AUSTRALIAN PRODUCT INFORMATION - NOUMED FUROSEMIDE (FUROSEMIDE) 40MG TABLETS

1. NAME OF THE MEDICINE

Furosemide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Noumed Furosemide tablets contain 40mg of the active ingredient furosemide. They also contain the inactive ingredients maize starch, lactose monohydrate, sodium starch glycollate, microcrystalline cellulose and magnesium stearate.

3. PHARMACEUTICAL FORM

Noumed Furosemide 40mg tablets –White, round tablets, slightly convex with a score notch on one side.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Oedema
Adults. Treatment of oedema associated with congestive heart failure, cirrhosis of the liver and renal disease, including the nephrotic syndrome. Noumed Furosemide is particularly useful when an agent with greater diuretic potential than that of those commonly employed is desired.

Hypertension
Adults. Noumed Furosemide tablets may be used in adults for the treatment of hypertension alone or in combination with other antihypertensive agents. Hypertensive patients who cannot be adequately controlled with thiazides will probably also not be adequately controlled with Noumed Furosemide alone.

4.2 DOSE AND METHOD OF ADMINISTRATION

Oedema
Therapy should be individualised according to patient's response. This therapy should be titrated to gain maximal therapeutic response with the minimum dose possible to maintain that diuretic response.

Adults. The usual initial daily dose is 20 to 80mg given as a single dose. If the diuretic response to a single dose of 20 to 80mg is not satisfactory, increase this dose by

increments of 20 to 40mg, not sooner than six to eight hours after the previous dose, until the desired diuretic effect is obtained. This individually determined dose should be given once or twice (e.g. at 8am and 2pm) daily. The dose of Noumed Furosemide may be carefully titrated up to 400mg/day (except in advanced renal failure) in those patients with severe clinical oedematous states. The mobilisation of oedema may be most efficiently and safely accomplished by giving Noumed Furosemide on two to four consecutive days each week.

When doses exceeding 80mg/day are given for prolonged periods, careful clinical laboratory observations are particularly advisable.

Hypertension
Therapy should be individualised according to the patient's response. This therapy should be titrated to gain maximal therapeutic response with the minimum dose possible to maintain that therapeutic response.

Adults. The usual initial daily dose of Noumed Furosemide for hypertension is 80mg, usually divided into 40mg twice a day. Dosage should then be adjusted according to response. If response is not satisfactory, add other antihypertensive agents.

Changes in blood pressure must be carefully monitored when Noumed Furosemide is used with other antihypertensive drugs, especially during initial therapy.

To prevent an excessive drop in blood pressure, the dosage of other agents should be reduced by at least 50% when Noumed Furosemide is added to the regimen. As the blood pressure falls under the potentiating effect of Noumed Furosemide, a further reduction in dosage or even discontinuation of other antihypertensive drugs may be necessary.

4.3 CONTRAINDICATIONS

Known hypersensitivity to furosemide or sulfonamides or any of the inactive ingredients (see Section 2 QUALITATIVE AND QUANTITATIVE COMPOSITION). Patients allergic to sulfonamides (e.g. sulfonamide antibiotics or sulfonylureas) may show cross-sensitivity to furosemide.

Complete renal shutdown, impaired renal function or anuria. If increasing azotaemia and oliguria occur during treatment of severe progressive renal disease, discontinue furosemide. Severe hypokalaemia, hyponatraemia, hypovolaemia, dehydration or hypotension must be regarded as contraindications until serum electrolytes, fluid balance and blood pressure have been restored to normal levels.

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

In breastfeeding or pregnant women.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Furosemide (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.

Cases of reversible or irreversible tinnitus or hearing impairment 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 furosemide 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 furosemide therapy. It is also 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.

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

In patients with prostatic hypertrophy or if disturbances of micturition exist or are suspected, or where consciousness is impaired, furosemide (frusemide) 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.

Particularly careful monitoring is required in patients with gout, 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.

