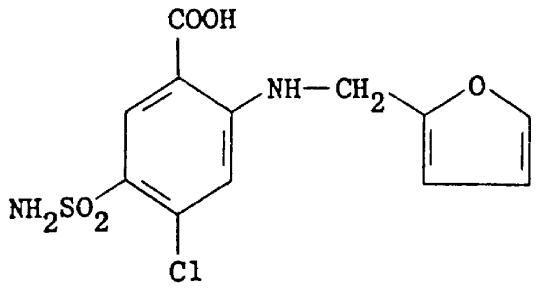
NEW ZEALAND DATA SHEET

UREX FORTE (frusemide 500 mg tablets)

NAME OF THE DRUG:

Chemically, FRUSEMIDE it is 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid. The chemical structure is below.



CAS Registry No.: 54-31-9

DESCRIPTION:

Frusemide is an anthranilic acid derivative. Frusemide is a sulphonamide-type loop diuretic and occurs as a white to slightly yellow, odourless crystalline powder with a pKa of 3.9. It is only slightly soluble in water, sparingly soluble in alcohol and freely soluble in alkali hydroxides.

Urex Forte tablets contain the following excipients; lactose, starch-maize, silica-colloidal anhydrous, magnesium stearate and maltodextrin.

Urex tablets and Urex-M tablets contain the following excipients; lactose, maize starch and magnesium stearate.

PHARMACOLOGY:

Frusemide is a potent diuretic. It inhibits sodium reabsorption in the ascending limb of Henle's loop and in both the proximal and distal tubules. The action on the distal tubule is independent of any inhibitory effect on carbonic anhydrase or aldosterone. The high degree of efficacy is due to this unique site of action.

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. Frusemide is rapidly absorbed from the upper gastrointestinal tract. Absorption rates in healthy subjects have been reported from 60-69%; 45% in patients with end stage renal

failure; and 34-80 in patients with congestive heart failure.

Bioavailability in healthy subjects is 60-69%.

The mean apparent volume of distribution in the steady state ranges from 0.07 to 0.18 L/kg body weight in healthy subjects.

Recent evidence suggests that frusemide glucuronide is the only or at least the major biotransformation product of frusemide in man. Frusemide is extensively bound to plasma proteins, mainly to albumin. Plasma concentrations ranging from 1 to 400 □g/mL are 91 to 99% bound in healthy individuals. The unbound fraction averages 2.3 to 4.1% of therapeutic concentrations.
Frusemide's diuretic effect is apparent within 1 hour following oral administration and the peak effect occurs in the first or second hour. The duration of action is 4 to 5 hours but may continue up to 8 hours.

At the peak of diuretic response 30 to 40% of the filtered sodium load may be excreted, along with some potassium and with chloride as the major anion. Frusemide augments the potassium output as a result of increased distal potassium secretion. Its diuretic action is independent of changes in acid-base balance. Under conditions of acidosis or alkalosis the diuretic produces a chloruresis without augmentation of bicarbonate excretion.

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.

The following table summarises frusemide's elimination kinetics in both normal subjects and patients with renal insufficiency:

Subjects	Administration Route	Dose (mg)	Administration Rate	Biliary Excretion	Max. Serum Conc..	$t_{1/2}$ hr.
Normal	Oral	40	-	10 to 15%	<1 □g/mL	4.0
Normal	I.V.	40	bolus	10 to 15%	2.5 □g/mL	4.5
Renal insufficiency	I.V.	1000	25 mg/min	60%	53 □g/mL	13.5
Renal insufficiency	I.V.	1000	4 mg/min	-	29 □g/mL	-

Frusemide administration may induce extracellular metabolic alkalosis, primarily by virtue of the disproportionate loss of chloride but also, in part, as a result of the variable depletion of potassium.

