GENRX FRUSEMIDE TABLETS

NAME OF THE MEDICINE
Frusemide.

Chemical Name: 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid.

Structural Formula:

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\text{[Structural formula image]}
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Molecular Formula: $\text{C}_{12}\text{H}_{11}\text{ClN}_{2}\text{O}_{5}\text{S}$
Molecular Weight: 330.70
CAS Registry Number: 54-31-9

DESCRIPTION
Frusemide is an anthranilic acid derivative.

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.

PHarmacology

Pharmacodynamics
Frusemide is a potent diuretic. It inhibits sodium and chloride absorption in the ascending limb of the loop of Henle and in both the proximal and the distal tubule. 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.

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.

Pharmacokinetics

Absorption
Frusemide is rapidly absorbed from the gastrointestinal tract. Absorption rates have been reported to be from 60 to 69% in healthy subjects and from 43 to 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. In fasted normal men, the mean bioavailability of frusemide from frusemide tablets is 64% of that from an intravenous injection of the drug. Peak plasma concentrations increase with increasing dose but times to peak do not differ among doses.

Distribution
Frusemide is extensively bound to plasma proteins, mainly to albumin. Plasma concentrations ranging from 1 to 400 μg/mL are 91 to 99% bound in healthy individuals. The unbound fraction averages 2.3 to 4.1% at therapeutic concentrations.
Metabolism
Recent evidence suggests that frusemide glucuronide is the only or at least the major biotransformation product of frusemide in humans.

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 intravenous injection than after tablet administration.

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

INDICATIONS

- **Oedema - Adults and Children**
  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 with frusemide should be reserved for patients unable to take oral medication or for patients in emergency clinical situations. If gastrointestinal absorption is impaired or oral medication is not practical for any reason, frusemide is indicated by the intravenous or intramuscular route. Parenteral use should be replaced with oral frusemide as soon as practical.

- **Hypertension - Adults**
  Oral frusemide 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 frusemide alone.

CONTRAINDICATIONS

- Known hypersensitivity to frusemide, sulfonamides or any of the inactive ingredients (see PRESENTATION AND STORAGE CONDITIONS). Patients allergic to sulfonamides (e.g. sulfonamide antibiotics or sulfonyleureas) may show cross-sensitivity to frusemide.
- Complete renal shutdown; impaired renal function or anuria. If increasing azotaemia and oliguria occur during treatment of severe progressive renal disease, discontinue frusemide. Severe hypokalaemia, 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, frusemide therapy should not be instituted until the underlying conditions have been corrected or ameliorated.
- Do not administer frusemide to new born infants with jaundice or to infants with conditions which might induce hyperbilirubinaemia or kernicterus (e.g. Rhesus incompatibility, familial non-haemolytic jaundice) because of frusemide’s in vitro potential to displace bilirubin from albumin.
- Breast-feeding women
PRECAUTIONS

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

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. In hepatic coma and in states of electrolyte depletion, therapy should not be instituted until the basic condition is improved. 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. Supplemental potassium chloride and, if required, an aldosterone antagonist are helpful in preventing hypokalemia and metabolic alkalosis.

Cases of reversible or irreversible tinnitus or hearing impairment have been reported. Usually reports indicate that frusemide ototoxicity is associated with 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 frusemide may be weakened and its ototoxicity potentiated. Cautious dose titration is required.

Caution should be exercised when administering curare or its derivatives to patients undergoing frusemide therapy. Frusemide has a tendency to antagonize the skeletal muscle relaxing effects and may potentiate the action of succinylcholine. 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 prostatic hypertrophy or impairment of micturition. Urinary outflow must be secured. Increased production of urine may provoke or aggravate complaints.

Particularly careful monitoring is required in patients with gout, patients with partial obstructions of urinary outflow (e.g. in patients with bladder-emptying disorders, prostatic hyperplasia or narrowing of the urethra), in patients at risk from hypotension (e.g. patients with coronary artery stenosis), 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 Botall’s duct. As with any effective diuretic, electrolyte depletion may occur during therapy with frusemide, especially in patients receiving higher doses and a restricted salt intake. Periodic determinations of serum electrolytes to detect possible imbalance should be performed at appropriate intervals, as well as creatinine, blood urea and CO₂ content.
All patients receiving frusemide therapy should be observed for signs of fluid or electrolyte imbalance, namely hyponatraemia, hypochloraeic alkalosis, hypomagnesaemia, hypocalcaemia and hypokalaemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids.

