

This product is no longer marketed in New Zealand and this data sheet may not be up to date. A more up-to-date data sheet for a product with the same active ingredient may be available on the Medsafe website.

## Data Sheet

### DIURIN 500

500mg tablets

Furosemide

---

#### Presentation

---

Tablets, 500mg: Off-white flat bevel edged tablet 1/2" diameter, with a bisect on one side.

---

#### Uses

---

##### **Actions**

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

Furosemide may produce a prompt diuresis in cases which have previously proved resistant to other diuretics.

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

##### **Pharmacokinetics**

###### **Absorption:**

Furosemide is rapidly absorbed from the gastrointestinal tract. Absorption rates in healthy subjects have been reported from 60-69% and from 43-46% in patients with end stage renal failure. The onset of diuresis following oral administration is within 1 hour. The peak effect occurs within the first or second hour. The duration of diuretic effect is 4 to 6 hours.

In fasted normal men, the mean bioavailability of furosemide from furosemide tablets is 64% of that from an intravenous injection of the medicine. Although furosemide is more rapidly absorbed from the oral solution (50 minutes) than from the tablet (87 minutes), peak plasma levels and area under the plasma concentration-time curves do not differ significantly. Peak plasma concentrations increase with increasing dose but times-to-peak do not differ among doses.

###### **Distribution:**

Furosemide 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 furosemide glucuronide is the only, or at least the major, biotransformation product of furosemide in man.

###### **Excretion:**

In patients with normal renal function, approximately 80% of an intravenous or intramuscular dose is excreted in the urine within 24 hours. Urinary excretion is accomplished both by glomerular filtration and proximal tubular secretion, which accounts for roughly 66% of the ingested dose, the remainder being excreted in the faeces. A small fraction is metabolised by cleavage of the side chain.

**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 premature and full term infants.

**Indications**

The high-dosage preparation diurin 500mg tablets is intended exclusively for administration to patients with severely impaired renal function. Use under strict medical supervision only within the hospital setting (see Dosage and Administration). High doses of diurin 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 postoperative 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; and in selected patients with the nephrotic syndrome with severe impairment of renal function (e.g. in chronic glomerular nephritis, lupus erythematosus and Kimmelstiel-Wilson syndrome). If diuresis is less than 2.5 L/day, dialysis has to be used.

---

**Dosage and Administration**

---

The high dose preparation is intended exclusively for administration to patients with greatly reduced glomerular filtration rate (GFR less than 20 ml/min but greater than 5 ml/min). Normal doses of frusemide are usually adequate in patients with greatly reduced GFR if functional oliguria is observed. Therefore test a normal dose of frusemide first before administering diurin high dose. Before treatment of patients in shock is started, hypovolaemia and hypotension should be dealt with by suitable measures. Similarly markedly disturbed serum electrolytes and acid-base balance should first be corrected.

When treating patients with conditions likely to interfere with micturition such as prostatic hypertrophy or disturbed consciousness, it is absolutely essential to ensure free urinary drainage. Because of the wide and unpredictable individual variations in responsiveness it is important to adjust dosage and route of administration to individual needs.

Once the desired rise in urinary output has begun, exact balance of water intake and water output must be maintained throughout the course of treatment so as to avoid hypovolaemia or hypotension. Careful electrolyte replacement is also necessary.

The dosage of high dose frusemide 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)

**Initial Dose:**

The dose which has been found to produce an effective diuresis when given IV is used as the initial dose orally.

**Additional Dose:**

Should the initial dose fail to produce an adequate increase (at least 40 to 50ml) in urinary output within 4-6 hours, the dose may be raised by 250 to 500mg at a time.

For selected patients with advanced chronic renal failure, diuretic therapy may be started with frusemide orally. If conventional doses (80 to 160mg orally) fail to produce an adequate diuresis, a single dose of 250mg is given as a starting dose. If satisfactory diuresis does not ensue within 4 to 6 hours, the dose may be doubled to 500mg. The criterion of optimal dosage is a urinary output of at least 2.5 L/day.

