UREX® FORTE (furosemide 500 mg tablets)

1 NAME OF THE MEDICINE

UREX® FORTE (Furosemide) 500mg tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Furosemide is an anthranilic acid derivative. Furosemide 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 tablets are available in 500 mg (Urex Forte).

For the full list of excipients, **see Section 6.1 List of excipients**.

3 PHARMACEUTICAL FORM

UREX® FORTE - Each tablet contains furosemide 500mg. white round uncoated tablet, one face plain, one face with a break-bar.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

UREX FORTE (furosemide 500 mg):

Furosemide 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 **4.2 Dose and Method of Administration**). High doses of furosemide may be used as an adjuvant treatment of oliguria and in the promotion of diuresis in the treatment of oedema; in selected patients with acute renal failure, e.g. in the post-operative phase and in association with septic infections; in selected patients with chronic renal failure with fluid retention, both in the pre-dialysis phase and when dialysis has become unavoidable, especially in the presence of acute pulmonary oedema; 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

UREX FORTE (furosemide 500mg):

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 furosemide, 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 furosemide in children has been associated with permanent deafness **(see 4.4 Special Warnings and Precautions for use)**. 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 furosemide preparations such as UREX FORTE tablets should not be used in children. However, normal doses may be used (refer to **4.2 Dose and Method of administration**, 1. UREX (furosemide 40 mg), UREX-M (furosemide 20 mg), above).

4.3 CONTRAINDICATIONS

Known hypersensitivity to furosemide or sulfonamides or to any of the components of Urex (see **6.1 List of Excipients**). Patients allergic to sulfonamides (e.g. sulfonamide antibiotics or sulfonylureas) may show cross-sensitivity to Urex.

Complete renal shutdown, impaired renal function or anuria. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease discontinue furosemide.

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

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

In breastfeeding or pregnant women (see **4.6 Fertility, Pregnancy and Lactation - Use in Lactation, Use in Pregnancy**).

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

Particular contraindications for UREX FORTE (furosemide 500 mg)

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.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Excessive loss of potassium in patients receiving cardiac glycosides may precipitate digitalis toxicity.

In patients with hepatic cirrhosis and ascites, initiation of therapy with furosemide 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 with hypotension or who are at particular risk from a pronounced fall in blood pressure (e.g. patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain), in patients with latent or manifest diabetes mellitus, in patients with hepatorenal syndrome or in patients with hypoproteinaemia (e.g. associated with nephrotic syndrome). Dose titration, especially in this latter case, is required. In premature infants, there is the possible development of nephrocalcinosis/nephrolithiasis and therefore renal function must be monitored and renal ultrasonography must be performed. In premature infants furosemide administered during the first weeks of life may increase the risk of persistence of Botallo's duct.

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

Cases of reversible or irreversible tinnitus and deafness have been reported. Usually, reports indicate that furosemide ototoxicity is associated with rapid injection, 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 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 furosemide therapy.

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

Caution should be exercised and the risks and benefits of combining risperidone with furosemide or other potent diuretics should be considered prior to the decision to treat.

As with any effective diuretic, electrolyte depletion may occur during therapy with furosemide, especially in patients receiving higher doses and a restricted salt intake. All patients receiving Furosemide therapy should be observed for signs of fluid or electrolyte imbalance; namely hyponatraemia, hypochloraemic alkalosis, and hypokalaemia. Thus, strict restriction of sodium intake is not advisable in patients receiving furosemide. 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 furosemide 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 at high risk of developing electrolyte imbalances (e.g. receiving parental fluids) or in case of significant additional fluid loss, such as vomiting, diarrhea and intense sweating. 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 furosemide 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 furosemide therapy may be necessary.

During long-term therapy, a high potassium diet is recommended. Potassium supplements may be required, especially when high doses are used for prolonged periods. Particular caution with potassium is necessary when the patient is on digitalis glycosides, potassium depleting steroids, or in the case of infants and children. Potassium supplementation, diminution in dose, or discontinuation of furosemide therapy may be required.

