AUSTRALIAN PRODUCT INFORMATION – LASIX® HIGH DOSE (FUROSEMIDE)

1 NAME OF THE MEDICINE

Furosemide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Lasix High Dose injection contains 250 mg/25 mL furosemide in water for injection (without solubiliser, pH about 9)

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Furosemide is a white to off-white odourless crystalline powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Furosemide high-dosage formulations are intended exclusively for patients with severely impaired renal function. Use under strict medical supervision only within a hospital setting (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). High doses of furosemide may be used as an adjuvant treatment of oliguria and in the promotion of diuresis in the treatment of oedema; in selected patients with acute renal failure (e.g. in the post-operative phase and in association with septic infections), in selected patients with chronic renal failure with fluid retention, both in the pre-dialysis phase and when dialysis has become unavoidable, especially in the presence of acute pulmonary oedema; and in selected patients with the nephrotic syndrome with severe impairment of renal function (e.g. in chronic glomerular nephritis, lupus erythematous and Kimmelstiel-Wilson syndrome). If diuresis is less than 2.5 L/day, dialysis has to be used.

4.2 DOSE AND METHOD OF ADMINISTRATION

The high dosage preparations are intended exclusively for administration to patients with greatly reduced glomerular filtration rate (GFR less than 20 mL/min but greater than 5 mL/min). Normal doses of Lasix are usually adequate in patients with greatly reduced GFR if functional oliguria or anuria is observed. Thus, test a normal dose of Lasix first, before administering Lasix High Dose.

Furosemide is given intravenously only when oral administration is not feasible or is ineffective or if 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 furosemide infusion is generally preferred to repeated bolus injections.

Before treatment of patients in shock is started, hypovolaemia and hypotension should be dealt with by suitable measures. Similarly, disturbed serum electrolytes and acid-base balance should first be corrected.

When treating patients with conditions likely to interfere with micturition, such as prostatic hypertrophy or disturbed consciousness, it is absolutely essential to ensure free urinary drainage. Because of the wide and unpredictable individual variations in responsiveness it is important to adjust dosage and route of administration to individual needs.

Once the desired rise in urinary output has begun, exact balance of water intake and water output must be maintained throughout the course of treatment so as to avoid hypovolaemia or hypotension. Careful electrolyte replacement is also necessary.

The dosage of high strength furosemide given below is for adults only. The dosage regimen for children has not yet been determined. The administration of large doses of furosemide in children has been associated with permanent deafness (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Intravenous Infusion

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

Infusion fluid Lasix High Dose for IV use is a mildly buffered alkaline solution. Lasix High Dose can be added to 5% Dextrose in water Isotonic Saline or Lactated Ringer's Injection when mixed as directed and prepared immediately before use. Furosemide may precipitate in, and therefore is incompatible with, solutions in which the pH of the resulting mixture is less than 5.5. Furosemide 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.

Initial dose

The contents of one ampoule (250 mg/25 mL) are infused together with 250 mL of neutral to alkaline isotonic solution. The rate of infusion should not exceed 4 mg/minute, otherwise there is a risk of ototoxicity (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Thus the duration of infusion should be about 60 minutes. The diuresis should start during the infusion.

Additional dose

Should the initial dose fail to produce an adequate increase (at least 40 to 50 mL/hour) in urinary output, a second infusion of 500 mg (appropriately diluted) may be given 1 hour after completion of the first.

The duration of this infusion is determined by the maximum rate of furosemide 4 mg/minute. A maximum daily dose of 1000 mg should not be exceeded.

For hypervolaemic patients, it is advisable to give the high-dosage formulation of furosemide undiluted, or in a suitable volume (e.g. 250 mg in 50 mL) of infusion fluid, so as to avoid the risk of over-hydration. IV infusions of the undiluted solution must be given with the aid of a motor-driven precision syringe, so as to make sure that the upper limit of furosemide 4 mg (0.4mL) /minute is not exceeded.

If a satisfactory diuretic response is achieved (40 to 50 mL/hour), the effective dose can be repeated every 24 hours.

4.3 CONTRAINDICATIONS

Patients with a history of hypersensitivity to furosemide or sulphonamides or any of the ingredients (see Section 6.1 LIST OF EXCIPIENTS). Patients allergic to sulphonamides (eg sulphonamide antibiotics or sulfonylureas) may show cross-sensitivity to furosemide.

Lasix High Dose is contraindicated in 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, (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS), hypovolaemia, dehydration or hypotension until electrolytes, volume and blood pressure have returned to normal.

Lasix High Dose is contraindicated in patients with normal renal function because there is a risk of severe fluid and electrolyte loss.

Hepatic cirrhosis; existing or impending hepatic coma. Jaundiced infants or infants with conditions which might induce hyperbilirubinaemia or kernicterus (e.g. Rhesus incompatibility, familial non-haemolytic jaundice etc).

Lasix High Dose must not be used in breast-feeding or pregnant women.

