PRODUCT INFORMATION – FUROSEMIDE – AFT (FUROSEMIDE) INJECTION

1 NAME OF THE MEDICINE

Furosemide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Furosemide 20 mg/ 2 mL solution for injection. Contains 160 µmol/mL of sodium.

Furosemide is an anthranilic acid derivative. Chemically, it is 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid.

For the full list of excipients, see 6.1 List of excipients

3 PHARMCEUTICAL FORM

Furosemide – AFT injection is a glass ampoule containing clear, colourless or light yellowish solution. The drug product has a pH of 8.0-9.3.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

- Oedema due to cardiac and hepatic diseases (ascites)
- Oedema due to renal disease (in the nephrotic syndrome, therapy of the underlying diseases has precedence)
- Acute cardiac insufficiency, especially in pulmonary oedema (administration in conjunction with other therapeutic measures)
- Reduced urinary output due to gestoses (pregnancy-related nephrosis), after restoring the fluid volume to normal
- Supportive measures in brain oedema
- Oedema due to burns
- Hypertensive crisis (in addition to other antihypertensive measures)
- To support forced diuresis in poisoning

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults

Parenteral therapy with Furosemide – AFT should be used only in patients unable to take oral medication or in emergency situations and should be replaced with oral therapy as soon as practical. To achieve optimum efficacy and suppress counter-regulation, a continuous furosemide (frusemide) infusion is generally preferred to repeat bolus injections.

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

Oedema

The usual initial dose of Furosemide – AFT is 20 to 40 mg given as a single dose, injected intramuscularly or intravenously. The intravenous dose should be given slowly (see Section 4.4 Special warnings and precautions for use). Ordinarily a prompt diuresis ensues. If needed, another dose may be administered in the same manner 2 hours later, or the dose may be increased. The dose may be raised by 20 mg and given not sooner than 2 hours after the previous dose, until the desired diuretic effect has been obtained. This individually determined single dose should then be given once or twice daily.

Therapy should be individualised according to patient response to gain maximal therapeutic response and to determine the minimal dose needed to maintain that response. Close medical supervision is necessary. If the physician elects to use high dose parenteral therapy, add the Furosemide – AFT to either Sodium Chloride Injection or Lactated Ringer's Injection, and administer as a controlled intravenous infusion at a rate not greater than 4 mg/min. Furosemide – AFT is a buffered alkaline solution.

Acute Pulmonary Oedema

The usual initial dose of Furosemide – AFT is 40 mg injected slowly intravenously (see Section 4.4 Special warnings and precautions for use). If a satisfactory response does not occur, a further dose of 20-40 mg is injected after 20 minutes. If necessary, additional therapy (e.g. digitalis, oxygen) may be administered concomitantly.

Infants and Children

Parenteral therapy should be used only in patients unable to take oral medication or in emergency situations, and should be replaced with oral therapy as soon as practical.

The recommended dose of Furosemide – AFT (intravenously or intramuscularly) in infants and children is 1 mg/kg body weight and should be given slowly under close medical supervision up to a maximum of 20 mg.

Furosemide-AFT Injection should be inspected visually for particulate matter and discolouration before administration. Do not use if solution is discoloured.

Furosemide-AFT is for single use in one patient only. Discard any residue.

Although the chemical stability of diluted Furosemide – AFT (diluted with 0.9 % NaCl or Lactated Ringer's Injection to concentration 1 mg/ml of furosemide) has been demonstrated for storage at 30 °C for 24 hours, the diluted solution should be used as soon as practicable to reduce risk of microbiological hazard. The diluted solution must be protected from light.

4.3 CONTRAINDICATIONS

Known hypersensitivity to furosemide or sulfonamides or any of the inactive ingredients (see Section 6.1 List of excipients description). Patients allergic to sulfonamides (e.g. sulfonamide antibiotics or sulfonylureas) may show cross-sensitivity to Furosemie – AFT.

Renal failure with oligoanuria not responding to furosemide. Renal failure as a result of poisoning by nephrotoxic or hepatotoxic agents. If increasing azotaemia and oliguria occur during treatment of severe progressive renal disease, discontinue furosemide.

Severe hypokalaemia, (see Section 4.8 Adverse effects (undesirable effects), hyponatraemia, hypovolaemia, dehydration or hypotension must be regarded as contraindications until serum electrolytes, fluid balance and blood pressure have been restored to normal levels.

