

PACKAGE LEAFLET
for medical use of medicinal product

ADRENALIN-DARNITSA

Qualitative and quantitative composition:

active substance: epinephrine.

1 ml of solution contains epinephrine hydrotartrate (adrenaline tartrate) 1.8 mg.

Excipients: sodium metabisulfite (E 223), sodium chloride, water for injections.

Pharmaceutical form Solution for injection.

Basic physicochemical properties: clear colourless or slightly coloured liquid.

Pharmacotherapeutic group

Non-glycoside cardiotonic agents. Adrenergic and dopaminergic agents. ATC Code: C01CA24

Pharmacological properties

Pharmacodynamic properties

The substance belongs to natural hormones. It is created thru the methylation of noradrenalin and depositing of the produced adrenaline in the chromaffin tissues of adrenal medulla. It is an adrenoreceptor agonist affecting the α - and β -adrenoreceptors. Adrenaline shows great similarity in relation to the α_2 -, β_2 - and β_3 - adrenoreceptors and, to a lesser extent, in relation to the α_1 - and β_1 - adrenoreceptors.

The action is caused by the activation of adenylate cyclase at the internal surface of the cellular membrane and the increase in the intracellular concentration of the cAMP and Ca^{2+} . In very low doses with the introduction speed lower than 0.01 mcg/kg/min, it may lower the arterial blood pressure due to the broadening of the vessels in the skeletal muscles. With the introduction speed being 0.04 to 0.1 mcg/kg/min, it increases the frequency and strength of the heart rate as well as the stroke volume and the minute volume and lowers the [general] peripheral vascular resistance. At the introduction speed of 0.02 mcg/kg/min, the drug narrows the vessels, and increases the arterial blood pressure (mainly, the systolic) and the [general] peripheral vascular resistance.

The pressor effect may cause a short-term reflexory slowdown of the heart rate. The drug eases the plain muscles of bronchi. The doses exceeding 0.3 mcg/kg/min decrease the renal blood flow, the blood supply to internal organs, the tonus, and the motility of gastrointestinal tract. The drug dilates pupils and facilitates the decreases in the production of intraocular liquid and in the intraocular pressure. It also causes hyperglycemia (strengthens glycogenolysis and glycogenesis) and increases the content of free fatty acids in plasma. The drug also improves the conductivity, irritability and automatism of myocardium, and increases the myocardium oxygen demand.

The drug inhibits the antigen-induced release of histamine and leukotrienes, and removes the spasms of bronchioles, and prevents the development of swollen mucosa. It influences the α -adrenoreceptors located in the skin, in the mucosa, and in the internal organs, and it also causes the narrowing of vessels and the lowering of the speed of local anesthesia agents, and it increases the length and decreases the toxic effect of local anesthesia. The stimulation of the β_2 -adrenoreceptors is accompanied by an increased release of the K^+ from a cell and may result in hypoglycemia. When administered intracavernously, the drug decreases the blood-filling of cavernous bodies.

The therapeutic effect develops almost instantly in the event of intravenous administration (the effect remains for 1 to 2 minutes); the effect develops in 5 to 10 minutes after a subcutaneous administration (the maximum effect is reached for after 20 minutes); and the commencement time for the drug effect is variable when administered intramuscularly.

Pharmacokinetics properties

Absorption. Good absorption when administered intramuscularly or subcutaneously. The time

required to reach the maximum concentration in blood (TC_{max}) constitutes 3-10 minutes when administered subcutaneously and intravenously.

Distribution. The drug penetrates the breast milk thru placenta, and it does not penetrate the hematoencephalic barrier.

Metabolism. The drug is metabolized mainly by two ferments (enzymes); the catechol-O-methyltransferase, which transforms adrenaline into metanephrine in liver and in other tissues, and the monoaminooxidase, which takes part in its transformation into vanillylmandelic acid.

Excretion. The metabolites are excreted mainly in the form of conjugates with sulfuric acid and, to a lesser extent, with urine in the form of glucuronides. The elimination half-life ($T_{1/2}$) constitutes 1-2 minutes.

Clinical particulars

Therapeutic indications

Allergic reactions of immediate type: the anaphylactic shock developing in the event of administration of pharmaceutical drugs and sera, and in the event of contact with allergens. Bronchial asthma – rapid relief of symptoms. Asystolia; heart arrest; prolongation of local anesthetic action; acutely developing AV-block of the III stage.

Contraindications

Increased individual sensitivity to the components of the drug. Hypertrophic obstructive cardiomyopathy; severe aortic stenosis; tachyarrhythmia; ventricular fibrillation; pheocromocytoma; closed-angle glaucoma; shock (except for the anaphylactic option); general anesthesia with the administration of inhalation agents, such as halothane, cyclopropane, and chloroform; administration to various parts of hands and legs, nose, and genitals.

