NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Furosemide-AFT 20 mg/ 2 mL solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

3 PHARMCEUTICAL FORM

Furosemide – AFT solution for injection is a colourless or light yellow, clear, sterile aqueous solution contained in a 2 mL amber glass ampoule.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Oedema:

Furosemide – AFT is indicated in adults, infants and children for the treatment of oedema associated with congestive heart failure, cirrhosis of the liver and renal disease including the nephrotic syndrome. It is particularly useful when an agent with greater diuretic potential than that of those commonly employed is desired. Parenteral therapy should be reserved for patients unable to take oral medication or for patients in emergency clinical situations.

Furosemide – AFT solution for injection is also indicated as adjunctive therapy in acute pulmonary oedema and cerebral oedema where intense and rapid onset of diuresis is desired. If gastrointestinal absorption is impaired or oral medication is not practical for any reason, Furosemide – AFT is indicated by the intravenous route. Parenteral use should be replaced with oral furosemide (frusemide) as soon as practical.

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.

If a test dose of 40 to 80 mg furosemide (frusemide), injected slowly IV over about 2 to 5 minutes, does not lead to increased diuresis within 30 minutes, infusion treatment with furosemide (frusemide) High Dose 250 mg is indicated.

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 within 1 hour, the dose may be increased to 80 mg injected slowly intravenously. If necessary, additional therapy (e.g. digitalis, oxygen) may be administered concomitantly.

Cerebral Oedema

The following procedure is recommended, pending further experience:

Intravenous injection of 20 to 40 mg three times daily. A more uniform diuretic action is obtained if the same doses are infused. The rate of infusion must be determined individually in accordance with the diuretic action and the neurological findings.

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. If the diuretic response to the initial dose is not satisfactory, dosage may be increased by 1 mg/kg not sooner than 2 hours after the previous dose, until the desired effect has been obtained. Doses of greater than 6 mg/kg body weight are not recommended.

Furosemide-AFT solution for 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.

The chemical stability of diluted Furosemide – AFT (diluted with 0.9% sodium chloride solution or Ringer's lactate solution) has been demonstrated for storage at 25 °C for 6 hours. The diluted solution must be protected from light and should be used as soon as practicable to reduce risk of microbiological hazard.

Furosemide (frusemide) may precipitate in, and therefore is incompatible with, solutions in which the pH of the resulting mixture is less than 5.5. Furosemide (frusemide) should not be added into the tubing of a running infusion solution. Also, it should not be mixed with any other drugs in the infusion bottle.

4.3 CONTRAINDICATIONS

Furosemide-AFT solution for injection is contraindicated in patients with:

- Known hypersensitivity to furosemide (frusemide) or sulfonamides or any of the inactive ingredients (see Section 6.1 List of excipients). Patients allergic to sulfonamides (e.g. sulfonamide antibiotics or sulfonylureas) may show cross-sensitivity to Furosemide – AFT.
- Complete renal shutdown; impaired renal function; anuria; glomerular filtration rate below 5 mL/ min or above 20 mL/ min and renal failure due to poisoning with nephrotoxic or hepatotoxic substances; severe hyponatraemia, hypokalaemia, hypovolaemia, dehydration or hypotension until electrolytes, volume and blood pressure have returned to normal.
- Patients with normal renal function because there is a risk of severe fluid and electrolyte loss.
- Hepatic cirrhosis; existing or impeding hepatic coma. Jaundiced infants or infants with conditions or precoma and conditions which might induce hyperbilirubinaemia or kernicterus (e.g. Rhesus incompatibility, familial non-haemolytic jaundice etc).
- In breast-feeding or pregnant women.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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.

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

In patients with hepatic cirrhosis and ascites, initiation of therapy with furosemide (frusemide) 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.

Cases of reversible or irreversible tinnitus or hearing impairment have been reported. Usually, reports indicate that furosemide (frusemide) 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, ethacrynic acid, or other ototoxic medicines. In patients with hypoproteinaemia, e.g. associated with nephrotic syndrome, the effect of furosemide (frusemide) 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 4mg furosemide (frusemide) per minute must be used; for adults with

impaired renal function [creatinine > 5mg/dL], an infusion rate of no greater than 2.5mg per minute must be used).

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

Caution should be exercised and the risks and benefits of combining risperidone with furosemide (frusemide) 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 (frusemide) 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 (frusemide) 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 (frusemide).

Furosemide (frusemide) 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 urinate outflow (e.g. in patients with bladder emptying disorders, prostatic hyperplasia or narrowing of the uretha), increased production of urine may provoke or aggravate complaints. These patients require careful monitoring.

Particularly careful monitoring is required in patients with gout, with partial obstruction of urinary outflow, in patients with hypotension or at risk from hypotension (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. 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 (frusemide) administered during the first weeks of life may increase the risk of persistence of Botallo's duct.

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 (frusemide) 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 (frusemide).

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 (frusemide) therapy may be required.

