

PACKAGE LEAFLET
for medical use of a medicinal product

FURODAR-DARNITSA

Qualitative and quantitative composition:

active ingredient: furosemide;

Each tablet contains Furosemide 40mg;

excipients: potato starch, lactose monohydrate, croscarmellose sodium, sodium lauryl sulfate, magnesium stearate.

Pharmaceutical form

Tablets.

Basic physical and chemical properties: White to off white, flat, round tablets.

Pharmacotherapeutic group. Highly active diuretics. Simple sulfamide drugs. Furosemide. Code ATX C03C A01.

Pharmacological properties

Pharmacodynamic properties

Furosemide is a loop diuretic of rapid action, which causes a relatively strong and short-term diuretic effect. The furosemide blocks the $\text{Na}^+ \text{K}^+ 2\text{Cl}^-$ co-transporter, located in the basal membranes of the thick segment of the ascending part of the Henle loop: the effectiveness of the saluretic action of the furosemide, therefore, depends on whether the drug reaches the tubule in the lumen of the anion-transport mechanism. The diuretic effect results from inhibition of sodium chloride reabsorption in this segment of the Henle loop. As a result, fractional sodium excretion can reach 35 % glomerular filtration of sodium. Secondary effects of increased sodium excretion include increased urinary excretion (due to osmotically bound water) and increased distal tubular secretion of potassium. It also increases the excretion of calcium and magnesium ions.

Furosemide induces dose-dependent stimulation of the renin-angiotensin-aldosterone system. In case of heart failure, furosemide results in a sharp decrease in cardiac preload (by narrowing the capacious venous vessels). This early vascular effect is prostaglandin-mediated and involves an adequate renal function with the activation of the renin-angiotensin system and the intact synthesis of prostaglandins. In addition, due to its natriuretic effect, furosemide reduces vascular reactivity relative to catecholamines, which is increased in patients with arterial hypertension.

The antihypertensive efficacy of furosemide is due to increased sodium excretion, reduced blood volume and reduced response of smooth muscle vessels to stimulation by vasoconstrictors or vasoconstrictors.

The onset of the diuretic effect is observed within 1 hour after the oral administration of the dose of the medicinal product.

The dose-dependent increase in diuresis and sodium urine was observed in healthy volunteers receiving furosemide at doses of 10-100 mg. The duration of action in healthy volunteers is approximately 3-6 hours after the oral administration of 40 mg furosemide.

The effect of furosemide is reduced if there is a reduced tubular secretion or binding of a medicinal product to albumin inside the tubules.

Pharmacokinetic properties

Furosemide is rapidly absorbed from the gastrointestinal tract. Furosemide is absorbed between 1 and 1.5 hours at most. Absorption of the medicinal product indicates significant individual variability.

Bioavailability of furosemide in tablets ranges between approximately 50 to 70% in healthy volunteers. The bioavailability of the medicinal product depends on various factors in patients, including existing diseases. For example, in the case of nephrotic syndrome, the bioavailability may be reduced by up to 30%.

Taking furosemide simultaneously with food can affect the medicinal product absorption.

The volume of distribution of furosemide is from 0.1 to 0.2 liters per 1 kg of body weight. The volume of distribution may be higher depending on the disease.

Furosemide (over 98 %) forms strong compounds with blood plasma proteins, especially albumin.

Furosemide is excreted primarily as an unchanged drug through secretion in the proximal tubule. Metabolite furosemide - glucuronide - is 10-20 % of substances contained in the urine. The residual dose is excreted with feces, presumably through biliary secretion.

The terminal half-life of furosemide after intravenous administration is approximately 1 to 1.5 hours.

Furosemide penetrates breast milk, through the placental barrier and slowly falls into the fetus. Furosemide is defined in the fetus or in newborns at the same concentrations as the mother of the child.

Kidney disease.

In renal failure, the output of furosemide is delayed, and the half-life is prolonged; The terminal half-life may last up to 24 hours in patients with severe renal insufficiency.

With nephrotic syndrome, reduced concentrations of plasma protein proteins lead to an increase in the concentration of unbound (free) furosemide. On the other hand, the efficacy of furosemide in these patients is reduced by binding to intratubular albumin and understated tubular secretion.