A maximum daily dose of 1000mg should not be exceeded.

Use in Children:

Diurin high dose preparations are not to be used in children. However, normal doses of diurin may be used.

---

## Contraindications

---

Diurin high dose 500mg tablets are contraindicated in patients with normal renal function because in these cases there is a danger of severe fluid and electrolyte loss.

Known hypersensitivity to frusemide or sulphonamides or any of the inactive ingredients. Patients allergic to sulphonamides (e.g. sulphonamide antibiotics or sulfonyleureas) may show cross sensitivity to frusemide.

Complete renal shutdown.

If increasing azotaemia and oliguria occur during treatment of severe progressive renal disease, discontinue frusemide.

Severe hypokalaemia, hyponatraemia, hypovolaemia 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 pre-coma and conditions producing electrolyte depletion, frusemide therapy should not be instituted until the underlying conditions have been corrected or ameliorated.

In breast feeding women.

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

Diurin 500mg tablets must not be used unless the patient has a marked reduction in glomerular filtration. Otherwise there is a risk of excessive fluid and electrolyte losses.

---

## Warnings and 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 and frusemide is best carried out in hospital. Sudden alterations of fluid and electrolyte balance in patients with cirrhosis may precipitate hepatic coma, therefore, strict observation is necessary during the period of diuresis.

Cases of reversible or irreversible tinnitus or hearing impairment have been reported.

Usually, reports indicate that frusemide ototoxicity is associated with rapid injection, severe renal impairment, hypoproteinaemia, doses exceeding several times the usual recommended dose, or concomitant therapy with aminoglycoside antibiotics, ethacrynic acid, or other ototoxic medicines.

In patients with hypoproteinaemia, e.g. associated with nephrotic syndrome, the effect of frusemide may be weakened and its ototoxicity potentiated. Cautious dose titration is required.

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

Rigid sodium restriction is conducive to both hyponatraemia and hypokalaemia, thus strict restriction of sodium intake is not advisable in patients receiving frusemide.

Frusemide should be used with care, especially in the initial stages, in patients with impairment of micturition (e.g. prostatic hypertrophy). Urinary outflow must be secured. Particularly careful monitoring is required in patients with gout, 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 ultrasonography performed.

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 CO<sub>2</sub> content.

All patients receiving frusemide therapy should be observed for signs of fluid or electrolyte imbalance; namely hyponatraemia, hypochloraemic alkalosis, and hypokalaemia.

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. This may require temporary discontinuation of frusemide.

During long-term therapy, a high potassium diet is recommended (lean meat, potatoes, banana, tomatoes, cauliflower, spinach, dried fruit etc.). Potassium supplements may be required, especially when high doses are used for prolonged periods. Particular caution with potassium is necessary when the patient is on digitalis glycosides, potassium depleting steroids or in the case of infants and children. Potassium supplementation, diminution in dose, or discontinuation of frusemide therapy may be required.

Periodic checks on urine and blood glucose should be made in diabetics and even those suspected of latent diabetes when receiving frusemide. Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and 2-hour post prandial sugar have been observed, and rare cases of precipitation of diabetes mellitus have been reported.

Frusemide may lower calcium levels, and rare cases of tetany have been reported. Accordingly, periodic serum calcium levels should be obtained.

In children, urge to defecate, complaints of abdominal pain and cramping have been reported after IV frusemide. An association of these symptoms with a low serum calcium and/or a low calcium/protein ratio is possible.

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

Reversible elevations of blood urea may be seen. These have been observed in association with dehydration, which should be avoided, particularly in patients with renal insufficiency.

Frusemide increases cholesterol and triglycerides short-term. It is not clear whether this effect persists long-term; however, the current evidence does not indicate this.

As with many other medicines, patients should be observed regularly for the possible occurrence of blood dyscrasias, liver damage, or other idiosyncratic reactions.

