

DATA SHEET

1 PRODUCT NAME

Lasix Oral solution 10mg/mL

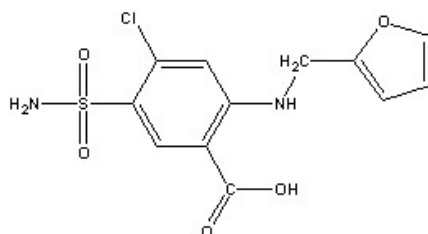
Lasix High Dose Solution for infusion 10mg/mL

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Furosemide (frusemide) Oral solution 10mg/mL

Furosemide (frusemide) High Dose Solution for infusion 10mg/mL in water for injection (without solubiliser, pH about 9)

Chemical Structure



CAS Number

54-31-9

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Lasix is an anthranilic acid derivative. Chemically, it is 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid. Furosemide (Frusemide) is a white to off-white odourless crystalline powder. It is practically insoluble in water, sparingly soluble in alcohol, freely soluble in dilute alkali solutions and insoluble in dilute acids.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Oedema

Lasix 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. Lasix 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.

Lasix 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, Lasix is indicated by the intravenous route. Parenteral use should be replaced with oral Lasix as soon as practical.

Hypertension

Oral Lasix may be used in adults for the treatment of hypertension alone or in combination with other antihypertensive agents. Hypertensive patients who cannot be adequately controlled with thiazides will probably also not be adequately controlled with Lasix alone.

4.2 DOSE AND METHOD OF ADMINISTRATION

Lasix Oral Administration

Oedema

Therapy should be individualised according to patient's response. This therapy should be titrated to gain maximal therapeutic response with the minimum dose possible to maintain that diuretic response.

Adults:

The usual initial daily dose is 20 to 80 mg given as a single dose. If the diuretic response to a single dose of 20 to 80 mg is not satisfactory, increase this dose by increments of 20 to 40 mg, not sooner than 6 to 8 hours after the previous dose, until the desired diuretic effect is obtained. This individually determined dose should be given once or twice (e.g. at 8 am and 2 pm) daily. The dose of Lasix may be carefully titrated up to 400 mg/day (except in advanced renal failure) in those patients with severe clinical oedematous states. The mobilisation of oedema may be most efficiently and safely accomplished by giving Lasix on 2 to 4 consecutive days each week.

When doses exceeding 80 mg/day are given for prolonged periods, careful clinical laboratory observations are particularly advisable.

Infants and Children:

The usual initial dose of oral Lasix for infants and children is 2mg/kg body weight given as a single dose. If the diuretic response is not satisfactory, the dose may be increased by 1 to 2 mg/kg no sooner than 6 to 8 hours after the previous dose. Doses of greater than 6 mg/kg body weight are not recommended.

For maintenance therapy in infants and children, the dose should be adjusted to the minimum effective level.

Hypertension

Therapy should be individualised according to the patient's response. This therapy should be titrated to gain maximal therapeutic response with the minimum dose possible to maintain that therapeutic response.

Adults:

The usual initial daily dose of Lasix for hypertension is 80 mg, usually divided into 40 mg twice a day. Dosage should then be adjusted according to response. If response is not satisfactory, add other antihypertensive agents.

Changes in blood pressure must be carefully monitored when Lasix is used with other antihypertensive drugs, especially during initial therapy.

To prevent an excessive drop in blood pressure, the dosage of other agents should be reduced by at least 50% when Lasix is added to the regimen. As the blood pressure falls under the potentiating effect of Lasix, a further reduction in dosage or even discontinuation of other antihypertensive drugs may be necessary.

Lasix High Dose Parenteral 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 (frusemide) 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 (frusemide) 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 (frusemide) given below is for adults only. The dosage regimen for children has not yet been determined. The administration of large doses of furosemide (frusemide) in children has been associated with permanent deafness (see **Section 4.4**).

Lasix High Dose - 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 (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.

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**). 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 (frusemide) 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 (frusemide) 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 motordriven precision syringe, so as to make sure that the upper limit of furosemide (frusemide) 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.

Use in Children

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

4.3 CONTRAINDICATION

Known hypersensitivity to furosemide (frusemide) or sulfonamides or any of the inactive ingredients. Patients allergic to sulfonamides (e.g. sulfonamide antibiotics or sulfonyleureas) may show cross-sensitivity to Lasix.

Lasix

Complete renal shutdown, impaired renal function or anuria. If increasing azotaemia and oliguria occur during treatment of severe progressive renal disease, discontinue furosemide (frusemide). Severe hypokalaemia, (see **Section 4.8**), 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 (frusemide) therapy should not be instituted until the underlying conditions have been corrected or ameliorated.