Furosemide is poorly dialyzable in patients undergoing hemodialysis, peritoneal dialysis and chronic peritoneal dialysis in outpatient settings.

Hepatic insufficiency.

In case of hepatic failure, the half-life of furosemide is increased by 30-90 %, mainly due to the greater volume of distribution. It should also be noted that a wide variety of all pharmacokinetic parameters is observed in this group of patients.

Congestive heart failure, severe arterial hypertension, elderly patients.

Furosemide withdrawal is delayed due to decreased kidney function in these patients.

Premature and infant infants. Depending on the level of kidney formation, excretion of furosemide may be delayed. Metabolism of the drug also decreases if infants have an ability to glucuronize. The terminal half-life lasts less than 12 hours in a fetus aged 33 weeks after fertilization of the egg. In infants aged 2 months, the terminal clearance is similar to clearance in adult patients.

Therapeutic indications

Indications

- Edema in chronic congestive heart failure (if treatment with diuretics is necessary).
- Edema in nephrotic syndrome (if treatment with diuretics is necessary).
- Edema in chronic renal insufficiency.
- Acute renal failure, including during pregnancy or during childbirth.
- Edema with liver disease (if necessary, to complement treatment with the use of aldosterone antagonists).
- Hypertension.

Contraindications

▪ Hypersensitivity to furosemide or to other components that are part of the medicinal product. Patients with sulfonamide allergy (example sulfonamide antibiotics or sulfonylureas) may experience cross-sensitivity to furosemide.

- Hypovolemia or dehydration.
- Renal insufficiency in the form of anuria if there is no therapeutic response to furosemide.

- Renal insufficiency due to poisoning with nephrotoxic or hepatotoxic drugs.
- Severe hypokalemia.
- Severe hyponatremia.
- Preecomatous or comatose states associated with hepatic encephalopathy.
- Addison's disease.
- Digitalis intoxication.
- Breastfeeding.

Interaction with other medicinal products and other forms of interaction

Unsolicited combinations.

In some cases, taking furosemide within 24 hours of chloral hydrate may cause tiredness, increased sweating, excitement, nausea, increased blood pressure and tachycardia. Consequently, the simultaneous use of furosemide and chloral hydrate is not recommended.

Furosemide can potentiate ototoxicity of *aminoglycosides and other ototoxic drugs*. Since this can lead to damage that is irreversible, these medicines should not be used simultaneously with furosemide. Furosemide may reduce serum *vancomycin* levels. Furosemide *when combined with antihistamines* may cause hypokalemia and increase the risk of cardiac toxicity.

Combinations requiring precautionary measures.

In the case of co-administration of *cisplatin* and furosemide there is a risk of ototoxic effects. In addition, the nephrotoxicity of cisplatin may be increased if furosemide is not prescribed in low doses (for example, 40 mg in patients with normal renal function) and with a positive fluid balance when the drug is used to achieve the effect of forced diuresis during cisplatin therapy.

The intake of oral furosemide and sucralfate should be separated by at least two hours, as sucralfate decreases the absorption of furosemide from the intestine and so reduces its effect.

Furosemide reduces the elimination of lithium salts and may lead to increased levels of lithium in serum, which results in an increased risk of lithium toxicity, including a higher risk of cardiotoxic and neurotoxic effects of lithium. Therefore, it is recommended that thorough monitoring of lithium levels be performed in patients receiving this combination therapy.

Patients receiving diuretics may suffer from severe arterial hypotension and impaired renal function, including renal failure, especially when first using an *angiotensin converting enzyme inhibitor (ACE inhibitor)* or an *angiotensin II receptor antagonist*, or at the first dose of these drugs at an increased dose. It is necessary to decide whether to temporarily stop using furosemide, at least reduce the dose of furosemide 3 days prior to treatment or increase the dose of an ACE inhibitor or angiotensin II receptor antagonist.

Antipsychotics: furosemide-induced hypokalaemia increase the likelihood of cardiotoxicity. Avoid co-administration with *pimozide*; increased risk of ventricular arrhythmias with *amisulpiride* or *sertindole*. An enhanced hypotensive effect may be seen when administered with *phenothiazine derivatives (chlorpromazine)*.

Risperidone: Caution should be exercised and careful to weigh the risk and benefit before deciding whether to use combination therapy or to be co-administered with furosemide or other potent diuretics.

