Approved Professional Information for FRUSEMIDE 250 mg/25 ml FRESENIUS.

SCHEDULING STATUS S3

1. NAME OF THE MEDICINE

FRUSEMIDE 250 mg/25 ml FRESENIUS solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 25 ml contains 250 mg furosemide.

Sugar free.

For the full list of excipients, see section 6.1.

Excipient with known effect:

Sodium chloride.

3. PHARMACEUTICAL FORM

Solution for injection.

A clear colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oliguria in acute or chronic renal failure, chronic renal insufficiency.

4.2 Posology and method of administration

Posology

Oliguria in acute or chronic renal failure:

The effective dose (up to 1 g) may be given daily.

Dosage is then adjusted according to patient's response.

Patients not responding to 1 g **FRUSEMIDE 250 mg/25 ml FRESENIUS** probably require dialysis.

Method of administration

Slow intravenous infusion.

250 mg **FRUSEMIDE 250 mg/25 ml FRESENIUS** diluted to 250 ml in a suitable diluent infused over one hour. Suitable diluents include dextrose 5 %; ringers' lactate; sodium chloride 0,9 % or dextrose 10 % or 20 % in water.

If urine output is insufficient within an hour, this dose may be followed by 500 mg **FRUSEMIDE 250 mg/25 ml FRESENIUS** added to an infusion fluid, the volume of which must be governed by the patient's state of hydration and infused over 2 hours. If urine output is still not satisfactory within 1 hour of the end of the second infusion, a third dose of 1 g **FRUSEMIDE 250 mg/25 ml FRESENIUS** may be infused over 4 hours.

In oliguria or anuric patients with significant fluid overload, the injection may be given directly into the vein at an administration rate never to exceed 4 mg/minute.

4.3 Contraindications

- Hypersensitivity to furosemide, amiloride, sulphonamides, sulphonamide derivatives (cross-sensitivity exists between sulphonamides and furosemide) or to any of the excipients listed in section 6.1.
- Hypovolaemia and dehydration (with or without accompanying hypotension) (see section 4.4).
- Severe hypokalaemia, severe hyponatraemia (see section 4.4).
- Comatose or pre-comatose states associated with hepatic cirrhosis (see section 4.4).
- Pregnancy and lactation (see section 4.6).

- **FRUSEMIDE 250 mg/25 ml FRESENIUS** should not be given in anuria or in renal failure due to nephrotoxic or hepatotoxic medicines nor in renal failure associated with hepatic coma.
- Impaired renal function with a creatinine clearance below 30 ml/min per 1,73 m^2 body surface area (see section 4.4).
- **FRUSEMIDE 250 mg/25 ml FRESENIUS** should not be given to patients with Addison's disease or pre-existing hypercalcaemia.
- Digoxin intoxication (see section 4.5).
- Porphyria.

4.4 Special warnings and precautions for use

Conditions requiring correction before treatment with FRUSEMIDE 250 mg/25 ml FRESENIUS is started (see section 4.3):

- Hypotension.
- Hypovolaemia.
- Severe electrolyte disturbances – particularly hypokalaemia, hyponatraemia and acid-base disturbances. Fluid and electrolyte imbalance should be monitored during therapy.

FRUSEMIDE 250 mg/25 ml FRESENIUS contains 90,76 mg sodium per ampoule, equivalent to 4% of the WHO recommended daily intake of 2 g sodium for an adult.

The maximum daily dose of this product is equivalent to 18 % of the WHO recommended maximum daily intake for sodium.

FRUSEMIDE 250 mg/25 ml FRESENIUS is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

FRUSEMIDE 250 mg/25 ml FRESENIUS is not recommended:

- In patients at high risk for radiocontrast nephropathy – **FRUSEMIDE 250 mg/25 ml FRESENIUS** should not be used for diuresis as part of the preventative measures against radiocontrast-induced nephropathy. Except as a single trial dose in acute anuria in the absence of obstruction, **FRUSEMIDE 250 mg/25 ml FRESENIUS** should be avoided in anuric patients.