Breast-feeding or pregnant women.

Do not administer furosemide (frusemide) to newborns presenting jaundice or to infants with conditions which might induce hyperbilirubinaemia or kernicterus (e.g. Rhesus incompatibility, familial nonhaemolytic jaundice etc.) because of furosemide's (frusemide's) 'in vitro' potential to displace bilirubin from albumin.

Lasix High Dose

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

Breast-feeding or pregnant women.

Lasix 250 mg 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.

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.

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, ethacrynic 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 (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 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 (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 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 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 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 (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 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 (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 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.

Excipient Warning

Ethanol (Alcohol) – Lasix Oral Solution (not requiring refrigeration) contains 12.7% v/v ethanol (alcohol). The safety of ethanol at a concentration of 12.7% v/v in a medicine intended for use in children has not been established. This should be taken into consideration when deciding whether to prescribe Lasix Oral Solution in this age group.

The ethanol content of this formulation (0.5g per 5ml dose) is harmful to those suffering from alcoholism. This should also be taken into account in pregnant or breast feeding women, children and high-risk groups such as patients with liver disease, or epilepsy.

The sorbitol present in the vehicle may cause diarrhoea (especially in children) when higher doses of Lasix Oral Solution are given.

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.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

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.

Interactions with other Medicines

Combinations that are not recommended

Lasix may increase the ototoxic and nephrotoxic potential of certain antibiotics (eg. 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 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.

Precautions for use

Lasix should not be used concomitantly with ethacrynic 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.

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.

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

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 (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 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.

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** regarding increased mortality in elderly patients with dementia concomitantly receiving risperidone.

High doses of furosemide (frusemide) may inhibit binding of thyroid hormones to carrier proteins when administered with levothyroxine, 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.

Take into account

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**). Carbenoxolone, corticosteroids, prolonged use of laxatives or ingestion of liquorice in large amounts may also predispose a patient to hypokalaemia.

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.

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 mg/kg) enhance the neuromuscular blockade of tubocurarine and succinylcholine. High doses (1-5mg/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.

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

Lasix may decrease arterial responsiveness to noradrenaline. 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 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 (frusemide).

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.

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.

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

It should be borne in mind that the effect of antidiabetics or of pressor amines (e.g. adrenaline, noradrenaline) may be attenuated by furosemide (frusemide) (see **Section 4.4**).

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.

Concomitant use of cyclosporine A and furosemide (frusemide) is associated with increased risk of gouty arthritis secondary to furosemide-induced (frusemide-induced) hyperuricemia and cyclosporine impairment of renal urate excretion.

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 patients who received only intravenous hydration prior to receiving radiocontrast.

4.6 FERTILITY, PREGNANCY AND LACTATION

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 thrombocytopenia 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 UNDESIRABLE EFFECTS

a. Summary of the safety profile

Whenever adverse reactions are moderate or severe, furosemide (frusemide) 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 (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 4.4**) 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 Lasix 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. Treatment with furosemide (frusemide) has occasionally caused reduced glucose tolerance and deterioration in cases of manifest diabetes, or made latent diabetes manifest.

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. 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.

b. 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: $\geq 10\%$; 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	<p>Common: haemoconcentration</p> <p>Uncommon: thrombocytopenia</p> <p>Rare: eosinophilia, thrombophlebitis, haemolytic or aplastic anaemia, leukopaenia and agranulocytosis</p>
Immune system disorders	<p>Rare: severe anaphylactic or anaphylactoid reactions (e.g. with shock), but is acutely lifethreatening if it does occur</p> <p>Not known: exacerbation or activation of systemic lupus erythematosus</p>
Metabolism and nutritional disorders	<p>Very common: electrolyte disturbances (including symptomatic), dehydration and hypovolaemia especially in elderly patients, increased blood creatinine and increased blood triglycerides</p> <p>Common: hyponatremia, hypochloremia, hypokalaemia, blood cholesterol increased, blood uric acid increased and attacks of gout, urine volume increased</p> <p>Uncommon: impaired glucose tolerance-</p> <p>Not known:</p> <p>Latent diabetes mellitus may manifest.</p> <p>Pseudo-Bartter syndrome in the context of misuse and/or long-term use of furosemide (frusemide).</p> <p>Hypomagnesaemia, blood urea increased, hypocalcemia and metabolic alkalosis</p>