In hepatic coma or precoma and conditions producing electrolyte depletion, furosemide therapy should not be instituted until the underlying conditions have been corrected or ameliorated.

In breast-feeding women.

Do not administer furosemide to new-borns presenting jaundice or to infants with conditions which might induce hyperbilirubinemia or kernicterus (e.g. Rhesus incompatibility, familial non-haemolytic jaundice etc.) because of furosemide's *in vitro* potential to displace bilirubin from albumin.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

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

Particularly careful monitoring is required in patients with gout, patients with partial obstruction of urinary outflow, in patients with hypotension or who are at particular 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), in patients with latent or manifest diabetes mellitus, in patients with hepatorenal syndrome or in patients with hypoproteinaemia (e.g. associated with nephrotic syndrome). Dose titration, especially in this latter case, is required.

Cases of reversible or irreversible tinnitus or hearing impairment have been reported. Usually, reports indicate that furosemide ototoxicity is associated with rapid injection or infusion, severe renal impairment, hypoproteinaemia, doses exceeding several times the usual recommended dose, or concomitant therapy with aminoglycoside antibiotics, etacrynic acid, or other ototoxic drugs. In patients with hypoproteinaemia, e.g. associated with nephrotic syndrome, the effect of furosemide may be weakened, and its ototoxicity potentiated. Cautious dose titration is required. If the physician elects to use high dose parenteral therapy, controlled intravenous infusion is advisable (for adults with normal renal function, an infusion rate not exceeding 4 mg Furosemide – AFT per minute must be used; for adults with impaired renal function [creatinine > 5 mg/dL], an infusion rate of no greater than 2.5 mg per minute must be used).

Caution should be exercised when administering curare or its derivatives to patients undergoing furosemide therapy. It is also advisable to discontinue furosemide for one week prior to any elective surgery.

Caution should be exercised and the risks and benefits of combining risperidone with Furosemide – AFT or other potent diuretics should be considered prior to the decision to treat. In the 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 to 97) compared to treatment with risperidone alone (3.1% ; mean age 84 years, range 70 to 96) or furosemide alone (4.1%; mean age 80 years, range 67 to 90). Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low doses) was not associated with similar mortality findings. No pathophysiological mechanism has been identified to explain this finding and no consistent pattern for cause of death was observed. Nevertheless, caution is advised. Irrespective of treatment, dehydration was an overall risk factor for mortality and should, therefore, be carefully avoided in elderly patients with dementia.

Rigid sodium restriction is conducive to both hyponatraemia and hypokalaemia, thus strict restriction of sodium intake is not advisable in patients receiving furosemide.

Excessive loss of potassium in patients receiving cardiac glycosides may precipitate digitalis toxicity.

During long-term therapy, a high potassium diet is recommended. Potassium supplements may be required, especially when high doses are used for prolonged periods. Particular caution with potassium is necessary when the patient is on digitalis glycosides, potassium depleting steroids or in the case of infants and children. Potassium supplementation, diminution in dose, or discontinuation of furosemide therapy may be required.

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

The possibility exists of exacerbation or activation of systemic lupus erythematosus.

When Furosemide – AFT is administered parenterally, a maximum injection rate of 4 mg/minute should be used to minimise the risk of ototoxicity.

Intramuscular administration of Furosemide – AFT must be limited to exceptional cases where neither oral nor intravenous administration are feasible. Intramuscular administration is not suitable for acute conditions such as pulmonary oedema.

Use in hepatic impairment

In patients with hepatic cirrhosis and ascites, initiation of therapy with Furosemide – AFT is best carried out in hospital. 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.

Use in renal impairment

Furosemide should be used with care, especially in the initial stages, in patients with impairment of micturition (e.g. prostatic hypertrophy). Urinary outflow 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. Thus, these patients require careful monitoring.

Patients who were at high risk for 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.

Use in the elderly

See "Identified precautions" and Section 4.8 Adverse effects (undesirable effects) "Metabolism and Nutritional Disorders", "Renal and Urinary Disorders" and "Vascular Disorders".

Paediatric use

In premature infants, there is the possible development of nephrocalcinosis/ nephrolithiasis and therefore renal function must be monitored and renal ultrasonography performed. In premature infants, furosemide administered during the first weeks of life may increase the risk of persistence of Botallo's duct.

