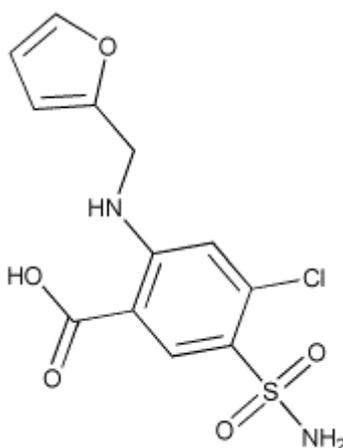

PRODUCT INFORMATION
FRUSEMIDE SANDOZ® INJECTION 20MG/2ML

NAME OF THE MEDICINE

Generic name: frusemide (furosemide)

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

Chemical structure:



CAS: 54-31-9

C₁₂H₁₁ClN₂O₅S

MW: 330.7423

DESCRIPTION

A white or almost white, crystalline powder, practically insoluble in water, soluble in acetone, sparingly soluble in alcohol, practically insoluble in methylene chloride. It dissolves in dilute solutions of alkali hydroxides. It melts at about 210°C, with decomposition.

Frusemide Sandoz Injection also contains the inactive ingredients:

Sodium Hydroxide, Sodium Chloride and Water for injection.

PHARMACOLOGY

Site and Mode of Action

Frusemide (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.

Frusemide (furosemide) may promote diuresis in cases which have previously proved resistant to other diuretics.

Frusemide (furosemide) has no significant pharmacological effects other than on renal function.

Pharmacokinetics

Absorption

Frusemide (furosemide) has a rapid onset of action. Following intravenous administration, diuresis occurs within five minutes (longer following intramuscular administration), peaks within 30 minutes, and lasts approximately two hours. In patients with severely impaired renal function, the diuretic response may be prolonged.

Distribution

Frusemide (furosemide) is extensively bound to plasma proteins, mainly 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.

The drug crosses the placenta and is present in breast milk.

Metabolism

Recent evidence suggests that frusemide (furosemide) glucuronide is the only or at least the major biotransformation product of frusemide (furosemide) in humans.

Excretion

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

Frusemide (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 and in newborn infants.

INDICATIONS

Treatment of oedema associated with congestive heart failure, cirrhosis of the liver and renal disease, including the nephrotic syndrome and as adjunctive therapy in acute pulmonary oedema and cerebral oedema.

Parenteral therapy with frusemide (furosemide) should be reserved for patients in emergency clinical situations, or for patients unable to take oral medication or if

gastrointestinal absorption is impaired. Oral formulations of frusemide (furosemide) should be commenced as soon as practicable.

CONTRAINDICATIONS

Known hypersensitivity to frusemide (furosemide), sulfonamides or any of the inactive ingredients (see DESCRIPTION). Patients allergic to sulfonamides (e.g. sulfonamide antibiotics or sulfonyleureas) may show cross sensitivity to frusemide (furosemide).

Complete renal shutdown, impaired renal function or anuria. If increasing azotaemia and oliguria occur during treatment of severe progressive renal disease, discontinue frusemide (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, frusemide (furosemide) therapy should not be instituted until the underlying conditions have been corrected or ameliorated.

In breast-feeding and pregnant women.

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

PRECAUTIONS

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

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

In patients with hepatic cirrhosis and ascites, initiation of therapy with frusemide (furosemide) 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 (furosemide) ototoxicity is associated with rapid injection or infusion, 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 effects of frusemide (furosemide) may be weakened and its ototoxicity potentiated. Cautious dose titration

is required. If the physician elects to use high-dose parenteral therapy, controlled intravenous infusion is advisable (for adults with normal renal function, an infusion rate not exceeding 4mg frusemide (furosemide) per minute must be used; for adults with impaired renal function (creatinine > 5mg/dL), an infusion rate of no greater than 2.5mg per minute must be used).

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

Caution should be exercised and the risks and benefits of combining risperidone with frusemide or other potent diuretics should be considered prior to the decision to treat. In the risperidone placebo-controlled trials in elderly patients with dementia, a higher incidence of mortality was observed in patients treated with frusemide plus risperidone (7.3% ; mean age 89 years, range 75 to 97) compared to treatment with risperidone alone (3.1% ; mean age 84 years, range 70 to 96) or frusemide alone (4.1% ; mean age 80 years, range 67 to 90). Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low doses) was not associated with similar mortality findings. No pathophysiological mechanism has been identified to explain this finding and no consistent pattern for cause of death was observed. Nevertheless, caution is advised. Irrespective of treatment, dehydration was an overall risk factor for mortality and should, therefore, be carefully avoided in elderly patients with dementia.