Levothyroxine: High doses of furosemide may inhibit the binding of thyroid hormones to carrier proteins, and therefore initially lead to a temporary increase in the levels of free thyroid hormone fractions followed by an overall decrease in total thyroid hormone fraction levels.

Thyroid hormone levels should be monitored.

Combinations to be used with caution.

The simultaneous use of *non-steroidal anti-inflammatory drugs, including acetylsalicylic acid*, may reduce the effect of furosemide. In patients with dehydration or hypovolaemia, non-steroidal anti-inflammatory drugs can lead to acute heart failure. The action of furosemide may increase the toxicity of salicylate.

Indomethacin and *ketorolac* may antagonize the effects of furosemide. In patients with dehydration or hypovolemia, NSAIDs may cause acute renal failure.

Reducing the efficacy of furosemide may occur after co-administration of *phenytoin*.

The use of *corticosteroids*, *carbenoxolone*, *licorice root* in large doses and long-term administration of *laxatives* may increase the risk of hypokalemia.

Some electrolyte imbalances (such as hypokalemia, hypomagnesaemia) may increase the toxicity of certain other drugs (such as *digitalis drugs* and *drugs causing QT prolongation syndrome*).

If *antihypertensive drugs*, *diuretics* or other medicines that have the ability to lower blood pressure, to be co-administered with furosemide, an even greater reduction in blood pressure should be expected.

Probenecid, *methotrexate*, and other medicinal products, such as furosemide, undergo significant tubular secretion in the kidneys, may reduce the effectiveness of furosemide. Conversely, furosemide may reduce the release of these drugs by the kidneys. Conducting treatment with high doses (including furosemide and other drugs) may increase their serum levels and increase the risk of side effects caused by furosemide or the use of concomitant therapy.

The effectiveness of *antidiabetic drugs* and *sympathomimetics* that have the potential to increase blood pressure (example epinephrine, norepinephrine) may decrease.

The effect of *curarelike muscle relaxants* or *theophylline* may be intensified.

It is possible to increase the harmful effect of *nephrotoxic drugs* on the kidneys.

Renal impairment may develop in patients receiving concomitant furosemide therapy and high doses of certain *cephalosporins*.

The simultaneous administration of *cyclosporin A* and furosemide is associated with an increased risk of gouty arthritis, secondary to hyperuricemia induced by furosemide, and a cessation of renal excretion of urates caused by cyclosporine.

In patients who were at high risk for nephropathy due to radiocontrast therapy, furosemide treatment had a greater rate of deterioration of renal function after receiving contrast media compared with those in high-risk patients who only received intravenous hydration prior to the appointment of *radiocontrast substances*.

Alcohol increases the risk of potassium loss.

Special warnings and precautions for use

During treatment with furosemide it is necessary to ensure constant outflow of urine. Patients with partial urinary outflow obstruction require close attention, especially at the initial stages of treatment.

Treatment with furosemide requires regular medical supervision of the patient. Extremely careful monitoring is required:

- patients with arterial hypotension;
- patients who are at high risk because of a significant reduction in blood pressure, such as patients with severe stenosis of the coronary arteries or blood vessels supplying the blood to the brain;
- patients with latent or severe form of diabetes mellitus;
- patients with gout;
- patients with hepatorenal syndrome, that is, with functional renal failure associated with severe liver disease;
- patients with hypoproteinemia, for example, associated with nephrotic syndrome (the effect of furosemide may be diminished simultaneously with the potentiation of ototoxicity). Necessary cautious titration of the dose;
- Premature infants (possible nephrocalcinosis/nephrolithiasis development); monitor kidney function and perform ultrasonography of the kidneys.

Regular monitoring of sodium, potassium and serum creatinine is generally recommended during furosemide therapy. Patients with a high risk of developing electrolyte imbalances or in the event of significant additional fluid loss (for example, as a result of vomiting, diarrhea, or intense sweating) require particularly careful monitoring. Hypovolemia or dehydration of the body, as well as any significant violations of electrolyte and acid-base balance, should be corrected. This may require a temporary cessation of therapy with furosemide.

The development of electrolyte imbalance affects factors such as existing diseases (e.g. cirrhosis of the liver, heart failure), concomitant use of drugs and nutrition. For example, as a result of vomiting or diarrhea, there may be a lack of potassium.

