

APPROVED
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Health of Ukraine
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PACKAGE LEAFLET
for medical use of a medicinal product

FUROSEMID-DARNITSA

Qualitative and quantitative composition:

active substance: furosemide;

1 ml of solution contains furosemide 10 mg;

List of excipients: sodium chloride, sodium hydroxide, water for injections.

Pharmaceutical form. Solution for injection.

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

Pharmacotherapeutic group. High-ceiling diuretics. Sulfonamides, plain.

ATC code C03C A01.

Pharmacological properties.

Pharmacodynamic properties.

Furosemide is a fast-acting loop diuretic that causes a relatively strong and short-term diuretic effect. Furosemide blocks the $\text{Na}^+\text{K}^+2\text{Cl}^-$ cotransporter located in the basal membranes of cells of the thick segment of the ascending part of Henle's loop: the effectiveness of the saluretic effect of furosemide, therefore, depends on whether the medicinal product enters to the tubules in the lumen by anion transport mechanism. The diuretic effect occurs as a result of inhibition of the reabsorption of sodium chloride in this segment of Henle's loop. As a result, fractional sodium excretion may reach 35 % glomerular sodium filtration. Secondary effects of increased sodium excretion are increased urinary excretion (due to the osmotically bound water) and increased distal tubular secretion of potassium. The excretion of calcium and magnesium ions also increases. Furosemide causes dose-dependent stimulation of renin-angiotensin-aldosterone system. In heart failure, furosemide leads to an acute decrease in cardiac overload (by narrowing of capacitance venous vessels). This early vascular effect is prostaglandin-mediated and occurs with adequate renal function with activation of renin-angiotensin system and intact prostaglandin synthesis. In addition, due to its inherent natriuretic effect, furosemide reduces the reactivity of blood vessels with respect to catecholamines, increased in patients with arterial hypertension.

Antihypertensive efficacy of furosemide is explained by an increased sodium excretion, decreased blood volume, and decreased response of vascular smooth muscles to stimulation with vasoconstrictors.

The onset of the diuretic effect is observed within 15 minutes after the intravenous dose of the medicinal product.

Dose-dependent increase in diuresis and natriuresis was observed in healthy volunteers receiving furosemide at a dose of 10–100 mg. The duration of action in healthy volunteers is approximately 3 hours after intravenous administration of 20 mg of furosemide.

In patients, the relationship between the concentrations of unbound (free) furosemide within the tubular organs (determined based on the rate of excretion of furosemide in urine) and the natriuretic

effect is expressed in the form of a sigmoid curve with a minimum effective rate of excretion of furosemide, which is approximately 10 micrograms per minute. Thus, continuous intravenous infusion of furosemide is more effective than repeated bolus injections. Moreover, apart from a certain bolus dose of the medicinal product, there is no significant increase in effect. The effect of furosemide is reduced, if there is an underestimated tubular secretion or the interaction of the medicinal product with albumin inside the tubules.

Pharmacokinetic properties.

The distribution volume 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 (more than 98 %) forms strong compounds with plasma proteins, especially with albumin.

Furosemide is excreted mainly in the form of an unmodified medicinal product by secretion into the proximal tubule. After intravenous administration, from 60 % to 70 % of the administered dose of furosemide is excreted in this way. The metabolite of furosemide – glucuronide – accounts for 10 – 20 % of the substances contained in urine. The residual dose is excreted in the feces, probably by biliary secretion.

The terminal half-life of furosemide after intravenous administration is approximately 1 to 1.5 hours. Furosemide is excreted into the breast milk; penetrates the placental barrier and slowly enters to the fetus. Furosemide is determined in the fetus or in the newborn in the same concentrations as in child's mother.

Renal disorders with renal failure, furosemide excretion is delayed, and the elimination half-life is elongated; the final elimination half-life could be up to 24 hours in patients with severe renal failure. In nephrotic syndrome, the reduced concentrations of plasma proteins lead to an increase in the concentration of unbound (free) furosemide. On the other hand, the effectiveness of furosemide in these patients is reduced due to binding to intratubular albumin and low tubular secretion.

Furosemide is difficult for dialysis in patients who undergo hemodialysis, peritoneal dialysis and chronic peritoneal dialysis on an outpatient basis.

