

PACKAGE LEAFLET
for medical use of the medicinal product

Gentamicin sulfat-Darnitsa

Qualitative and quantitative composition:

active substance: gentamicin;

1 ml of solution contains gentamicin sulfate 40 mg;

List of excipients: sodium metabisulfite (E 223), disodium edetate, water for injections.

Pharmaceutical form. Solution for injection.

Main physical and chemical properties: clear colorless or slightly colored liquid.

Pharmacotherapeutic group. Antibacterial agents for systemic use. Aminoglycosides. Gentamicin. ATC code J01G B03.

Pharmacological properties.

Pharmacodynamic properties.

Gentamicin is a broad-spectrum aminoglycoside antibiotic. The mechanism of action is associated with inhibition of the 30S ribosomal subunits. *In vitro* tests confirm its activity against different types of gram-positive and gram-negative microorganisms: *Escherichia coli*, *Proteus spp.* (indole-positive and indole-negative), *Pseudomonas aeruginosa*, *Klebsiella spp.*, *Enterobacter spp.*, *Serratia spp.*, *Citrobacter spp.*, *Salmonella spp.*, *Shigella spp.* and *Staphylococcus spp.* (including penicillin- and methicillin-resistant strains). The following microorganisms are usually resistant to gentamicin: *Streptococcus pneumoniae*, most other species of streptococci, enterococci, *Neisseria meningitidis*, *Treponema pallidum* and anaerobic microorganisms such as *Bacteroides sp.* or *Clostridium spr.*

Pharmacokinetic properties.

The maximum plasma concentration in 0.5-2 hours after intramuscular administration of 80 mg gentamicin is 4-12 µg/ml. Similar concentrations are achieved after intravenous administration. The half-life is 2.5 hours and increases with impaired renal excretory function. Plasma protein binding is 20-30 %. The volume of distribution is 0.25 L/kg. Normally, gentamicin does not pass well through the blood-brain barrier; with meningitis, the concentration in the cerebrospinal fluid increases.

Gentamicin crosses the placenta. The concentrations observed in the fetal blood are approximately 40% of the concentration found in the mother's blood.

Gentamicin is not metabolized in the body. It is excreted unchanged in the urine, mainly by glomerular filtration, and partially by glomerular secretion.

Clinical particulars.

Therapeutic indications.

Given the limited therapeutic breadth of Gentamicin-Darnitsa, it should be used in cases where microorganisms are resistant to safer antibiotics.

Bacterial infections caused by gentamicin-sensitive microflora, in particular: lower respiratory tract infections, complicated urogenital infections, bone and joint infections, including osteomyelitis, skin

and soft tissue infections, infected burn wounds, abdominal infections (peritonitis), central nervous system infections, including meningitis in combination with β -lactam antibiotics, septicemia.

Contraindications.

Hypersensitivity to the active substance and to other components of the medicinal product; auditory nerve neuritis; chronic renal failure with azotemia and uremia; myasthenia gravis; parkinsonism; botulism (gentamicin can cause neuromuscular disorders, which can lead to further weakening of skeletal muscles); elderly age; previous treatment with ototoxic medicinal products. Acute renal failure is a limitation to the use of the medicinal product.

Interaction with other medicinal products and other forms of interaction

In case of concomitant use of medicinal product with other medicinal products, it is possible:

with ototoxic agents (including capreomycin, cisplatin, teicoplanin, vancomycin, potent diuretics: furosemide, ethacrynic acid) - increased ototoxic effect, this combination is not recommended;

with neurotoxic or nephrotoxic agents (in particular streptomycin, neomycin, kanamycin, capreomycin, tobramycin, cephaloridin, paromomycin, biomyacin, polymyxin B, colistin, amikacin, vancomycin, teicoplanin, tacrolimus, amphotericin B, cyclosporin, clindamycin, piperacillin, methoxyflurane, foscarnet, radiocontrast agents for intravenous administration, cisplatin) - increased neurotoxic or nephrotoxic effect, this combination is not recommended;

with non-depolarizing muscle relaxants - enhancing the muscle relaxant effect of curare-like medicinal products;

with methoxyflurane, polymyxins for parenteral administration, drugs that block neuromuscular transmission (inhalation medicinal products for general anesthesia, narcotic analgesics, transfusion of large amounts of blood with citrate preservatives) - an increase in the risk of respiratory arrest due to increased neuromuscular blockade;

with botulinum toxin - increased risk of toxicity due to increased neuromuscular blockade;

with medicinal products that increase muscle tone - a decrease in the effectiveness of the latter;

with cephalosporins - increased nephrotoxic effect; monitoring of renal function is recommended during therapy;

with penicillins - an increased bactericidal effect;

with bisphosphonates - an increase in the risk of developing hypocalcemia;

with indomethacin (parenteral administration) - an increase in the risk of developing the toxic effect of gentamicin due to an increase in the half-life and a decrease in clearance.