System organ class	Frequency and symptom
Nervous system disorders	<p>Common: hepatic encephalopathy in patients with hepatocellular insufficiency</p> <p>Rare: paraesthesia</p> <p>Not known: headache, dizziness, fainting or loss of consciousness have been reported.</p> <p>Reactions such as vertigo, and blurred vision occasionally accompany Lasix induced diuresis.</p>
Ear and labyrinth disorders	<p>Uncommon: hearing disorders although usually transitory and cases of deafness , sometimes irreversible.</p> <p>Rare: permanent tinnitus and impairment of hearing</p>
Vascular disorders	<p>Very common: hypotension including orthostatic hypotension</p> <p>Rare: vasculitis</p> <p>Not known: thrombosis</p>
Gastrointestinal disorders	<p>Uncommon: anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhoea and constipation.</p> <p>In isolated cases, acute pancreatitis has been observed.</p>
Hepato-biliary disorders	<p>In isolated cases increases in transaminases have been observed.</p> <p>Not known: cholestasis and jaundice</p> <p>Furosemide (Frusemide) may increase the bile flow and distend the biliary tree which is already obstructed.</p>

System organ class	Frequency and symptom
Skin and subcutaneous tissue disorders	<p>Uncommon: allergic reactions including dermatitis bullous, rashes, urticaria, pruritus, photosensitivity reactions, pemphigoid, erythema multiforme, purpura and exfoliative dermatitis.</p> <p>Rare: cases of necrotising angitis, Steven-Johnson syndrome, toxic epidermal necrolysis.</p> <p>Not known: Itching, AGEP (acute generalized exanthematous pustulosis), lichenoid reactions and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms).</p>
Musculoskeletal and connective tissue disorders	<p>Not known: cases of rhabdomyolysis, often in the context of severe hypokalaemia (see Section 4.3).</p>
Renal and urinary disorders	<p>Rare: tubulointerstitial nephritis</p> <p>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.</p> <p>Existing conditions of obstructed micturition may be triggered or aggravated.</p>
Congenital and familial/genetic disorders	<p>Not known: The persistence of patent ductus arteriosus when furosemide (frusemide) has been administered to a premature infant during the first weeks.</p>
General disorders and administration site conditions	<p>Rare: fever</p> <p>Not known: restlessness and following intramuscular injection, local reactions such as pain</p>

Reporting of suspected adverse reactions

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

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 hypochloreaemic 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 (frusemide) elimination.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Site and Mode 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 (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

Furosemide (Frusemide) 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 (frusemide) from Lasix Tablets and Lasix Oral Solution is 64% and 60% respectively of that from an intravenous injection of the drug. Although furosemide (frusemide) 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 (Frusemide) is extensively bound to plasma proteins, mainly to albumin. Plasma concentrations ranging from 1 to 400 $\mu\text{g/ml}$ are found 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, biotransformation 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. There are no significant differences between the two oral formulations in the amount of unchanged drug excreted in urine.

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.

5.3 PRECLINICAL SAFETY DATA

No further relevant information other than that which is included in the other sections of the Data Sheet.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Lasix Oral Solution

Inactive ingredients include sorbitol, glycerol, sodium hydroxide, methyl parahydroxybenzoate, propyl parahydroxybenzoate, ethanol, quinoline yellow, sunset yellow S E110, orange flavour, purified water.

Ethanol (Alcohol) – This medicinal product contains 12.7% v/v ethanol (alcohol), i.e. up to 0.5g per 5ml of dose (See **Section 4.4**).

Lasix High Dose

Inactive ingredients include mannitol and sodium hydroxide. Contains 0.03 mmol/mL of sodium.

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

Lasix Oral Solution: 24 months from date of manufacture. Once opened 8 weeks.

Lasix High Dose: 36 months from date of manufacture.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Lasix Oral Solution should be stored below 25°C. Protect from light.

Lasix High Dose should be stored below 25°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Lasix Oral Solution for paediatric use, 10 mg/mL glass bottle (orange flavoured, 35% sorbitol solution): 30 mL.

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

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

No special requirements

7 MEDICINE SCHEDULE

Prescription Only Medicine

8 SPONSOR

sanofi-aventis new zealand limited
Level 8, 56 Cawley Street
Ellerslie, Auckland
Freecall No: 0800 283 684

9 DATE OF FIRST APPROVAL

Lasix Oral Solution: 19 December 1977

Lasix High Dose: 4 February 1970

10 DATE OF REVISION OF THE TEXT

23 August 2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
6.3	Updated Lasix High Dose shelf life