Hepatic failure. In case of liver failure, the half-life of furosemide increases by 30 – 90 %, mainly due to the large volume of distribution. It should also be noted that in this group of patients, there is a wide variety of all pharmacokinetic parameters.

Congestive heart failure, severe arterial hypertension, elderly patients. The excretion of furosemide is delayed due to a decrease in renal function in patients with congestive heart failure, severe arterial hypertension and in elderly patients.

Premature and full-term newborns. Depending on the level of kidney formation, furosemide excretion may be delayed. Depending on the level of kidney formation, furosemide excretion may be delayed. The final half-life lasts less than 12 hours in fetuses older than 33 weeks after fertilization of the ootid. In infants 2 months and older, the final clearance is similar to that of adults.

Clinical particulars.

Therapeutic indications.

Edema in chronic congestive heart failure (if treatment with diuretics is necessary).

Edema in acute congestive heart failure.

Edema in chronic renal failure.

Acute renal failure, including pregnant women or during the childbirth.

Edema in liver diseases (if necessary, for supplementation treatment with aldosterone antagonists).

Hypertensive crisis (as a maintenance medicinal product).

Forced diuresis support.

Contraindications.

Hypersensitivity to furosemide or other components that contained in the medicinal product. Patients with allergy to sulfonamides (e.g. sulfonamide antibiotics or sulfonylurea) may have cross-sensitivity to furosemide.

Hypovolemia or dehydration.

Renal failure in the form of anuria in the absence of a therapeutic response to furosemide.

Renal failure due to the poisoning with nephrotoxic or hepatotoxic medicinal products.
Severe hypokalemia.
Severe hyponatremia.
Precoma or coma associated with hepatic encephalopathy.

Interaction with other medicinal products and other forms of interaction

Not recommended combinations.

In some cases, the administration of furosemide within 24 hours after administration of *chloral hydrate* may cause hot flushes, increased sweating, an excited state, nausea, high blood pressure and tachycardia. Therefore, concomitant use of furosemide and chloral hydrate is not recommended.

Furosemide may enhance the ototoxicity of aminoglycosides and other ototoxic medicinal products. Since this can lead to irreversible damage, these medicinal products should not be used concomitantly with furosemide.

Combinations requiring preventive action.

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

Furosemide reduces the excretion of lithium salts and may lead to an increase in serum lithium levels, resulting in an increased risk of lithium toxicity, including a greater risk of cardiotoxic and neurotoxic effects. Therefore, it is recommended that careful monitoring of lithium levels in patients receiving this combination therapy.

Patients receiving diuretics may suffer from severe arterial hypotension and impaired renal function, including cases of renal failure, especially when using an angiotensin-converting enzyme inhibitor (ACE inhibitor) or an angiotensin II receptor antagonist for the first time, or when using these medicinal products for the first time in an increased dose. It must be decided whether to temporarily stop administration of furosemide or, at least, reduce the dose of furosemide 3 days before the start of treatment, or increase the dose of an ACE inhibitor or angiotensin II receptor antagonist.

Risperidone: caution should be exercised, and the risks and benefits carefully considered before deciding on whether to administer the combination therapy or concomitant administration of furosemide or other potent diuretics.

Combinations to be used with caution.

Concomitant administration of *non-steroidal anti-inflammatory drugs (NSAIDs)*, including *acetylsalicylic acid*, may reduce the effect of furosemide. In patients with dehydration or hypovolemia, non-steroidal anti-inflammatory drugs may lead to acute heart failure. Under the influence of furosemide, the toxicity of salicylate may increase.

A decrease in the effectiveness of furosemide may occur after concomitant administration with phenytoin.

Administration of *corticosteroids*, *carbenoxolone*, *licorice root* in large doses and prolonged administration of laxatives increases the risk of hypokalemia.

Some electrolyte imbalances (such as hypokalemia, hypomagnesemia) may increase the toxicity of certain other drugs (e.g., *digitalis medicinal products and medicinal product that cause QT prolongation syndrome*).

If *antihypertensive medicinal products*, *diuretics*, or other medicinal products that tend to lower blood pressure are used simultaneously with furosemide, an even greater decrease in blood pressure (BP) should be expected.