Particular caution and/or dose reduction required:

- Symptomatic hypotension leading to dizziness, fainting or loss of consciousness can occur in patients treated with **FRUSEMIDE 250 mg/25 ml FRESENIUS**, particularly in the elderly, patients using other medicines which can cause hypotension, and patients with other medical conditions that are risks for hypotension.
- Elderly people (lower initial dose as particularly susceptible to side effects, see section 4.2).
- Difficulty with micturition, including prostatic hypertrophy (increased risk of urinary retention: consider lower dose). Closely monitor patients with partial occlusion of the urinary tract.
- Diabetes mellitus (latent diabetes may become overt; insulin requirements in established diabetes may increase; stop **FRUSEMIDE 250 mg/25 ml FRESENIUS** before a glucose tolerance test).
- Pregnancy (see section 4.6).
- Patients with hepatorenal syndrome.
- Caution should be exercised in patients with impaired hepatic function or renal impairment (see section 4.3 and below – monitoring required).
- **FRUSEMIDE 250 mg/25 ml FRESENIUS** may enhance the nephrotoxicity of cephalosporin and aminoglycoside antibiotics (see section 4.5). Hypoproteinaemia e.g. nephritic

syndrome (effect of furosemide, as in **FRUSEMIDE 250 mg/25 ml FRESENIUS**, may be impaired and its ototoxicity potentiated – cautious dose titration required).

- Acute hypercalcaemia (dehydration results from vomiting and diuresis – correct before giving **FRUSEMIDE 250 mg/25 ml FRESENIUS**). Treatment of hypercalcaemia with a high dose of furosemide results in fluid and electrolyte depletion – meticulous fluid replacement and correction of electrolytes required.
- Patients who are at risk from a pronounced fall in blood pressure.
- **FRUSEMIDE 250 mg/25 ml FRESENIUS** has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.
- Caution should be exercised in patients with gout (furosemide, as in **FRUSEMIDE 250 mg/25 ml FRESENIUS**, may raise uric acid levels/precipitate gout).
- Patients on restricted sodium intake are particularly susceptible to excessive dehydration and hypotension.
- Patients sensitive to sulphonamides may develop allergic dermatological and vasculitic reactions to **FRUSEMIDE 250 mg/25 ml FRESENIUS**.
- Caution must be exercised in administering **FRUSEMIDE 250 mg/25 ml FRESENIUS** to infants, particularly for extended periods. Premature infants (possible development of nephrocalcinosis or nephrolithiasis; renal function must be monitored, and renal ultrasonography performed).

Laboratory monitoring requirements:

Serum sodium

Particularly in elderly people or in patients liable to electrolyte deficiency.

Serum potassium

The possibility of hypokalaemia should be taken into account, in particular in patients with cirrhosis of the liver, those receiving concomitant treatment with corticosteroids, those with an

unbalanced diet and those who abuse laxatives. Regular monitoring of the potassium, and if necessary, treatment with a potassium supplement, is recommended in all cases, but is essential at higher doses and in patients with impaired renal function. It is especially important in the event of concomitant treatment with digoxin, as potassium deficiency can trigger or exacerbate the symptoms of digitalis intoxication (see section 4.5). A potassium-rich diet is recommended during long-term use.

Frequent checks of the serum potassium are necessary in patients with impaired renal function and creatinine clearance below 60 ml/min per 1,73m^2 body surface area, as well as in cases where furosemide is taken in combination with certain other medicines which may lead to an increase in potassium levels (see section 4.5 and refer to section 4.8 for details of electrolyte and metabolic abnormalities).

Renal function

Frequent blood urea nitrogen (BUN) in the first few months of treatment, periodically thereafter. Long-term/high-dose BUN should regularly be measured. Marked diuresis can cause reversible impairment of kidney function in patients with renal dysfunction. Adequate fluid intake is necessary in such patients. Serum creatinine and urea levels tend to rise during treatment.

Glucose

Adverse effect on carbohydrate metabolism – exacerbation of existing carbohydrate intolerance or diabetes mellitus. Regular monitoring of blood glucose levels is desirable.