In children, urge to defecate, complaints of abdominal pain and cramping have been reported after IV furosemide. An association of these symptoms with a low serum calcium and/ or a low calcium/ protein ratio is possible.

Renal calcifications (from barely visible on X-ray to staghorn) have occurred in some severely premature infants treated with intravenous furosemide for oedema due to patent ductus arteriosus and hyaline membrane disease. The concurrent use of chlorothiazides has been reported to decrease hypercalciuria and to dissolve some calculi.

Effects on laboratory tests

As with any effective diuretic, electrolyte depletion may occur during therapy, especially in patients receiving higher doses and a restricted salt intake. All patients receiving furosemide therapy should be observed for signs of fluid or electrolyte imbalance; namely hyponatraemia, hypochloraemic alkalosis, and hypokalaemia. Periodic determinations of serum electrolytes to detect a possible imbalance should be performed at appropriate intervals, as well as creatinine, blood urea and CO_2 content determinations. This is particularly important when the patient is at high risk of developing electrolyte imbalances (e.g. receiving parenteral fluids) or in case of significant additional fluid loss such as vomiting diarrhoea and intense sweating. Warning signs of an imbalance, irrespective of cause include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, arrhythmia, and gastrointestinal disturbances such as nausea and vomiting. Hypovolaemia or dehydration as well as any significant electrolyte and acid-base disturbances must be corrected. This may require temporary discontinuation of Furosemide – AFT.

Periodic checks on urine and blood glucose should be made in diabetics and even those suspected of latent diabetes when receiving Furosemide – AFT. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and 2-hour post prandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported.

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

Reversible elevations of blood urea may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency.

Furosemide increases cholesterol and triglycerides short-term. It is not clear whether this effect persists long-term, however, the current evidence does not indicate this.

Asymptomatic hyperuricaemia can occur and rarely, gout may be precipitated.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Combinations that are not recommended

Antibiotics

Furosemide – AFT may increase the ototoxic and nephrotoxic potential of certain antibiotics (e.g. aminoglycosides and certain cephalosporins (e.g. cephaloridine)) and other ototoxic drugs, especially in the presence of impaired renal function, therefore the simultaneous administration of these drugs is not advisable.

Anticonvulsants

Anticonvulsants may decrease the response to furosemide. 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.

Combinations that require precautions

Etacrynic acid or cisplatin

Furosemide – AFT should not be used concomitantly with etacrynic acid or cisplatin because of the possibility of ototoxicity. In addition, 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.

Lithium salts

Furosemide 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.

Antihypertensives

The action of other antihypertensive drugs may be potentiated by Furosemide – AFT, especially in combination with ACE inhibitors. The administration of ACE inhibitors to patients pre-treated with furosemide may lead to a deterioration in renal function including renal failure, or may result in severe hypotension 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 Furosemide – AFT temporarily or at least reducing the dose of Furosemide – AFT for 3 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 risperidone with Furosemide – AFT or other potent diuretics should be considered prior to the decision to use. See Section 4.4 Special warnings and precautions for use, regarding increased mortality in elderly patients with dementia concomitantly receiving risperidone.

Levothyroxine sodium

High doses of furosemide may inhibit binding of thyroid hormones to carrier proteins when administered with levothyroxine sodium, and thereby lead to an initial transient increase in free thyroid hormones, followed by an overall decrease in total thyroid hormone levels. It is recommended that thyroid hormones be monitored.

Other combinations to consider

Drugs inducing QT interval prolongation

The effects of digitalis preparations and drugs inducing QT interval prolongation syndrome may be potentiated by changes in electrolyte concentrations (e.g. hypokalaemia, hypomagnesaemia) due to furosemide. When a cardiac glycoside is administered concurrently, it should be remembered that potassium or magnesium deficiency increases the sensitivity of the myocardium to digitalis, and may increase the toxicity of drugs which induce QT interval prolongation syndrome. When a glucocorticoid is administered during diuretic treatment, the potassium-lowering effect of the steroid should be borne in mind (see Section 4.4 Special warnings and precautions for use). Carbenoxolone, corticosteroids, prolonged use of laxatives or ingestion of liquorice in large amounts may also predispose a patient to hypokalaemia.

Salicylates

Patients receiving high doses of salicylates, as in rheumatic disease, in conjunction with Furosemide – AFT may experience salicylate toxicity at lower doses because of competitive renal excretory sites.

