SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FUROMID 20 mg/2 ml IM/IV Ampoules
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule solution of 2 ml contains
Active substance:
Furosemide……...20 mg

Excipients:
Sodium chloride……15 mg
Sodium hydroxide……6 mg
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
Clear solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Fluid retention associated with chronic congestive heart failure (if diuretic treatment is required)
- Fluid retention associated with acute congestive heart failure
- Fluid retention associated with chronic renal failure
- Maintenance of fluid extraction in acute renal failure, including that due to pregnancy or burns
- Fluid retention associated with nephrotic syndrome (if diuretic treatment is required)
- Fluid retention associated with liver disease (if necessary to supplement treatment with aldosterone antagonists)
- Hypertension
- Hypertensive crisis (as a supportive measure)
- Support of forced diuresis

4.2 Posology and method of administration

Posology and frequency and duration of administration
The dose used must be the lowest that is sufficient to achieve the desired effect.

Furosemide is given intravenously only when oral administration is not feasible or is ineffective (e.g. in impaired intestinal absorption) or if a rapid effect is required.
If intravenous therapy is used, it is recommended that transfer to oral therapy be carried out as soon as possible.

To achieve optimum efficacy and suppress counter-regulation, a continuous FUROMID infusion is generally to be preferred to repeated bolus injections.

Where continuous FUROMID infusion is not feasible for follow-up treatment after one or several

acute bolus doses, a follow-up regimen with low doses given at short intervals (approximately 4 hours) is to be preferred to a regimen with higher bolus doses at longer intervals.

In adults, the recommended maximum daily dose of FUROMID for both oral and intravenous administration is 1500 mg.

The duration of treatment depends on the indication and is determined on an individual basis by physician.

Route of administration:
Intravenous injection/infusion:
Intravenous FUROMID must be injected or infused slowly; a rate of 4 mg/minute must not be exceeded. In patients with severe impairment of renal function (serum creatinine >5 mg/dl), it is recommended that an infusion rate of 2.5 mg /minute is not exceeded.

In order to dilute the concentration of 10 mg/ml of FUROMID to a concentration of 1 mg/ml, 0.9% w/v sodium chloride solution for injection or Ringer Lactate solution for injection should be used directly. Diluted solutions should be used as soon as possible. The infusion solution should be prepared in aseptic conditions and by professional healthcare professionals. FUROMID should not be added to a flowing infusion solution and should not be used as an infusion with any other medication. Except for the conditions and diluents given in product information, no other application method and/or different or additional drugs should be used.

Intramuscular injection:
Intramuscular administration must be restricted to exceptional cases where neither oral nor intravenous administration is feasible. It must be noted that intramuscular injection is not suitable for the treatment of acute conditions such as pulmonary edema.

FUROMID must not be mixed with other drugs in the same injection syringe.

FUROMID has a pH of about 9; it has no buffering capacity. Therefore, the active ingredient may precipitate at pH values <7. If this solution is to be diluted, care must be taken to ensure that the pH of the solution is within the slightly alkaline to neutral range.

Diluted solutions should be used as soon as possible.

Additional information on special populations:
Renal/Hepatic impairment:
Fluid retention associated with chronic renal impairment:
The natriuretic response to furosemide depends on a number of factors, including severity of renal failure and the sodium balance, and, therefore, the effect of a dose cannot be accurately predicted. In patients with chronic renal failure, the dose must be carefully titrated so that the initial loss of fluid is gradual. For adults, this means a dose, which leads to a loss of approx. 2 kg body weight (approx. 280 mmol Na+) per day.

The recommended initial oral dose is 40 mg to 80 mg daily. This may be adjusted as necessary according to response. The total daily dose may be given as a single dose or two divided doses.

In dialysis patients, the usual oral maintenance dose is 250 mg to 1500 mg daily.

In intravenous treatment, the dose of FUROMID may be determined by starting with a continuous intravenous infusion of 0.1 mg per minute and then gradually increasing the rate every half hour according to response.

Maintenance of fluid extraction in acute renal impairment:
Hypovolemia, hypotension, and significant electrolyte and acid-base imbalances must be corrected before starting furosemide. It is recommended that transfer from the intravenous to the oral route of administration is carried out as soon as possible.

The recommended initial dose is 40 mg given as an intravenous injection. If this does not lead to the desired increase in fluid excretion, FUROMID may be given as a continuous intravenous infusion, starting with a rate of 50 mg to 100 mg per hour.

Fluid retention associated with nephrotic syndrome:
The recommended initial oral dose is 40 mg to 80 mg daily. This may be adjusted as necessary according to response. The total daily dose may be given as a single dose or several divided doses (see section 4.4).

