission disorders.

Verapamil hydrochloride should be used with caution in the presence of neuromuscular transmission disorders (*myasthenia gravis*), Lambert-Eaton syndrome, Duchenne progressive muscular dystrophy).

Patients with atrial fibrillation/flutter and additional pathways (e.g., Wolff-Parkinson-White syndrome) may rarely experience increased conduction via the abnormal pathway, and ventricular tachycardia may be increased.

Renal impairment.

Although data from confirmed comparative studies have shown that renal failure does not affect the pharmacokinetics of verapamil in patients with end-stage renal failure, there have been several reports suggesting that patients with renal insufficiency should use verapamil with caution and under close supervision. Verapamil is not removed during hemodialysis.

Hepatic impairment.

Since verapamil is extensively metabolized in the liver, it is necessary to carefully titrate the dose of verapamil in patients with liver disorders.

Patients with significant hepatic impairment should use verapamil with caution (see section "Posology and method of administration").

Relevant information on excipients.

This medicinal preparation contains lactose, so patients with rare hereditary forms of galactose intolerance, lactase deficiency or glucose-galactose malabsorption syndrome should not use the

drug.

This medicine contains sodium, so patients who follow a controlled sodium diet should be careful when using it.

Fertility, pregnancy and lactation.

Pregnancy.

There are no clear and well-studied data on verapamil use in pregnant women. Animal studies of verapamil have shown no reproductive toxicity. Since data obtained from reproductive studies in animals not always can be extrapolated to humans, the drug should be used during pregnancy only if absolutely necessary.

Verapamil passes through the placenta and is detected in the umbilical cord blood.

During treatment, it is necessary to take into account the effect of verapamil to cause uterine muscle relaxation.

Lactation.

Verapamil and its metabolites pass into breast milk. Limited data with human participation indicate that the dose of verapamil that enters the newborn's body is low (0.1–1 % of the oral dose taken by the mother), so the use of verapamil may be compatible with breast-feeding, but the risk for newborns cannot be excluded. Given the risk of serious adverse reactions in newborns, verapamil during breast-feeding can only be used if absolutely necessary for the mother.

Effects on ability to drive and use machines.

Due to the antihypertensive effect of verapamil hydrochloride, depending on the individual reaction, the ability to drive vehicles, work with mechanisms or work in dangerous conditions may be impaired due to a feeling of drowsiness, especially at the beginning of treatment, in case of increasing the dose, changing the antihypertensive drug, as well as simultaneous use of the drug with alcohol. Verapamil has been shown to increase the blood levels of alcohol and slow its elimination. Therefore, the effects of alcohol may be exaggerated.

Posology and method of administration.

Doses should be selected individually for each patient. The drug should be taken without dissolving or chewing with a sufficient amount of liquid (for example, 1 cup of water, in no case grapefruit juice), preferably during or immediately after a meal.

Adults and adolescents with body weight more than 50 kg.

Coronary heart disease, paroxysmal supraventricular tachycardia, atrial flutter/fibrillation.

The recommended daily dose is 120-480 mg, divided into 3-4 administrations. The maximum daily dose is 480 mg.

Arterial hypertension.

The recommended daily dose is 120-360 mg, divided into 3 administrations.

Older preschool children under 6 years of age, only with heart rhythm disorders.

The recommended dosage is in the range of 80–120 mg per day, divided into 2–3 administrations.

Children aged 6-14 years, only with cardiac arrhythmias. The recommended dosage is in the range of 80–360 mg per day, divided into 2–4 administrations.

Impaired renal function.

The available data is described in the "Special warnings and precautions for use" section. In patients with renal insufficiency, verapamil hydrochloride should be used with caution and under close supervision.

Impaired liver function.

In patients with impaired liver function, depending on the severity, the effect of verapamil hydrochloride increases and prolongs due to slowing down the breakdown of the drug. Therefore, in such cases, the dosage should be determined with extreme caution and should begin with low doses (for patients with limited liver function, at the beginning – 40 mg 2–3 times a day, respectively 80–120 mg per day (see Section "Special warnings and precautions for use").

If it is necessary to use a dose of 40 mg, the drug should be used in the appropriate dosage.

Do not lie down immediately after taking medicine.

Verapamil hydrochloride should not be administered to patients with myocardial infarction during

first 7 days after the event.

After long-term therapy the drug should be discontinued gradually.

The duration of treatment is determined by the doctor individually and depends on the patient's condition and the course of the disease.

Children.

The drug in this dosage form can only be used in children with cardiac arrhythmias (see section "Posology and method of administration").

Overdose.

The course of symptoms of verapamil intoxication depends on the amount taken, the point in time at which detoxification measures are taken, and myocardial contractility (age-related).

Symptoms: hypotension (sometimes to values not detectable), shock symptoms, loss of consciousness, grade I and II AV block (often as a Wenckebach phenomenon with or without escape rhythms), total AV block with total AV dissociation, escape rhythm, asystole, bradycardia up to high degree AV block and sinus node arrest, hyperglycemia, stupor and metabolic acidosis. Lethal cases due to overdose have been reported.