Special warnings and precautions for use.

Gentamicin is one of the main treatments for severe suppurative infections caused by resistant gram-negative flora. Due to the broad spectrum of action, gentamicin can be prescribed for the mixed infections, as well as in cases where the pathogen is not identified, usually in combination with semi-synthetic penicillins: ampicillin, carbenicillin.

Treatment of medicinal product should only be prescribed by a physician and under close clinical supervision due to the potential toxicity of gentamicin.

During treatment with gentamicin, blood tests should be performed regularly to determine plasma medicinal product concentrations to ensure adequate and avoid potentially toxic blood levels of the medicinal product.

Sufficient fluids should be consumed during treatment.

Like other aminoglycosides, gentamicin is potentially nephro- and neurotoxic. The risk of developing these side effects is higher in patients with impaired renal function, as well as when the medicinal product is prescribing in large doses or for a long time. Therefore, regular (1 or 2 times a week, and in patients receiving higher doses or those who are treated for more than 10 days - daily) should monitor renal function. In order to avoid the development of hearing impairment, it is recommended to regularly (1 or 2 times a week) conduct a study of vestibular function or determine the hearing loss at high frequencies.

In some cases, hearing impairment may occur after the end of treatment.

It is necessary to inform the doctor about the following symptoms: a feeling of any hearing loss, a ringing or ringing in the ears, dizziness, impaired coordination of movements, numbness, tingling of the skin, muscle twitching, convulsions at any time during treatment. This may indicate the development of neurological side effects.

Symptoms of impaired renal function or damage to the auditory or vestibular apparatus require stopping gentamicin therapy or, in exceptional cases, only adjusting its dose.

The medicinal product should be used with caution in patients with dehydration, hypocalcemia, patients with impaired renal function, obesity.

Due to little clinical experience, it is not recommended to administer the entire daily dose of gentamicin in such conditions: burns with an area of more than 20%, cystofibrosis, ascites, endocarditis, chronic renal failure with hemodialysis, sepsis.

Rapid direct intravenous administration of the drug may initially lead to a potentially neurotoxic concentration of gentamicin, and it is very important to administer the dose at the recommended intervals.

Cross-hypersensitivity is possible among aminoglycoside antibiotics.

Against the background of treatment, resistance of microorganisms may develop. In such cases, it is necessary to cancel the medicinal product and conduct a study of the sensitivity of microorganisms to antibiotics.

Fertility, pregnancy and lactation

Due to the fact that gentamicin sulfate penetrates the placenta and can have a nephrotoxic effect on the fetus, the medicinal product is contraindicated for use during pregnancy.

The medicinal product passes into breast milk, so if you need to prescribe gentamicin to the mother should either stop breastfeeding, or stop using the medicinal product.

Effects on ability to drive and use machines

The medicinal product affects the speed of neuromuscular conduction, therefore, during treatment with the medicinal product should refrain from driving and working with mechanisms that require special attention.

Posology and method of administration.

Gentamicin should be administered intramuscularly or intravenously. The dose, route of administration and intervals between administrations depend on the severity of the disease and the patient's condition. The dose regimen is calculated based on the patient's body weight.

Adults and children over 14 years.

The usual daily dose of gentamicin for patients with moderate to severe infections is 3 mg/kg body weight intramuscularly, divided into 2-3 injections. The maximum daily dose for adults is 5 mg/kg body weight, divided into 3-4 injections. The usual duration of the medicinal product administration for all patients is 7-10 days.

In severe and complicated infections, the course of therapy can be continued as needed. In such cases, it is recommended to monitor the function of the kidneys, hearing and vestibular apparatus, as the toxicity of the medicinal product is manifested itself after its use for more than 10 days.

Calculation of body weight to which gentamicin should be prescribed.

Calculate the dose based on actual body weight (ABW) if the patient is not overweight (that is, no more than 20% of the ideal body weight (IBW)). If the patient is overweight, the dose is calculated for the following body weight (DBW) according to the formula:

$$DBW = IBW + 0.4 (ABW - IBW).$$

In case of renal impairment, it is necessary to change the dosage regimen of the medicinal product so that it guarantees the therapeutic adequacy of the treatment. The serum gentamicin concentration should be monitored whenever possible. Serum concentrations should be 5-10 µg/ml 30-60 minutes after intramuscular administration.

The initial single dose for patients with stable chronic renal failure is 1-1.5 mg/kg body weight, then the dose and interval between injections should be determined depending on creatinine clearance.

