רופא/ה רוקח/ת נכבד/ה,

חברת ביואבניר מבקשת ליידע אתכם על עדכון העלון לרופא של התכשיר:

FUROVENIR 250 MG/25 ML (FUROSEMIDE 250 MG/25 ML)

<u>התוויה הרשומה לתכשיר בישראל :</u>

Furosemide is a potent diuretic indicated for use when a prompt and effective diuresis is required. Furosemide is appropriate for use in emergencies or where oral therapy is not feasible. The indications include cardiac, pulmonary, hepatic, and renal oedema.

<u>מהות העדכון:</u>

עדכוני בטיחות ועדכוני נוסח בהתאם לעלוני האסמכתא וכן התאמה לפורמט העלונים הנדרש לפי הנחיות משרד הבריאות.

העלון נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלו מודפס ע"י פניה לבעל הרישום ביואבניר בע"מ , דוד המלך 1 הרצליה פיתוח או בטלפון 09-9544129.

בכבוד רב,

לירון שמש

רוקחת ממונה

ביואבניר בע"מ

BioAvenir

עלון לרופא

FuroVenir 250 mg/25 ml (Solution for injection)

[…]

4.3 Contraindications

Hypersensitivity to amiloride, sulphonamides or sulphonamide derivatives.

Hypovolemia and dehydration (with or without accompanying hypotension) (see section 4.4).

Severe hypokalemia: severe hyponatremia (see section 4.4).

Comatose or pre-comatose states associated with hepatic cirrhosis (see section 4.4).

[…]

Impaired renal function with a creatinine clearance below 30ml/min per 1.73 m^2 body surface area (see section 4.4).

[…]

4.4 Special warnings and precautions for useConditions requiring correction before furosemide is started (see also section 4.3)

Hypotension.

Hypovolaemia.

Severe electrolyte disturbances – particularly hypokalemia, hyponatremia and acid-base disturbances.

Furosemide is not recommended in patients at high risk for radiocontrast nephropathy - it should not be used for diuresis as part of the preventative measures against radiocontrast-induced nephropathy.

Particular caution and/or dose reduction required:

Symptomatic hypotension leading to dizziness, fainting or loss of consciousness can occur in patients treated with furosemide, particularly in the elderly, patients on other medications which can cause hypotension and patients with other medical conditions that are risks for hypotension.

Elderly people (lower initial dose as particularly susceptible to side-effects - see section 4.2)

difficulty with micturition including prostatic hypertrophy (increased risk of urinary retention: consider lower dose). Closely monitor patients with partial occlusion of the urinary tract

[…]

adrenal disease

4.5 Interaction with other medicinal products and other forms of interaction

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Vasodilators – enhanced hypotensive effect with moxisylyte (thymoxamine) or hydralazine.

Other diuretics – profound diuresis possible when furosemide given with metolazone. Increased risk of hypokalemia with thiazides.

Renin inhibitors – aliskiren reduces plasma concentrations of furosemide.

Nitrates – enhanced hypotensive effect.

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Chelating agents – sucralfate may decrease the gastro-intestinal absorption of furosemide – the 2 drugs should be taken at least 2 hours apart.

NSAIDs – increased risk of nephrotoxicity. Indomethacin and ketorolac may antagonize the effects of furosemide (avoid, if possible, see section 4.4). NSAIDs may attenuate the action of furosemide and may cause acute renal failure in cases ofpre-existing hypovolaemia or dehydration.

Salicylates – effects may be potentiated by furosemide. Salicylic toxicity may be increased by furosemide.

Antibiotics – increased risk of ototoxicity with aminoglycosides, polymyxins or vancomycin - only use concurrently if compelling reasons. Increased risk of nephrotoxicity with aminoglycosides or cefaloridine. Furosemide can decrease vancomycin serum levels after cardiac surgery. Increased risk of hyponatremia with trimethoprim. Impairment of renal function may develop in patients receiving concurrent treatment with furosemide and high doses of certain cephalosporins.

Antidepressants – enhanced hypotensive effect with MAOIs. Increased risk of postural hypotension with TCAs (tricyclicantidepressants). Increased risk of hypokalemia with reboxetine.