Lasix High Dose injection must not be used as a bolus injection. It must only be infused using volume or rate controlled infusion pumps to reduce the risk of accidental overdose.

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.

Cases of reversible or irreversible tinnitus or hearing impairment have been reported. Usually, reports indicate that Lasix 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 Lasix 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 Lasix 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 Lasix 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.

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.

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. 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.

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 Lasix 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 CO2 content determinations. This is particularly important when the patient is at high risk of developing electrolyte imbalances

(eg. 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 Lasix.

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.

Periodic checks on urine and blood glucose should be made in diabetics and even those suspected of latent diabetes when receiving Lasix. 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.

Lasix 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. 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 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 drugs, 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 Lasix 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 Lasix is administered parenterally, a maximum injection rate of 4 mg/minute should be used to minimise the risk of ototoxicity.

Intramuscular administration of Lasix 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.

During treatment with furosemide in high-dosage formulations, extreme care must always be taken to adjust dosage to individual requirements. Rate of infusion must not exceed 4 mg/min.

Use in hepatic impairment

In patients with hepatic cirrhosis and ascites, initiation of therapy with Lasix 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 the elderly

No data available

Paediatric use

High dose Lasix preparations should not be used in children. However, normal doses of Lasix may be used (refer to Lasix Product Information).

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Combinations that are not recommended

Antibiotics

Lasix 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

Lasix 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 Lasix 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.

Sucralfate

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

Antihypertensives

The action of other antihypertensive drugs may be potentiated by Lasix, especially in combination with ACE inhibitors. The administration of ACE inhibitors to patients pretreated 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 Lasix temporarily or at least reducing the dose of Lasix 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 Lasix 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 Combination 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 Lasix 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 (amphotericin)

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

Noradrenaline (norepinephrine)

Lasix 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 Lasix, 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 Lasix 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 effects 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.

Radiocontrast

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.

Interactions with Food

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available

Use in pregnancy

Category C

Lasix 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. 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 must only be used in patients with a marked reduction in glomerular filtration.

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 (UNDESIRABLE EFFECTS)

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

Metabolism and Nutritional 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 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, dermatitis bullous, 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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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 Lasix has been determined in mice, rats and dogs. In all three, the oral LD50 exceeded 1000 mg/kg body weight, while the intravenous LD50 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 Lasix in biological fluids associated with toxicity or death is not known.

No specific antidote to Lasix 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Diuretics, ATC code: C03CA01

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Lasix 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.

Clinical trials

No data available

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Furosemide is rapidly absorbed from the GIT. Absorption rates in healthy subjects have been reported from 60-69% and from 43-46% in patients with end stage renal failure.

The onset of diuresis following oral administration is within 1 hour. The peak effect occurs within the first or second hour. The duration of diuretic effect is 6 to 8 hours.

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.

In fasted normal men, the mean bioavailability of furosemide from Lasix Tablets and Lasix Oral Solution is 64% and 60% respectively of that from an intravenous injection of the drug. Although furosemide is more rapidly absorbed from the oral solution (50 minutes) than from the tablet (87 minutes), peak plasma levels and area under the plasma concentration-time curves do not differ significantly. Peak plasma concentrations increase with increasing dose but times-to-peak do not differ among doses.

Distribution

Furosemide is extensively bound to plasma proteins, mainly to albumin. Plasma concentrations ranging from 1 to 400 mg/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. There are no significant differences between the two oral formulations in the amount of unchanged drug excreted in urine.

Furosemide has a biphasic half life in the plasma with t1/2 ranging up to 100 minutes; t1/2 is prolonged by renal and hepatic insufficiency and in new born infants.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available

Carcinogenicity

No data available

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mannitol
Sodium hydroxide
Contains 0.03 mmol/mL of sodium
Water for injections

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Ampoules: Store below 25°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Lasix High Dose 250 mg/25 mL ampoules (in water for injection without solubiliser, pH about 9): 6 amber glass ampoules.

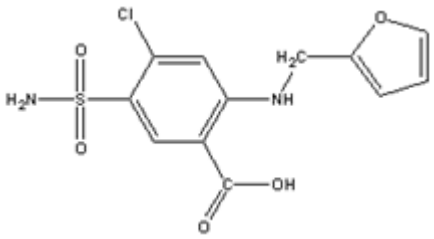
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Lasix is an anthranilic acid derivative. Chemically it is 4-chloro-N-furfuryl-5-sulphamoylanthranilic acid. It is practically insoluble in water, sparingly soluble in alcohol, freely soluble in dilute alkali solutions and insoluble in dilute acids.

Chemical structure



CAS number

54-31-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

sanofi-aventis australia pty ltd
International Tower 3, Level 23
300 Barangaroo Avenue
Sydney NSW 2000
Freecall: 1800 818 806
Email: medinfo.australia@sanofi.com

9 DATE OF FIRST APPROVAL

01 August 1991

10 DATE OF REVISION

02 June 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Sponsor details updated