This leaflet format has been determined by the Ministry of Health and the content thereof has been checked and approved.” Date of approval: February 2011.

**Composition**

Each ampoule of 2 ml contains:

*Active Ingredient*
- Furosemide 20 mg

*Other Ingredients*
- Sodium chloride, sodium hydroxide, water for injection.

Sodium content: 7.7 mg per ampoule of 2 ml.

**Action**

Furosemide is a potent diuretic which inhibits the reabsorption of sodium at the proximal and distal tubules, as well as the ascending limb of Henle's loop. It is characterized by a high degree of efficacy and rapid onset of action, with comparatively short duration.

The onset of diuresis is within 5 minutes following i.v. administration, and somewhat longer after i.m. administration. The peak effect occurs within the first 30 minutes, and the duration of diuretic effect is approximately 2 hours.

**Indications**

Fusid injection is indicated when a rapid onset and an intense diuresis is desired in the following clinical situations:
- Treatment of edema associated with congestive heart failure, cirrhosis of the liver, and renal disease, including the nephrotic syndrome.
- Adjunctive therapy in acute pulmonary edema.
- Fusid injection is also indicated when oral therapy is precluded, as in impairment of gastrointestinal absorption, and where oral administration is not practical for any reason.

**Contraindications**

Known hypersensitivity to furosemide or sulfonamides.
- Electrolyte deficiency (e.g. severe hypokalaemia, severe hyponatraemia).
- Hypovolaemia, dehydration
- Renal failure due to nephrotoxic or hepatotoxic agents.
- Renal failure associated with hepatic coma.
- Pre-comatose and comatose states associated with hepatic encephalopathy/liver cirrhosis.
- Anuria or renal failure with anuria not responding to furosemide.
- Breastfeeding.

As furosemide may be capable of displacing bilirubin from albumin at least "in vitro", it should not be administered to jaundiced newborn infants or to infants suffering from diseases (e.g. Rh incompatibility, familial non-hemolytic jaundice, etc.) with the potential of causing hyperbilirubinemia and possibly kernicterus.
Warnings

FUROSEMIDE IS A POTENT DIURETIC WHICH IF GIVEN IN EXCESSIVE AMOUNTS CAN LEAD TO A PROFOUND DIURESIS WITH WATER AND ELECTROLYTE DEPLETION. THEREFORE, CAREFUL MEDICAL SUPERVISION IS REQUIRED, AND DOSE AND DOSE SCHEDULE HAVE TO BE ADJUSTED TO THE INDIVIDUAL PATIENT'S NEEDS.

Note: Steps should be taken to correct hypotension or hypovolemia before commencing therapy.

In patients with hepatic cirrhosis and ascites, initiation of therapy with furosemide is best carried out in a hospital. In hepatic coma and states of electrolyte depletion, therapy should not be instituted until the basic condition is improved. Sudden alterations of fluid and electrolyte balance in patients with cirrhosis may precipitate hepatic coma. Therefore, strict observation is necessary during the period of diuresis. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis.

If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, the drug should be discontinued.

Patients with prostatic hypertrophy or impairment of micturition have an increased risk of developing acute retention.

Cases of tinnitus and reversible or irreversible hearing impairment have been reported. Usually, reports indicate that furosemide ototoxicity is associated with rapid injection, severe renal impairment, doses exceeding several times the usual recommended dose, or concomitant therapy with aminoglycoside antibiotics, ethacrynic acid or other ototoxic drugs. If high-dose parenteral therapy is to be used, controlled intravenous infusion is recommended (for adults, an infusion rate not exceeding 4 mg furosemide per minute has been used).

Use in Pregnancy

Safety of use in pregnancy has not been established. Furosemide should be used during pregnancy only if the potential benefit to the mother outweighs the possible risk to the fetus. Treatment during pregnancy requires monitoring of fetal growth because of the potential for higher birth weights.

Furosemide has been shown to cause unexplained maternal deaths and abortions in rabbits at 2, 4 and 8 times the maximal recommended human dose.

Use in Breastfeeding

(see Contraindications)

Furosemide appears in breast milk. Therefore, having taken into account the importance of the drug to the mother, either discontinue nursing or discontinue the drug.

Furosemide may inhibit lactation.

Use in Pediatrics

Renal calcifications have occurred in some severely premature infants treated with intravenous furosemide for edema due to patent ductus arteriosus and hyaline membrane disease.