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

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 furosemide.

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.

Furosemide may lower serum 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 intravenous furosemide. An association of these symptoms with a low serum calcium and/or a low calcium/protein ratio is possible.

Transient rises in creatinine levels have also been observed, reflecting a fall in glomerular filtration rate on a haemodynamic basis. Furosemide increases cholesterol and triglyceride short-term. It is not clear whether this effect persists long-term, however, the current evidence does not indicate this.

In patients with prostatic hypertrophy or if disturbances of micturition exist or are suspected, or where consciousness is impaired, furosemide should be used with care and urinary outflow must be secured. Symptoms of obstructed urine flow (e.g. in hydronephrosis, or ureteric stenosis) may become manifest or intensified in the course of diuretic therapy. In patients with a partial obstruction of urinary outflow (e.g. in patients with bladder-emptying disorders, prostatic hyperplasia or narrowing of the urethra), increased production of urine may provoke or aggravate complaints. Thus, these patients require careful monitoring.

Renal calcifications (from barely visible on X-ray to staghorn) have occurred in some premature infants treated with intravenous furosemide 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 furosemide (e.g. an undesirable pronounced fall in blood pressure) may impair the patient's 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).

Particular precautions for UREX FORTE (furosemide 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.

Use in hepatic impairment: In patients with hepatic cirrhosis and ascites, initiation of therapy with furosemide 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.

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

Hearing impairment is more likely to occur in patients with severely reduced renal functions who are given large doses of furosemide parenterally, at a rate exceeding 4 mg/min or in patients who are also receiving drugs known to be ototoxic.

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.

Use in elderly: In the risperidone placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone compared to treatment with risperidone alone or furosemide alone. 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.

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.

Paediatric Use:

The use of furosemide in children has been established (refer 4.2 Dose and Method of Adminstration for details).

Effects on laboratory tests: No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Interactions with Foods:

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

Interactions with Other Medicines:

Combinations that are not recommended:

Furosemide may increase the ototoxic and nephrotoxic potential of certain antibiotics, for example aminoglycosides (e.g. kanamycin, gentamicin and tobramycin) and certain cephalosporins (e.g. cephaloridine, cephalothin), and other ototoxic drugs, especially in patients with impaired renal function. Except in life-threatening situations, avoid this combination.The simultaneousadministration of these drugs is therefore not advisable.

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

Precautions for use:

Furosemide 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) and with positive fluid balance when used to achieve forced diuresis during cisplatin treatment.

Furosemide decreases the excretion of lithium salts and may cause increased serum lithium levels, resulting in increased risk of lithium toxicity, including increased risk of cardiotoxic and neurotoxic effects of lithium. Therefore, it is recommended that lithium levels are carefully monitored in patients receiving this combination.

Simultaneous administration of sucralfate and oral furosemide must not be taken within two hours of each other because sucralfate decreases the absorption of furosemide from the intestine and hence, reduces its effect. Patients receiving both drugs should be observed closely to determine if the desired diuretic and/or antihypertensive effect of Urex has been achieved.

The action of other antihypertensive drugs may be potentiated by furosemide; especially in combination with angiotensin converting enzyme (ACE) inhibitors. The administration of ACE inhibitors to patients pretreated with furosemide may lead to a deterioration in renal function including renal failure, or may result in severe hypotension, especially when an ACE inhibitor or angiotensin II receptor antagonist is given for the first time, or for the first time at an increased dose. 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, 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 furosemide or other potent diuretics should be considered prior to the decision to use. See **4.4 Special Warnings and Precautions for use** regarding increased mortality in elderly patients with dementia concomitantly receiving risperidone.

