Furesix® 40

Furosemide

FORMS AND PRESENTATION
Furesix® 40: Tablets: Box of 30.
COMPOSITION
Furesix® 40: Each tablet contains Furosemide 40mg.
Excipients: Lactose monohydrate, microcrystalline cellulose, mannitol, croscarmellose sodium, polyvinylpyrrolidone, talc, magnesium stearate.
PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic Group: Cardiovascular apparatus. Antihypertensives. Diuretics, Diuretics of loop;
ATC code: C03CA01
The evidence from many experimental studies suggests that furosemide acts along the entire nephron with the exception of the distal exchange site. The main effect is on the ascending limb of the loop of Henley with a complex effect on renal circulation. Blood-flow is diverted from the juxta-medullary region to the outer cortex.
The principle renal action of furosemide is to inhibit active chloride transport in the thick ascending limb. Re-absorption of sodium chloride from the nephron is reduced, hypotonic or isotonic urine is produced.
It has been established that prostaglandin (PG) biosynthesis and the renin-angiotensin system are affected by furosemide administration and that furosemide alters the renal permeability of the glomerulus to serum proteins.
Pharmacokinetic properties
Furosemide is rapidly but incompletely absorbed (60-70%) on oral administration and its effect is largely over within 4 hours. The optimal absorption site is the upper duodenum at pH 5.0. Furosemide is bound to plasma albumin and little biotransformation takes place. It is mainly eliminated via the kidneys (80-90%); a small fraction of the dose undergoes biliary elimination and 10-15% of the activity can be recovered from the faeces.
Renal insufficiency: In case of renal insufficiency, the elimination of furosemide is slower and its half-life is prolonged.
In case of nephrotic syndrome, the lower concentration of plasma proteins leads to higher concentrations of unconjugated (free) furosemide. Per On the other hand, the efficacy of furosemide is reduced in these patients, due to the intratubular albumin and decreased tubular secretion.
Furosemide is poorly dialysable in patients receiving hemodialysis, dialysis peritoneal or CAPD (Chronic Ambulatory Peritoneal Dialysis).
Hepatic insufficiency: In case of hepatic impairment, the half-life of furosemide is 30% to 90%. Elimination of furosemide is slowed due to reduced renal function in patients with congestive heart failure, severe hypertension or in the elderly.
INDICATIONS
Furesix® 40 is a potent diuretic with rapid action.
Furesix® 40 is indicated for:
• The treatment of fluid retention associated with heart failure, including left ventricular failure, cirrhosis of the liver and renal disease, including nephrotic syndrome.
• The treatment of mild to moderate hypertension when brisk diuretic response is required. Alone or in combination with other anti-hypertensive agents in the treatment of more severe cases.
• The treatment of oedema: diuresis lasts for approximately four hours following administration and hence the time of administration can be adjusted to suit the patient's requirements.
CONTRAINDICATIONS
- Hypersensitivity to furosemide, amiloride, sulphonamides or sulphonamide derivatives, and/or any of the excipients of the product.
- Hypovolemia and dehydration.
- Severe hypokalemia: severe hyponatremia.
- Comatose or pre-comatose states associated with hepatic cirrhosis.
- Anuria or renal failure with anuria not responding to furosemide, renal failure as a result of poisoning by nephrotoxic or hepatotoxic agents or renal failure associated with hepatic coma.
- Impaired renal function with a creatinine clearance below 30ml/min per 1.73 m^2 BSA.
- Addison's disease.
- Digitalis intoxication.
- Concomitant potassium supplements or potassium sparing diuretics.
- Porphyria
- Breast-feeding women.
PRECAUTIONS
Conditions requiring correction before furosemide is started: Hypotension, hypovolemia, 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.
• In patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
Particular caution and/or dose reduction required
• elderly patients.
• difficulty with micturition including prostatic hypertrophy (increased risk of urinary retention). Closely monitor patients with partial occlusion of the urinary tract.
• diabetes mellitus (latent diabetes may become overt: insulin requirements in established diabetes may increase: stop furosemide before a glucose tolerance test).
• pregnancy.
• gout.
• patients with hepatorenal syndrome.
• impaired hepatic or renal function.
• adrenal disease (contraindication in Addison's disease).
• hypoproteinemia e.g. nephrotic syndrome (effect of furosemide may be impaired and its ototoxicity potentiated).
• acute hypercalcemia (dehydration results from vomiting and diuresis). Treatment of hypercalcemia with a high dose of furosemide results in fluid and electrolyte depletion.
• patients who are at risk from a pronounced fall in blood pressure.
• premature infants (possible development of nephrocalcinosis/nephrolithiasis.
• Symptomatic hypotension (dizziness, fainting, loss of consciousness) can occur particularly in the elderly, patients on other medications which can cause hypotension and patients with other medical conditions that are risks for hypotension.
Laboratory monitoring requirements:
• *Serum sodium and serum potassium:* Particularly in the elderly or in patients liable to electrolyte deficiency, in patients with cirrhosis of the liver, those receiving concomitant treatment with corticosteroids, those with an unbalanced diet and those who abuse laxatives.
• *Renal function:* Frequent BUN (blood urea nitrogen) in first few months of treatment, periodically thereafter. Long-term/high-dose BUN should regularly be measured.
• *Glucose:* Exacerbation of existing carbohydrate intolerance or diabetes mellitus.
• *Other electrolytes:* Patients with hepatic failure/alcoholic cirrhosis are particularly at risk of hypomagnesia, as well as hypokalemia. During long-term therapy, magnesium, calcium, chloride, bicarbonate and uric acid should be regularly measured.
• *Serum cholesterol and triglycerides* may rise but usually return to normal within 6 months of starting furosemide.
Clinical monitoring requirements:
Regular monitoring for blood dyscrasias, liver damage and idiosyncratic reactions.
Concomitant use with risperidone
In risperidone placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3%; mean age 89 years, range 75-97 years) when compared to patients treated with risperidone alone (3.1%; mean age 84 years, range 70-96 years) or furosemide alone (4.1%; mean age 80 years, range 67-90 years).
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 affected should not drive, operate machinery or take part in activities where these effects could put them or others at risk.
PREGNANCY AND LACTATION
Pregnancy
There is clinical evidence of safety of the drug in the third trimester of human pregnancy & furosemide has been given after the first trimester of pregnancy for oedema, hypertension and toxemia of pregnancy without causing fetal or newborn adverse effects. However, furosemide crosses the placental barrier and should not be given during pregnancy unless there are compelling medical reasons.
Lactation
Furosemide is contraindicated as it passes into breast milk and may inhibit lactation.
DRUG INTERACTIONS
Antihypertensives – enhanced hypotensive effect possible with all types.
Antipsychotics –Avoid concurrent use with pimozide. Increased risk of ventricular arrhythmias with amisulpride or sertindole. Enhanced hypotensive effect with phenothiazines.
Anti-arrhythmics –risk of cardiac toxicity because of furosemide-induced hypokalemia. The effects of lidocaine, tocainide or mexiletine may be antagonized by furosemide.
Cardiac glycosides – hypokalemia and hypomagnesia increase the risk of cardiac toxicity.
Drugs that prolong Q-T interval – increased risk of toxicity with furosemide-induced electrolyte disturbances.
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. Contraindicated with potassium sparing - increased risk of hyperkaliemia.
Renin inhibitors – aliskiren reduces plasma concentrations of furosemide.
Nitrates – enhanced hypotensive effect.
Lithium - serum lithium levels may be increased when lithium is given concomitantly with furosemide, resulting in increased lithium toxicity, including increased risk of cardiotoxicity and neurotoxicity.
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. Indometacin and ketorolac may antagonize the effects of furosemide.
Salicylates – effects may be potentiated by furosemide.
Antibiotics – increased risk of ototoxicity with aminoglycosides, polymixins or vancomycin. 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 tricyclic antidepressants. Increased risk of hypokalemia with reboxetine.
Antidiabetics – hypoglycemic effects antagonized by furosemide.
Antiepileptics – increased risk of hyponatremia with carbamazepine. Diuretic effect