Neuromuscular blockers

Interactions between furosemide and neuromuscular blocking agents have been reported. These appear to be dependent on the dose of furosemide and the neuromuscular blocking agent involved. Low doses of furosemide (0.1 - 10 µg/kg) enhance the neuromuscular blockade of tubocurarine and succinylcholine. High doses (1 - 5 mg/kg) of furosemide have a tendency to antagonise the skeletal muscle relaxing effect of tubocurarine but may potentiate the action of succinylcholine. The clinical relevance of these findings is uncertain.

Amphotericin B

The combination of furosemide and amphotericin B (amphotericin) may result in an excessive loss of potassium.

Noradrenaline (norepinephrine)

Furosemide – AFT may decrease arterial responsiveness to noradrenaline (norepinephrine). This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

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

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs including acetylsalicylic acid may reduce the natriuretic and antihypertensive effects of Furosemide – AFT in some patients by inhibiting prostaglandin synthesis. In patients with dehydration or pre-existing hypovolaemia, non-steroidal anti-inflammatory drugs may cause acute renal failure. Salicylate toxicity may be increased by furosemide.

Drugs eliminated by renal tubular secretion

Phenytoin, methotrexate, probenecid 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 the case of high dose treatment (in particular of both furosemide and the other drugs), this may lead to an increased risk of adverse effects due to furosemide or the concomitant medication.

Theophylline

IV furosemide was shown to increase the steady state concentration of theophylline by 20% in a small number of asthmatic patients; hence it is appropriate to measure serum theophylline levels when both drugs are given together.

Muscle relaxants

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

Antidiabetic agents and adrenaline (epinephrine)

It should be borne in mind that the effect of antidiabetics or of pressor amines (e.g. adrenaline (epinephrine), noradrenaline (norepinephrine)) may be attenuated by furosemide (see Section 4.4 Special warnings and precautions for use).

Cephalosporins

Impairment of renal function may develop in patients receiving concurrent treatment with furosemide and high doses of certain cephalosporins. The harmful effects of nephrotoxic drugs on the kidney may be increased.

Ciclosporin

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available

Use in pregnancy

Category C

Furosemide – AFT must not be given during pregnancy unless there are compelling medical reasons. Treatment during pregnancy requires monitoring of foetal growth.

Thiazides, related diuretics and loop diuretics enter the foetal circulation and may cause electrolyte disturbances. Neonatal thrombocytopaenia has been reported with thiazides and related diuretics. Loop diuretics, like furosemide and bumetanide, are probably also associated with this risk.

Use in lactation

Furosemide passes into the breast milk and inhibits lactation. Women must not breast feed if being treated with furosemide.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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 ADVERSE EFFECTS (UNDESIREABLE EFFECTS)

Whenever adverse reactions are moderate or severe, furosemide dose should be reduced or therapy withdrawn.

Metabolism and nutrition disorders

As with other diuretics, electrolytes and water balance may be disturbed during therapy with furosemide, especially in patients receiving high doses for a prolonged period. The serum potassium concentration may decrease, especially at the commencement of treatment (owing to the earlier onset of action of furosemide).

Excessive diuresis may give rise, especially in elderly patients and children, to circulatory disturbances such as headache, dizziness, dry mouth or visual impairment, as symptoms of hypovolaemia. In extreme cases, hypovolaemia and dehydration may lead to hypotension, circulatory collapse and, in elderly patients in particular, thrombophilia. However, with individualised dosage, acute haemodynamic reactions are generally not to be expected, although diuresis sets in rapidly.

All saluretics may cause hypokalaemia, mainly in cases of low potassium diet, vomiting or chronic diarrhoea.

Factors such as underlying diseases (liver cirrhosis, cardiac failure), concomitant medication (see Section 4.5 Interactions with other medicines and other forms of interactions) or nutritional inadequacies (excessive restriction of salt intake), may lead to sodium (hyponatremia), chloride (hypochloremia), or other electrolyte or fluid deficiencies which may produce a fall in orthostatic blood pressure, calf muscle spasms, anorexia, weakness, dizziness, drowsiness, apathy, vomiting and confusion.

Furosemide may lower the serum calcium level (hypocalcemia) which may trigger a state of increased neuromuscular irritability. Furosemide may cause a rise in serum cholesterol and triglyceride.

Hypomagnesaemia and, in rare cases, tetany or cardiac arrhythmias have been observed as a consequence of increased renal magnesium loss.