Treatment of verapamil hydrochloride overdose: mainly supportive and individual. The main measures that are used to eliminate the symptoms of deliberate overdose with oral administration of verapamil hydrochloride: elimination of cardiodepressive effects, hypotension or bradycardia by β -adrenergic stimulation. The specific antidote is calcium, for example, 10-20 ml of a 10% calcium gluconate solution should be administered intravenously (2.25–4.5 mmol), repeated if necessary, or administered as a continuous drip infusion (for example, 5 mmol/h).

Therapeutic measures that should be taken depend on the point of time at which verapamil was taken, the type and severity of intoxication symptoms. In cases of intoxication with a large number of slow-release drugs, the release of the active drug and absorption in the intestine can take more than 48 hours.

It should be noted that along the entire length of the gastrointestinal tract there may be some lumps of incompletely dissolved tablets that function as active drug depots (depending on the time elapsed after administration).

General measures to be taken: Gastric lavage along with usual precautions, even later than 12 hours after ingestion, if no gastrointestinal motility (peristaltic sounds) is detectable.

If intoxication with a modified release drug is suspected, measures such as induced vomiting, removal of stomach and small intestine contents under endoscopy, intestinal lavage, the use of laxatives, and cleansing enemas are indicated. Routine intensive resuscitation measures, such as cardiopulmonary resuscitation, defibrillation, and/or pacemaker therapy, are used.

In case of significant arterial hypotension or high-grade AV block, it is necessary to use drugs that increase blood pressure (for example, dopamine, dobutamine, norepinephrine).

In case of asystole, grade II or III AV block, sinus bradycardia, β -adrenergic stimulation (for example, isoprenaline, orciprenaline), other measures aimed at increasing blood pressure, pacing, or restoring heart activity and breathing should be used simultaneously with the usual measures.

If there are signs of prolonged myocardial insufficiency – use dopamine, dobutamine, if necessary – repeated injections of calcium.

Verapamil hydrochloride is not eliminated by hemodialysis.

Undesirable effects.

The following adverse reactions have been reported in clinical trials, with post-marketing use of verapamil, or in phase IV clinical trials.

For each organ system, adverse reactions are classified according to the frequency of reports: very common ($\geq 1/10$), common ($\geq 1/100 < 1/10$), uncommon ($\geq 1/1000$ to $< 1/1,000$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), unknown (frequency cannot be determined from available data).

The most common adverse reactions were: headache, dizziness; gastrointestinal disorders: nausea, constipation and abdominal pain; also bradycardia, tachycardia, palpitations, decreased blood pressure, hyperemia, peripheral oedema and fatigue.

Ear and labyrinth disorders: rare – tinnitus; unknown – vertigo.

Respiratory, thoracic and mediastinal disorders: unknown – bronchoconstriction, dyspnoea.

Gastrointestinal tract disorders: common – nausea, constipation; uncommon – abdominal pain; rare – vomiting, unknown – abdominal discomfort, intestinal obstruction, gum hyperplasia (gingivitis and bleeding). Gum hyperplasia may develop very rarely when the drug is used for a long period of time and completely disappears after its withdrawal.

Kidney and urinary system disorders: unknown – renal failure.

Metabolism and nutrition disorders: unknown – hyperkalemia.

Nervous system disorders: common – dizziness, headache; rare – paresthesia, tremor; unknown – extrapyramidal disorders, paralysis (tetraparesis)*, epileptic seizures.

Cardiovascular system disorders: common – bradycardia, hyperemia, hot flashes, decreased blood pressure, dystonia; uncommon – palpitations, tachycardia; unknown – I, II or III degree AV block, heart failure, sinus node arrest, sinus bradycardia, asystole, bradyarrhythmia in atrial fibrillation.

Immune system disorders: unknown – hypersensitivity.

Skin and subcutaneous tissue disorders: rare – hyperhidrosis; unknown – angioedema, Stevens-Johnson syndrome, erythema multiforme, maculopapular rash, alopecia, urticaria, pruritus, purpura, erythromegaly.

Musculoskeletal and connective tissue disorders: unknown – myalgia, arthralgia, muscle weakness.

Reproductive system and breast disorders: unknown – erectile dysfunction, gynecomastia, galactorrhea. Gynecomastia was observed in very rare cases in elderly men during long-term therapy with verapamil and was completely reversible in all cases of drug withdrawal.

General disorders: common – peripheral oedema; uncommon – fatigue.

Laboratory particulars: unknown – increased levels of liver enzymes and prolactin levels in the blood serum.

*Paralysis (tetraparesis) associated with the combined use of verapamil and colchicine has been reported once in post-marketing observations. This may be caused by penetration of colchicine through the blood-brain barrier due to inhibition of CYP3A4 and P-gp by verapamil (see section "Interactions with other drugs and other types of interactions").

Reported suspected adverse reactions.

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

Shelf life: 3 years.

Special precautions for storage.

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

Keep out of reach of children

Nature and contents of container.

10 tablets in a blister package; 3 blister packages 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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