When using furosemide, it is advisable to recommend high-potassium foods (baked potatoes, bananas, tomatoes, spinach, dried fruit) to the patient. It should be remembered that the use of furosemide may require a medical compensation for potassium deficiency.

Co-administration with risperidone. In placebo-controlled studies of risperidone among elderly patients with dementia, higher lethality was observed in patients receiving furosemide concomitantly with risperidone compared with patients receiving risperidone or furosemide alone.

Caution should be exercised and careful to weigh the risks and benefits before deciding whether to use such a combination or co-treatment with other potent diuretics. Avoid dehydration.

Medicinal product administration must be discontinued prior to glucose tolerance test.

Important information on excipients.

This medicinal product contains lactose monohydrate. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Fertility, pregnancy and lactation

Pregnancy. Furosemide penetrates through the placental barrier. It should not be prescribed during pregnancy, except for cases of treatment for vital signs. Treatment with a medicament during pregnancy requires monitoring of the growth and development of the fetus.

Breast feeding. Furosemide penetrates breast milk and can suppress lactation. Women should stop breastfeeding during treatment with furosemide.

Effects on ability to drive and use machines

Some side effects (such as an unexpected significant decrease in blood pressure) may interfere with the patient's ability to concentrate and rate of response.

Therefore, it should be kept for a period of treatment from driving or working with other mechanisms.

Posology and method of administration

The mode of application is determined by the physician individually depending on the severity of the water-electrolyte balance disorders, the size of the glomerular filtration, the severity of the patient's condition.

Medicinal product is usually taken before food.

In adults, the recommended maximum daily dose of Furodar-Darnitsa administration should not exceed 1500 mg.

Special dosage recommendations for adults.

Edema in chronic congestive heart failure. The recommended starting dose of the drug for oral administration is 40 mg per day. If necessary, the dose can be adjusted in accordance with the patient's therapeutic response. It is recommended that the daily dose be divided into 2 or 3 doses.

Edema in chronic renal insufficiency. The dose should be carefully titrated to ensure gradual initial fluid loss. For adult patients, this means the use of such a dose, resulting in a daily reduction in body weight of about 2 kg (about 280 mmol Na⁺). The recommended starting dose of the drug for oral administration is 40-80 mg per day. If necessary, the dose can be adjusted in accordance with the patient's therapeutic response. The overall daily dose can be administered once or divided into 2 doses. For hemodialysis patients, the total daily oral dose is 250-1500 mg.

In acute renal failure, before starting to use furosemide, hypovolemia, arterial hypotension and significant electrolyte and acid-base imbalance should be compensated. It is recommended to move as soon as possible from intravenous to oral administration.

Edema with nephrotic syndrome. The recommended starting dose of the drug for oral administration is 40-80 mg per day. If necessary, the dose can be adjusted in accordance with the patient's therapeutic response. The overall daily dose can be administered once or divided into 2 doses.

Edema with diseases of the liver. Furodar-Darnitsa is administered as an add-on to aldosterone

antagonist therapy in cases where the use of aldosterone antagonists is inadequate. To prevent complications such as orthostatic hypotension or electrolyte and acid-alkaline balance disruption, the dose should be carefully titrated to provide a gradual initial loss of fluid. For adult patients, this means the administration of such a dose, which leads to a daily reduction in body weight of about 0.5 kg. The recommended starting dose of the drug for oral administration is 40-80 mg per day. If necessary, the dose can be adjusted in accordance with the patient's therapeutic response. The overall daily dose can be administered once or divided into 2 doses.

For children not able take the oral dosage form, such as premature infants and newborns, the administration of the parenteral dosage form should be considered.

For children, the recommended oral dose of furosemide is 2 mg/kg body weight, but the maximum daily dose should not exceed 40 mg. The dose should be reduced in accordance with the body weight.

Children

The medicinal product in this dosage form should be prescribed to children weighing more than 10 kg (see section "Method of administration and dose").

Overdose

Symptoms: The clinical picture of acute or chronic overdosing depends mainly on the degree and effects of electrolyte and fluid loss and includes such symptoms as hypovolemia, dehydration, hemoconcentration, cardiac arrhythmias (including AV block and ventricular fibrillation). The symptoms of these disorders include severe arterial hypotension (progressing to shock), acute renal failure, thrombosis, delusions, peripheral paralysis, apathy and confusion of consciousness.