Treatment with Furosemide – AFT may lead to transitory increases in urine volume, blood creatinine and urea levels. Serum levels of uric acid (hyperuricaemia) may increase and attacks of gout may occur.

Pre-existing metabolic alkalosis (e.g. due to decompensated liver cirrhosis) may be aggravated during furosemide treatment. Metabolic alkalosis has been reported with furosemide use.

Treatment with furosemide has occasionally caused reduced glucose tolerance and deterioration in cases of manifest diabetes, or made latent diabetes manifest.

Pseudo-Bartter syndrome in the context of misuse and/or long-term use of furosemide has been reported.

Very common: electrolyte disturbances (including symptomatic), dehydration and hypovolaemia especially in elderly patients, increased blood creatinine, increased blood triglycerides

Common: hyponatremia, hypochloremia, hypokalaemia, blood cholesterol increased, blood uric acid increased and attacks of gout, urine volume increased

Uncommon: impaired glucose tolerance. Latent diabetes mellitus may manifest

Gastrointestinal disorders and hepato-biliary disorders

Reactions with normal doses are uncommon with furosemide. They include anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhoea and constipation.

In isolated cases, acute pancreatitis and increases in transaminases have been observed. Additionally, cholestasis and jaundice have been reported. Furosemide may increase the bile flow and distend the biliary tree which is already obstructed.

Central nervous system disorders

Reactions such as dizziness, vertigo, paraesthesia, headache and blurred vision occasionally accompany furosemide – induced diuresis.

Ear and labyrinth disorders

Reversible hearing impairment and tinnitus and rarely, permanent tinnitus and impairment of hearing have been observed, especially in patients with markedly reduced

renal function or hypoproteinaemia (e.g. in nephrotic syndrome). This occurs particularly when the recommended rate of injection or infusion of 4 mg per minute (normal renal function) or 2.5 mg per minute (impaired renal function) is exceeded, or in patients who are also receiving drugs known to be ototoxic.

Cases of deafness, sometimes irreversible have been reported after oral or IV administration of furosemide.

Skin and subcutaneous tissue disorders

Uncommon allergic reactions include dermatitis, bullous dermatitis, rashes, urticaria, pruritus, photosensitivity reactions, pemphigoid, erythema multiforme, purpura and exfoliative dermatitis. Itching may occur and rare cases of necrotising angitis, Steven-Johnson syndrome, toxic epidermal necrolysis. AGEP (acute generalized exanthematous pustulosis), lichenoid reactions and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) has been reported with furosemide use.

Blood and the lymphatic system disorders

Common: haemoconcentration

Uncommon: thrombocytopenia

The following rare adverse reactions have been reported: eosinophilia, thrombophlebitis, haemolytic or aplastic anaemia, leukopaenia and agranulocytosis.

Congenital and familial/ genetic disorders

The persistence of patent ductus arteriosus when furosemide has been administered to a premature infant during the first weeks of life has been reported.

Renal and urinary disorders

Excessive diuresis and dehydration could cause transient elevation of creatinine and BUN and reduction of GFR. Rare cases of tubulointerstitial nephritis have been reported. In elderly men with prostatic hypertrophy, acute urinary retention with overflow incontinence may occur. Symptoms of existing conditions of obstructed micturition, such as ureterostenosis or hydronephrosis, may be triggered or aggravated by pronounced diuresis. Interstitial nephritis has also been reported with furosemide use. In premature infants, calcium salts may be deposited in the renal tissue (nephrocalcinosis/ nephrolithiasis). In patients with a partial obstruction of urinary outflow, acute retention of urine may occur.

Increases in sodium and/or chloride urine levels, and renal failure has been reported with furosemide use.

Vascular disorders

Very common (especially for intravenous infusion), orthostatic hypotension may occur and may be aggravated by alcohol, narcotics and barbiturates. Due to the possibility of side effects such as hypotension, patients' ability to drive or operate machinery may be impaired, especially at the commencement of therapy. Ischaemic complications have also been reported in elderly patients. A tendency for thromboses has been reported. If

furosemide is administered to premature infants during the first weeks of life, it may increase the risk of persistence of patent ductus arteriosus.

Rare: vasculitis

Cases of thrombosis have been reported.

Immune system disorders

Severe anaphylactic or anaphylactoid reactions (e.g. with shock) is rare, but is acutely life-threatening if it does occur.

Cases of exacerbation or activation of systemic lupus erythematosus have been reported.