Hepatic impairment
Fluid retention associated with liver disease
FUROMID is used to supplement treatment with aldosterone antagonists in cases where these alone are not sufficient. In order to avoid complications such as orthostatic intolerance or electrolyte and acid-base imbalances, the dose must be carefully titrated so that the initial loss of fluid is gradual. For adults, this means a dose, which leads to a loss of approximately 0.5 kg body weight per day.

The recommended initial oral dose is 20 mg to 80 mg daily. This may be adjusted as necessary according to response. The daily dose may be given as a single dose or divided doses. If intravenous treatment is absolutely necessary, the initial single dose is 20 mg to 40 mg.

Other
Fluid retention associated with chronic congestive heart failure
The recommended initial oral dose is 20 mg to 80 mg daily. This may be adjusted as necessary according to response. It is recommended that the daily dose is given as 2 or 3 divided doses.

Fluid retention associated with acute congestive heart failure
The recommended initial dose is 20 to 40 mg given as an intravenous bolus injection. The dose may be adjusted as necessary according to response.

Hypertension
FUROMID can be used alone or in combination with other antihypertensive agents.
The usual oral maintenance dose is 20 mg to 40 mg daily. In hypertension associated with chronic renal failure, higher doses may be required.

Hypertensive crisis
The recommended initial dose of 20 mg to 40 mg is given as an intravenous bolus injection. This may be adjusted as necessary according to response.

Support of forced diuresis in poisoning

FUROMID is given intravenously in addition to infusions of electrolyte solutions. The dose is dependent on the response to FUROMID. Fluid and electrolyte losses must be corrected before and during treatment. In case of poisoning with acid or alkaline substances, elimination can be increased further by alkalization or acidification respectively, of the urine.

The recommended initial dose is 20 mg to 40 mg given intravenously.

Pediatric population
In infants and children under 15 years of age, FUROMID should only be used parenterally in exceptionally life-threatening situations. The average daily dose for parenteral administration is 0.5 mg/kg body weight. Exceptionally, furosemide can be administered intravenously at up to 1 mg/kg body weight.

Geriatric population
The dose adjustment for the elderly patient with dementia should be cautious.

4.3 Contraindications

FUROMID must not be used in:
- Patients with hypersensitivity to furosemide or any of the excipients of FUROMID (see section 6.1). Patients allergic to sulfonamides (e.g. sulfonamide antibiotics or sulfonylureas) may show cross-sensitivity to furosemide.
- Patients with hypovolemia or dehydration.
- Patients with anuric renal failure not responding to furosemide.
- Patients with renal failure as a result of poisoning by nephrotoxic or hepatotoxic agents.
- Patients with renal failure associated with hepatic coma
- Patients with severe hypokalemia (see section 4.8).
- Patients with severe hyponatremia.
- Patients with pre-comatose and comatose states associated with hepatic encephalopathy.
- Breast-feeding women.

For use during pregnancy, see section 4.6

4.4 Special warning and precautions for use

Urinary output must be secured. In patients with a partial obstruction of urinary outflow (e.g. in patients with bladder-emptying disorders, prostatic hyperplasia or narrowing of the urethra) increased production of urine may provoke or aggravate complaints. These patients require careful monitoring, especially at the beginning of treatment for these patients.

Treatment with FUROMID necessitates regular medical supervision. Particularly careful monitoring is necessary in:

- Patients with hypotension.
- Patients who are at risk from a pronounced fall in blood pressure. e.g. patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain.
- Patients with latent or manifest diabetes mellitus (regular monitoring of blood glucose levels necessary).
- Patients with gout and hyperuricaemia (regular monitoring of uric acid levels in serum necessary)
- Patients with hepatorenal syndrome, i.e. functional renal failure associated with severe liver disease.

- Patients with hypoproteinemia (e.g. associated with nephrotic 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).
- Co-administration with lithium salts (monitoring of lithium levels is required, see section 4.5)
- Acute porphyria (the use of diuretics is considered to be unsafe in acute porphyria and caution should be exercised)

In premature infants with respiratory distress syndrome, diuretic treatment with FUROMID during the first weeks of life can increase the risk of persistent ductus arteriosus.

Symptomatic hypotension leading to dizziness, fainting or loss of consciousness may develop in patients treated with FUROMID, especially the elderly, patients taking other medications that may cause hypotension, and patients with medical conditions that pose a risk for hypotension.

FUROMID may be used in patients with impaired micturition (e.g. in prostatic hypertrophy) only if diuresis is not impaired, as sudden polyuria may lead to ischuria with overextension of the bladder.

FUROMID causes an increase in the excretion of sodium and chloride and therefore an increase in water excretion. There is also an increase in the excretion of other electrolytes (especially potassium, calcium and magnesium). Since disturbances in body fluid balance and electrolyte imbalance are frequently observed during FUROMID treatment due to increased electrolyte excretion, serum electrolytes must be monitored regularly.