Nephrocalcinosis/nephrolithiasis has also been observed in children under 4 years of age with no history of prematurity who have been treated chronically with furosemide. Monitor renal function, and renal ultrasonography should be considered, in pediatric patients receiving furosemide.

If furosemide is administered to premature infants during the first weeks of life, it may increase the risk of persistence of patent ductus arteriosus.
The concurrent use of chlorothiazide has been reported to decrease hypercalciuria and to dissolve some calculi.

Hearing loss in neonates has been associated with the use of furosemide injection.

**Use in the Elderly**

Controlled clinical studies of furosemide did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for the elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Elderly patients may be more sensitive to the hypotensive and electrolyte effects of diuretics. The excessive diuresis induced by the loop diuretic, furosemide, may result in dehydration and in reduction of blood volume, with circulatory collapse and with the possibility of vascular thrombosis and embolism. Elderly patients are also more likely to have age-related renal function impairment. Adjustment of dosage or of the dosing interval is required.

**Adverse Reactions**

Adverse reactions are categorized below by organ system and listed by decreasing severity.

**Gastrointestinal System Reactions**

(1) hepatic encephalopathy in patients with hepatocellular insufficiency (2) pancreatitis, (3) jaundice (intrahepatic cholestatic jaundice), (4) increased liver enzymes, (5) anorexia, (6) oral and gastric irritation, (7) cramping, (8) diarrhea, (9) constipation, (10) nausea, (11) vomiting.

**Systemic Hypersensitivity Reactions**

(1) Severe anaphylactic or anaphylactoid reactions (e.g. with shock), (2) systemic vasculitis, (3) interstitial nephritis, (4) necrotizing angitis.

**Central Nervous System Reactions**

(1) tinnitus and hearing loss, (2) paresthesias, (3) vertigo, (4) dizziness, (5) headache, (6) blurred vision, (7) xanthopsia.

**Hematologic Reactions**

(1) aplastic anemia, (2) thrombocytopenia, (3) agranulocytosis, (4) hemolytic anemia, (5) leucopenia, (6) anemia, (7) eosinophilia.

**Dermatologic-Hypersensitivity Reactions**

(1) exfoliative dermatitis, (2) bullous pemphigoid, (3) erythema multiforme, (4) purpura, (5) photosensitivity, (6) urticaria, (7) rash, (8) pruritus, (9) Stevens-Johnson Syndrome, (10) toxic epidermal necrolysis.

**Cardiovascular Reactions**

(1) Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates, or narcotics, (2) increase in cholesterol and triglyceride serum levels.

**Other Reactions**

(1) Hyperglycemia, (2) glycosuria, (3) hyperuricemia, (4) muscle spasm, (5) weakness, (6) restlessness, (7) urinary bladder spasm, (8) thrombophlebitis, (9) fever.
Whenever adverse reactions are moderate or severe, furosemide dosage should be reduced or therapy withdrawn.

**Miscellaneous**

Transient pain at the injection site following IM injection. Blood urea nitrogen (BUN) levels may be increased. Serum calcium, magnesium, potassium and sodium levels may be decreased.

**Metabolism and Nutrition Disorders:** Transitory increases in blood creatinine and urea levels, increase in cholesterol and triglyceride serum levels, increase in uric acid serum levels and attacks of gout, decrease of glucose tolerance.

**Vascular Disorders:** Hypotension including orthostatic hypotension, tendency for thromboses.

**Congenital and Familiar/Genetic Disorders:** Increased risk of persistence of patent ductus arteriosus when furosemide is administered to premature infants during the first weeks of life.

**Precautions**

Where indicated, steps should be taken to correct hypotension or hypovolemia before commencing therapy.

Excessive diuresis may result in dehydration and reduction in blood volume with circulatory collapse, together with the possibility of vascular thrombosis and embolism, particularly in elderly patients.

Electrolyte depletion may occur during therapy, especially in patients receiving higher doses and a restricted salt intake. Frequent serum electrolyte, CO₂ and BUN determinations should be performed during the first few months of therapy and periodically thereafter, in order to correct abnormalities or if necessary, withdraw the drug temporarily.

Furosemide may lower serum calcium levels and rare cases of tetany have been reported. Accordingly, periodic serum calcium levels should be obtained.