Nervous system disorders

Common: hepatic encephalopathy in patients with hepatocellular insufficiency

Rare: paraesthesia

Headache, dizziness, fainting or loss of consciousness have been reported.

Musculoskeletal and connective tissue disorders

Cases of rhabdomyolysis have been reported, often in the context of severe hypokalaemia (see Section 4.3 Contraindications).

General disorders and administration site conditions

Rarely, fever may occur. Following intramuscular injection, local reactions such as pain may occur. Restlessness has also been reported.

4.9 OVERDOSE

The clinical picture in acute or chronic overdose depends primarily on the extent and consequences of electrolyte and fluid loss; e.g. dehydration, blood volume reduction, hypotension, electrolyte imbalance, cardiac arrhythmias (including A-V block and ventricular fibrillation), hypokalaemia and hypochloraemic alkalosis, and extensions of its diuretic action. Symptoms of these disturbances include severe hypotension (progressing to shock), acute renal failure, thrombosis, delirious states, flaccid paralysis, apathy and confusion.

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 fluids associated with toxicity or death is not known.

No specific antidote to Furosemide – AFT is known. If ingestion has only just taken place, attempts may be made to limit further systemic absorption of the active ingredient by measures such as activated charcoal.

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). Haemodialysis does not accelerate furosemide elimination.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Furosemide is a potent diuretic. It inhibits sodium and chloride absorption in the ascending limb of Henle's loop and in both the proximal and distal tubules. The high degree of efficacy is due to this unique site of action. The action on the distal tubule is independent of any inhibitory effect on carbonic anhydrase or aldosterone.

Furosemide may promote diuresis in cases which have previously proved resistant to other diuretics.

Furosemide has no significant pharmacological effects other than on renal function.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

The onset of diuresis following intravenous administration is within 5 minutes and somewhat later after intramuscular administration. The peak effect occurs within the first half hour. The duration of diuretic effect is approximately 2 hours.

Distribution

Furosemide is extensively bound to plasma proteins, mainly to albumin. Plasma concentrations ranging from 1 to 400 µg/mL are 91 to 99% bound in healthy individuals. The unbound fraction averages 2.3 to 4.1% at therapeutic concentrations.

Metabolism

Recent evidence suggests that furosemide glucuronide is the only, or at least the major, bio-transformation product of furosemide in man.

Excretion

In patients with normal renal function, approximately 80% of an intravenous or intramuscular dose is excreted in the urine within 24 hours. Urinary excretion is accomplished both by glomerular filtration and proximal tubular secretion, which accounts for roughly 66% of the ingested dose, the remainder being excreted in the faeces. A small fraction is metabolised by cleavage of the side chain.

Significantly more furosemide is excreted in urine following the IV injection than after the tablet or oral solution.

Furosemide (Frusemide) has a biphasic half-life in the plasma with $t_{1/2}$ ranging up to 100 minutes; $t_{1/2}$ is prolonged by renal and hepatic insufficiency and in new-born infants.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The active ingredient in Furosemide – AFT is Furosemide. It also contains sodium chloride, sodium hydroxide and water for injection.

6.2 INCOMPATIBILITIES

Furosemide may precipitate out of solution in fluids of low pH (e.g. dextrose solutions).

6.3 SHELF LIFE

Please refer to the outer carton for expiry date.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

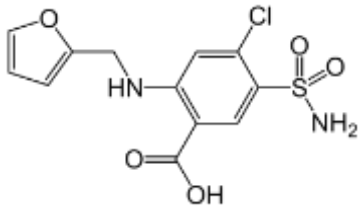
Store below 30 °C in original packaging. Protect from light. Do not freeze.

6.5 NATURE AND CONTENTS OF CONTAINER

Furosemide – AFT injections are presented in amber, Type I glass ampoules. 5 ampoules are placed in the contour-cell-type packing (PVC blister). Two contour-cell-type packings together with the product information are placed in a carton.

6.6 PHYSICOSHEMICAL PROPERTIES

Chemical structure



CAS number

54-31-9

ATC code

C03CA01

7 MEDICINE SCHEDULE

Prescription only medicine

8 MANUFACTURER

PrJSC “Pharmaceutical Firm “Darnitsa”

Address: 13 Boryspilska Str.,

Kiev, 02093, Ukraine.

9 DATE OF FIRST APPROVAL

XXX

10 DATE OF REVISION

XXX