Serum electrolytes (especially potassium, sodium, calcium), bicarbonate, creatinine, urea and uric acid, as well as blood sugar, should be monitored regularly, especially during long-term FUROMID treatment.

Regular monitoring of serum sodium, potassium and creatinine is generally recommended during furosemide therapy; particularly close monitoring is required in patients at high risk of developing electrolyte imbalances or in case of significant additional fluid loss (e.g. due to vomiting, diarrhea or over-sweating). Hypovolemia or dehydration as well as any significant electrolyte and acid-base disturbances must be corrected. This may require temporary discontinuation of FUROMID.

The possible development of electrolyte disturbances is affected by underlying diseases (e.g. liver cirrhosis, heart failure), concomitant medication use (see section 4.5) and diet. Weight loss caused by increased urine excretion should not exceed 1 kg/day, regardless of the amount of urine excretion.

Dosage should be determined carefully as there may be an increased risk of side effects in nephrotic syndrome.

NSAIDs may reduce the diuretic effect of FUROMID and other diuretics. Concomitant use of NSAIDs with diuretics may increase the risk of nephrotoxicity.

Simultaneous administration of sorbitol and FUROMID may cause increased dehydration. Sorbitol may trigger diarrhea, causing further fluid loss.

Cases of photosensitivity reactions have been reported with furosemide. If photosensitivity reaction occurs during treatment, it is recommended to stop the treatment. If a re-administration is deemed

necessary, it is recommended to protect exposed areas to the sun or to artificial UVA.

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). 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. Nevertheless, caution should be exercised and the risks and benefits of this combination or co-treatment with other potent diuretics should be considered prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant treatment with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be avoided in elderly patients with dementia (see section 4.3).

There is a possibility of activation or exacerbation of systemic lupus erythematosus.

The use of FUROMID may cause a positive response in doping tests. Additionally, misuse of FUROMID as a doping agent may pose a health hazard.

The following emergency measures are to be taken in the event of anaphylactic shock:
At the first signs of shock like hypotension, sudoresis, nausea, and cyanosis, interrupt the injection immediately, but leave the venous cannula in place or perform venous cannulation. In addition to the usual emergency measures, ensure that the patient remains lying down, with the legs raised and airways patent.

Emergency drug therapy:
Immediately epinephrine (adrenaline) IV:
Dilute 1 ml of commercially available epinephrine solution 1:1000 to 10 ml. In the first instance slowly inject 1 ml of this dilution (equivalent to 0.1 mg epinephrine) while monitoring pulse and blood pressure (watch for disturbances of cardiac rhythm). The administration of epinephrine may be repeated (See package leaflet).

Then glucocorticoids IV, e.g. 250-1000 mg methylprednisolone-21-hydrogen-succinate. The glucocorticoid administration may be repeated (See Summary of Product Characteristics of these drugs).

Subsequently IV volume substitution, e.g. plasma expanders, human albumin, balanced electrolyte solution should be made.

Other therapeutic measures:
Artificial respiration, oxygen inhalation, antihistaminics. A pre-existing metabolic alkalosis (e.g. decompensated liver cirrhosis) may be aggravated upon treatment with furosemide.

This medicinal product contains less than 1 mmol (23 mg) sodium per ampoule; i.e essentially. "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

Foods:
Whether and to what extent the absorption of FUROMID is affected by taking it with food seems to depend on the pharmaceutical formulation of furosemide. It is recommended that oral formulations of furosemide be taken on an empty stomach.

Not recommended associations:
In isolated cases, intravenous administration of FUROMID within 24 hours of taking chloral hydrate may lead to flushing, sweating attacks, restlessness, nausea, increase in blood pressure, and tachycardia. Use of FUROMID concomitantly with chloral hydrate is therefore not recommended.

FUROMID may potentiate the ototoxicity of aminoglycosides (e.g. kanamycin, gentamicin, tobramycin) and other ototoxic drugs if used simultaneously. Since this may lead to irreversible damage, these drugs must only be used with FUROMID if there are compelling medical reasons.

Precautions for use
There is a risk of ototoxic effects if cisplatin and FUROMID are given concomitantly. In addition, nephrotoxicity of cisplatin may be enhanced if FUROMID 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.

Oral FUROMID and sucralfate must not be taken within two hours of each other because sucralfate decreases the absorption of FUROMID from the intestine and hence, reduces its effect.

FUROMID decreases the excretion of lithium salts and may cause increased serum lithium levels, resulting in increased risk of lithium toxicity, including increased risk of cardiotoxic and neurotoxic effects of lithium. Therefore, it is recommended that lithium levels are carefully monitored in patients receiving this combination.