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

Symptomatic hypotension leading to dizziness, fainting or loss of consciousness can occur in patients treated with furosemide, particularly in the elderly, patients on other medications which can cause hypotension and patients with other medical conditions that are risks for hypotension.

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 a possible imbalance should be performed at appropriate intervals, as well as creatinine, blood urea and CO_2 content determinations. This is particularly important when the patient is at high risk of developing electrolyte imbalances (eg. receiving parenteral fluids) or in case of significant additional fluid loss such as vomiting, diarrhoea and intense sweating. Warning signs of an imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, arrhythmia and gastrointestinal disturbances, e.g. nausea and vomiting. Hypovolaemia or dehydration as well as any significant electrolyte and acid-base disturbances must be corrected. This may require temporary discontinuation of furosemide.

Hypokalaemia may develop with furosemide (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.

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 or on potassium depleting steroids. Potassium supplementation, diminution in dose or discontinuation of furosemide therapy may be required.

Periodic checks on urine and blood glucose should be made in diabetic patients, and even in those suspected of having latent diabetes, who are receiving 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 calcium levels, and rare cases of tetany have been reported. Accordingly, periodic serum calcium levels should be obtained.

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

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

The possibility exists of exacerbation or activation of systemic lupus erythematosus. Asymptomatic hyperuricaemia can occur and rarely gout may be precipitated.

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
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.

See Section 4.3 CONTRAINDICATIONS.

Use in the 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 (7.3% ; mean age 89 years, range 75 to 97) compared to treatment with risperidone alone (3.1% ; mean age 84 years, range 70 to 96) or furosemide alone (4.1% ; mean age 80 years, range 67 to 90). Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low doses) was not associated with similar mortality findings. No pathophysiological mechanism has been identified to explain this finding and no consistent pattern for cause of death was observed. Nevertheless, caution is advised. Irrespective of treatment, dehydration was an overall risk factor for mortality and should, therefore, be carefully avoided in elderly patients with dementia.

Paediatric Use
No data available.

Effects on laboratory tests
No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Interactions with food:
Whether and to what extent the absorption of furosemide is affected by taking it with food seems to depend on the pharmaceutical formulation of furosemide. It is recommended that furosemide 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 (e.g. aminoglycosides and certain cephalosporins (e.g cephaloridine)) and other ototoxic drugs, especially in the presence of impaired renal function, therefore the simultaneous administration of these drugs are not advisable.

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

Precautions for use
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.

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.

Furosemide and sucralfate 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 furosemide 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 in an increased dose. Therefore consideration must be given to

interrupting the administration of furosemide temporarily or at least reducing the dose of furosemide for three 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 Section 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 of 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 Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Carbenoloxone, corticosteroids, prolonged use of laxatives or ingestion of liquorice in large amounts may also predispose a patient to hypokalaemia.

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

Interactions between furosemide and neuromuscular blocking agents have been reported. These appear to be dependent on the dose of furosemide and the neuromuscular blocking agent involved. Low doses of furosemide (0.1 to 10microgram/kg) enhance the neuromuscular blockade of tubocurarine and succinylcholine. High doses (1 to 5mg/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.

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

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 furosemide, a more pronounced fall in blood-pressure must be anticipated.

Non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylic acid 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 drugs which, like furosemide, undergo significant renal tubular secretion may attenuate the effects of furosemide. Conversely, furosemide may decrease renal elimination of these drugs. In the case of high-dose treatment (in particular of both furosemide and the other drugs), this may lead to an increased risk of adverse effects due to furosemide or the concomitant medication.

The effects of curare-type muscle relaxants or of theophylline may be increased.

It should be borne in mind that the effect of antidiabetics and pressor amines (e.g. adrenaline and noradrenaline) may be attenuated by furosemide (see Section 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 cyclosporin A and furosemide is associated with increased risk of gouty arthritis secondary to furosemide-induced hyperuricaemia and cyclosporin impairment of renal urate excretion.