Interaction with other medicinal products and other forms of interaction

The epinephrine antagonist are the blocking agents of the α - and β -adrenoreceptors.

The following occurrences are possible if the drug is administered simultaneously with:

narcotic analgesics and sleeping medicines – weakening of their respective effects.

cardiac glycosides, quidinine, tricyclic antidepressants, dopamine, inhalation anesthetics (chloroform, enflurane, isoflurane, methoxyflurane), and cocaine, – an increased risk of development of the arrhythmias.

other sympathomimetic agents – strengthened manifestations of side effects in the cardiovascular system.

antihypertensive agents (including diuretics) – a decrease in their efficiency.

inhibitors of monoamine oxidase (including furazolidone, procarbazine, and selegiline) – a sudden and manifest increase in arterial pressure, hyperpyretic crises, headache, cardiac arrhythmias, and vomiting.

nitrates – weakening of their therapeutic effects.

phenoxybenzamine – an increased hypotensive effect and tachycardia.

phenytoin – a sudden decrease of arterial pressure and bradycardia depending on the dose and speed of administration of adrenaline.

thyroid hormones-based drugs – mutual strengthening of the effects.

astemizole, cisapride, and terfenadine – an elongation of the QT interval in ECG.

diatrizoate and iotalamic or ioxaglic acid – strengthening of neurological effects.

alkaloids – strengthening of the vasoconstrictor effect, leading up to a manifest ischemia and gangrenosis.

hypoglycemic agents (including insulin) – a decreased hypoglycemic effect.

Special warnings and precautions for use

Intracardiac introduction may be used in the event of asystolia if other methods to eliminate it are inaccessible. In this case, however, there is an increased risk of development of cardiac tamponade and pneumothorax.

If an infusion is required, it is necessary to use a device with a measuring instrument in order to control the infusion rate. The infusion should be conducted at one of the great veins, whereby a central vein is the best choice.

In the course of the infusion, it is recommended to monitor the K^+ concentration in the blood serum as well as the arterial pressure, the diuresis, the ECG, the central venous pressure, and the pulmonary artery pressure.

The administration of the drug increases glycemia in diabetic patients, and thus larger doses of insulin or sulfonylurea are required.

It is not advised to administer adrenaline for long time, since it may cause the narrowing of the peripheral vessels, leading to the development of necrosis or gangrene.

When the treatment is coming to its end, the adrenaline dose should be lowered gradually because an abrupt termination of the therapy may result in severe hypotension.

The drug required due care when administered to patients with ventricular arrhythmia, ischemic heart disease, auricular fibrillation, arterial hypertension, pulmonary hypertension, in the event of a myocardial infarction (if it is required to administer the drug in the event of a myocardial infarction, it should be remembered that adrenaline may increase ischemia due to an increased myocardial oxygen demand), metabolic acidosis, hypercapnia, hypoxia, hypovolemia, thyrotoxicosis, and to patients with occlusive vascular disease (arterial embolism, atherosclerosis, Buerger disease, freezing injury, diabetic endarteritis, Raynaud disease; since there is a risk of development of necrosis and gangrene, it is necessary to control the condition of the peripheral blood circulation), and to patients with cerebral atherosclerosis, Parkinson disease, convulsive syndrome, and prostatic hypertrophy.

In the event of hypovolemia, it is necessary to properly hydrate the patients prior to the administration of sympathomimetic agents.

Fertility, pregnancy and lactation

There have been no controlled studies regarding the application of adrenaline during pregnancy.

No application is allowed during delivery for the purposes of correction of arterial hypotensia since this drug may cause an extension of the II period of delivery due to the relaxation of the uterus muscles. When applied in large quantities in order to ease the uterus contractions, the drug may cause a prolonged atonia of the uterus accompanied by bleedings. When it is necessary to apply the drug, breast feeding should be discontinued.

Effects on ability to drive and use machines

During the medical treatment with this drug, it is not recommended to drive motor vehicles and to perform any other potentially dangerous operations that require increased concentration of attention and fast psychomotor ability.

Posology and method of administration

The drug should be prescribed for subcutaneous and intramuscular administration, and sometimes intravenously or intravenously in drops.

For adults.

Anaphylactic shock: The drug is administered intravenously at slow rate in the dose of 0.5 ml in a solution form (a one-time dose is diluted in 20 ml of the 40 % glucose solution). Further, if necessary, the intravenous administration in drops should be continued at the rate of 1 mcg/min, and to this effect as much as 1 ml of adrenaline solution should be diluted in 400 ml of the 0.9 % sodium chloride solution or in the 5 % glucose. If the patient's condition allows, it looks more expedient to administer the drug intramuscularly or subcutaneously, with 0.3-0.5 ml of the drug in a diluted or undiluted form.

