NEW ZEALAND DATA SHEET

1 FUROSEMIDE-BAXTER (10mg/mL solution for injection)

Furosemide-Baxter 10mg/mL solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Furosemide-Baxter solution for injection contains 10mg frusemide per mL.

Furosemide-Baxter is available in 2mL and 5mL ampoules which contain 20mg/2mL and 50mg/5mL respectively.

Excipients with known effect
Sodium chloride and sodium hydroxide.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Appearance
Furosemide-Baxter solution for injection is a clear colourless solution for injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Oedema
Furosemide-Baxter solution for injection 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.

Frusemide 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-Baxter 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, frusemide is indicated by the intravenous route. Parenteral use should be replaced with oral frusemide as soon as practical.

4.2 Dose and method of administration

Adults
Parenteral therapy with **Furosemide-Baxter** solution for injection 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.

Oedema
The usual initial dose of **Furosemide-Baxter** is 20 to 40mg given as a single dose, injected intramuscularly or intravenously. The intravenous dose should be given slowly (see section 4.4). 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 20mg, 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-Baxter** to either Sodium Chloride Injection or Lactated Ringer's Injection, and administer as a controlled intravenous infusion at a rate not greater than 4mg/min. **Furosemide-Baxter** solution for injection is a buffered alkaline solution.

Acute Pulmonary Oedema

The usual initial dose of **Furosemide-Baxter** is 40mg injected slowly intravenously (see section 4.4). If a satisfactory response does not occur within 1 hour, the dose may be increased to 80mg 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 40mg 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-Baxter** solution for injection (intravenously or intramuscularly) in infants and children is 1mg/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 1mg/kg not sooner than 2 hours after the previous dose, until the desired effect has been obtained. Doses of greater than 6mg/kg body weight are not recommended.

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

Furosemide-Baxter solution for injection is for single use in one patient only. Discard any residue.

Although the chemical stability of diluted **Furosemide-Baxter** solution for injection has been demonstrated for storage at 25°C for 24 hours, the diluted solution should be used as soon as practicable to reduce risk of microbiological hazard. If storage is necessary, hold the diluted solution at 2 - 8°C for not more than 24 hours.

4.3 Contraindications

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

- Known hypersensitivity to frusemide or sulfonamides or any of the inactive ingredients (see section 6.1). Patients allergic to sulfonamides (e.g. sulfonamide antibiotics or sulfonylureas) may show cross-sensitivity to frusemide.
- Complete renal shutdown; impaired renal function; anuria; glomerular filtration rate below 5mL/min or above 20mL/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.
- **Furosemide-Baxter** 250mg solution for 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 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 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 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 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 frusemide therapy. It is also advisable to discontinue frusemide for one week prior to any elective surgery.

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

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 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 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 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 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.

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 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.

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

Intramuscular administration of 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 Interaction with other medicines and other forms of interaction

Combinations that are not recommended

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

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

Precautions for use

Frusemide 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 frusemide is not given in low doses (e.g. 40mg in patients with normal renal function) and with positive fluid balance when used to achieve forced diuresis during cisplatin treatment.

Frusemide decreases the excretion of lithium salts and my 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.

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

The action of other antihypertensive medication may be potentiated by frusemide, especially in combination with ACE inhibitors. The administration of ACE inhibitors to patients pre-treated with 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 frusemide temporarily or at least reducing the dose of frusemide 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 frusemide 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 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.

To be considered

The effects if digitalis preparations and medications inducing QT interval prolongation syndrome may be potentiated by changes in electrolyte concentrations e.g. hypokalaemia, hypomagnesaemia due to 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 medicines 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 frusemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites.

Interactions between frusemide and neuromuscular blocking agents have been reported. These appear to be dependent on the dose of frusemide and the neuromuscular blocking agent involved. Low doses of frusemide (0.1 - 10µg/kg) enhance the neuromuscular blockade of tubocurarine and succinylcholine. High doses (1 - 5mg/kg) of 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 frusemide and amphotericin may result in an excessive loss of potassium.

Frusemide 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 medications with blood-pressure lowering potential are given concomitantly with frusemide, 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 frusemide in some patients by inhibiting prostaglandin synthesis. In patients with dehydration or pre-existing hypovolaemia, non-steroidal anti-inflammatory drugs may cause renal failure. Salicylate toxicity may be increased by frusemide.

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

IV 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 medicines 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 frusemide (see section 4.4).

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

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

Patients who were at high risk for radiocontrast nephropathy treated with 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

Fertility

No information on fertility is available.

Pregnancy - Pregnancy category C

Frusemide 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 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, frusemide must only be used in patients with a marked reduction in glomerular filtration.

Breast-feeding

Frusemide passes into the breast milk and inhibits lactation. Women must not breast feed if being treated with 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, 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 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 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 (hyponatraemia), chloride (hypochloraemia), 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.