If other antihypertensive agents, diuretics, or drugs with blood pressure-lowering potential are used concurrently with furosemide, a significant decrease in blood pressure should be expected. Patients who are receiving diuretics may suffer severe hypotension and deterioration in renal function, including cases of renal failure, especially when an angiotensin converting enzyme inhibitor (ACE inhibitor) or angiotensin II receptor antagonist is given for the first time or for the first time in an increased dose. Consideration must be given to interrupting the administration of FUROMID temporarily or at least reducing the dose of FUROMID for three days before starting treatment with, or increasing the dose of, an ACE inhibitor or angiotensin II receptor antagonist.

Risperidone: Caution should be exercised and the risks and benefits of treating a patient on this combination or other potent diuretics should be considered prior to the decision to use (See section 4.4; regarding increased mortality in elderly patients with dementia concomitantly receiving risperidone).

Levothyroxine: High doses of furosemide may inhibit the binding of thyroid hormones to carrier proteins, thereby causing an initial transient increase in free thyroid hormones followed by an overall decrease in total thyroid hormone levels. Thyroid hormone levels should be monitored.

<u>Points to consider:</u>

Concomitant non-steroidal anti-inflammatory drugs including acetylsalicylic acid may reduce the effects of furosemide. In patients with dehydration or pre-existing hypovolemia, non-steroidal anti-inflammatory drugs may cause acute renal failure. If FUROMID is used simultaneously with salicylates, the toxicity of salicylates at high doses may increase.

Attenuation of the effect of FUROMID may occur following concurrent administration of phenytoin.

Concomitant use of FUROMID and glucocorticoids, carbenoxolone or laxatives may cause an increase in potassium depletion with the risk of developing hypokalemia. In this respect, large amounts of liquorice may act like carbenoxolone.

When hypokalemia and/or hypomagnesemia develop during FUROMID treatment when given simultaneously with cardiac glycosides, it should be taken into consideration that myocardial sensitivity to cardiac glycosides may increase. In the presence of electrolyte disturbances, the risk of ventricular arrhythmia (including torsades de pointes) will be higher if FUROMID and drugs that cause QT interval prolongation syndrome (e.g. terfenadine, some class I and class III antiarrhythmic agents) are used concomitantly.

If antihypertensive agents, diuretics or other drugs with blood-pressure lowering potential are given concomitantly with FUROMID, a more pronounced fall in blood pressure must be anticipated.

Probenecid and methotrexate other drugs which, like furosemide, undergo significant renal tubular secretion may reduce the effect of FUROMID.

Conversely, FUROMID may decrease renal elimination of these drugs. In the case of high dose treatment (in particular of both FUROMID and the other drugs), this may lead to increase of serum levels and an increased risk of adverse effects due to furosemide or the concomitant medication.

The effects of antidiabetic drugs and sympathomimetics that increase blood pressure (e.g., epinephrine, norepinephrine) may be reduced when used together with FUROMID.

The effects of curare-type muscle relaxants or theophylline may be increased by FUROMID.

The harmful effects of nephrotoxic drugs (e.g. antibiotics such as aminoglycosides, cephalosporins, polymyxins) on the kidney may increase when used together with FUROMID.

Renal dysfunction may develop in patients receiving high doses of certain cephalosporins and concomitant treatment with FUROMID.

Concomitant use of ciclosporin A and FUROMID is associated with increased risk of gouty arthritis secondary to furosemide induced hyperuricemia and cyclosporine impairment of renal urate excretion.

Patients who are at high risk of radiocontrast nephropathy treated with furosemide experienced 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.

Concomitant use of carbamazepine or aminoglutethimide with FUROMID may increase the risk of hyponatremia.

As a result of the interaction of FUROMID and thiazides, a synergetic effect occurs in diuresis.

Metformin blood levels may increase with FUROMID. In contrast, metformin may reduce the concentration of FUROMID. This risk is associated with an increased occurrence of lactic acidosis in cases of functional renal failure.

If used simultaneously (especially in hypoalbuminemia), blood levels of FUROMID and fibric acid derivatives (e.g. clofibrate and fenofibrate) may increase. The increase in the effect/toxicity of this situation should be monitored.

4.6 Fertility, pregnancy and lactation

General recommendation
Pregnancy category is C.

Women of child-bearing potential/Birth Control (Contraception)
There are no data on its use in women of childbearing potential.

Pregnancy
There are no adequate data from the use of furosemide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Since furosemide crosses the placenta, it should be used during pregnancy only after very careful weighing of the expected benefit against possible risks and for short periods only.

Diuretics are not suitable for routine treatment of hypertension and edema in pregnancy because they impair placental perfusion and therefore intrauterine growth.