INDICATIONS:

Urex Forte (frusemide 500mg):
Frusemide in a high-dosage formulation such as UREX FORTE (500 mg tablets) is intended exclusively for patients with severely impaired renal function. For use under strict

medical supervision only within a hospital setting (see Dosage and Administration). High doses of frusemide may be used as an adjuvant treatment of oliguria and in the promotion of diuresis in the treatment of oedema; in selected patients with acute renal failure, e.g. in the post-operative phase and in association with septic infections; in selected patients with chronic renal failure with fluid retention, both in the pre-dialysis phase and when dialysis has become unavoidable, especially in the presence of acute pulmonary oedema; in selected patients with the nephrotic syndrome with severe impairment of renal function e.g. in chronic glomerulonephritis, lupus erythematous and Kimmelstiel-Wilson syndrome. If diuresis is less than 2.5 L/day dialysis has to be used.

CONTRAINDICATIONS:

Known hypersensitivity to frusemide or sulfonamides or to any of the components of Urex. Patients allergic to sulfonamides (e.g. sulfonamide antibiotics or sulfonylureas) may show cross-sensitivity to Urex.

Anuria or complete renal shutdown. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease discontinue frusemide.

In hepatic coma or precoma and conditions producing electrolyte depletion, frusemide therapy should not be instituted until the underlying condition has been corrected or ameliorated.

Severe hypokalaemia, hyponatraemia, hypovolaemia or hypotension must be regarded as contraindications until serum electrolytes and fluid balance and blood pressure have been restored to normal levels.

In breastfeeding women. (see Precautions - Use in Lactation).

Do not administer frusemide to newborn presenting jaundice or to infants with conditions which might induce hyperbilirubinaemia or kernicterus (Rh incompatibility, familial nonhemolytic jaundice etc.) because of frusemide's "in vitro" potential to displace bilirubin from albumin.

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

Normal renal function or impaired renal function with glomerular filtration rates below 5 mL/minute or in excess of 20 mL/minute due to the possibility of severe fluid and electrolyte loss, and renal failure due to poisoning with nephrotoxic or hepatotoxic substances. Hepatic cirrhosis; breast feeding.

PRECAUTIONS:

Frusemide is a potent diuretic, which, if given in excessive amounts, can lead to a profound diuresis.

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 or precoma and states of electrolyte depletion, therapy should not be initiated 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 hypokalaemia and metabolic alkalosis.

Particularly careful monitoring is required in patients with gout, in patients with partial obstruction of urinary outflow, in patients at risk from hypotension (e.g. patients with coronary artery stenosis), 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 ultasonography must be performed. In premature infants frusemide administered during the first weeks of life may increase the risk of persistence of Botallo's duct.

If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, the drug should be discontinued.

Patients with known sulphonamide sensitivity may show allergic reactions to frusemide.

Cases of tinnitus and reversible or irreversible deafness have been reported. Usually, reports indicate that frusemide ototoxicity is associated with rapid injection, severe renal impairment, 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 Urex may be weakened and its ototoxicity potentiated. Cautious dose titration is required. There have also been some reports of cases, the majority in children undergoing renal transplantation, in which permanent deafness has occurred. In these latter cases, the onset of deafness is usually insidious and gradually progressive up to 6 months after frusemide therapy. Hearing impairment is more likely to occur in patients with severely reduced renal functions who are given large doses of frusemide parenterally, at a rate exceeding 4 mg/min or in patients who are also receiving drugs known to be ototoxic.

Caution should be exercised when administering curare or its derivatives to patients undergoing frusemide therapy and it is advisable to discontinue frusemide for one week prior to any elective surgery.

As with any effective diuretic, electrolyte depletion may occur during therapy with frusemide, especially in patients receiving higher doses and a restricted salt intake. Thus, strict restriction of sodium intake is not advisable in patients receiving frusemide. Periodic determinations of serum electrolytes to detect possible imbalance, should be performed at appropriate intervals, as well as creatinine and blood urea and CO_2 content.