Renal calcifications (from barely visible on x-ray to staghorn) have occurred in some severely premature infants treated with intravenous frusemide for oedema due to patent ductus arteriosus and hyaline membrane disease. The concurrent use of chlorothiazides has been reported to decrease hypercalciuria and to dissolve some calculi.

The possibility exists of exacerbation or activation of systemic lupus erythematosus.

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

### ***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).

### ***Use in the 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.

### ***Pregnancy and Lactation:***

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

Thiazides, related diuretics and loop diuretics enter the foetal circulation and may cause electrolyte disturbances. Neonatal thrombocytopaenia has been reported with thiazides and related diuretics. Loop diuretics, like frusemide and bumetanide, are probably also associated with this risk. During the latter part of pregnancy, products of this type should only be given on sound indications, and then in the lowest effective dose.

The use of frusemide in lactating mothers should be avoided as it passes into the breast milk and inhibits lactation.

---

## **Adverse Effects**

---

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.

Excessive diuresis may give rise especially in elderly patients and children, to circulatory disturbances such as headache, dizziness, dry mouth or visual impairment, as symptoms of hypovolaemia. In extreme cases, hypovolaemia and dehydration may lead to hypotension, circulatory collapse and in elderly patients in particular thrombophilia. However, with individualised dosage, acute haemodynamic reactions are generally not 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 Interactions) or nutritional inadequacies (excessive restriction 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.

Furosemide may lower the serum calcium level. This 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 arrhythmia have been observed as a consequence of increased renal magnesium losses.

Treatment with furosemide may lead to transitory increases in blood creatinine and urea levels and to an increase in cholesterol and triglyceride serum levels. Serum levels of uric acid may increase and attacks of gout may occur.

### ***Gastrointestinal System:***

Reactions with normal doses are uncommon with furosemide. They include anorexia, oral and gastric irritation, nausea, vomiting, cramping, diarrhoea and constipation.

### ***Hepatic System:***

Isolated cases of acute pancreatitis and increases in liver transaminases have been observed. Additionally, intrahepatic cholestasis and jaundice have been reported, however, relationship to the medicine has not been established. Furosemide may increase the bile flow and distend the biliary tree which is already obstructed.

### ***Central Nervous System:***

Reactions such as dizziness, vertigo, paraesthesia, headache and blurred vision occasionally accompany furosemide induced diuresis. Tinnitus, reversible impairment and rarely, permanent impairment of hearing have been observed with markedly reduced renal function or hypoproteinaemia (e.g. in nephrotic syndrome).

This occurs particularly when the recommended rate of injection or infusion of 4mg per minute (normal renal function) or 2.5mg per minute (impaired renal function) is exceeded, or in patients who are also receiving medicines known to be ototoxic.

### ***Dermatologic:***

Allergic reactions may occasionally occur in the form of dermatitis, including rash, urticaria and rare cases of exfoliative dermatitis, necrotising angitis, bullous eruption, erythema multiforme and purpura and pruritus.

Photosensitivity reactions have occasionally been reported.

### ***Haematologic:***

The following rare adverse reactions have been reported: eosinophilia, thrombophlebitis, haemolytic or aplastic anaemia, leukopaenia, thrombocytopaenia, agranulocytosis. Vasculitis may also occur.

### ***Urinary System:***

Excessive diuresis and dehydration could cause transient elevation of creatinine and BUN and reduction of GFR. In elderly men with prostatic hypertrophy, acute urinary retention with overflow incontinence may occur. Interstitial nephritis has also been reported with furosemide use.

Symptoms of existing obstructed micturition in patients with conditions such as uretostenosis or hydronephrosis may be triggered or aggravated by pronounced diuresis.

### **Cardiovascular:**

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

### **Other:**

Restlessness, hyperuricaemia, fever, transient rise in serum cholesterol and triglyceride, transient pain at the injection site following intramuscular injection. Treatment with frusemide has occasionally caused reduced glucose tolerance and deterioration in cases of manifest diabetes, or made latent diabetes manifest. Pre-existing metabolic alkalosis (e.g. due to decompensated liver cirrhosis) may be aggravated during frusemide treatment. Uricaemia may occur and lead to gout attacks in predisposed patients (see Precautions).