However, if the use of FUROMID is necessary for maternal heart failure or renal failure, electrolytes and hematocrit as well as fetal development should be accurately monitored. In case of hyperbilirubinemia, an increased risk of kernicterus has been observed as a result of the separation of bilirubin from albumin associated with furosemide.

Fetal urine production can be stimulated in utero.

Urolithiasis and nephrocalcinosis have been observed following treatment of premature infants with furosemide.

No relevant embryotoxic or teratogenic effects were revealed in various mammalian species including mouse, rat, cat, rabbit and dog after treatment with furosemide. Retarded renal maturation - a reduction in the number of differentiated glomeruli - has been described in the progeny of rats treated with 75 mg furosemide per kg body weight during days 7 to 11 and 14 to 18 of pregnancy.

Furosemide crosses the placental barrier and in umbilical cord blood it attains 100% of maternal serum concentrations. To date, no malformations have been detected in humans which might be linked with exposure to furosemide. However, sufficient experience has not been gained to permit a conclusive assessment of possible harmful effects on the embryo/fetus.

Breast-feeding
Furosemide passes into the breast milk and may inhibit lactation. No studies have been conducted to

assess the effects on the infant of furosemide when ingested with the breast milk. Women treated with FUROMID should not breastfeed their babies. If necessary, they should discontinue breastfeeding (see section 4.3).

Reproductive ability / Fertility
Furosemide did not impair fertility of male and female rats at daily doses of 90 mg/kg body weight and of male and female mice at daily doses of 200 mg/kg body weight orally.

4.7 Effects on ability to drive and use machines

Even when used correctly, this medicinal product may affect movement to a degree that may impair the ability to drive, use machines, or work without protection. This is especially true at the beginning of treatment, when increasing the dose or when switching to another preparation, or when taking the drug with alcohol.

Some adverse effects (e.g. an undesirable pronounced fall in blood pressure) may impair the patient's ability to concentrate and react and therefore constitute a risk in situations where these abilities are of special importance (e.g. operating a vehicle or machinery).

4.8 Undesirable effects

The frequencies are derived from literature data referring to studies where furosemide is used in a total of 1387 patients, at any dose and in any indication. When the frequency category for the same ADR was different, the highest frequency category was selected.

The following frequency rating is used, when applicable:

Very common (≥1/10); Common (≥1/100 and <1/10); Uncommon (≥1/1000 and <1/100); Rare (≥1/10000 and <1/1000); Very rare (<1/10000); Not known (cannot be estimated from available data).

Blood and lymphatic system disorders
Common: Hemoconcentration (if diuresis is excessive)
Uncommon: Thrombocytopenia
Rare: Leukopenia, eosinophilia
Very rare: Agranulocytosis, aplastic anemia or hemolytic anemia (Symptoms of agranulocytosis may include fever with chills, mucosal changes, and sore throat)

Immune system disorders
Uncommon: Mucocutaneous reactions (see Skin and subcutaneous tissue disorders)
Rare: Severe anaphylactic or anaphylactoid reactions (e.g. with shock) (for treatment see section 4.9)

Initial symptoms of shock include flushing, skin reactions such as urticaria, restlessness, headache, sweating, nausea, and cyanosis.

Metabolism and nutritional disorders
Very common: Electrolyte disturbances (including symptomatic), hypovolemia and dehydration especially in elderly patients, blood creatinine increased, and serum triglyceride increased
Common: Hyponatremia, hypochloremia (especially if sodium chloride intake is limited), hypokalemia (especially when potassium intake is simultaneously reduced and/or in patients with increased potassium loss (e.g. with vomiting or chronic diarrhea)) and blood cholesterol increased,

serum uric acid increased and gout attacks
Uncommon: Glucose tolerance impaired and hyperglycemia. In diabetes mellitus patients, this situation may cause to disturbances of metabolic control; latent diabetes mellitus may become manifest.
Not known: Hypocalcemia, hypomagnesemia, blood urea increased, metabolic alkalosis, Pseudo-Bartter syndrome in the context of misuse and/or long-term use of furosemide.

Common symptoms of hyponatremia are apathy, calf cramps, anorexia, asthenia, dizziness, vomiting and confusion.

Hypokalemia can manifest itself as neuromuscular (muscle weakness, paresthesia, paresis), intestinal (vomiting, constipation, meteorism), renal (polyuria, polydipsia) and cardiac (impulse formation and conduction disorders) symptoms. Severe potassium deficiency can cause paralytic intestinal obstruction, impaired consciousness, and even coma.

Hypocalcemia can trigger tetany in rare cases.

Tetany or cardiac arrhythmia have been observed in rare cases as a result of hypomagnesemia.