reduced by phenytoin.
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 and increased risk of hypokalemia
Glychyrrizin – (in liquorice) may increase the risk of developing hypokalemia.
Carbenoxolone -may increase the risk of developing hypokalemia.
Cytotoxics – increased risk of nephrotoxicity and ototoxicity with platinum compounds/cis-platin.
Anti-metabolites – effects of furosemide may be reduced by methotrexate and furosemide may reduce renal clearance of methotrexate.
Potassium salts – contraindicated - increased risk of hyperkaliemia.
Dopaminergics – enhanced hypotensive effect with levodopa.
Immunomodulators – enhanced hypotensive effect with aldesleukin. Increased risk of hyperkalemia with ciclosprin and tacrolimus. Increased risk of gouty arthritis with ciclosporin.
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 hyperkaliemia.
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.
Alcohol – enhanced hypotensive effect.
Laxative abuse - increases the risk of potassium loss.
Others: Concomitant administration of aminoglutethimide may increase the risk of hyponatremia.
Concomitant administration of colestyramine and colestipol with furosemide should be considered (administer 2 to 3 hours apart).

ADVERSE EFFECTS

Undesirable effects can occur with the following frequencies: very common (> 1/10), common (> 1/100, < 1/10), uncommon (> 1/1,000, < 1/100), rare (> 1/10,000, < 1,000) and very rare (< 1/10,000, including isolated reports).