High doses of furosemide 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 digitalis preparations and drugs inducing QT interval prolongation syndrome may be potentiated by changes in electrolyte concentrations (e.g. hypokalaemia, hypomagnesaemia) due to furosemide. When a cardiac glycoside is administered concurrently, it should be remembered that potassium or magnesium deficiency increases the sensitivity of the myocardium to digitalis and may increase the toxicity of drugs which induce QT interval prolongation syndrome. When a glucocorticoid is administered during diuretic treatment, the potassium-lowering effect of the steroid should be borne in mind (see **4.4 Special Warnings and Precautions for use**). Carbenoxolone, corticosteroids, prolonged use of laxatives or ingestion of liquorice in large amounts may also predispose a patient to hypokalaemia.

Patients receiving high doses of salicylates, as in rheumatic diseases, in conjunction with furosemide may experience salicylate toxicity at lower doses because of competitive renal excretory sites.

Interactions between furosemide and neuromuscular blocking agents have been reported. The interaction appears to be dependent on the dose of furosemide and the neuromuscular blocking agent involved. Low doses of furosemide (0.1 to 10 µg/kg) enhance the neuromuscular blockade of tubocurarine and succinylcholine. High doses (1-5 mg/kg) of furosemide have a tendency to antagonise the skeletal muscle relaxing effect of tubocurarine but may potentiate the action of succinylcholine. The clinical relevance of these findings is uncertain.

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

Furosemide may decrease arterial responsiveness to noradrenaline. This diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

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

Non-steroidal anti-inflammatory drugs including acetylsalicylic acid and indomethacin may reduce the natriuretic and antihypertensive effects of furosemide in some patients by inhibiting prostaglandin synthesis. In patients with dehydration or pre-existing hypovolaemia, non-steroidal anti-inflammatory drugs may cause acute renal failure. Salicylate toxicity may be increased by furosemide.

Phenytoin, methotrexate, probenecid and other drugs which, like furosemide, undergo significant renal tubular secretion, may attenuate the effects of furosemide. 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.

Intravenous furosemide was shown to increase the steady state concentration of theophylline 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(epinephrine), noradrenaline(norepinephrine)) may be attenuated by furosemide (see **4.4 Special Warnings and Precautions for use**).

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

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

Patients who are at high risk for radiocontrast nephropathy treated with furosemide experienced a higher incidence of deterioration in renal function after receiving radiocontrast compared to high-risk patients who received only intravenous hydration prior to receiving radiocontrast.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Data not available.

Use in pregnancy (Category C)

Urex must not be given during pregnancy unless there are compelling medical reasons. Treatment during pregnancy requires monitoring of foetal growth.

Thiazides, related diuretics and loop diuretics enter the foetal circulation and may cause electrolyte disturbances. Neonatal thrombocytopenia has been reported with thiazides and related diuretics. Loop diuretics, like furosemide and bumetanide, are probably also associated with this risk. During the latter part of pregnancy, products of this type should only be given on sound indications, and then in the lowest effective dose. In pregnancy, furosemide must only be used in patients with a marked reduction in glomerular filtration.

Use in lactation.

Furosemide passes into the breast milk and inhibits lactation. Women must not breastfeed if being treated with furosemide.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Due to possible hypotension, the patient's ability to drive or operate machinery may be impaired, especially at the commencement of therapy.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Metabolism and Nutritional Disorders

Disturbances in electrolytes and water balance may occur during furosemide therapy, especially in patients receiving high doses for a prolonged period. The serum potassium concentration may decrease, especially at the commencement of treatment (owing to the earlier onset of action of furosemide).

Excessive diuresis may cause, especially in elderly patients and children, 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. Although diuresis occurs rapidly, because of individualised dosage, acute haemodynamic reactions are generally not expected.

All salurectics may cause hypokalaemia, mainly in cases of low potassium diet, vomiting or chronic diarrhea.