Nervous system disorders
Common: Hepatic encephalopathy in patients with hepatocellular insufficiency
Rare: Paresthesia, vertigo, somnolence, confusion, feeling of pressure in the head
Not known: Dizziness, fainting and loss of consciousness, headache

Eye disorders
Rare: Progression of myopia, blurred vision, visual disturbances with symptoms of hypovolemia

Ear and labyrinth disorders
Uncommon: Hearing disorders, and tinnitus, 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. Cases of deafness, sometimes irreversible have been reported after oral or intravenous administration of furosemide.
Rare: Tinnitus

Vascular disorders
Very common (especially for intravenous infusion): Hypotension including orthostatic hypotension
Rare: Vasculitis
Not known: Thrombosis (especially in elderly patients)

If diuresis is too intense, circulatory complaints (including circulatory collapse) may occur, especially in elderly patients and children. These complaints mostly manifest as headache, dizziness, visual disturbances, dry mouth and thirst, hypotension and orthostatic dysregulation.

Gastrointestinal disorders
Uncommon: Nausea
Rare: Vomiting, diarrhea
Very rare: Acute pancreatitis

Hepatobiliary disorders
Very rare: Intrahepatic cholestasis, cholestatic jaundice, hepatic ischemia, increased hepatic

transaminases

Skin and subcutaneous tissue disorders
Uncommon: Pruritus, urticaria, rash, bullous dermatitis, erythema multiforme, pemphigoid, exfoliative dermatitis, purpura, photosensitivity reaction
Not known: Steven-Johnson syndrome, toxic epidermal necrolysis, AGEP (acute generalized exanthematous pustulosis) and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms)

Musculoskeletal, connective tissue and bone disorders
Rare: Leg muscle cramps, asthenia, chronic arthritis
Not known: Cases of rhabdomyolysis, most often in the form of severe hypokalemia, have been reported (see section 4.3).

Renal and urinary disorders
Very common: Increased blood creatinine
Common: Urine volume increased.
Rare: Tubulointerstitial nephritis.
Not known: Increased sodium in the urine, increased chloride in the urine, increased urea in the blood, signs of urinary obstruction (e.g. in patients with prostatic hypertrophy, hydronephrosis, ureteric stenosis) and even urinary retention with secondary complications (see section 4.4), nephrocalcinosis and/or nephrolithiasis in premature infants, renal impairment

Congenital and familial/genetic disorders
Not known: Increased risk of persistence of patent ductus arteriosus when furosemide is administered to premature infants during the first weeks of life.

General disorders and administration site conditions:
Rare: Fever
Not known: Following intramuscular injection, local reactions such as pain may occur.

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

4.9 Overdose

Symptoms:
In acute or chronic overdose, the clinical picture varies mainly depending on the degree and consequences of electrolyte and fluid loss. Overdose may cause hypotension, orthostatic dysregulation, electrolyte disturbances (hypokalemia, hyponatremia, hypochloremia) or alkalosis. In case of more severe dehydration, hemoconcentration may develop, with a tendency to marked hypovolemia, dehydration, circulatory collapse and thrombosis. Delirium may be observed in rapid water and electrolyte losses. In rare cases, anaphylactic shock (symptoms; sweating, nausea, cyanosis, severe drop in blood pressure, confusion and even coma) may occur.

Treatment:
Clinically relevant disturbances in electrolyte and fluid balance must be corrected. Together with the prevention and treatment of serious complications resulting from such disturbances and of other effects

on the body, this corrective action may necessitate general and specific intensive medical monitoring and therapeutic measures. Hemodialysis does not accelerate the elimination of furosemide.

In case of overdose or signs of hypovolemia (hypotension, orthostatic dysregulation) FUROMID treatment should be stopped immediately.

In addition to monitoring vital signs, recurring checks should be made for water and electrolyte balance, acid-base balance, blood sugar, and nitrogen-containing compounds in the urine, and deviations should be corrected as necessary.

Free flow of urine should be ensured in patients with micturition disorders (e.g. patients with prostatic hyperplasia) because the sudden flow of large amounts of urine can cause urinary retention with overdistention of the bladder.

Hypovolemia treatment: volume replacement

Hypokalemia treatment: potassium replacement

Treatment of circulatory collapse: supine position with legs in the air, shock treatment if necessary

Emergency measures to be taken in case of anaphylactic shock:
When the first symptoms appear (e.g. flushing, skin reactions such as urticaria, restlessness, headache, sweating, nausea, cyanosis), the following should be applied:

- Injection/infusion is stopped and vascular access is kept open.
- In addition to general emergency measures, the patient is placed in a supine position with legs up, the airways are kept open and oxygen is administered.
- If necessary, emergency intensive care measures are applied (including adrenaline (epinephrine), volume replacement fluids, glucocorticoids).