Blood and lymphatic system disorders
Uncommon: thrombocytopenia.
Rare: Eosinophilia, leukopenia, bone marrow depression.
Very Rare: Aplastic anemia or hemolytic anemia, agranulocytosis.
Nervous system disorders
Rare: Paresthesia, hyperosmolar coma.
Not known: Dizziness, fainting and loss of consciousness.
Endocrine disorder
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.
Eye disorders
Uncommon: visual disturbance.
Ear and labyrinth disorders
Rare: Hearing disorders and tinnitus, usually transitory, may occur in patients with renal failure, hypoproteinemia and/or when intravenous furosemide has been given too rapidly.
Uncommon: Deafness.
Cardiac disorders
Uncommon: Cardiac arrhythmias.
Furosemide may cause a reduction in blood pressure which, may cause signs and symptoms (impairment of concentration and reactions, light headedness, sensations of pressure in the head, headache, dizziness, drowsiness, weakness, disorders of vision, dry mouth, orthostatic intolerance).
Hepatobiliary disorders
In isolated cases, intrahepatic cholestasis, an increase in liver transaminases or acute pancreatitis may develop. Hepatic encephalopathy in patients with hepatocellular insufficiency may occur.
Vascular Disorder
Rare: Vasculitis
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: Acute Generalized Exanthematous Pustulosis (AGEP)
Metabolism and nutrition disorders
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.
Metabolic acidosis can also occur; the risk increases at higher dosages.
Symptomatic electrolyte disturbances and metabolic alkalosis may develop when higher furosemide doses are administered to patients with normal renal function.
Sodium deficiency can occur; this can manifest itself in the form of confusion, muscle cramps/weakness, loss of appetite, dizziness, drowsiness and vomiting.
Potassium deficiency manifests itself in neuromuscular, intestinal, renal or cardiac symptoms. Severe potassium depletion can result in paralytic ileus, confusion, or coma.
Magnesium and calcium deficiency result very rarely in tetany and heart rhythm disturbances.
Nephrocalcinosis/Nephrolithiasis has been reported in premature infants.
Serum cholesterol and triglyceride levels may rise during furosemide treatment. They usually return to normal within six months.
Treatment with furosemide may lead to transitory increase in blood creatinine, urea levels and attacks of gout may occur.
The diuretic action of furosemide may lead to hypovolemia and dehydration, especially in elderly patients, thus hemoconcentration with a tendency for thromboses to develop.
General disorders and administration site conditions
Uncommon: Fatigue.
Rare: Severe anaphylactic or anaphylactoid reactions, fever, malaise.
Gastrointestinal disorders
Uncommon: dry mouth, thirst, nausea, bowel motility disturbances, vomiting, diarrhea, constipation.
Rare: Acute Pancreatitis.
Renal and urinary disorders
Uncommon: Serum creatinine and urea levels can be temporarily elevated.
Rare: Interstitial nephritis, acute renal failure.
Increased urine production, urinary incontinence (in patients with urinary tract obstruction).
Acute urine retention (in patients with bladder disorders, prostatic hyperplasia or narrowing of the urethra).
Pregnancy, puerperium and perinatal conditions
In premature infants with respiratory distress syndrome, administration of furosemide in the initial weeks after birth entails an increased risk of a persistent patent ductus arteriosus.
In premature infants, furosemide can be precipitated as nephrocalcinosis/kidney stones.
Rare complications may include minor psychiatric disturbances.

DOSAGE AND ADMINISTRATION

Adults and children over 12 years:
Oedema: Initially 40mg daily in the morning; ordinarily a prompt diuresis ensues and the starting dose can then be maintained or even reduced.
Diuresis lasts for approximately four hours following administration and hence the time of administration can be adjusted to suit the patient's requirements. Maintenance dose is 20mg daily or 40mg on alternate days, increased in resistant oedema to 80mg daily.
Hypertension: 20-40mg twice daily; if 40mg twice daily does not lead to a clinically satisfactory response, the addition of other antihypertensive agents, rather than an increase in the dose of furosemide should be considered.
Children under 12 years: A more suitable dosage form should be used in this age group.
Elderly: Furosemide is generally eliminated more slowly. The dosage should be titrated until the required response is achieved.
Method of Administration:
For oral administration.
Dosage adjustment may be necessary in patients with hypoproteinemia and/or liver dysfunction.

OVERDOSAGE

Signs and symptoms:
The clinical picture depends primarily on the extent and consequences of loss of electrolytes and fluids. (e.g. hypovolemia, dehydration, hemoconcentration, cardiac arrhythmia - including A-V block and ventricular fibrillation). Symptoms of these changes include: severe hypotension (and progression to shock), acute renal failure, thrombosis, delirious states, flaccid paralysis, apathy and confusion.
Treatment:
There is no known specific antidote for furosemide. Attempts may be made to limit more extensive systemic absorption of active substance, through measures such as gastric lavage or other measures intended to reduce absorption (e.g. use of activated charcoal).
Changes in clinically relevant fluid and electrolyte balance must be corrected. Together with the prevention and treatment of serious complications resulting from such imbalances and other effects on the body, this corrective action may require intensive generalist and specific medical monitoring, as well as of therapeutic measures.

STORAGE CONDITIONS

Store below 30°C.
Keep in original pack in intact conditions.

Marketing Authorization Holder and Manufacturer
Benta S.A.L.
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