All patients receiving frusemide therapy should be observed for signs of fluid or electrolyte imbalance: namely hyponatraemia, hypochloraemic alkalosis, hypokalaemia, hypomagnesemia or hypocalcaemia. Serum and urine electrolyte determinations are

particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs, 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 such as nausea and vomiting. Hypovolaemia or dehydration as well as any significant electrolyte and acid-base disturbances must be corrected, which may require temporary discontinuation of Urex.

Hypokalaemia may develop with frusemide as with any other potent diuretic, especially with brisk diuresis, when cirrhosis is present, during long-term therapy or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalaemia. Digitalis therapy may exaggerate metabolic effects of hypokalaemia, especially with reference to myocardial effects. Caution with potassium is necessary for infants and children; a reduction in dose or discontinuation of frusemide therapy may be necessary.

A potassium rich diet is recommended that will help prevent hypokalaemia, although occasionally potassium supplements or potassium-sparing diuretics may be required, especially in cases of hepatic cirrhosis.

Since rigid sodium restriction is conductive to both hyponatraemia and hypokalaemia, strict restriction in sodium intake is not advisable in patients receiving frusemide.

Asymptomatic hyperuricaemia can occur and rarely, gout may be precipitated.

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

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. Transient rises in creatinine levels have also been observed, reflecting a fall in glomerular filtration rate on a haemodynamic basis. There may also be rises in cholesterol and triglyceride levels but these will usually return to normal during long-term treatment with frusemide, within 6 months. It is not clear whether this effect persists long-term.

In patients with prostatic hypertrophy or if disturbances of micturition exist or are suspected, or where consciousness is impaired, care has to be taken for an uninterrupted flow of urine. Symptoms of obstructed urine flow (e.g. in hydronephrosis, or ureteric stenosis) may become manifest or intensified in the course of diuretic therapy.

Renal calcifications (from barely visible on X-ray to staghorn) have occurred in some premature infants treated with intravenous frusemide for oedema due to patent ductus arteriosus (PDA) 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 erythematous.
As with many other drugs, patients should be observed regularly for the possible occurrence

of blood dyscrasias, liver or kidney damage, or other idiosyncratic reactions.

Some adverse effects associated with the use of frusemide (e.g. an undesirable pronounced fall in blood pressure) may impair the patients ability to concentrate and react. This constitutes a risk in situations where these abilities are of special importance (e.g. operating a vehicle or machinery).

In premature infants, frusemide administered during the first weeks of life may increase the risk of persistence of Botallo's duct.

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.

Particular precautions for UREX FORTE (frusemide 500 mg):

During therapy with high dose UREX FORTE, careful laboratory control is essential and extreme care must always be taken to adjust dosage to individual requirements. Fluid balance and electrolytes should be carefully controlled and, in particular, in patients with shock, measures should be taken to correct blood pressure and blood volume before UREX FORTE therapy.

Paediatric Use:
The use of frusemide in children has been established (refer Dosage and Administration for details).

Use in Pregnancy: Category C
Urex must not be given during pregnancy unless there are compelling medical reasons, such as marked reduction in glomerular filtration. 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 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.

Use in Lactation:
The use of frusemide in lactating mothers should be avoided as it passes into the breast milk and may inhibit lactation.

INTERACTIONS:

Interactions with Foods:
The extent to which the absorption of frusemide is affected by taking it with food seems to depend on the pharmaceutical formulation. It is recommended that oral formulations of frusemide, such as Urex, be taken on an empty stomach.

Interactions with Other Drugs:
Combinations that are not recommended:
Concurrent administration of frusemide and aminoglycosides (e.g. kanamycin, gentamicin and tobramycin) may result in an increased incidence of ototoxicity, especially in patients

with a decrease in renal function. Except in life-threatening situations, avoid this combination.

It has been reported in the literature that diuretics such as frusemide may enhance the nephrotoxicity of certain antibiotics (e.g. aminoglycosides, cephaloridine, cephalosporin and cephalothin), especially if both are in high doses. The simultaneous administration of these drugs is therefore not advisable.