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Antihistamines – hypokalemia with increased risk of cardiac toxicity

Antifungals – increased risk of hypokalemia and nephrotoxicity with amphotericin

Anxiolytics and hypnotics – enhanced hypotensive effect. Chloral or triclorfos may displace thyroid hormone from binding site.

CNS stimulants (drugs used for ADHD) – hypokalemia increases the risk of ventricular arrhythmias.
Corticosteroids – diuretic effect antagonized (sodium retention) and increased risk of hypokalemia.
Glychyrrizin - (contained in liquorice) may and increase the risk of developing hypokalemia.

Cytotoxics – increased risk of nephrotoxicity and ototoxicity with platinum compounds/cisplatin. Nephrotoxicity of cisplatin may be enhanced if furosemide is not given in low doses (e.g. 40 mg in patients with normal renal function) and with positive fluid balance when used to achieve forced diuresis during cisplatin treatment.

Anti-metabolites – effects of furosemide may be reduced by methotrexate and furosemide may reduce renal clearance of methotrexate.

Dopaminergics – enhanced hypotensive effect with levodopa.

Immunomodulators – enhanced hypotensive effect with aldesleukin. Increased risk of hyperkalaemia with cyclosporine and tacrolimus. Increased risk of gouty arthritis with cyclosporin

Muscle relaxants – enhanced hypotensive effect with baclofen or tizanidine. Increased effect of curare-like muscle relaxants.

Oestrogens – diuretic effect antagonized.

Progestogens (drosperidone) – increased risk of hyperkalemia.

Prostaglandins – enhanced hypotensive effect with alprostadil.

Sympathomimetics – increased risk of hypokalemia with high doses of beta 2 sympathomimetics.

Theophylline – enhanced hypotensive effect.

Probenecid – effects of furosemide may be reduced by probenecid and furosemide may reduce renal clearance of probenecid.

Anesthetic agents – general anesthetic agents may enhance the hypotensive effects of furosemide. The effects of curare may be enhanced by furosemide.

Alcohol – enhanced hypotensive effect.

Laxative abuse - increases the risk of potassium loss.

Others: Concomitant administration of aminoglutethimide may increase the risk of hyponatremia.

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4.7 Effects on ability to drive and use machines.

Reduced mental alertness, dizziness and blurred vision have been reported, particularly at the start of treatment, with dose changes and in combination with alcohol. Patients should be advised that if affected, they should not drive, operate machinery or take part in activities where these effects could put themselves or others at risk.

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4.8 Undesirable effects

MedDRA system organ class database	Frequency	Undesirable effects
Blood and lymphatic system disorders	Uncommon	Thrombocytopenia
	Rare	Eosinophilia Leukopenia Bone marrow depression (necessitates withdrawal of treatment). The haemopoietic status should therefore be regularly monitored.
	Very Rare	Aplastic anemia or hemolytic anemia Agranulocytosis
Nervous system disorders	Rare	Paresthesia Hyperosmolar coma
	Not known	Dizziness, syncope and loss of consciousness (caused by symptomatic hypotension).
Eye disorders	Uncommon	Visual disturbance
Ear and labyrinth disorders	Uncommon	Deafness (sometimes irreversible)
	Rare	Hearing disorders and tinnitus[1]
Cardiac arrhythmias	Uncommon	Cardiac arrhythmias
Hepatobiliary disorders	Not known	Cholestasis Intrahepatic (In isolated cases) Hepatic encephalopathy in patients with hepatocellular insufficiency may occur (see Section 4.3).
Vascular Disorder	Uncommon	Hypotension[2]
	Rare	Vasculitis
	Not Known	Thrombosis[8]
Skin and subcutaneous tissue disorders	Uncommon	Photosensitivity
	Rare	Skin and mucous membrane reactions may occasionally occur, e.g., Itching, urticaria, other rashes or bullous lesions, fever, hypersensitivity to light, exudative erythema multiforme (Lyell's syndrome and Stevens-Johnson syndrome), bullous exanthema, exfoliative dermatitis, purpura, AGEP (acute generalized exanthematous pustulosis) and DRESS (Drug rash with eosinophilia and systemic symptoms)