Warning signs of fluid or electrolyte imbalance, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, arrhythmia and gastrointestinal disturbances, e.g. 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 diabetic patients, and even in those suspected of having latent diabetes, who are receiving frusemide. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and 2 hour postprandial 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 defaecate, complaints of abdominal pain and cramping have been reported after intravenous 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 drugs, patients should be observed regularly for the possible occurrence of blood dyscrasias, hepatic 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.

**Use in 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 fetal circulation and may cause electrolyte disturbances. Neonatal thrombocytopenia 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 deterioration in glomerular filtration.
Australian Categorisation Definition of Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Use in Lactation
Frusemide passes into the breast milk and inhibits lactation. Women must not breast feed if being treated with frusemide.

Driving a Vehicle or Performing Other Potentially Hazardous Tasks
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).

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

Interactions with Other Medicines

Combinations that are Not Recommended.

Frusemide may increase the ototoxic potential of antibiotics, especially in the presence of impaired renal function. Except in life-threatening situations, avoid this combination.

Since frusemide may enhance nephrotoxicity of certain antibiotics (e.g. aminoglycosides, and high doses of certain cephalosporins e.g. cephaloridine), especially in the presence of impaired renal function, therefore the simultaneous administration of these drugs 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. 40 mg in patients with normal renal function) and with positive fluid balance when used to achieve forced diuresis during cisplatin treatment.

Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity, including increased risk of cardiotoxic and neurotoxic effects of lithium. If given, lithium levels should be 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 drugs may be potentiated by frusemide, especially in combination with angiotensin converting enzyme (ACE) inhibitors. The administration of ACE inhibitors to patients pretreated with frusemide may lead to a deterioration in renal function including renal failure, or may result in severe hypotension especially when an ACE inhibitor or an angiotensin II receptor antagonist is given for the first time in an increased dose. Therefore 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 an ACE inhibitor or angiotensin II receptor antagonist or increasing its dose.
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 PRECAUTIONS regarding increased mortality in elderly patients with dementia concomitantly receiving risperidone.

**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 frusemide.

When a cardiac glycoside is administered concurrently with frusemide, 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 increase 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 PRECAUTIONS). Carbenoxolone, corticosteroids ingestion of liquorice in large amounts or prolonged use of laxatives 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 to 10 μg/kg) enhance the neuromuscular blockade of tubocurarine and suxamethonium. High doses (1 to 5 mg/kg) of frusemide have a tendency to antagonise the skeletal muscle relaxing effect of tubocurarine but may potentiate the action of suxamethonium. 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 pressor amines such as adrenaline or 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 frusemide, a more pronounced fall in blood pressure must be anticipated.

Non-Steroidal Anti-Inflammatory Drugs (e.g. indomethacin, aspirin) may reduce the natriuretic and antihypertensive effects of frusemide in some patients by inhibiting prostaglandin synthesis and may cause renal failure in the case of dehydration or pre-existing hypovolaemia. Salicylate toxicity may be increased by frusemide.

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

Intravenous 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) might be attenuated by frusemide (see PRECAUTIONS).

Impairment of renal function may develop in patients receiving concurrent treatment with 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 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 patients who received only intravenous hydration prior to receiving radiocontrast.

**Effect on Laboratory tests**
Frusemide may produce falsely low values for urinary glucose by the Clinistix and Diastix methods but not with Tes-tape.

**ADVERSE EFFECTS**
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, e.g. 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 PRECAUTIONS - Interactions With Other Medicines) or nutritional inadequacies (excessive restrictions of salt intake) may lead to sodium 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 which may trigger a state of increased neuromuscular irritability (in very rare cases, tetany has been observed).

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 blood creatinine and urea levels. Serum levels of uric acid may increase (hyperuricaemia) and attacks of gout may occur.

Pre-existing metabolic alkalosis (e.g. due to decompensated hepatic cirrhosis) may be aggravated during frusemide treatment.

Treatment with frusemide has occasionally caused reduced glucose tolerance and deterioration in cases of manifest diabetes, or made latent diabetes manifest.
Gastrointestinal Disorders and Hepato-biliary Disorders
Reactions with normal doses are uncommon with frusemide. They include anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhoea and constipation. In isolated cases acute pancreatitis and increases in liver transaminases have been observed. Additionally, intrahepatic cholestasis and jaundice have been reported. Frusemide may increase the bile flow and distend a biliary tree, which is already obstructed.