Other electrolytes

Patients with hepatic failure/alcoholic cirrhosis are particularly at risk of hypomagnesaemia (as well as hypokalaemia). During long-term therapy (especially at high doses) magnesium, calcium, chloride, bicarbonate and uric acid should be regularly measured.

Clinical monitoring requirements (see also section 4.8):

Regular monitoring for blood dyscrasias. If these occur, stop **FRUSEMIDE 250 mg/25 ml FRESENIUS** immediately:

- liver damage
- idiosyncratic reactions.

Other alterations in laboratory values

- Serum cholesterol and triglycerides may rise, but usually return to normal within 6 months of starting **FRUSEMIDE 250 mg/25 ml FRESENIUS**.
- Concomitant use with risperidone (see section 4.5).

  In risperidone placebo-controlled trials in elderly people with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone, when compared to patients treated with risperidone alone or furosemide alone. Concomitant use of risperidone with other diuretics (mainly thiazide diuretics, used in low dose) was not associated with similar findings.

  No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination or co-treatment with other potent diuretics should be considered, prior to the decision to use. There was no increased incidence of mortality among patients taking other diuretics as concomitant treatment with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be avoided in elderly patients with dementia (see section 4.3).

4.5 Interaction with other medicines and other forms of interaction

General: The dosage of concurrently administered digoxin, diuretics, antihypertensives or other medicines with blood pressure-lowering potential may require adjustment, as a more

pronounced fall in blood pressure must be anticipated if given concomitantly with **FRUSEMIDE 250 mg/25 ml FRESENIUS.**

Solutions for injection are alkaline and should not be mixed or diluted with glucose injection or other acidic solutions.

FRUSEMIDE 250 mg/25 ml FRESENIUS may enhance the nephrotoxicity of cephalosporin antibiotics and can enhance the ototoxicity of aminoglycoside antibiotics and other ototoxic medicines.

Neuromuscular blockers – the neuromuscular blocking action of competitive neuromuscular blockers, such as atracurium, may be enhanced.

Antihypertensives – enhanced hypotensive effect possible with all types. Concurrent use with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor antagonists can result in marked falls in blood pressure, **FRUSEMIDE 250 mg/25 ml FRESENIUS** should be stopped, or the dose reduced before starting an ACE inhibitor or angiotensin II receptor antagonists (see section 4.4).

Antipsychotics – furosemide-induced hypokalaemia increases the risk of cardiac toxicity. Avoid concurrent use with pimozide. Increased risk of ventricular dysrhythmias with amisulpride or sertindole. Enhanced hypotensive effect with phenothiazines.

When administering risperidone, caution should be exercised and the risks and benefits of the combination or co-treatment with furosemide or with other potent diuretics should be considered prior to the decision to use. See section 4.4 regarding increased mortality in elderly patients with dementia concomitantly receiving risperidone.

Anti-dysrhythmics (including amiodarone, disopyramide, flecanaide and sotalol) – risk of cardiac toxicity (because of furosemide-induced hypokalaemia).

Lidocaine (lignocaine), tocainide or mexiletine – the effects of lidocaine (lignocaine), tocainide or mexiletine may be antagonised by furosemide, as in **FRUSEMIDE 250 mg/25 ml FRESENIUS**.

Digoxin – hypokalaemia and electrolyte disturbances (including hypomagnesaemia) increase the risk of cardiac toxicity.

Medicines that prolong QT interval – increased risk of toxicity with furosemide-induced electrolyte disturbances.

Vasodilators – enhanced hypotensive effect with moxisylyte (thymoxamine) or hydralazine.

Other diuretics – profound diuresis is possible when furosemide, as in **Frusemide Fresenius 250 mg/25 ml**, is given with metolazone. Increased risk of hypokalaemia with thiazides.

Renin inhibitors – aliskiren reduces plasma concentrations of furosemide, as in **FRUSEMIDE 250 mg/25 ml FRESENIUS**.

Nitrates – enhanced the hypotensive effect of **FRUSEMIDE 250 mg/25 ml FRESENIUS**.

Alcohol, barbiturates or opioids – orthostatic hypotension associated with **FRUSEMIDE 250 mg/25 ml FRESENIUS** may be enhanced by alcohol, barbiturates or opioids.