	Not Known	Bullous Pemphigoid
Metabolism and nutrition disorders	Not Known	Symptomatic electrolyte disturbances and Metabolic alkalosis[3] Metabolic acidosis[4] Hyponatremia[5] Hypokalemia[6] Reduction of serum HDL-cholesterol, elevation of serum LDL-cholesterol and elevation of serum triglycerides. During long term therapy they will usually return to normal within six months. Hypocalcemia and Hypomagnesemia[7] Hypovolemia and dehydration[8]
Psychiatric disorders	Rare	Mental disorder
Congenital, familial and genetic disorders	Not Known	Patent ductus arteriosus[9]
General disorders and administration site conditions	Uncommon	Fatigue
	Rare	Severe anaphylactic or anaphylactoid reactions (e.g., with shock) occurs rarely. fever Malaise
Gastrointestinal disorders	Uncommon	dry mouth, thirst, nausea, bowel motility disturbances, vomiting, diarrhea, constipation[10]
	Rare	Acute Pancreatitis
Renal and urinary disorders	Rare	Interstitial nephritis Acute renal failure Increased urine production, Urinary incontinence and urinary obstruction [11] Acute urine retention[12]
	Not known	Nephrocalcinosis/Nephrolithiasis has been reported in premature infants
Investigations	Uncommon	Blood creatinine increased and Blood urea increased[13]
	Not known	Transaminases increased (In isolated cases) Glucose tolerance decreased [14]

[1] Although usually transitory, may occur in rare cases, particularly in patients with renal failure, hypoproteinemia (e.g. in nephritic syndrome) and/or when intravenous furosemide has been given too rapidly.

[2] Furosemide may cause a reduction in blood pressure which, if pronounced may cause signs and symptoms such as impairment of concentration and reactions, light headedness, sensations of pressure in the head, headache, dizziness, drowsiness, weakness, disorders of vision, dry mouth, orthostatic intolerance.

[3] As with other diuretics, electrolytes and water balance may be disturbed as a result of diuresis after prolonged therapy. Furosemide leads to increased excretion of sodium and chloride and consequently increase excretion of water. In addition, excretion of other electrolytes (in particular potassium, calcium and magnesium) is increased. Symptomatic electrolyte disturbances and metabolic alkalosis may develop in the form of a gradually increasing electrolyte deficit or e.g. where higher furosemide doses are administered to patients with normal renal function, acute severe electrolyte losses

[4] The risk of this abnormality increases at higher dosages and is influenced by the underlying disorder (e.g. cirrhosis of the liver, heart failure), concomitant medication (see section 4.5) and diet.

[5] Sodium deficiency can occur; this can manifest itself in the form of confusion, muscle cramps, muscle weakness, loss of appetite, dizziness, drowsiness and vomiting.

[6] 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.

[7] Magnesium and calcium deficiency result very rarely in tetany and heart rhythm disturbances. Serum calcium levels may be reduced; in very rare cases tetany has been observed.

[8] The diuretic action of furosemide may lead to or contribute to hypovolemia and dehydration, especially in elderly patients. Severe fluid depletion may lead to hemoconcentration with a tendency for thromboses to develop.

[9] If furosemide is administered to premature infants (including those with respiratory distress syndrome) during the first weeks of life, it may increase the risk of persistent patent ductus arteriosus.

[10] Gastro-intestinal disorder such as nausea, malaise or gastric upset (vomiting or diarrhea) and constipation may occur.

but not usually severe enough to necessitate withdrawal of treatment.

[11] Increased urine production, urinary incontinence, can be caused or symptoms can be exacerbated in patients with urinary tract obstruction.

[12] Acute urine retention, possibly accompanied by complications, can occur for example in patients with bladder disorders, prostatic hyperplasia or narrowing of the urethra.

[13] As with other diuretics, treatment with furosemide may lead to transitory increase in blood creatinine and urea levels. Serum levels of uric acid may increase, and attacks of gout may occur

[14] Glucose tolerance may decrease with furosemide. In patients with diabetes mellitus this may lead to a deterioration of metabolic control; latent diabetes mellitus may become manifest. Insulin requirements of diabetic patients may increase.

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