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

Frusemide (furosemide) should be used with care, especially in the initial stages, in patients with prostatic hypertrophy or impairment of micturition. Urinary outflow must be secured. 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 at risk from hypotension or who are at particular risk from a pronounced fall in blood pressure (e.g. patients with significant stenoses of the coronary artery 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.

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

In premature infants, there is the possible development of nephrocalcinosis/nephrolithiasis and therefore renal function must be monitored and

renal ultrasonography performed. In premature infants, frusemide (furosemide) administered during the first weeks of life may increase the risk of persistence of Botallo's duct.

As with any effective diuretic, electrolyte depletion may occur during therapy with frusemide (furosemide), especially in patients receiving higher doses and a restricted salt intake. All patients receiving frusemide (furosemide) therapy should be observed for signs of fluid or electrolyte imbalance, namely hyponatraemia, hypochloraemic alkalosis and hypokalaemia. Periodic determinations of serum electrolytes to detect possible imbalance should be performed at appropriate intervals, as well as creatinine, blood urea and CO₂ 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, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, arrhythmia and gastrointestinal disturbances, e.g. nausea and vomiting. Hypovolaemia or dehydration as well as any significant electrolyte and acid-base disturbances must be corrected. This may require temporary discontinuation of frusemide (furosemide).

During long-term therapy a high potassium diet is recommended. Potassium supplements may be required especially when high doses are used for prolonged periods. Particular caution with potassium is necessary when the patient is on digitalis glycosides, potassium depleting steroids or in the case of infants and children. Potassium supplementation, diminution in dose or discontinuation of frusemide (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 frusemide (furosemide). Increases in blood glucose and alterations in glucose tolerance tests with abnormalities of the fasting and two-hour postprandial sugar have been observed and rare cases of precipitation of diabetes mellitus have been reported.

Frusemide (furosemide) 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 intravenous frusemide (furosemide) treatment. An association of these symptoms with a low serum calcium and/or a low calcium: protein ratio is possible.

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

Frusemide (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.

Renal calcifications (from barely visible on X-ray to staghorn) have occurred in some severely premature infants treated with intravenous frusemide (furosemide) 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.

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

When frusemide (furosemide) is administered parenterally, a maximum injection rate of 4mg/minute should be used to minimise the risk of ototoxicity.

Intramuscular administration of frusemide (furosemide) must be limited to exceptional cases where neither oral nor intravenous administration are feasible. Intramuscular administration is not suitable for acute conditions such as pulmonary oedema.

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 pregnancy (Category C)

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.

Frusemide (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 frusemide (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.

In pregnancy, frusemide (furosemide) must only be used in patients with a marked deterioration in glomerular filtration.

Use in lactation

Frusemide (furosemide) passes into the breast milk and inhibits lactation. Women must not breastfeed if being treated with frusemide (furosemide).

INTERACTIONS WITH OTHER MEDICINES

Combinations that are not recommended

Frusemide (furosemide) may increase the ototoxic and nephrotoxic potential of 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 frusemide (furosemide). In isolated cases intravenous administration of frusemide (furosemide) within 24 hours of taking chloral hydrate may lead to flushing, sweating attacks, restlessness, nausea, increase in blood pressure and tachycardia. Use of frusemide (furosemide) concomitantly with chloral hydrate is, therefore, not recommended.

Precautions for use

Frusemide (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 frusemide (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.

Frusemide (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.

The action of other antihypertensive drugs may be potentiated by frusemide (furosemide), especially in combination with angiotensin converting enzyme (ACE) inhibitors. The administration of ACE inhibitors to patients pretreated with frusemide (furosemide) may lead to 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 frusemide (furosemide) temporarily or at least reducing the dose of frusemide (furosemide) for three days before starting treatment with an ACE inhibitor 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 frusemide (furosemide) or other potent diuretics should be considered prior to the decision to use. See PRECAUTIONS regarding increased mortality in elderly patients with dementia concomitantly receiving risperidone.