Periodic checks on urine and blood glucose should be made in diabetics and even those suspected of latent diabetes when receiving. 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 (frusemide) may lower calcium levels, and rare cases of tetany have been reported. Accordingly, periodic serum calcium levels should be obtained.

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

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

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

Renal calcifications (from barely visible on X-ray to staghorn) have occurred in some severely premature infants treated with intravenous furosemide (frusemide) 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.

The possibility exists of exacerbation or activation of systemic lupus erythematosus. Asymptomatic hyperuricaemia can occur and rarely, gout may be precipitated.

When furosemide (frusemide) is administered parenterally, a maximum injection rate of 4mg/minute should be used to minimise the risk of ototoxicity.

Intramuscular administration of furosemide (frusemide) 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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Combinations that are not recommended

Antibiotics

Furosemide (frusemide) 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 (frusemide). In isolated cases intravenous administration of furosemide (frusemide) within 24 hours of taking chloral hydrate may lead to flushing, sweating attacks, restlessness, nausea, increase in blood pressure and tachycardia. Use of furosemide (frusemide) concomitantly with chloral hydrate is, therefore, not recommended.

Combinations that require precautions

Etacrynic acid or cisplatin

Furosemide (frusemide) 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 (frusemide) 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 (frusemide) 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.

Sucralfate

Administration of furosemide (frusemide) and sucralfate within two hours of each other should be avoided, as sucralfate reduces the absorption of furosemide (frusemide) and hence, reduces its effect.

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 (frusemide) 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 (frusemide) 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 (frusemide). 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 (frusemide) and neuromuscular blocking agents have been reported. These appear to be dependent on the dose of furosemide (frusemide) and the neuromuscular blocking agent involved. Low doses of furosemide (frusemide) (0.1 - 10 µg/kg) enhance the neuromuscular blockade of tubocurarine and succinylcholine. High doses (1 - 5 mg/kg) of furosemide (frusemide) 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 (amphotericin)

The combination of furosemide (frusemide) 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 (frusemide).

Drugs eliminated by renal tubular secretion

Phenytoin, methotrexate, probenecid and other drugs which, like furosemide (frusemide), undergo significant renal tubular secretion may reduce the effect of furosemide (frusemide). Conversely, furosemide (frusemide) may decrease renal elimination of these drugs. In the case of high dose treatment (in particular of both furosemide (frusemide) and the other drugs), this may lead to an increased risk of adverse effects due to furosemide (frusemide) or the concomitant medication.

Theophylline

IV furosemide (frusemide) 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 (frusemide) (see Section 4.4 Special warnings and precautions for use).

Cephalosporins

Impairment of renal function may develop in patients receiving concurrent treatment with furosemide (frusemide) 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 (frusemide) is associated with increased risk of gouty arthritis secondary to furosemide (frusemide) – induced hyperuricemia and ciclosporin impairment of renal urate excretion.

Radiocontrast

Patients who were at high risk for radiocontrast nephropathy treated with furosemide (frusemide) experienced a higher incidence of deterioration in renal function after receiving radiocontrast compared to high-risk patient who received only intravenous hydration prior to receiving radiocontrast.

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 (frusemide) and bumetanide, are probably also associated with this risk. During the latter part of pregnancy, products of this type should only be given on sound indications, and then in the lowest effective dose. In pregnancy, furosemide (frusemide) must only be used in patients with a marked reduction in glomerular filtration.

Use in lactation

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

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 (UNDESIRABLE EFFECTS)

Whenever adverse reactions are moderate or severe, furosemide (frusemide) 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 (frusemide), 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 (frusemide)).

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 (frusemide) may lower the serum calcium level (hypocalcemia) which may trigger a state of increased neuromuscular irritability. Furosemide (frusemide) 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 (frusemide) treatment. Metabolic alkalosis has been reported with furosemide (frusemide) use.

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 (frusemide).

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

Tabulated list of adverse reactions

The following undesirable effects have been reported. They are presented in the following table by system organ class (SOC) and ranked under heading of frequency.

The following CIOMS frequency rating is used:

Very common: ≥ 10%

Common: ≥ 1 and < 10%;

Uncommon: ≥ 0.1 and < 1%;

Rare: ≥ 0.01 and < 1.0%;

Very rare: < 0.01%;

Not known: cannot be estimated from available data.