Patients who were 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
No data available.

Use in pregnancy
Category C: Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.

Furosemide 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

Some adverse effects (e.g. an undesirable pronounced fall in blood pressure) may impair the patient's ability to concentrate and react and therefore constitute a risk in situations where these abilities are of special importance (e.g. operating a vehicle or machinery).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

Metabolism and nutritional disorders
As with other diuretics, electrolytes and water balance may be disturbed during therapy with furosemide, 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 give rise, especially in elderly patients and children, to circulatory disturbances, e.g. headache, dizziness, dry mouth or visual impairment, as symptoms of hypovolaemia. In extreme cases, hypovolaemia and dehydration may lead to hypotension, circulatory collapse and in elderly patients in particular, thrombophilia. However, with individualised dosage, acute haemodynamic reactions are generally not to be expected, although diuresis sets in rapidly.

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

Factors such as underlying diseases (liver cirrhosis, cardiac failure), concomitant medication (see Section 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 (hypochloraemia),or other electrolyte or fluid deficiencies which may produce a fall in orthostatic blood pressure, leg cramps, calf muscle spasms, sweating, bladder spasms, anorexia, weakness, dizziness, drowsiness, apathy, lethargy, vomiting and confusion.

Furosemide may lower the serum calcium level (hypocalcaemia), which may trigger a state of increased neuromuscular irritability. 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.

Treatment with furosemide may lead to transitory increases in urine volume, blood creatinine and urea levels. Serum levels of uric acid (hyperuricaemia) may increase and attacks of gout may occur.

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

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), dehydration and hypovolaemia especially in elderly patients, increased blood creatinine, increased blood triglycerides
Common: hyponatraemia, hypochloraemia, hypokalaemia, blood cholesterol increased blood uric acid increased and attacks of gout, urine volume increased.
Uncommon: impaired glucose tolerance. Latent diabetes mellitus may manifest

In addition, the following rare adverse reactions have been reported: sweet taste, paradoxical swelling, and emboli: however, relationship to the drug has not been definitely established.

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

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

Central nervous system disorders

Reactions such as dizziness, vertigo, paraesthesia, headache, blurred vision and xanthopsia occasionally accompany furosemide-induced diuresis.

Ear and labyrinth disorders
Reversible tinnitus and hearing impairment and rarely, permanent tinnitus and impairment of hearing have been observed, especially in patients with markedly reduced renal function or hypoproteinaemia (e.g. in nephrotic syndrome). This occurs particularly in patients who are also receiving drugs known to be ototoxic.

Cases of deafness, sometimes irreversible, have been reported after oral administration of furosemide.

Skin and subcutaneous tissue disorders
Allergic reactions may occur in the form of dermatitis including rash, itching, urticaria, pruritus and rare cases of exfoliative dermatitis, necrotising angitis, bullous lesions or eruptions, pemphigoid, Steven-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme and purpura. 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.

Blood and the lymphatic system disorders
Common: haemoconcentration
Uncommon: thrombocytopenia
The following rare adverse reactions have been reported: eosinophilia, thrombophlebitis, haemolytic or aplastic anaemia, leukopaenia and agranulocytosis.

Renal and urinary disorders
Excessive diuresis and dehydration could cause transient elevation of serum urea, creatinine and BUN and reduction of glomerular filtration rate (GFR). Rare cases of tubulointerstitial nephritis have been reported. In elderly men with prostatic hypertrophy, acute urinary retention with overflow incontinence may occur. Symptoms of existing conditions of obstructed micturition, such as uretostenosis or hydronephrosis, may be triggered or aggravated by pronounced diuresis. Interstitial nephritis has also been reported with furosemide use. In patients with a partial obstruction of urinary outflow, acute retention of urine may occur. Increases in sodium and/or chloride urine levels, and renal failure has been reported with furosemide use.