Nonsteroidal anti-inflammatory drugs (NSAIDs) – the antihypertensive effect may be antagonised by medicines that cause fluid retention, such as nonsteroidal anti-inflammatory drugs (NSAIDs). The nephrotoxicity of NSAIDs may be enhanced. Indomethacin and ketorolac may antagonise the effects of furosemide (avoid, if possible, see section 4.4). NSAIDs may attenuate the action of furosemide, as in **FRUSEMIDE 250 mg/25 ml FRESENIUS**, and may cause acute renal failure in cases of pre-existing hypovolaemia or dehydration.

Lithium – **FRUSEMIDE 250 mg/25 ml FRESENIUS** should not be used with lithium.

Allopurinol – the toxicity of allopurinol may be increased.

Tetracycline antibiotics – the toxicity of tetracyclines may be increased.

Chelating medicines – sucralfate may decrease the gastrointestinal absorption of furosemide, as in **FRUSEMIDE 250 mg/25 ml FRESENIUS**. Sucralfate and **FRUSEMIDE 250 mg/25 ml FRESENIUS** should be used at least 2 hours apart.

Salicylates – the effects of salicylates may be potentiated by furosemide, as in **FRUSEMIDE 250 mg/25 ml FRESENIUS**. Salicylic toxicity may be increased by **FRUSEMIDE 250 mg/25 ml FRESENIUS**.

Antibiotics – increased risk of ototoxicity with aminoglycosides, polymyxins or vancomycin; only use concurrently if these are compelling reasons. Increased risk of nephrotoxicity with aminoglycosides or cefaloridine. Furosemide, as in **FRUSEMIDE 250 mg/25 ml FRESENIUS**, can decrease vancomycin serum levels after cardiac surgery. Increased risk of hyponatraemia with trimethoprim. Impairment of renal function may develop in patients receiving concurrent treatment with furosemide and high doses of certain cephalosporins.

Antidepressants – enhanced hypotensive effect with monoamine oxidase inhibitors (MAOIs). Increased risk of postural hypotension with tricyclic antidepressants (TCAs). Increased risk of hypokalaemia with reboxetine.

Antidiabetics – **FRUSEMIDE 250 mg/25 ml FRESENIUS** may alter the requirements for hypoglycaemics in diabetic patients.

Antiepileptics – increased risk of hyponatraemia with carbamazepine. Concurrent administration of phenytoin may reduce the clinical effects of **FRUSEMIDE 250 mg/25 ml FRESENIUS**.

Antihistamines – hypokalaemia with increased risk of cardiac toxicity.

Antifungals – increased risk of hypokalaemia and nephrotoxicity with amphotericin.

Anxiolytics and hypnotics – enhanced hypotensive effect. Chloral or triclofos may displace thyroid hormone from binding site.

Central nervous system (CNS) stimulants (medicines used for attention deficit hyperactivity disorder (ADHD)) – hypokalaemia increases the risk of ventricular dysrhythmias.

Corticosteroids and corticotrophin – diuretic effect antagonised (sodium retention) and increased risk of hypokalaemia.

Glycyrrhizin – (contained in liquorice) may increase the risk of developing hypokalaemia.

Cytotoxics – increased risk of nephrotoxicity and ototoxicity with platinum compounds/cisplatin.

Nephrotoxicity of cisplatin may be enhanced if **FRUSEMIDE 250 mg/25 ml FRESENIUS** is not given in low doses (e.g. 40 mg in patients with normal renal function) and with positive fluid balance when used to achieve forced diuresis during cisplatin treatment.

Anti-metabolites – effects of **FRUSEMIDE 250 mg/25 ml FRESENIUS** may be reduced by methotrexate and **FRUSEMIDE 250 mg/25 ml FRESENIUS** may reduce renal clearance of methotrexate.

Dopaminergics – enhanced hypotensive effect with levodopa.

Immunomodulators – enhanced hypotensive effect with aldesleukin. Increased risk of hyperkalaemia with ciclosporin and tacrolimus. Increased risk of gouty arthritis with ciclosporin.