Hypokalemia may develop with furosemide especially with brisk diuresis, inadequate oral electrolyte intake, concomitant use of laxatives, when liver cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Digitalis therapy may exaggerate metabolic effects of hypokalemia, especially myocardial effects.

All patients receiving furosemide therapy should be observed for these signs or symptoms of fluid or electrolyte imbalance (hyponatremia, hypochloremic alkalosis, hypokalemia, hypomagnesemia or hypocalcemia): dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, patients who are at risk from a pronounced fall in blood pressure, oliguria, tachycardia, arrhythmia, or gastrointestinal disturbances such as nausea and vomiting. Increases in blood glucose and alterations in glucose tolerance tests (with abnormalities of the fasting and 2-hour postprandial sugar) have been observed, and rarely, precipitation of diabetes mellitus has been reported.

In patients with severe symptoms of urinary retention (because of bladder emptying disorders, prostatic hyperplasia, urethral narrowing), the administration of furosemide can cause acute urinary retention related to increased production and retention of urine. Thus, these patients require careful monitoring, especially during the initial stages of treatment. In patients at high risk for radiocontrast nephropathy furosemide can lead to a higher incidence of deterioration in renal function after receiving radiocontrast compared to high-risk patients who received only intravenous hydration prior to receiving radiocontrast.

In patients with hypoproteinemia (e.g., associated with nephrotic syndrome) the effect of furosemide may be weakened and its ototoxicity potentiated.
Asymptomatic hyperuricemia can occur, and gout may rarely be precipitated. Patients allergic to sulfonamides may also be allergic to furosemide. The possibility exists of exacerbation or activation of systemic lupus erythematosus. Serum cholesterol and triglyceride levels may rise during furosemide treatment.

Careful monitoring is also necessary in:
- patients with hypotension.
- patients who are at risk from a pronounced fall in blood pressure.
- patients where latent diabetes may become manifest or the insulin requirements of diabetic patients may increase.
- patients with gout
- patients with hepatorenal syndrome
- patients with hypoproteinaemia, e.g. associated with nephritic syndrome (the effect of furosemide may be weakened and its ototoxicity potentiated). Cautious dose titration is required.
- premature infants (possible development nephrocalcinosis/nephrolithiasis; renal function must be monitored and renal ultrasonography performed).

As with many other drugs, patients should be observed regularly for the possible occurrence of blood dyscrasias, liver damage, or other idiosyncratic reactions.

In patients who are at high risk for radiocontrast nephropathy, furosemide is not recommended to be used for diuresis as part of the preventative measures against radiocontrast-induced nephropathy.

**Drug Interactions**

**Furosemide/Other Antihypertensive Drugs:** Furosemide may intensify the therapeutic effect of other antihypertensive drugs. Concurrent administration requires dosage adjustment.

**Furosemide/Salicylates in High Doses:** Furosemide and salicylates have competitive renal excretory sites. Therefore patients receiving high doses of salicylates concomitantly administered with furosemide, such as in rheumatic diseases, may experience salicylate toxicity in lower furosemide doses than usual. Therefore, caution should be exercised when administering this combination.

**Furosemide/Ototoxic and/or Nephrotoxic Medications** Concurrent and/or sequential administration of furosemide with ototoxic and/or nephrotoxic medications such as parenteral amphotericin B, aminoglycoside antibiotics, the cephalosporin antibiotics cephaloridine and cephalothin, parenteral amphotericin, and cisplatin, should be avoided because of the potential for these toxicities being increased. This is especially important in patients presenting with renal function impairment. Impairment of renal function may develop in patients receiving concurrent treatment with furosemide and high doses of certain cephalosporins.

**Furosemide/Cardiac Glycosides:** Concurrent use may increase the possibility of digitalis toxicity associated with hypokalemia.

**Furosemide/Risperidone:** Caution should be exercised and the risks and benefits of the combination or co-treatment with furosemide or with other potent diuretics should be considered prior to the decision to use.

In risperidone placebo controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone when compared to patients treated with risperidone alone or furosemide alone. Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings. No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Cautions should be exercised and the risks and benefits of this combination or co-treatment should be considered prior to the decision to use. Dehydration should be avoided.
**Furosemide/ACE Inhibitors/Angiotensin II Receptor Antagonists:** A marked fall in blood pressure and deterioration in renal function may be seen when ACE inhibitors or angiotensin II receptor antagonists are added to furosemide therapy, or their dose level increased. The dose of furosemide should be reduced for at least three days, or the drug stopped, before initiating the ACE inhibitor or angiotensin II receptor antagonist or increasing their dose.