Clearance creatinine ml/min	All following doses (% of initial dose)	Interval between injections, hour
70	100	8
40-69	100	12
30-39	50	8
20-29	50	12
15-19	50	16
10-14	50	24
5-9	50	36

For adult patients with bacterial infection who are on dialysis, the medicinal product is prescribed at a dose of 1-1.5 mg/kg body weight at the end of each dialysis.

For peritoneal dialysis in adults, add 1 mg of gentamicin to 2 liters of dialysis solution.

For intravenous administration, the dose of the medicinal product should be diluted with a solvent. The usual volume of solvent (sterile saline or 5% glucose solution) for adults is 50-300 ml, for children the volume of solvent should be reduced accordingly. The duration of intravenous infusion is 1-2 hours.

The concentration of gentamicin in the solution should not exceed 1 mg/ml (0.1%).

Children.

Gentamicin sulfate should be prescribed to children under 3 years of age only with life-threatening conditions.

The usual daily dose of gentamicin is: newborns and children under 1 year - 2-5 mg/kg body weight, children aged 1 to 5 years - 1.5-3 mg/kg body weight, children aged 6-14 years - 3 mg/kg body weight. The maximum daily dose for children of all ages is 5 mg/kg body weight, divided into 2-3 injections. The average duration of treatment is 7-10 days.

Children.

The medicinal product can be used in children. Gentamicin can be prescribed to children under 3 years of age only with life-threatening conditions.

Overdose.

Symptoms: dizziness, nausea, vomiting, nephrotoxic and ototoxic manifestations, blockade of neuromuscular conduction (respiratory arrest).

Treatment: For adults – intravenously inject proserine, as well as 10% calcium chloride solution or 5% calcium gluconate solution. Before the introduction of proserine pre-intravenous atropine at a dose of 0.5-0.7 mg, expect an increase in pulse rate and after 1.5-2 minutes, 1.5 mg (3 ml of 0.05% solution) of proserine is injected intravenously. If the effect of this dose is insufficient, re-inject the same dose of proserine (if bradycardia occurs, give an additional injection of atropine). In severe cases of respiratory depression, artificial lung ventilation is necessary. It can be excreted by hemodialysis (more effective) and peritoneal dialysis.

Undesirable effects.

Ear and labyrinth disorders: ototoxicity (lesions of the VIII pair of cranial nerves, especially if the treatment lasts 2-3 months) - tinnitus, hearing loss, vestibular and labyrinthine disorders, irreversible deafness.

Respiratory, thoracic and mediastinal disorders: sore throat, shortness of breath.

Gastrointestinal disorders: nausea, vomiting, increased thirst, loss of appetite, stomatitis, in some cases - pseudomembranous colitis.

Hepatobiliary disorders: increased activity of hepatic transaminases, hyperbilirubinemia.

Renal and urinary disorders: nephrotoxicity (renal dysfunction) - oliguria, azotemia, proteinuria, microhematuria, interstitial nephritis, renal failure, in some cases - renal tubular necrosis.

Metabolism and nutrition disorders: hypomagnesemia, hypocalcemia, hypokalemia, hyponatremia.

Nervous system disorders: headache, drowsiness, confusion, muscle twitching, paresthesia, feeling of numbness, convulsions, epileptic seizures, peripheral neuropathy, encephalopathy, neuromuscular disorders.

Psychiatric disorders: depression, hallucinations, in children - psychosis.

Cardiac disorders: lowering blood pressure.

Blood and lymphatic system disorders: anemia, leukopenia, granulocytopenia, thrombocytopenia, eosinophilia, purpura.

Immune system disorders: hypersensitivity reactions, including rash, pruritus, hyperemia, urticaria, Quincke's edema, anaphylactic shock, development of superinfections.

General disorders and administration site conditions: general weakness, muscle pain, edema, fever, chills, increased salivation, disorders at the injection site (including hyperemia, tightness of the skin, atrophy or necrosis of the subcutaneous tissue, with intravenous administration - the development of phlebitis and periphlebitis).

Shelf life 3 years.

Do not use this medicinal product after the expiry date which is indicated on the package.

Special precautions for storage

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

Incompatibilities.

It is undesirable to mix the medicinal product with other medicinal products. Pharmaceutically incompatible with other aminoglycosides, amphotericin B, heparin, ampicillin, benzylpenicillin, cloxacillin, carbenicillin, capreomycin.

Nature and contents of container.

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

Category of release

Prescription only medicine.

Manufacturer/Applicant

PrJSC "Pharmaceutical firm "Darnitsa".

The manufacturer's location and address of the place of business.

13, Boryspilska Street, Kyiv, 02093, Ukraine..

Date of the last revision.

28.04.2017