Frusemide may lower the serum calcium level (hypocalcaemia) which may trigger a state of increased neuromuscular irritability. 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 frusemide 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 frusemide treatment. Metabolic alkalosis has been reported with frusemide use. Treatment with 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 4mg per minute (normal renal function) or 2.5mg per minute (impaired renal function) is exceeded, or in patients who are also receiving medications known to be ototoxic. Cases of deafness, sometimes irreversible have been reported after administration of 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 uretostenosis 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 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 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
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 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 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 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).
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 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 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

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 frusemide has been determined in mice, rats and dogs. In all three, the oral LD_{50} exceeded 1000mg/kg body weight, while the intravenous LD_{50} ranged from 300 - 680mg/kg. The acute intragastric toxicity in neonatal rats is 7 to 10 times that of adult rats. The concentration of frusemide in biological fluids associated with toxicity or death is not known.

Treatment

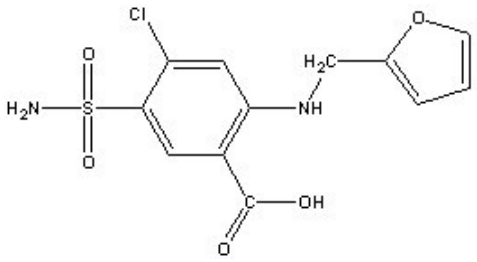
No specific antidote to frusemide is known. If ingestion has only just taken place, attempts may be made to limit further systemic absorption of the active ingredient by measures such as activated charcoal.

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 frusemide elimination.

For advice on the management of overdose please contact the National Poisons Centre on phone number: 0800 764 766 [0800 POISON] in New Zealand (or 131126 in Australia).

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.
Appearance	Frusemide is a white to off-white odourless crystalline powder.
Solubility	Practically insoluble in water, sparingly soluble in alcohol, freely soluble in dilute alkali solutions and insoluble in dilute acids.

Mechanism of action
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
Frusemide may promote diuresis in cases which have previously proved resistant to other diuretics.

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

5.2 Pharmacokinetic properties

Absorption
Frusemide is rapidly absorbed from the gastrointestinal tract. 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 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
Frusemide is extensively bound to plasma proteins, mainly to albumin. Plasma concentrations ranging from 1 - 400µg/mL are 91 - 99% bound in healthy individuals. The unbound fraction averages 2.3 - 4.1% at therapeutic concentrations.

Metabolism
Recent evidence suggests that frusemide glucuronide is the only, or at least the major, bio-transformation product of 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 frusemide is excreted in urine following the IV injection than after oral administration.

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 information other than that which is contained in other sections of the data sheet.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid
Sodium chloride
Sodium hydroxide
Water for injections.

6.2 Incompatibilities
In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life
3 years from date of manufacture.

6.4 Special precautions for storage
Store below 25°C. Protect from light.

Occasionally crystal deposits may be seen when **Furosemide-Baxter** ampoules are stored at low temperatures. Dissolve crystals by warming to 40°C and injection may be used.

Although the chemical stability of diluted **Furosemide-Baxter** solution for injection has been demonstrated for storage at 25°C for 24 hours, the diluted solution should be used as soon as practicable to reduce the risk of microbiological hazard. If storage is necessary, hold the diluted solution at 2 - 8°C (under refrigeration) for not more than 24 hours.

6.5 Nature and contents of container
Furosemide-Baxter solution for injection 10mg/mL ampoules are available in the following pack sizes:

- **20mg/2mL**: packs of 5 or 25 ampoules containing 2mL solution for injection.
- **50mg/5mL**: packs of 5 or 25 ampoules containing 5mL solution for injection.

Not all pack sizes may be available.

6.6 Special precautions for disposal and other handling
No special requirements.

7 MEDICINE SCHEDULE
Prescription only medicine.

8 SPONSOR
Furosemide-Baxter is distributed in New Zealand by:

Baxter Healthcare Ltd
33 Vestey Drive
Mt Wellington
Auckland 1060.

Baxter Healthcare Ltd
PO Box 14 062
Panmure
Auckland 1741

Phone (09) 574 2400.

Furosemide-Baxter is distributed in Australia by:
Baxter Healthcare Pty Ltd [ABN: 43 000 392 781]
1 Baxter Drive
Old Toongabbie, NSW 2146.

9 DATE OF FIRST APPROVAL
Date of publication in the New Zealand Gazette of consent to distribute the medicine:
22 October 2010.

10 DATE OF REVISION OF THE TEXT

15 October 2019.

SUMMARY TABLE OF CHANGES

Section	Summary of new information
ALL	Trade name changed. API name changed to BAN. Editorial changes: formatting, consistent use of units and headings.
3	Appearance information moved to correct section.
4.3, 4.4, 4.8	Safety information updated, including tabulation of undesirable effects.
5.1	Pharmacodynamic properties included.
6.4	Storage condition updated.

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.