1 ml of a 1/1000 adrenaline solution is diluted to 10 ml and 1 ml of this solution (0.1 mg adrenaline) is injected slowly, controlling pulse and blood pressure and monitoring possible arrhythmia. Adrenaline administration can be repeated if necessary.

A glucocorticoid (e.g. 250 mg methylprednisolone) is then administered intravenously. Glucocorticoid doses are repeated if necessary.

In children, the above mentioned doses are adjusted according to body weight.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: High-ceiling diuretics, sulphonamides (plain)
ATC code: C03CA01

Mechanism of action:
Furosemide is a loop diuretic that produces a comparatively powerful and short-lived rapid-onset diuresis. Furosemide blocks the transport system located in the luminal cell membrane of the thick ascending limb of the loop of Henle; therefore, the effectiveness of the saluretic effect of furosemide depends on the drug reaching the tubular lumen via an anion transport mechanism.
The diuretic action results from inhibition of the reabsorption of sodium chloride in this segment of the loop of Henle. As a result, fractional sodium excretion may be as much as 35% of glomerular

sodium filtration. The secondary effects of increased sodium excretion are increased urine excretion (due to osmotically bound water) and increased distal tubular potassium secretion. The excretion of calcium and magnesium ions is also increased.

Furosemide interrupts the tubulo-glomerular feedback mechanism in the macula densa, with the result that there is no attenuation of saluretic activity. Furosemide causes dose-dependent stimulation of the rennin-angiotensin-aldosterone system.

In case of heart failure, furosemide induces an acute reduction of cardiac pre-load. This early vascular effect seems to be mediated by prostaglandins and assumes an adequate renal function with activation of the renin-angiotensin system and an intact synthesis of prostaglandins. Due to its natriuretic effect, furosemide reduces the vascular reactivity to catecholamine that is increased in hypertensive patients.

The antihypertensive effectiveness of furosemide is attributable to increased sodium excretion, reduced blood volume and reduced responsiveness of vascular smooth muscle to vasoconstrictor stimuli.

Pharmacodynamic properties:
The diuretic effect of furosemide occurs within 15 minutes of an intravenous dose and within 1 hour of an oral dose.

A dose-dependent increase in diuresis and natriuresis has been demonstrated in healthy individuals receiving furosemide in doses of 10 mg to 100 mg. The duration of action in healthy individuals after the administration of an intravenous 20 mg dose of furosemide is approximately 3 hours and 3 to 6 hours, when an oral 40 mg dose is given.

In patients, the relationship between intratubular concentrations of unbound (free) furosemide (estimated using the urinary excretion rate of furosemide) and its natriuretic effect is in the form of a sigmoid curve, with the minimal effective excretion rate of furosemide being approximately 10 micrograms/minute. Consequently, a continuous infusion of furosemide is more effective than repeated bolus injections. Above a certain bolus administration dose, the drug's effects do not significantly increase. The efficacy of furosemide is decreased in cases of reduced tubular secretion or in cases of intra-tubular binding of the drug to albumin.

5.2 Pharmacokinetic properties

General properties

Absorption:
Furosemide is rapidly absorbed from the gastrointestinal tract. The absorption of the drug shows large inter- and intra-individual variability. The bioavailability of furosemide in healthy volunteers is approximately 50% to 70% for tablets and approximately 80% for the oral solution. In patients, the bioavailability of the drug is influenced by various factors including underlying diseases, and it may be reduced to 30% (e.g. in nephrotic syndrome).

Whether and to what extent the absorption of furosemide is affected by taking it with food seems to depend on the pharmaceutical formulation.

Distribution:
The volume of distribution of furosemide is 0.1-0.2 liters per kg body weight. The volume of distribution may be higher depending on the underlying disease.

Furosemide is strongly (more than 98%) bound to plasma protein, mainly albumin.

Biotransformation:
A glucuronide metabolite of furosemide accounts for 10-20% of the substances recovered in the urine.

Elimination:
Furosemide is eliminated mainly as the unchanged drug, primarily by secretion into the proximal tubule. After intravenous administration 60-70% of the furosemide dose is excreted in this way. The remaining dose is excreted in the feces, probably following biliary secretion.

In normal renal function, the elimination half-life of furosemide is approximately 1 hour; in terminal renal failure, it may take up to 24 hours.

Furosemide is excreted in breast milk. Furosemide passes the placental barrier and transfers to the fetus slowly. It is found in the fetus or newborn in the same concentrations as in the mother.

Characteristics in patients
Renal/Hepatic insufficiency:
In renal failure, the elimination of furosemide is slowed down and the half-life prolonged; the terminal half-life may be up to 24 hours in patients with severe renal failure.