Anticonvulsants may decrease the response to frusemide. A combination of frusemide and chloral hydrate may lead to diaphoresis, sensation of heat, flushes, tachycardia and elevation of blood pressure. As a result, this combination is not recommended.

Precautions for use:
Frusemide should not be used in combination with ethacrynic acid or cisplatin because of the possibility of ototoxicity. In addition, nephrotoxicity of cisplatin may be enhanced if Urex is not given in sufficiently low doses (e.g. 40 mg in patients with normal renal function) It may also be enhanced with positive fluid balance used to achieve forced diuresis during cisplatin treatment.

Lithium generally should not be given with diuretics because they reduce lithium's renal clearance and add a high risk of lithium toxicity.

Simultaneous administration of sucralfate and frusemide may reduce the natriuretic and antihypertensive effects of frusemide. Patients receiving both drugs should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Urex has been achieved. The intake of frusemide and sucralfate should be separated by at least two hours.

The action of other antihypertensive drugs may be potentiated by frusemide; especially in combination with ACE inhibitors. The administration of ACE inhibitors to patients pretreated with frusemide may lead to a deterioration in renal function or may result in severe hypotension. Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Therefore consideration must be given to interrupting the administration of Urex temporarily or at least reducing the dose of Urex for 3 days before starting treatment with an ACE inhibitor or increasing its dose.

To be considered:
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 Precautions).** 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 diseases, in conjunction with frusemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites.

Frusemide has been reported to interact with neuromuscular blocking agents. The interaction appears to be dependent on the dose of frusemide and the neuromuscular blocking agent involved. Low doses of frusemide (0.1 to 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.

Concomitant use of frusemide and amphotericin may result in an excessive potassium loss.

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 or other drugs with blood-pressure lowering potential are given concomitantly with Urex, a more pronounced fall in blood pressure must be anticipated.

It has been reported that coadministration of non-steroidal anti-inflammatory drugs (e.g. indomethacin, acetylsalicylic acid) may antagonise the action of frusemide and may cause renal failure in case of preexisting hypovolaemia. Thus, patients receiving both indomethacin and frusemide should be observed closely to determine if the desired diuretic and/or antihypertensive effect of frusemide is achieved. Phenytoin or drugs which undergo significant renal tubular secretion such as methotrexate or probenicid, may attenuate the effects of frusemide. Conversely Urex may decrease renal elimination of these drugs. In the case of high dose treatment (in particular of both Urex and the other drugs), this may lead to an increased risk of adverse effects due to Urex or the concomitant medication.

The effects of curare-type muscle relaxants 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 Precautions).

Non-steroidal anti-inflammatory medicines (e.g. indomethacin, acetylsalicylic acid) may reduce the natriuretic and antihypertensive effects of frusemide in some patients by inhibiting prostaglandin synthesis. NSAIDs may also cause renal failure in case of pre-existing hypovolaemia. Phenytoin or drugs which undergo significant renal tubular secretion such as methotrexate and probenecid, may attenuate the effects of frusemide.

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.

ADVERSE EFFECTS:

Disturbances in electrolytes and water balance may occur during frusemide therapy, especially in patients receiving high doses for a prolonged period.

Excessive diuresis may cause, especially in elderly patients and children, circulatory disturbances such as headache, dizziness, dry mouth or visual impairment because of hypovolaemia. In extreme cases hypovolaemia may lead to dehydration, hypotension, circulatory collapse and in elderly patients in particular, and thrombophilia. Although diuresis occurs rapidly, because of individualised dosage, acute haemodynamic reactions are generally not expected.