In patients with cirrhosis, overdose can lead to hepatic coma.

Treatment: no specific antidote for furosemide. Therapy is symptomatic. Treatment should be aimed at fluid replacement and correction of electrolyte imbalance.

Undesirable effects

The following classification is used to assess the adverse reaction frequency: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); frequency not known (cannot be estimated from the available data).

Eye disorders:

rare: visual disturbances, decreased acuity, blurred vision.

Ear and labyrinth disorders:

uncommon: hearing impairment, which is usually transient, especially in patients with renal insufficiency, hypoproteinemia (for example, with nephrotic syndrome) and/or in case of too fast intravenous administration of furosemide. There have been reported cases of deafness, sometimes irreversible, after oral administration or intravenous administration of furosemide.

rare: tingle.

Gastrointestinal disorders:

uncommon: nausea;

rare: vomiting, diarrhea;

very rare: acute pancreatitis;

frequency not known: dry mouth, impaired intestinal motility, constipation.

Hepatobiliary disorders:

very rare: cholestasis, increased levels of transaminases.

Renal and urinary disorders:

common: urine volume increase;

rare: tubulo-interstitial nephritis;

frequency not known:

- urine sodium levels increase;
- urine chlorine uptake, urinary retention (in patients with partial urinary drainage obstruction);
- nephrocalcinosis/nephrolithiasis in preterm infants;

- renal insufficiency;
- enuresis;
- creatine level increase in blood.

Metabolism and nutrition disorders:

very common: electrolyte imbalance disorders (including clinical manifestations), dehydration and hypovolemia, especially in elderly patients;

common: hyponatremia, hypochloremia, hypokalemia, elevated blood cholesterol, elevated blood urea, gout attacks;

uncommon: decreased glucose tolerance, diabetes mellitus can turn from a latent form to a pronounced, tetany;

frequency not known: hypocalcemia, hypomagnesemia, elevated blood uric acid, metabolic alkalosis, Bartter's pseudosyndrome due to improper and/or prolonged use of furosemide.*

Nervous system disorders:

rare: paresthesia, headache;

common: hepatic encephalopathy in patients with hepatocellular insufficiency;

frequency not known: dizziness, loss of consciousness (caused by symptomatic hypotension).

Cardiac disorders:

very common: (when used as an intravenous infusion): hypotension, including orthostatic hypotension;

rare: vasculitis;

frequency not known: thrombosis.

Blood and lymphatic system disorders:

common: hemoconcentration;

uncommon: thrombocytopenia;

rare: leukopenia, eosinophilia;

very rare: agranulocytosis, aplastic anemia or hemolytic anemia.

Immune system disorders:

rare: severe anaphylactic and anaphylactoid reactions (including those that are accompanied by shock).

frequency not known: possibility of exacerbation or activation of systemic lupus erythematosus.

Skin and subcutaneous tissue disorders:

uncommon: itching, urticaria, rash, bullous dermatitis, erythema multiforme, pemphigoid, exfoliative dermatitis, purpura, photosensitivity reaction;

frequency not known: Steven-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and DRESS syndrome (medication rash with eosinophilia and systemic symptoms).

Musculoskeletal system and connective tissue disorders:

rare: muscle weakness, muscle cramps;

frequency not known: rhabdomyolysis, often with severe hypokalaemia (see section "Contraindications").

General disorders and administration site conditions:

fever, local reactions, eg pain after intramuscular injection.

Congenital and hereditary/genetic disorders:

frequency not known: an increased risk of non-arterial duct failure if furosemide is prescribed to preterm infants during the first days of life.

* Potassium deficiency manifests itself in neuromuscular symptoms (muscular weakness, paralysis), intestinal symptoms (vomiting, constipation, meteorism), renal symptoms (polyuria) or cardiac symptoms. Severe potassium depletion can result in paralytic ileus or confusion, which can result in coma.

Reporting of suspected adverse reactions.

Reporting suspected adverse reactions after marketing authorisation of the medicinal product is important procedure. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the national reporting system.

Shelf life

3 years.

Special precaution 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 blister; 3 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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02.10.2019