Probenecid, methotrexate and other medicinal products which, similar to furosemide, are subject to significant tubular secretion in the kidneys, may reduce the effectiveness of furosemide. Conversely furosemide may decrease the excretion of these medicinal products by the kidneys. Treatment with high doses (in particular, both furosemide and other medicinal products) may lead to an increase in their levels in blood serum and an increased risk of adverse effects caused by furosemide or the use of concomitant therapy.

The effectiveness of antidiabetic medicinal products and sympathomimetics, which tend to increase blood pressure (e.g., epinephrine, norepinephrine), may decrease. The effect of curare-containing muscle relaxants or theophylline may be enhanced.

Increased harmful effects of nephrotoxic medicinal products on the kidneys are possible.

Impaired renal function may develop in patients receiving furosemide therapy and high doses of certain cephalosporins.

Concomitant administration of ciclosporin A and furosemide is associated with an increased risk of gouty arthritis secondary to hyperuricemia caused by furosemide, and impaired renal excretion of urates caused by ciclosporin.

Patients who belong to a high risk group for nephropathy due to radiocontrast substances, when treated with furosemide, there was a greater frequency of deterioration of renal function after radiocontrast agents compared with that in patients at high risk who underwent only intravenous hydration before radiocontrast agents were prescribed.

Special warnings and precautions for use.

During treatment with the medicinal product Furosemide-Darnitsa, a constant outflow of urine should be ensured. Patients with partial obstruction of the urine outflow require close attention, especially in the initial stages of treatment.

Treatment with the medicinal product Furosemide-Darnitsa requires regular medical monitoring of the patient. Particular careful monitoring is required:

- patients with arterial hypotension;
- patients at particular risk due to a significant decrease in blood pressure, e.g., patients with severe stenosis of the coronary arteries or blood vessels that supply the brain;
- patients with latent or severe diabetes mellitus;
- patients with gout;
- patients with hepatorenal syndrome, i.e. with functional renal failure, is associated with severe liver disease;
- patients with hypoproteinemia, for example, associated with nephrotic syndrome (the effect of furosemide can be weakened simultaneously with the potentiation of ototoxicity). Careful dose titration is necessary;
- premature babies (developing of nephrocalcinosis is possible/nephrolithiasis); kidney monitoring and renal ultrasonography are needed.

Regular monitoring of serum sodium, potassium, and creatinine is recommended during furosemide therapy. Particularly careful monitoring is necessary for patients at high risk for electrolyte imbalances or in the event of significant additional fluid loss (e.g., as a result of vomiting, diarrhea, or intense sweating). Hypovolemia or dehydration of a body, as well as any significant alterations of the electrolyte and acid-base balance, should be adjusted. This may require a temporary discontinuation of furosemide therapy.

Factors such as existing diseases (e.g., cirrhosis of the liver, heart failure), and concomitant administration of medicinal products and nutrition affect the development of electrolyte imbalance. For example, deficiency may result from vomiting or diarrhea.

During the administration of the medicinal product Furosemide-Darnitsa, it is advisable to recommend to eat foods with high potassium content (baked potatoes, bananas, tomatoes, spinach, dried fruits). It should be remembered that during the administration of the medicinal product Furosemide-Darnitsa, there may be a necessity for medication compensation of potassium deficiency. In placebo-controlled studies of risperidone among elderly patients with dementia, a higher mortality rate was observed in patients receiving furosemide simultaneously with risperidone, compared with patients who received only risperidone or only furosemide.

Caution should be exercised and the risks and benefits carefully considered before deciding on the use of such a combination of concomitant treatment with other powerful diuretics. Dehydration should be avoided.

Avoid the simultaneous use of alcohol and the medicinal product Furosemide-Darnitsa.

Fertility, pregnancy and lactation

Pregnancy. Furosemide crosses the placental barrier. It should not be prescribed during pregnancy, except in in situations, with critical conditions, with life-threatening conditions The medicinal product treatment during pregnancy requires monitoring the growth and development of the fetus.

Breastfeeding period. Furosemide passes into breast milk and may suppress lactation. Women should stop breast-feeding during treatment with furosemide.

Effects on ability to drive and use machines

When using the medicinal product Furosemide-Darnitsa, some adverse reactions (for example, an unexpected significant decrease in blood pressure) can interfere with the patient's ability to concentrate and the speed of his reaction.