High doses of frusemide 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 frusemide (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 PRECAUTIONS).

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

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

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

Frusemide (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 frusemide (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 frusemide (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 frusemide (furosemide).

Phenytoin methotrexate, probenecid and other drugs which, like frusemide undergo significant renal tubular secretion may attenuate the effects of frusemide (furosemide). Conversely, frusemide (furosemide) may decrease renal elimination of these drugs. In the case of high-dose treatment (in particular of both frusemide (furosemide) and the

other drugs), this may lead to an increased risk of adverse effects due to frusemide (furosemide) or the concomitant medication.

Intravenous frusemide (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 drugs are given together.

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

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

Impairment of renal function may develop in patients receiving concurrent treatment with frusemide (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 frusemide (furosemide) is associated with increased risk of gouty arthritis secondary to frusemide (furosemide)-induced hyperuricaemia and cyclosporine impairment of renal urate excretion.

Patients who were at high risk for radiocontrast nephropathy treated with frusemide (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.

ADVERSE EFFECTS

Whenever adverse reactions are moderate or severe, the dose of frusemide (furosemide) administered should be reduced or therapy withdrawn.

Metabolism and nutritional disorders

As with other diuretics, electrolytes and water balance may be disturbed during therapy with frusemide (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 frusemide).

Excessive diuresis may give rise especially in elderly patients and children to circulatory disturbances, e.g. headache, dizziness, dry mouth or visual impairment, as symptoms of hypovolaemia. In extreme cases, hypovolaemia and dehydration may lead to hypotension, circulatory collapse and, in elderly patients in particular, thrombophilia. However, with individualised dosage, acute haemodynamic reactions are generally not to be expected, although diuresis sets in rapidly.

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

Factors such as underlying diseases (liver cirrhosis, cardiac failure), concomitant medication (see INTERACTIONS WITH OTHER MEDICINES) or nutritional inadequacies (excessive restrictions 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, calf muscle spasms, anorexia, weakness, dizziness, drowsiness, apathy, vomiting and confusion.

Frusemide (furosemide) may lower the serum calcium level (hypocalcaemia), which may trigger a state of increased neuromuscular irritability. Frusemide (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 frusemide (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 hepatic cirrhosis) may be aggravated during frusemide (furosemide) treatment. Metabolic alkalosis has been reported with frusemide use.

Treatment with frusemide (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 frusemide has been reported.

Very common: electrolyte disturbances (including symptomatic), dehydration and hypovolaemia especially in elderly patients, increased blood creatinine, increased blood triglycerides.

Common: hyponatremia, hypochloremia, hypokalaemia, blood cholesterol increased, blood uric acid increased and attacks of gout, urine volume increased.

Uncommon: impaired glucose tolerance. Latent diabetes mellitus may manifest

Gastrointestinal disorders and hepato-biliary disorders

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

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

Central nervous system disorders

Reactions such as dizziness, vertigo, paraesthesia, headache and blurred vision occasionally accompany frusemide (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 when the recommended rate of injection or infusion of 4mg per minute (for normal renal function) or 2.5mg per minute (for impaired renal function) is exceeded or in patients who are also receiving drugs known to be ototoxic.

Cases of deafness, sometimes irreversible, have been reported after oral or IV administration of frusemide.*

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. Photosensitivity reactions have been reported. AGEP (acute generalized exanthematous pustulosis) and DRESS (Drug Rash with Eosinophilia and Systemic Symptoms) have been reported with frusemide 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.

Congenital and familial/genetic disorders

The persistence of patent ductus arteriosus when frusemide has been administered to a premature infant during the first weeks of life has been reported.

Renal and urinary disorders

Excessive diuresis and dehydration could cause transient elevation of 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 ureterostenosis or hydronephrosis, may be triggered or aggravated by pronounced diuresis. Interstitial nephritis has also been reported with frusemide (furosemide) use. In premature infants, calcium salts may be deposited in the renal tissue (nephrocalcinosis/nephrolithiasis). In patients with a partial obstruction of urinary outflow, acute retention of urine may occur. Increases in sodium and/or chloride urine levels, and renal failure has been reported with frusemide use.