Vascular disorders
Very common, orthostatic hypotension may occur and may be aggravated by alcohol, narcotics and barbiturates. Due to the possibility of side effects such as hypotension, the patient's ability to drive or operate machinery may be impaired, especially at the commencement of therapy. Ischaemic complications have also been reported in elderly patients.
A tendency for thromboses has been reported.
Rare: vasculitis
Cases of thrombosis have been reported.

Immune system disorders
Severe anaphylactic or anaphylactoid reactions (e.g. with shock) are rare, but are 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 Section 4.3 CONTRAINDICATIONS).

General disorders
Rarely, fever may occur. Restlessness has also been reported.

Other Reactions
Hyperglycaemia, glycosuria, transient rise in serum cholesterol and triglyceride, muscle weakness.

Reporting suspected adverse effects
Reporting suspected adverse effects after registration of the 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 www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

Symptoms
The clinical picture in acute or chronic overdose depends 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 furosemide has been determined in mice, rats and dogs. In all three, the oral LD_{50} exceeded 1,000mg/kg bodyweight. 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 toxicity or death is not known.

Treatment
No specific antidote to furosemide 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 furosemide elimination.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

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 gastrointestinal tract. Absorption rates have been reported to be from 60 to 69% in healthy subjects and from 43 to 46% in patients with end stage renal failure.

The onset of diuresis following oral administration is within 1 hour. The peak effect occurs within the first or second hour. The duration of diuretic effect is 6 to 8 hours.

In fasted normal men, the mean bioavailability of furosemide tablets is 64% of that from an intravenous injection of the drug. Peak plasma concentrations increase with increasing dose but times to peak do not differ among doses.

Distribution
Furosemide is extensively bound to plasma proteins, mainly to albumin. Plasma concentrations ranging from 1 to 400microgram/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 humans.

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 by cleavage of the side chain.

Furosemide 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.

5.3 PRECLINICAL DATA

Genotoxicity
No data available

Carcinogenicity
No data available

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 – QUALITATIVE AND QUANTITATIVE COMPOSITION.

6.2 INCOMPATIBILITIES

Refer to Section 4.5 – INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

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

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australia Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.
Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Noumed Furosemide 40mg tablets –White, round tablets, slightly convex with a score notch on one side.

Available in PE bottles of 100 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

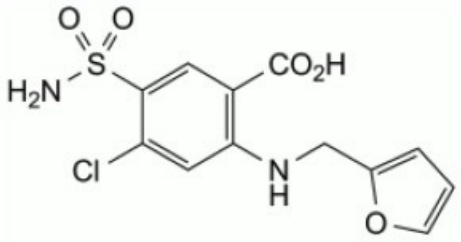
6.7 PHYSICOCHEMICAL PROPERTIES

Furosemide is an anthranilic acid derivative.

Furosemide is a white to off-white odourless crystalline powder. It is practically insoluble in water, sparingly soluble in alcohol, freely soluble in dilute alkali solutions and insoluble in dilute acids.

Chemical name: 4-chloro-*N*-furfuryl-5-sulfamoylanthranilic acid

Chemical structure:



Empirical formula: $C_{12}H_{11}ClN_2O_5S$ MW: 330.75

CAS Number: 54-31-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8. SPONSOR

Avallon Pharmaceuticals Pty Ltd
Level 5, 7 Eden Park Avenue,
Macquarie Park,
North Ryde, NSW 2113,

Supplied by:
Australian Pharmaceutical Industries
11 Grand Avenue
Camellia, NSW 2142
Australia

9. DATE OF FIRST APPROVAL

26/02/2018

10. DATE OF REVISION

12/07/2019

Summary table of changes

Section changed	Summary of new information
ALL	Reformatted in line with the revised Australian form for providing product information
8	Sponsor details updated to Avallon Pharmaceuticals Pty Ltd
4.4	Additional precautions added to align with the innovator PI
4.5	Additional interactions added to align with the innovator PI
4.8	Additional adverse events added to align with the innovator PI