Therefore, you should refrain from driving or working with other mechanisms for the period of treatment.

Posology and method of administration.

The dosage regimen is set by the doctor individually, depending on the severity of the disorders of the water-electrolyte balance, the value of glomerular filtration, and the severity of the patient's condition. In the process of using the medicinal product, the indicators of water-electrolyte balance should be adjusted taking into account the diuresis and the dynamics of the general condition of the patient.

Furosemide is administered intravenously only when oral administration is impractical or ineffective (e.g., in case of malabsorption in the intestine) or if a rapid effect is required. In the case of intravenous therapy, it is recommended to switch to oral therapy as soon as possible.

Continuous infusion of furosemide is generally preferred over repeated bolus injections to achieve optimal efficacy and inhibition of counter-regulation.

In cases where continuous infusion of furosemide is impractical for further treatment after the administration of one or more bolus doses, a further treatment regimen is preferred with the appointment of low doses, which are administered at short time intervals (about 4 hours), compared with large bolus doses, are administered at long intervals.

The maximum daily dose of furosemide is 1 500 mg for adults.

For children, the recommended dose of furosemide for parenteral administration is 1 m /kg body weight, but the maximum daily dose should not exceed 20 mg.

Special dosing recommendations.

The dosage for adults is generally based on the use of the recommendations below.

Edema in chronic congestive heart failure. The recommended initial dose of the medicinal product is 20 mg to 50 mg per day. If necessary, the dose could be adjusted depending on the therapeutic response of the patient. It is recommended to take a daily dose divided into 2 or 3 doses.

Edema in acute congestive heart failure. The recommended starting dose of the drug is 20 to 40 mg and is given as a bolus injection. If necessary, the dose could be adjusted depending on the therapeutic response of the patient.

Edema in chronic renal failure. The natriuretic effect of furosemide depends on a number of factors, including the severity of renal failure and sodium balance. Thus, it is impossible to accurately predict the effectiveness of the dose. Patients with chronic renal failure should carefully titrate the dose to ensure gradual initial fluid loss. For adult patients, this means the administration of such a dose that leads to a daily decrease in body weight of about 2 kg (about 280 mmol Na⁺).

In the case of intravenous administration, the dose of furosemide can be determined as follows: treatment begins with the introduction of a continuous intravenous infusion of 0.1 mg for 1 minute, then the infusion rate is increased every half hour depending on the patient's response.

In acute renal failure, before starting the use of furosemide, it is necessary to compensate hypovolemia, hypotension and significant electrolyte and acid-base imbalance.

It is recommended to switch from intravenous administration to oral administration as soon as possible.

Recommended initial dose of medicinal product is 40 mg and is given as an intravenous injection. If the appointment of this dose does not lead to the desired increase in fluid excretion, furosemide can be prescribed as a continuous intravenous infusion, starting with the introduction of 50 mg to 100 mg

of the drug in 1 hour.

Edema in liver disease. Furosemide is prescribed as an adjunct to therapy with aldosterone antagonists in cases where the use of aldosterone antagonists alone is insufficient. In order to prevent complications, such as orthostatic hypotension or electrolyte and acid-base disturbances, the dose should be carefully titrated to ensure a gradual initial loss of fluid. For adult patients, this means the administration of such a dose, which leads to a daily decrease in body weight by about 0.5 kg. If intravenous administration is absolutely necessary, the initial single dose is 20–40 mg.

Hypertensive crisis. The recommended starting dose of 20 mg to 40 mg is given as an intravenous bolus injection. If necessary, the dose could be adjusted depending on the therapeutic response of the patient.

Support of forced diuresis in case of poisoning. Furosemide is administered intravenously in addition to the administration of infusion of electrolyte solutions. The dose depends on the therapeutic response to furosemide. Fluid and electrolyte loss should be controlled before initiation and during treatment. In case of poisoning by acidic or alkaline substances, the excretion of fluid can be accelerated by alkalization or oxidation of urine, respectively.

The recommended starting dose is 20 mg to 40 mg and is given intravenously.

Special dosing recommendations.