Factors such as underlying diseases (liver cirrhosis, cardiac failure), concomitant medication (**see 4.5 Interactions with other Medicines and other forms of Interactions**) or nutritional inadequacies (excessive restriction of salt intake) may lead to sodium (hyponatraemia), chloride (hypochloremia), or other electrolyte or fluid deficiencies. This manifests itself by weakness, a fall in orthostatic blood pressure, dizziness, apathy, lethargy, leg cramps, calf muscle spasms, sweating, bladder spasms, anorexia, vomiting and/or mental confusion (see **4.4 Special warnings and precautions for use**).

Furosemide 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/ nephrolithiasis).

Furosemide may cause a rise in serum cholesterol and triglyceride.

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

Pre-exiting metabolic alkalosis (e.g. due to decompensated liver cirrhosis) may be aggravated during furosemide treatment. Metabolic alkalosis has been reported with furosemide use.

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

Treatment with Urex may lead to transitory increases in urine volume, blood creatinine 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. Paresthesia, 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 furosemide has occasionally caused reduced glucose tolerance and deterioration in cases of manifest diabetes, or made latent diabetes manifest.

Pseudo-Bartter syndrome in the context of misuse and/or long-term use of furosemide has been reported.

Very common: electrolyte disturbances (including symptomatic)

In addition, the following rare adverse reactions have been reported: sweet taste, paradoxicalswelling, 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 and Hepatic System Reactions: Reactions with normal doses of Urex are uncommon. They include: anorexia, oral and gastric irritation, cramping, diarrhoea, constipation, nausea, vomiting.

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

Central Nervous System Reactions: Reactions such as paresthesia, vertigo, dizziness, headache, blurred vision, and xanthopsia occasionally accompany furosemide induced diuresis.

Ear and Labyrinth Disorders: Tinnitus, reversible hearing impairment 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), or in patients who are also receiving drugs known to be ototoxic.

Cases of deafness, sometime irreversible, have been reported after oral or intravenous administration of furosemide.

Haematological Reactions: Common: haemoconcentration. Uncommon: thrombocytopenia. The following rare adverse reactions have been reported: aplastic anaemia, agranulocytosis, leucopoenia, anaemia, eosinophilia, thrombophlebitis, haemolytic anaemia.

Dermatologic Hypersensitivity Reactions: Allergic reactions may occur in the form of dermatitis, including rash, itching, urticaria, pruritus, and rare cases of necrotising angiitis (vasculitis, cutaneous vasculitis), exfoliative dermatitis, erythema multiforme, purpura, bullous lesions or eruptions, pemphigold, Steven-Johnson syndrome, and toxic epidermal necrolysis. Also photosensitivity reactions have been reported. AGEP (acute generalized exanthematous pustulosis) and DRESS (Drug

Rash with Eosinophilia and Systemic Symptoms) have been reported with furosemide use.

Cardiovascular Reactions: Very common (especially for intravenous infusion), orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Ischaemic complications have also been reported in elderly patients. A tendency for thromboses has been reported. If furosemide is administered to premature infants during the first weeks of life, it may increase the risk of persistence of the patent ductus arteriosus.

Rare: vasculitis

Cases of thrombosis have been reported.

Renal and Urinary System Disorders: Excessive diuresis and dehydration could cause transient elevation of serum urea, creatinine and BUN 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 furosemide use. In patients with a partial obstruction of urinary outflow, acute retension of urine may occur. Increase in sodium and/or chloride urine levels, and renal failure has been reported with furosemide use.

Immune System Disorders: Severe anaphylactic or anaphylactoid reactions (e.g. with shock) is rare, but is acutely life-threatening if it does occur. Cases of exacerbation or activation of systemic lupus erythematosus have been reported.

Nervous System Disorders

Common: hepatic encephalopathy in patients with hepatocellular insufficiency
Rare: paraesthesia
Headache, dizziness, fainting or loss of consciousness have been reported.

Musculoskeletal and Connective Tissue Disorders: Cases of rhabdomyolysis have been reported, often in the context of severe hypokalaemia (**see 4.3 Contraindications**).