**Furosemide/Carbamazepine/Aminoglutethimide:** Concomitant administration of carbamazepine or aminoglutethimide may increase the risk of hyponatremia.

**Furosemide/Hypoglycemics:** Furosemide may raise blood glucose levels or interfere with the hypoglycemic effects of these agents. For adult-onset diabetics, dosage adjustment of hypoglycemic medications may be necessary during and after therapy.

**Furosemide/Antigout Medications:** Furosemide may raise the level of blood uric acid. Dosage adjustment of antigout medications may be necessary to control hyperuricemia and gout.

**Furosemide/Corticosteroids or Corticotropin (ACTH)/Carbenoxolone/Liquorice/β₂ Sympathomimetics in Large Amounts/Prolonged Use of Laxatives, Reboxetine and Amphotericin:** Concurrent use of corticosteroids, carbenoxolone, liquorice, β₂ sympathomimetics in large amounts, prolonged use of laxatives, reboxetine and amphotericin may increase the risk of developing hypokalemia.

**Furosemide/Probenecid/Methotrexate:** Probenecid, methotrexate and other drugs which, like furosemide, undergo significant renal tubular secretion may reduce the effect of furosemide. Conversely, furosemide may decrease renal elimination of these drugs. In case of high-dose treatment (in particular, of both furosemide and the other drugs), this may lead to increased serum levels and an increased risk of adverse effects due to furosemide or the concomitant medication.

**Furosemide/Ciclosporin:** Concomitant use of ciclosporin and furosemide is associated with increased risk of gouty arthritis.

**Furosemide/Lithium Salts:** Concurrent use may provoke lithium toxicity because of reduced renal clearance. It is not recommended unless the patient can be closely monitored.

**Furosemide/Alcohol/Barbiturates/Narcotics:** Orthostatic hypotension due to furosemide may be aggravated by alcohol, barbiturates or narcotics.

**Furosemide/Indomethacin:** Literature reports indicate that co-administration of indomethacin may reduce the natriuretic and antihypertensive effects of furosemide in some patients by inhibiting prostaglandin synthesis. Indomethacin may also affect plasma renin levels, aldosterone excretion, and renin profile evaluation. Patients receiving both indomethacin and furosemide should be observed closely to determine if the desired diuretic and/or antihypertensive effect of furosemide is achieved.

**Furosemide/Other Non-Steroidal Anti-Inflammatory Agents (NSAIAs):** There are case reports of patients who developed increased BUN, serum creatinine, and serum potassium levels, and weight gain when furosemide was used in conjunction with NSAIAs.

**Furosemide/Tubocurarine:** Furosemide has a tendency to antagonize the skeletal muscle relaxing effect of tubocurarine and may potentiate the action of succinylcholine.

**Furosemide/Norepinephrine:** Furosemide may decrease arterial responsiveness to norepinephrine.

**Furosemide/Amiodarone:** Concurrent use may lead to an increased risk of arrhythmias associated with hypokalemia.

**Furosemide/Theophyllines:** Concurrent administration may lead to increased diuresis.

**Furosemide/Hydantoins (e.g. Phenytoin):** Concurrent administration may reduce the efficacy of furosemide.
**Furosemide/Chloral Hydrate:** In isolated cases intravenous administration of furosemide within 24 hours of taking chloral hydrate may lead to flushing, sweating attacks, restlessness, nausea, increase in blood pressure and tachycardia. Use of furosemide concomitantly with chloral hydrate is, therefore, not recommended.

**Furosemide/Metolazone:** Severe diuresis may occur if metolazone is administered concomitantly.

**Furosemide/Antidiabetics:** The effects of antidiabetic drugs may be reduced.

**Furosemide/Chlorothiazides:** The concurrent use of furosemide with chlorothiazide has been reported to decrease hypercalciuria and to dissolve some calculi.

**Oral Furosemide/Sucralfate:** Simultaneous administration of sucralfate and furosemide tablets may reduce the natriuretic and antihypertensive effects of furosemide. Patients receiving both drugs should be observed closely to determine if the desired diuretic and/or antihypertensive effect of furosemide is achieved. The intake of furosemide and sucralfate should be separated by at least two hours.