In nephrotic syndrome the reduced plasma protein concentration leads to a higher concentration of unbound (free) furosemide. On the other hand, efficacy of furosemide is reduced in these patients due to binding to intratubular albumin and lowered tubular secretion.

Furosemide is poorly dialyzable in patients undergoing hemodialysis, peritoneal dialysis and CAPD.

In liver failure, the half-life of furosemide is increased by 30% to 90% mainly due to a larger volume of distribution. Additionally, in this patient group there is a wide variation in all-pharmacokinetic parameters.

Other:
Congestive heart failure, severe hypertension, geriatric population:
The elimination of furosemide is slowed down due to reduced renal function in patients with congestive heart failure, severe hypertension or in the elderly.

Premature and full-term infants:
Depending on the maturity of the kidney, the elimination of furosemide may be slowed down. The metabolism of the drug is also reduced if the infant's glucuronidation capacity is impaired. The terminal half-life is below 12 hours in infants with a post-conceptional age of more than 33 weeks. In infants of 2 months and older, the terminal clearance is the same as in adults.

5.3 Preclinical safety data

Acute toxicity:
Studies conducted with oral and intravenous administration of furosemide in various rodent species and dogs revealed low acute toxicity. The oral LD_{50} of furosemide is between 1050 to 4600 mg/kg body weight in mice and rats, and 243 mg/kg body weight in guinea pigs. In dogs, the oral LD_{50} is approx. 2000 mg/kg body weight, and the IV LD_{50} is greater than 400 mg/kg body weight.

Chronic toxicity:
In rats and dogs after 6 and 12 months' administration, renal changes (including focal fibrosis, calcification) were encountered in the top dosage groups (10 to 20 times the therapeutic dose in humans).

Ototoxicity:
Furosemide may interfere with transport processes in the stria vascularis of the internal ear, possibly leading to a (generally reversible) hearing disorder.

Carcinogenicity
Furosemide in the approximate amount of 200 mg/kg body weight (14,000 ppm) daily was administered to female mice and rats over a 2-year period with their diet. An increased incidence of mammary adenocarcinoma was noted in the mice, but not in the rats. This dose is considerably greater than the therapeutic dose administered in human patients. Moreover, these tumors were morphologically identical to the spontaneously occurring tumors observed in 2% to 8% of control animals.

Thus, it appears unlikely that this incidence of tumors is relevant to the treatment of humans. Indeed, there is no evidence of increased incidence of human mammary adenocarcinoma following the use of furosemide. Based on epidemiological studies, a carcinogenicity classification for furosemide in humans is not possible.

In a carcinogenicity study, rats were administered furosemide in daily doses of 15 and 30 mg/kg body weight. Male rats in the 15 mg/kg-dose category, but not in the 30 mg/kg-dose category, showed a marginal increase in uncommon tumors. These findings are considered to be incidental.

Nitrosamine-induced urinary bladder carcinogenesis in rats yielded no evidence to suggest that furosemide is a promoting factor.

Mutagenicity:
In *in-vitro* tests on bacteria and mammalian cells, both positive and negative results have been obtained. Induction of gene and chromosome mutations, however, has been observed only where furosemide reached cytotoxic concentrations.

Reproductive toxicity:
Furosemide did not impair fertility of male and female rats at daily doses of 90 mg/kg body weight and of male and female mice at daily doses of 200 mg/kg body weight orally.

No relevant embryotoxic or teratogenic effects were revealed in various mammalian species including mouse, rat, cat, rabbit and dog after treatment with furosemide. Retarded renal maturation - a reduction in the number of differentiated glomeruli - has been described in the progeny of rats treated with 75 mg furosemide per kg body weight during days 7 to 11 and 14 to 18 of pregnancy.

Furosemide crosses the placental barrier and in umbilical cord blood it attains 100% of maternal serum concentrations. To date, no malformations which might be linked with exposure to furosemide have been detected in humans. However, sufficient experience has not been gained to permit a conclusive assessment of possible harmful effects on the embryo/fetus. Urine production in the fetus can be stimulated in uterus.

Urolithiasis and nephrocalcinosis have been observed following treatment of premature infants with furosemide.

No studies have been conducted to assess the effects on the infant of furosemide when ingested with the breast milk.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid solution
Sodium hydroxide
Sodium chloride
Water for injection

6.2 Incompatibilities

None

6.3 Shelf life

60 months.

6.4 Special precautions for storage

Store at room temperature below 25°C protected from light.

6.5 Nature and contents of container

Amber-colored 2 ml type I glass (high resistance borosilicate glass) ampoules with ring.
Each cardboard box contains 5 ampoules of 2 ml.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece/ISTANBUL - TURKEY

8. MARKETING AUTHORIZATION NUMBER

129/12

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

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Date of last renewal: 30.03.2006

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