Vascular disorders

Very common (especially for intravenous infusion), 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. If frusemide (furosemide) is administered to premature infants

during the first weeks of life, it may increase the risk of persistence of patent ductus arteriosus.

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

Not known: Dizziness, fainting and loss of consciousness (caused by symptomatic hypotension)

General disorders and administration site conditions

Rarely, fever may occur. Following intramuscular injection, local reactions such as pain may occur. Restlessness has also been reported.

DOSAGE AND ADMINISTRATION

Frusemide Sandoz Injection should be inspected visually for particulate matter before administration. Do not use if solution contains particulate matter.

Frusemide Sandoz Injection is for intravenous and intramuscular use.

Contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue.

Adults

Parenteral therapy with frusemide (furosemide) injection should only be used in patients unable to take oral medication or in emergency situations and should be replaced with oral therapy as soon as practical.

Oedema

The usual initial dose of frusemide (furosemide) is 20 to 40mg given as a single dose, injected intramuscularly or intravenously. The intravenous dose should be given slowly. Ordinarily a prompt diuresis ensues. If necessary, another dose may be given no sooner than two hours later. This second dose may be increased by 20mg. The resulting dose may then be repeated once or twice daily.

Therapy should be individualised according to patient response to gain maximal therapeutic effect and to determine the minimal dose needed to maintain that response. Close medical supervision is necessary.

For high-dose parenteral therapy, add the frusemide (furosemide) to either sodium chloride injection or lactated Ringer's injection and administer as a controlled intravenous infusion at a rate not greater than 4mg/minute.

Acute pulmonary oedema

The usual initial dose of frusemide (furosemide) is 40mg injected slowly intravenously. If a satisfactory response does not occur within one hour, the dose may be increased to 80mg injected slowly intravenously.

If necessary, additional therapy (e.g. digitalis, oxygen) may be administered concomitantly.

Cerebral oedema

The following procedure is recommended. An intravenous injection of 20 to 40mg, three times daily. A more uniform diuretic action is obtained if the same doses are infused. The rate of infusion must be determined individually in accordance with the diuretic action and the neurological findings.

Infants, children

Parenteral therapy should be used only in patients unable to take oral medication or in emergency situations and should be replaced by oral therapy as soon as practical.

The usual dose of frusemide (furosemide) injection (intravenously or intramuscularly) in infants and children is 1mg/kg bodyweight and should be given under close medical supervision. If the diuretic response after the initial dose is not satisfactory, the dosage may be increased by 1mg/kg not sooner than two hours after the previous dose, until the desired diuretic effect has been obtained. Doses greater than 6mg/kg bodyweight are not recommended.

OVERDOSAGE

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

Symptoms

The clinical picture in acute or chronic overdose depends primarily on the extent and consequences of electrolyte and fluid loss, e.g. dehydration, blood volume reduction, hypotension, electrolyte imbalance, cardiac arrhythmias (including AV block and ventricular fibrillation), hypokalaemia and hypochloreaemic 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 (furosemide) has been determined in mice, rats and dogs. In all three, the oral LD₅₀ exceeded 1,000mg/kg bodyweight, while the intravenous LD₅₀ ranged from 300 to 680mg/kg. The acute intragastric toxicity in neonatal rats is seven to ten times that of adult rats. The concentration of frusemide (furosemide) in biological fluids associated with toxicity or death is not known.

Treatment

No specific antidote to frusemide (furosemide) is known.

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

PRESENTATION AND STORAGE CONDITIONS

Frusemide Sandoz Injection 20mg/2mL - clear, colourless solution supplied in a brown glass ampoule.

Available in packs of 5 ampoules.

Store below 25 °C. Protect from light.

Inspect visually for particulate matter and discolouration before administration. Do not use if solution contains particulate matter or is discoloured. Although the chemical stability of diluted frusemide (furosemide) injection has been demonstrated for storage at 25°C for 24 hours, the diluted solution should be used as soon as practicable to reduce the risk of microbiological hazard. If storage is necessary, hold the diluted solution at 2-8°C for not more than 24 hours.

Contains no antimicrobial agent. Product is for single use in one patient only. Discard any residue.

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road
Macquarie Park, NSW 2113
Australia
Tel: 1800 634 500

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG): 05/01/2010

Date of most recent amendment: 29/01/2016

*Changes of clinical significance.