**Effects on Ability to Drive and Use Machines**
Reduced mental alertness may impair ability to drive or operate dangerous machinery.

**Diagnostic Interference**
Serum electrolytes (particularly potassium), CO₂, creatinine and BUN should be determined frequently during the first few months of furosemide therapy and periodically thereafter.

Serum and urine electrolyte determinations are particularly important when the patient is vomiting profusely or receiving parenteral fluids. Abnormalities should be corrected or the drug temporarily withdrawn. Other medications may also influence serum electrolytes.

Reversible elevations of BUN may occur and are associated with dehydration, which should be avoided, particularly in patients with renal insufficiency.

Urine and blood glucose should be checked periodically in diabetics receiving furosemide, even in those suspected of latent diabetes (including patients where latent diabetes may become manifest or the insulin requirements of diabetic patients may increase).

Furosemide may lower serum levels of calcium (rarely cases of tetany have been reported) and magnesium. Accordingly, serum levels should be determined periodically.

**Information for Patients**
Patients receiving furosemide should be advised that they may experience symptoms from excessive fluid and/or electrolyte losses. The postural hypotension that sometimes occurs can usually be managed by getting up slowly. Potassium supplements and/or dietary measures may be needed to control or avoid hypokalemia.

Patients with diabetes mellitus should be told that furosemide may increase blood glucose levels and thereby affect urine glucose tests. The skin of some patients may be more sensitive to the effects of sunlight while taking furosemide.

Hypertensive patients should avoid medications that may increase blood pressure, including over-the-counter products for appetite suppression and cold symptoms.

**Dosage and Administration**

*Parenteral drug products should be inspected visually for particulate matter and discoloration, prior to administration, whenever solution and container permit.*
Route of administration: intramuscular or intravenous

Since furosemide is a potent diuretic which, if given in excessive amounts, can lead to profound diuresis with water and electrolyte depletion, careful medical supervision is required. Dosage should be adjusted to the individual needs of each patient.

**Adults**

**Edema**

The usual initial dose is 20-40 mg, administered as a single dose, injected intramuscularly or intravenously. The intravenous injection should be administered slowly (over 1-2 minutes). If the patient's response is unsatisfactory, the following is recommended:

- a second dose may be administered in the same manner 2 hours later after the first dose.
- alternatively, the dose may be raised by increments of 20 mg administered not sooner than 2 hours after the previous dose, until the desired diuretic effect has been obtained.

This individually-determined dose should then be administered once or twice daily. If the high dose parenteral therapy is chosen, the drug should be administered as a controlled intravenous infusion at a rate not exceeding 4 mg/min.

**Acute Pulmonary Edema**

The usual initial dose is 40 mg, injected intravenously. The injection should be administered slowly (over 1-2 minutes). If a satisfactory response does not occur within 1 hour, the dose may be increased to 80 mg, administered intravenously (over 1-2 minutes).

**Infants and Children**

The usual initial dose injected intramuscularly or intravenously is 1 mg/kg body weight. It should be administered slowly, and under close medical supervision. If the diuretic response after the initial dose is unsatisfactory, dosage may be increased by 1 mg/kg body weight administered not sooner than 2 hours after the previous dose, until the desired diuretic effect has been obtained. Doses greater than 6 mg/kg body weight are not recommended.

**Overdosage**

**Manifestations**

The principal signs and symptoms of overdose with furosemide are dehydration, blood volume reduction, hypotension, electrolyte imbalance, hypokalemia and hypochloremic alkalosis, and are extensions of the diuretic action.

The acute toxicity of furosemide has been determined in mice, rats, and dogs. In all three, the oral LD 50 exceeded 1000 mg/kg body weight while the intravenous LD 50 ranged from 300 to 680 mg/kg. The acute intragastric toxicity in neonatal rats is 7 to 10 times that of adult rats. The concentration of furosemide in biological fluid associated with toxicity or death is not known.
Treatment
Treatment of overdosage is supportive and consists of replacement of excessive fluid and electrolyte losses. Serum electrolytes, carbon dioxide level and blood pressure should be determined frequently. Adequate drainage must be assured in patients with urinary bladder outlet obstruction (such as prostatic hypertrophy). Hemodialysis does not accelerate furosemide elimination.

Drug Registration No.: 052 74 24464 21.

Storage
Store below 25°C.
Store in the original container in order to protect from light.

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