Central Nervous system
Reactions such as dizziness, vertigo, paraesthesia, headache and blurred vision occasionally accompany frusemide induced diuresis.

Ear and Labyrinth Disorders
Reversible tinnitus and hearing impairment and rarely, permanent tinnitus and impairment of hearing have been observed, especially in patients in markedly reduced renal function or hypoproteinaemia (e.g. in nephrotic syndrome) or when patients were also receiving other drugs known to be ototoxic.

Skin and Subcutaneous Tissue Disorders
Various forms of dermatitis, including rash, itching, urticaria and rare cases of exfoliative dermatitis, necrotising angitis, bullous lesions or eruptions, bullous pemphigoid, Stevens - Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, purpura and pruritus have occurred. Also, photosensitivity reactions have been reported.

Blood and the Lymphatic System Disorders
The following rare adverse reactions have been reported: thrombophlebitis, haemolytic or aplastic anaemia, leucopenia, thrombocytopenia, eosinophilia, haemoconcentration and agranulocytosis.

Renal and Urinary Disorders
Excessive diuresis and dehydration could cause transient elevation of creatinine and BUN and reduction of glomerular filtration rate (GFR). 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 frusemide use. In premature infants, calcium salts may be deposited in the renal tissue (nephrocalcinosis/ nephrolithiasis). In patients with a partial obstruction of urinary outflow, acute retention of urine may occur.

Vascular Disorders
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. Vasculitis may also occur. If frusemide is administered to premature infants during the first weeks of life, it may increase the risk of persistence of patent ductus arteriosus.

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

Nervous System Disorders
Rarely paraesthesiae may occur. In patients with hepatocellular insufficiency, hepatic encephalopathy may occur.

General Disorders
Rarely, fever may occur. Restlessness has also been reported.
DOSAGE AND ADMINISTRATION

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 six to eight 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 frusemide 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 frusemide on two to four consecutive days each week. When doses exceeding 80 mg/day are given for prolonged periods, careful clinical laboratory observations are particularly advisable.

Children

The usual initial dose of oral frusemide for children is 2 mg/kg bodyweight given as a single dose. If diuretic response is not satisfactory, the dose may be increased by 1 to 2 mg/kg no sooner than six to eight hours after the previous dose. Doses greater than 6 mg/kg bodyweight are not recommended. For maintenance therapy in 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 frusemide 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 frusemide 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 frusemide is added to the regimen. As the blood pressure falls under the potentiating effect of frusemide, a further reduction in dosage or even discontinuation of other antihypertensive drugs may be necessary.
OVERDOSAGE

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 hypochloraeemic alkalosis, and extensions of its diuretic action. Symptoms of these disturbances include severe hypotension (progressing to shock), acute renal failure, thrombosis, delirious state, flaccid paralysis, apathy and confusion. The acute toxicity of frusemide has been determined in mice, rats and dogs. In all three, the oral LD50 exceeded 1,000 mg/kg bodyweight, 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 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, activated charcoal may reduce absorption of the drug if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

Treatment of overdose 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.

Contact the Poisons Information Centre on 13 11 26 (Australia) for advice on the management of overdose.
PRESENTATION AND STORAGE CONDITIONS

**GenRx Frusemide 20 mg tablets**
An off-white, round, flat bevelled edged tablet engraved 20 over a breakline on one side and plain on the other.
Bottles of 50 & 100*.
AUST R Number 75578

**GenRx Frusemide 40 mg tablets**
An off-white, round, flat bevelled edge tablet engraved with 40 over a breakline on one side and plain on the other.
Bottles of 100.
AUST R Number 75582

* Not all strengths, pack types and/or pack sizes may be available.

GenRx Frusemide tablets are intended for oral administration. Each tablet contains 20 mg or 40 mg frusemide. In addition, each tablet contains the following inactive ingredients: lactose, magnesium stearate, butyl hydroxybenzoate, microcrystalline cellulose, povidone, propyl hydroxybenzoate, silica–colloidal anhydrous, sodium starch glycollate.

**Storage**
Store below 30°C. Protect from light and moisture.

**POISONS SCHEDULE OF THE MEDICINE**
S4 – Prescription Only Medicine.

**NAME AND ADDRESS OF THE SPONSOR**
Apotex Pty Ltd
16 Giffnock Avenue
Macquarie Park NSW 2113

GenRx is a registered trade mark of Apotex Pty Ltd.

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