Factors such as underlying diseases (liver cirrhosis, cardiac failure), concomitant medication (see INTERACTIONS) or nutritional inadequacies (excessive restriction of salt intake) may lead to sodium or other electrolyte or fluid deficiencies. This manifests itself by weakness, a fall in orthostatic blood pressure, dizziness, lethargy, (leg cramps, sweating,

bladder spasms, anorexia, vomiting and/or mental confusion (see Precautions).

Frusemide may lower the serum calcium level which may trigger a state of increased neuromuscular irritability. In very rare cases, tetany has been observed. In premature infants, calcium salts may be deposited in the renal tissue (nephrocalcinosis).

Hypomagnesaemia and, in rare cases, tetany or cardiac arrhythmias have been observed as a consequence of increased renal magnesium loss.

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

Frusemide may cause hypokalaemia, mainly in cases of low potassium diet, vomiting or chronic diarrhoea.

Treatment with Urex may lead to transitory increases in blood creatine and urea levels. Serum levels of uric acid may increase and attacks of gout may occur.

Various forms of dermatitis, including urticaria and rare cases of exfoliative dermatitis and pruritus have occurred. Paresthesias, blurring of vision, postural hypotension, nausea, vomiting and diarrhoea have been reported. Anaemia, leucopoenia and thrombocytopenia (with purpura) have occurred, as well as rare cases of agranulocytosis which responded to treatment.

Treatment with frusemide has occasionally caused some deterioration in cases of manifest diabetes, or made latent diabetes manifest.

In addition, the following rare adverse reactions have been reported: sweet taste, oral and gastric burning, paradoxical swelling, headache, jaundice, acute pancreatitis, thrombophlebitis and emboli: however, relationship to the drug has not been definitely established.

Adverse reactions are categorised below by organ system and listed by decreasing severity.

Gastrointestinal System Reactions: Reactions with normal doses of Urex are uncommon. They include; pancreatitis, jaundice (intrahepatic cholestatic jaundice), anorexia, oral and gastric irritation, cramping, diarrhoea, constipation, nausea, vomiting.

Hepatic system: In isolated cases, acute pancreatitis and increases in liver transaminases have been observed. Additionally, intrahepatic chloestasis and jaundice have been reported. Frusemide may increase the bile flow and distend the biliary tree which is already obstructed.

Central Nervous System Reactions: tinnitus and hearing loss, paresthesias, vertigo, dizziness, headache, blurred vision, xanthopsia. Tinnitus, reversible impairment and rarely, permanent tinnitus and impairment of hearing have been observed, especially in patients with markedly reduced renal function or hypoproteinaemia, or in patients who are also receiving drugs known to be ototoxic.

Haematological Reactions: aplastic anaemia (rare), thrombocytopenia, agranulocytosis (rare), leucopoenia, anaemia, eosinophilia, thrombophlebitis, haemolytic anaemia.

Dermatologic Hypersensitivity Reactions: necrotising angiitis (vasculitis, cutaneous

vasculitis), exfoliative dermatitis, erythema multiforme, purpura, urticaria, rash, pruritus and bullous eruptions. Also photosensitivity reactions have been reported.

Cardiovascular Reactions: Orthostatic hypotension may occur and be aggravated by, alcohol, barbiturates or narcotics. Ischaemic
complications have also been reported in elderly patients.

Urinary System: Excessive diuresis and dehydration could cause transient elevation of serum urea and reduction of GFR. In elderly men with prostatic hypertrophy, acute urinary retention with overflow incontinence may occur. Symptoms of existing conditions of obstructed micturition, such as urethrostenosis or hydronephorosis, may be triggered or aggravated by pronounced diuresis. Interstitial nephritis has also been reported with frusemide use.