Muscle relaxants – enhanced hypotensive effect with baclofen or tizanidine. Increased effect of curare-like muscle relaxants.

Oestrogens – diuretic effect antagonised.

Progestogens (drosperidone) – increased risk of hyperkalaemia.

Prostaglandins – enhanced hypotensive effect with alprostadil.

Sympathomimetics – increased risk of hypokalaemia with high doses of beta$_2$ sympathomimetics, such as sotalol or salbutamol.

Theophylline – enhanced hypotensive effect.

Probenecid – effects of **FRUSEMIDE 250 mg/25 ml FRESENIUS** may be reduced by probenecid, and furosemide, as in **FRUSEMIDE 250 mg/25 ml FRESENIUS,** may reduce renal clearance of probenecid.

Anaesthetic medicines – general anaesthetic medicines may enhance the hypotensive effects of furosemide. The effects of curare may be enhanced by **FRUSEMIDE 250 mg/25 ml FRESENIUS**.

Laxative abuse – increases the risk of potassium loss.

Others – concomitant administration of aminoglutethimide may increase the risk of hyponatraemia.

The response of pressor amines e.g. noradrenaline (norepinephrine), has been reported to be diminished.

4.6 Fertility, pregnancy and lactation

The safety of **FRUSEMIDE 250 mg/25 ml FRESENIUS** in pregnancy and lactation has not been established (see section 4.3).

FRUSEMIDE 250 mg/25 ml FRESENIUS should not be used during pregnancy and lactation since it crosses the placenta and also appears in breast milk. **FRUSEMIDE 250 mg/25 ml FRESENIUS** may compromise placental perfusion by reducing maternal blood volume; it may also inhibit lactation.

4.7 Effects on ability to drive and use machines

Reduced mental alertness, dizziness and blurred vision have been reported, particularly at the start of treatment, with dose changes and in combination with alcohol. Patients should be advised that if affected, they should not drive a vehicle, operate machinery or take part in activities where these effects could put themselves or others at risk.

4.8 Undesirable effects

Blood and lymphatic system disorders:

Less frequent:

Bone marrow depression (necessitates withdrawal of treatment, the haemopoietic status should therefore be regularly monitored), aplastic anaemia or haemolytic anaemia, agranulocytosis, thrombocytopenia, leukopenia and eosinophilia.

Electrolyte imbalance: hyponatraemia, hypokalaemia and hypochloraemic alkalosis.

Immune systems disorders:

Less frequent: Allergy, hypersensitivity reactions including interstitial nephritis and fever.

Endocrine disorders:

Frequency unknown:

Hyperglycaemia and glycosuria.

Hyperuricaemia (with precipitated attacks of gout) and an increased excretion of calcium may occur.

Glucose tolerance may decrease with furosemide, as in **FRUSEMIDE 250 mg/25 ml FRESENIUS**. In patients with diabetes mellitus this may lead to a deterioration of metabolic control; latent diabetes mellitus may become manifest. Insulin requirements of diabetic patients may increase.

Metabolism and nutrition disorders:

Frequency unknown:

Electrolyte imbalance: hypovolaemic shock.

Nervous system disorders:

Less frequent:

Paraesthesia, hyperosmolar coma.

Frequency unknown:

Dizziness, headache, fainting and loss of consciousness (caused by symptomatic hypotension).

Electrolyte imbalance: headache, lethargy and restlessness.

Eye disorders:

Less frequent:

Visual disturbance.

Frequency unknown:

Blurred vision, yellow vision.

Ear and labyrinth disorders:

Less frequent:

Tinnitus and deafness may occur during rapid, high-dose therapy (faster than 4 mg/minute), although usually transitory, it may occur in rare cases, particularly in patients with renal failure or hypoproteinaemia (e.g. in nephritic syndrome).

Deafness may be permanent, particularly in patients with impaired renal function or when administered concomitantly with ototoxic medicine.

Cardiac disorders:

Less frequent:

Cardiac dysrhythmias.