Rarely, fever or paraesthesia and occasionally photosensitivity may occur.

In premature infants, frusemide may precipitate nephrocalcinosis/nephrolithiasis. If frusemide is administered to premature infants during the first weeks of life, it may increase the risk of persistence of patent ductus arteriosus.

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.

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

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

---

## **Interactions**

---

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

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 of 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 (0.1-10 mcg/kg) enhance the neuromuscular blockade of tubocurarine and succinylcholine.

High doses (1-5 mg/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.

Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity. If given, lithium levels should be monitored.

Furosemide may increase the ototoxic potential of antibiotics, especially in the presence of impaired renal function. Except in life-threatening situations, avoid this combination. Furosemide 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 furosemide is not given in low doses (e.g. 40mg in patients with normal renal function) and with positive fluid balance when used to achieve forced diuresis during cisplatin treatment.

Since furosemide may enhance nephrotoxicity of certain antibiotics (e.g. aminoglycosides, cephaloridine), the simultaneous administration of these medicines is not advisable.

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

Furosemide should not be used concomitantly with ethacrynic acid or cisplatin because of the possibility of ototoxicity. If furosemide is used in combination with cisplatin to force diuresis, care must be taken that only a low dose (e.g. 40mg where normal kidney function) of furosemide is used and that there is a positive fluid balance.

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

The action of other antihypertensive medicines may be potentiated by furosemide, especially in combination with ACE Inhibitors.

The administration of ACE Inhibitors to patients pretreated with furosemide may lead to a deterioration in renal function or may result in severe hypotension.

Non steroidal anti-inflammatory medicines (e.g. indomethacin, acetylsalicylic acid) may reduce the natriuretic and antihypertensive effects of furosemide 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 furosemide.

Conversely, furosemide may decrease renal elimination of these drugs. In case of high dose treatment (in particular of both furosemide and the other drugs), this may lead to increased risk of adverse effects due to furosemide or the concomitant medication.

IV furosemide 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.

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

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

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

---

## Overdosage

---

The clinical picture in acute or chronic overdose depend primarily on the extent and consequences of electrolyte and fluid loss; e.g. dehydration, blood volume reduction, hypotension, electrolyte imbalance, cardiac arrhythmias including AV block and ventricular fibrillation), hypokalaemia and hypochloraemic alkalosis, and extensions of its diuretic action.

Symptoms of these disturbances include severe hypotension (progressing to shock), acute renal failure, thrombosis, delirious states, flaccid paralysis, apathy and confusion. The acute toxicity of frusemide has been determined in mice, rats and dogs.

In all three, the oral LD<sub>50</sub> exceeded 1000 mg/kg body weight, while the intravenous LD<sub>50</sub> 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.

No specific antidote to frusemide is known.

If ingestion has only just taken place, attempts may be made to limit further systemic absorption of the active ingredient by measures such as gastric lavage or those designed to reduce absorption (e.g. activated charcoal).

Treatment of overdosage is supportive and consists of replacement of excessive fluid and electrolyte losses. Serum electrolytes, carbon dioxide level and blood pressure should be determined frequently. Adequate drainage must be assured in patients with urinary bladder outlet obstruction (such as prostatic hypertrophy). Haemodialysis does not accelerate frusemide elimination.

---

## Pharmaceutical Precautions

---

Store below 25°C. Protect from light.

---

## Medicine Classification

---

Prescription Medicine.

---

## Package Quantities

---

Tablet: 500mg, bottles of 50 tablets and 100 tablets.

---

## Further Information

---

Nil.

---

## Name and Address

---

Mylan New Zealand Ltd  
PO Box 11-183  
Ellerslie  
AUCKLAND  
Telephone: 09-579-2792

---

## Date of Preparation

---

2 February 2009