Other Reactions: interstitial nephritis, hyperglycaemia, glycosuria, hyperuricemia, fever, transient rise in serum cholesterol and triglyceride, muscle spasm, weakness, restlessness, urinary bladder spasm, thrombophlebitis. Treatment with frusemide has occasionally caused some deterioration in cases of manifest diabetes, or made latent diabetes manifest. Frusemide may lower the serum calcium level (in very rare cases, tetany has been observed). Rarely, fever or paraesthesia and occasionally photosensitivity may occur. In premature infants, calcium salts may be deposited in the renal tissue (nephrocalcinosis/nephrolithiasis). If Urex is administered to premature infants during the first weeks of life, it may increase the risk of persistence of patent ductus arteriosus. Pre-existing metabolic alkalosis (e.g. due to decompensated liver cirrhosis) may be aggravated during frusemide treatment. Due to possible hypotension, the patient's ability to drive or operate machinery may be impaired, especially at the commencement of therapy.

Anaphylactic shock is rare, but is acutely life-threatening if it does occur.

Whenever adverse reactions are moderate or severe, frusemide dosage should be reduced or withdrawn.

DOSAGE AND ADMINISTRATION

Urex Forte (frusemide 500 mg):
The high dosage preparation, UREX FORTE tablets, is intended exclusively for administration to patients with greatly reduced glomerular filtration rate. (G.F.R. less than 20 mL/minute but greater than 5 mL/minute). Normal dose may be adequate in patients with greatly reduced G.F.R. mainly if functional oliguria or anuria is observed. Thus, test a normal dose first before administering a high dose.

Before treatment of patients in shock is started, hypovolaemia and hypotension should be dealt with by normal 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 fluid 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 frusemide, UREX FORTE tablets, given below is for adults only. The dosage regimen for children has not yet been determined. The administration of large doses of frusemide in children has been associated with permanent deafness **(see Warnings)**. If conventional doses (80 to 160 mg orally) fail to produce an adequate diuresis, an initial dose of 250 mg may be given, increased, if necessary, in steps of 250 mg every 4 to 6 hours until adequate diuresis of at least 2.5 L/day is achieved. A maximum daily dose of 1000 mg should not be exceeded.

Use in Children: High dose frusemide preparations such as UREX FORTE tablets should not be used in children.

Use in elderly:
No requirement exists for special dosage recommendations in the elderly. However, the smaller peak effect of a single dose together with a delay in its effect in conjunction with reduced renal function, as well as possible need for closer monitoring of water and electrolyte balances in the elderly, must be taken into consideration.

OVERDOSAGE:

The clinical manifestations of 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 the diuretic action of frusemide. Symptoms of these disturbances include severe hypotension (progressing to shock), acute renal failure, thrombosis, delirious states, flaccid paralysis, apathy and confusion. In cirrhotic patients, overdosage may precipitate hepatic coma.

The acute toxicity of frusemide has been determined in mice, rats and dogs. In all three, the oral LD_{50} exceeded 1000 mg/kg body weight. 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 death is not known.

Treatment of overdosage:
No specific antidote to Urex 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 gastric lavage or those designed to reduce absorption (e.g. activated charcoal).

Treatment of overdosage is supportive. Discontinue the drug. Institute water and electrolyte replacements immediately and adjust in accordance with urine output. Haemodialysis does not accelerate frusemide elimination. Serum electrolytes, carbon dioxide level and blood pressure should be determined frequently. Adequate drainage must be assured in patients with urinary bladder obstruction (such as prostatic hypertrophy).

STORAGE:

Store below 30°C. Protect from light.

MEDICINE CLASSIFICATION

Prescription Medicine

PRESENTATION:

Urex Forte:
Tablets, 500 mg (white round uncoated tablet, one face plain, one face with a break-bar): 50's in blister packs.

NAME AND ADDRESS OF SPONSOR:

Arrotex Pharmaceuticals (NZ) Limited:

Address: C/o Quigg Partners

Level 7, The Bayleys Building

36 Brandon Street,

Wellington 6011, New Zealand

Distributor

Pharmacy Retailing (NZ) Limited trading as Healthcare Logistics
58 Richard Pearse Drive
Airport Oaks
Mangere
AUCKLAND

DATE OF PREPARATION:

18 January 2023