Intravenous injection/infusion: in the case of intravenous administration, furosemide must be administered as a slow injection or infusion at a rate not exceeding 4 mg in 1 minute. In patients with severe hepatic impairment (serum creatinine > 5 mg/dL), it is recommended to infuse at a rate not exceeding 2.5 mg per minute

Intramuscular injection: the administration of the medicinal product by intramuscular injection should be limited only to exceptional cases when oral and intravenous administration is inappropriate. It should be noted that the route of administration of the medicinal product by intramuscular injection is not indicated for the treatment of acute conditions such as pulmonary edema.

Furosemide-Darnitsa should not be infused with other medicines!

Furosemide-Darnitsa is a solution with a pH level from 8.8 to 9.8, which has no buffer capacity. Thus, the active ingredient can precipitate at pH values below 7. In the case of dilution of this solution, attention should be paid to ensure that the pH of the diluted solution remains in the range from weakly alkaline to neutral.

0.9 % sodium chloride solution can be used as a solvent. It is recommended to apply diluted solutions as soon as possible.

Children.

For children, the dose should be reduced according to body weight (see section "Posology and method of administration").

Overdose.

Symptoms: clinical picture of acute or chronic overdose depends mainly on the degree and consequences of electrolyte and fluid loss and includes signs such as hypovolemia, dehydration, blood concentration, cardiac arrhythmias (including AV blockade and ventricular fibrillation). Symptoms of these disorders include severe arterial hypotension (that progresses to shock), acute renal failure, thrombosis, delirium, peripheral paralysis, apathy, and confusion.

Treatment: there are no specific antidotes for furosemide. Therapy is symptomatic.

Undesirable effects.

Ear and labyrinth disorders: hearing impairment, which is usually transient, especially in patients with renal failure, hypoproteinemia (e.g., in nephrotic syndrome) and/or in the case of too fast intravenous administration of furosemide. Cases of deafness, sometimes irreversible, have been reported following the oral or intravenous administration of furosemide. Tinnitus.

Gastrointestinal disorders: nausea, vomiting, diarrhea, acute pancreatitis.

Hepatobiliary disorders: cholestasis, increased levels of transaminases.

Renal and urinary disorders: tubulo-interstitial nephritis, increased urine volume, increased urinary sodium, increased urinary chlorine, urinary retention (in patients with partial obstruction of urine outflow), nephrocalcinosis/nephrolithiasis in preterm infants, renal failure.

Metabolism and nutrition disorders: electrolyte imbalance (including clinical manifestations), dehydration and hypovolemia, especially in the elderly, hyponatremia, hypochloremia, hypokalemia, hypocalcemia, hypomagnesemia, metabolic alkalosis, elevated blood triglycerides, elevated blood cholesterol, elevated blood cholesterol in the blood, increased levels of uric acid in the blood, gout attacks, increased levels of urea in the blood, decreased glucose tolerance, the course of diabetes can go from latent to severe, Barter pseudosyndrome on the background of improper and/or long-term use of furosemide.

Nervous system disorders: paresthesia, hepatic encephalopathy in patients with hepatocellular insufficiency.

Cardiac disorders: hypotension, including orthostatic hypotension, vasculitis, thrombosis.

Blood and lymphatic system disorders: hemoconcentration, thrombocytopenia, leukopenia, eosinophilia, agranulocytosis, aplastic anemia or hemolytic anemia.

Immune system disorders: severe anaphylactic and anaphylactoid reactions (including those accompanied by shock).

Skin and subcutaneous tissue disorders: pruritus, urticaria, rash, bullous dermatitis, erythema multiforme, pemphigoid, exfoliative dermatitis, purpura, photosensitivity reaction, Steven-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis and DRESS syndrome (medicinal product eruptions and eruptions).

General disorders and administration site conditions: fever, local reactions such as pain after an intramuscular injection.

Congenital and hereditary/genetic disorders: increased risk of obstruction of the ductus arteriosus, if furosemide is given to premature newborns during first weeks of life.

Shelf life 3 years.

Special precautions for storage

Keep out of reach of children in the original packaging at a temperature not exceeding 25° C. Do not freeze.

Nature and contents of container.

2 ml in ampoules; 10 ampoules in a blister strip; 1 contour cell pack in a pack; 2 ml ampoules; 5 ampoules in a blister strip; 2 contour cell packs 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 the last revision.

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