Bronchial asthma: The drug should be administered subcutaneously in the doses of 0.3-0.5 ml in a diluted or undiluted form. If it is necessary to administer the drug again, the said dose may be applied every 20 minutes (maximum for 3 times). It is also possible to administer the drug intravenously in the amounts of 0.3-0.5 ml in a diluted form (with a one-time dose having been

diluted in 20 ml of the 40 % glucose solution).

As a vasoconstrictor agent: The drug should be administered intravenously in drops at the rate of 1 mcg/min (with a possible acceleration to 2-10 mcg/min).

Asystolia: The drug should be administered intracardially with the dose of 0.5 ml in a diluted form (a one-time dose is diluted in 10 ml of the 0.9 % sodium chloride solution).

Resuscitation procedure (cardiac arrest, severely developing AV block of the III stage): The drug should be administered intravenously at slow rate with 1 ml per 3-5 minutes in a diluted form.

Prolonged action of local anesthetics: The drug should be prescribed in the concentration of 1:50000 to 1:100000, and the dose is dependent on the kind of an anesthetic.

For children.

Asystolia in infants: The drug should be administered intravenously at slow rate with the doses of 10-30 mcg/kg of the body weight during each 3-5 minutes.

Anaphylactic shock: The drug should be administered subcutaneously or intramuscularly in the doses of 10 mcg/kg of the body weight (maximum up to 0.3 mg). If necessary, the drug may be applied again every 15 minutes (maximum for 3 times).

Bronchospasm: The drug should be administered subcutaneously in the doses of 10 mcg/kg of the body weight (maximum up to 0.3 mg). If necessary, the drug may be applied again every 15 minutes (up to 3-4 times) or every 4 hours.

Children

The drug may be administered to children.

Overdose

Symptoms: Abnormally increased arterial pressure; tachyarrhythmia followed by bradycardia; disturbances of heart rate (including auricular and ventricular fibrillation); cooling and paling of skin surfaces; vomiting; fear; anxiety; tremor; headache; metabolic acidosis; myocardial infarction; craniocerebral bleeding (especially in aged patients); pulmonary edema; renal insufficiency; and fatal outcome. If administered in large doses (with the minimum lethal dose in the event of subcutaneous introduction constituting 10 ml of the 0.18 % solution), mydriasis develops as well as a significantly increase in the arterial pressure and a tachycardia with a possible transition into ventricular fibrillation.

Treatment: The administration of the drug must be stopped. An overdose of adrenaline may be eliminated thru the administration of α - and β -adrenergic blocking agents and fast-working nitrates.

In the event of severe complications, a complex therapy is required. In the event of arrhythmia, the parenteral administration of β -adrenergic blocking agents must be prescribed.

Undesirable effects

When using the drug, the following adverse reactions may occur.

Gastrointestinal disorders: nausea, vomiting, anorexia.

Renal and urinary disorders: rarely, labored and painful urination (with hyperplasia of the prostate gland).

Metabolism and nutrition disorders: hypokalemia, hyperglycemia.

Nervous system disorders: headache, tremor, dizziness, nervousness, muscle twitching, patients with Parkinson's disease may increase rigidity and tremor.

Psychiatric disorders: anxiety, psychoneurotic disorders, psychomotor agitation, disorientation, memory impairment, aggressive or panic behavior, frustration like schizophrenia, paranoia, sleep disturbance.

Cardiac disorders: stenocardia, bradycardia or tachycardia, palpitation, dyspnea; At high doses - ventricular arrhythmias; Rarely - arrhythmia, pain in the chest; ECG changes (including a decrease in the amplitude of the T wave).

Vascular disorders: a decrease or increase in blood pressure (even with subcutaneous administration in usual doses due to increased blood pressure, possibly subarachnoid hemorrhage

and hemiplegia).

Immune system disorders: angioedema, bronchospasm.

Skin and subcutaneous tissue disorders: skin rash, erythema multiforme.

General disorders and administration site conditions: pain or burning at the site of intramuscular injection; Fatigue, increased sweating, violation of thermoregulation (sensation of cold or heat), cold extremities, repeated injections of adrenaline may be accompanied by necrosis due to the vasoconstrictor action of adrenaline (including necrosis of the liver or kidneys).

Shelf life. 2 years.

Special precautions for storage

Store in the original package at temperature 2 °C – 8 °C. Do not freeze.

Keep out of reach of children.

Incompatibilities

Do not mix in the same syringe with solutions of acids, alkalis and oxidants because of the possible chemical interaction of the active substance.

Nature and contents of container

1 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.

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