Other Reactions: hyperglycaemia, glycosuria, hyperuricaemia, fever, transient rise in serum cholesterol and triglyceride, muscle weakness, restlessness.

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

Reporting suspected adverse effects after registration of this medicinal product is important. It allows continued monitoring of the benefit-risk balance of this medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://pophealth.my.site.com/carmreportnz/s/.

4.9 OVERDOSE

Symptoms.

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 furosemide. 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 furosemide 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 furosemide in biological fluids associated with death is not known.

Treatment.

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 furosemide 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).

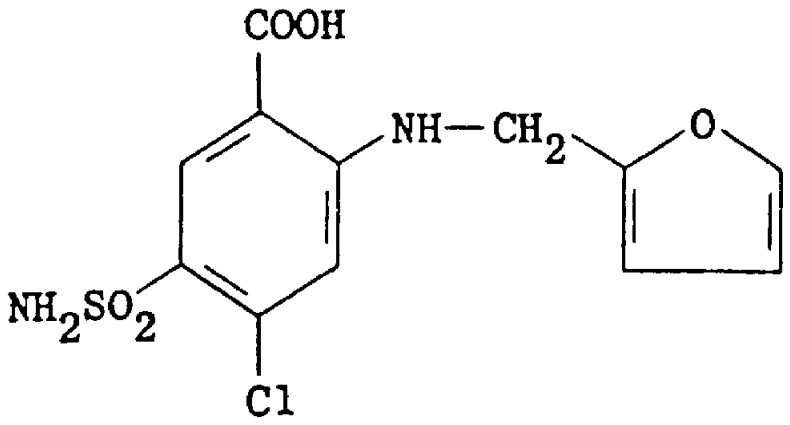
For information on the management of overdose, contact the the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Chemical structure

Chemically, FUROSEMIDE is 4-Chloro-2-[(furan-2-ylmethyl) amino]-5-sulfamoylbenzoic acid. The chemical structure is below.



CAS Number: 54-31-9

Molecular weight: 330.7

Mechanism of action

Furosemide 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.

Furosemide may promote diuresis in cases which have previously proved resistant to other diuretics.

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

Clinical trials

Data not available

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Furosemide 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%.

Distribution

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

Metabolism

Recent evidence suggests that furosemide glucuronide is the only or at least the major biotransformation product of furosemide in man. Furosemide 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% of therapeutic concentrations

Excretion

Furosemide'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. Furosemide 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 furosemide'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 μg/mL	4.0
Normal	I.V.	40	bolus	10 to 15%	2.5 μg/mL	4.5
Renal insufficiency	I.V.	1000	25 mg/min	60%	53 μg/mL	13.5
Renal insufficiency	I.V.	1000	4 mg/min	-	29 μg/mL	-

Furosemide 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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity – No data available

Carcinogenicity – No data available

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

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

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

In New Zealand, information on the shelf-life can be found on the public Public/Application Search on Medsafe website www.medsafe.govt.nz/regulatory/Dbsearch. The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30 ° C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

UREX FORTE:

Tablets, 500 mg: 50's in blister pack (PVC/PVDC-Al) and glass bottle*.

* Currently not marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription only medicine

8 SPONSOR

Arrotex Pharmaceuticals (NZ) Limited:
Address: C/o Quigg Partners
Level 7, The Bayleys Building
36 Brandon Street,
Wellington 6011, New Zealand

Phone: +64 9 918 5100

Distributor

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

9 DATE OF FIRST APPROVAL

UREX FORTE:

Bottle presentation: 17 June 2010

Blister pack presentation: 17 June 2010

10 DATE OF REVISION

14 June 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
1	Updated to include product name, strength and pharmaceutical form.
4.8	Updated web site address for reporting adverse effects.
4.9	Updated as per the New Zealand Data Sheet Template Explanatory Guide.
5.1	Information from Section 6.7 included.
6.7	Deleted Section
8	NZ sponsor contact phone number added.