System organ class	Frequency and symptom
Blood and the lymphatic system disorders	*Common*: haemoconcentration *Uncommon*: thrombocytopenia *Rare*: eosinophilia, thrombophlebitis, haemolytic or aplastic anaemia, leukopaenia and agranulocytosis
Immune system disorders	*Rare*: severe anaphylactic or anaphylactoid reactions (e.g. with shock), but is acutely life threatening if it does occur *Not known*: exacerbation or activation of systemic lupus erythematosus

System organ class	Frequency and symptom
Metabolism and nutritional disorders	*Very common*: electrolyte disturbances (including symptomatic), dehydration and hypovolaemia especially in elderly patients, increased blood creatinine and 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. *Not known*: Latent diabetes mellitus may manifest. Pseudo-Bartter syndrome in the context of misuse and/or long- term use of furosemide (frusemide). Hypomagnesaemia, blood urea increased, hypocalcemia and metabolic alkalosis
Nervous system disorders	*Common*: hepatic encephalopathy in patients with hepatocellular insufficiency *Rare*: paraesthesia *Not known*: headache, dizziness, fainting or loss of consciousness have been reported. Reactions such as vertigo, and blurred vision occasionally accompany furosemide (frusemide) induced diuresis.
Ear and labyrinth disorders	*Uncommon*: hearing disorders although usually transitory and cases of deafness, sometimes irreversible. *Rare*: permanent tinnitus and impairment of hearing
Vascular disorders	*Very common*: hypotension including orthostatic hypotension *Rare*: vasculitis *Not known*: thrombosis
Gastrointestinal disorders	*Uncommon*: anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhoea and constipation. In isolated cases, acute pancreatitis has been observed.
Hepato-biliary disorders	In isolated cases increases in transaminases have been observed. *Not known*: cholestasis and jaundice. Furosemide (frusemide) may increase the bile flow and distend the biliary tree which is already obstructed.
Skin and subcutaneous tissue disorders	*Uncommon*: allergic reactions including dermatitis bullous, rashes, urticaria, pruritus, photosensitivity reactions, pemphigoid, erythema multiforme, purpura and exfoliative dermatitis. *Rare*: cases of necrotising angitis, Steven-Johnson syndrome, toxic epidermal necrolysis. *Not known*: Itching, AGEP (acute generalized exanthematous pustulosis), lichenoid reactions and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms).
Musculoskeletal and connective tissue disorders	Not known: cases of rhabdomyolysis, often in the context of severe hypokalaemia (see Section 4.3).

System organ class	Frequency and symptom
Renal and urinary disorders	*Rare*: tubulointerstitial nephritis *Not known*: transient elevation of creatinine and BUN, reduction of GFR, urine retention (in patients with partial obstruction of urinary flow), nephrocalcinosis/ nephrolithiasis, increases in urine sodium and chloride, and renal failure. Existing conditions of obstructed micturition may be triggered or aggravated.
Congenital and familial/genetic disorders	*Not known*: The persistence of patent ductus arteriosus when furosemide (frusemide) has been administered to a premature infant during the first weeks.
General disorders and administration site conditions	*Rare*: fever *Not known*: restlessness and following intramuscular injection, local reactions such as pain

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

Symptoms

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 (frusemide) 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 (frusemide) in biological fluids associated with toxicity or death is not known.

Treatment

No specific antidote to furosemide (frusemide) 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.

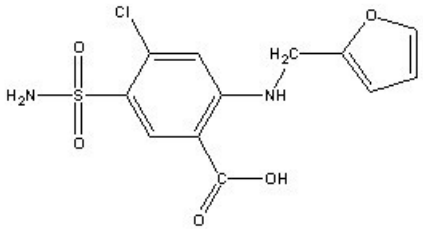
Treatment of overdosage is supportive and consists of replacement of excessive fluid and electrolyte losses. Serum electrolytes, carbon dioxide level and blood pressure should be determined frequently. Adequate drainage must be assured in patients with urinary

bladder outlet obstruction (such as prostatic hypertrophy). Haemodialysis does not accelerate furosemide (frusemide) elimination.

For advice on the management of overdose please contact the National Poisons Centre on phone number: 0800 764 766 [0800 POISON].

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group	Cardiovascular system, high-ceiling diuretic
ATC code	C03CA01
Chemical name	4-chloro-N-furfuryl-5-sulfamoylanthranilic acid
Chemical structure	
CAS number	54-31-9

Mechanism of action

Furosemide (frusemide) 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.

Pharmacodynamic effects

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

Furosemide (frusemide) 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 (frusemide) 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 (frusemide) glucuronide is the only, or at least the major, bio-transformation product of furosemide (frusemide) 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 (frusemide) 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 newborn infants.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available

Carcinogenicity

No data available

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

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

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30 °C in original packaging. Protect from light. Do not freeze. Occasionally crystal deposits may be seen when Furosemide-AFT ampoules are stored at low temperatures. Dissolve crystals by warming to 40 °C and injection may be used.

6.5 NATURE AND CONTENTS OF CONTAINER

Furosemide – AFT solution for injections are presented in 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 SPECIAL PRECAUTIONS FOR DISPOSAL

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

7 MEDICINE SCHEDULE

Prescription only medicine

8 SPONSOR

AFT Pharmaceuticals Ltd.
PO Box 33-203, Takapuna
Auckland 0740, New Zealand

Phone: 0800-423-823

Email: customer.service@aftpharm.com

9 DATE OF FIRST APPROVAL

15 August 2024

10 DATE OF REVISION

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