FRUSEMIDE 250 mg/25 ml FRESENIUS may cause a reduction in blood pressure which, if pronounced, may cause signs and symptoms such as impairment of concentration and reactions, light headedness, sensations of pressure in the head, headache, dizziness, drowsiness, weakness, disorders of vision, dry mouth and orthostatic intolerance. The diuretic effect of **FRUSEMIDE 250 mg/25 ml FRESENIUS** can result in hypovolaemia and dehydration, especially in the elderly. There is an increased risk of thrombosis.

Vascular disorders:

Less frequent:

Vasculitis.

Gastrointestinal disorders:

Less frequent:

Nausea, vomiting, diarrhoea, constipation, acute pancreatitis.

Electrolyte imbalance: dry mouth, thirst and gastrointestinal disturbances.

Hepato-biliary disorders:

Frequency unknown:

Jaundice, hepatic dysfunction and cholestatic jaundice.

In isolated cases, intrahepatic cholestasis, an increase in liver transaminases or acute pancreatitis may develop.

Hepatic encephalopathy in patients with hepatocellular insufficiency may occur (see section 4.3).

Skin and subcutaneous tissue disorders:

Less frequent:

Photosensitivity, skin rashes.

Skin and mucous membrane reactions may occasionally occur, e.g. itching, urticaria, other rashes or bullous lesions, fever, hypersensitivity to light, exudative erythema multiforme (Lyell's syndrome and Stevens-Johnson syndrome), bullous exanthema, exfoliative dermatitis, purpura, AGEP (acute generalised exanthematous pustulosis) and DRESS (drug rash with eosinophilia and systemic symptoms).

Frequency unknown:

Bullous pemphigoid.

Musculoskeletal and connective tissue disorders:

Frequency unknown:

Electrolyte imbalance: muscle cramps and weakness.

Renal and urinary disorders:

Less frequent:

Serum creatinine and urea levels can be temporarily elevated.

Interstitial nephritis, acute renal failure. Increased urine production and urinary incontinence can be caused, or symptoms can be exacerbated in patients with urinary tract obstruction. Acute urine retention, possibly accompanied by complications, can occur for example in patients with bladder disorders, prostatic hyperplasia or narrowing of the urethra.

Frequency unknown:

Renal stone formation has been reported in pre-term infants.

Electrolyte imbalance: dehydration and oliguria.

Pregnancy, puerperium and perinatal conditions

In premature infants with respiratory distress syndrome, administration of **FRUSEMIDE 250 mg/25 ml FRESENIUS** in the initial weeks after birth entails an increased risk of a persistent patent ductus arteriosus.

In premature infants, **FRUSEMIDE 250 mg/25 ml FRESENIUS** can be precipitated as nephrocalcinosis/ kidney stones.

Rare complications may include minor psychiatric disturbances.

Special population:

Patients with hepatic impairment

Pre-existing metabolic alkalosis (e.g. in decompensated cirrhosis of the liver) may be aggravated by **FRUSEMIDE 250 mg/25 ml FRESENIUS** treatment.

Reporting of suspected adverse reactions

Health care providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

Reporting suspected adverse reactions after authorisation of **FRUSEMIDE 250 mg/25 ml FRESENIUS** is important. It allows continued monitoring of the benefit/risk balance of **FRUSEMIDE 250 mg/25 ml FRESENIUS**. Health care providers are asked to report any suspected adverse reactions via the "**6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms

Overdose can cause massive diuresis resulting in dehydration, volume depletion and electrolyte disturbances with consequent hypotension and cardiac toxicity. High doses have the potential to cause transient deafness and may precipitate gout (disturbed uric acid secretion).

Treatment

Benefits of gastric decontamination are uncertain. In patients presenting within 1 hour of ingestion, consider activated charcoal (50 g for adults and 1 g/kg for children).

Observe for a minimum of 4 hours – monitor pulse and blood pressure.

Treat hypotension and dehydration with appropriate IV fluids.

Monitor urinary output and serum electrolytes (including chloride and bicarbonate). Correct electrolyte imbalances. Monitor 12 lead electrocardiogram (ECG) in patients with significant electrolyte disturbances.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 18.1 Diuretics.

Pharmacotherapeutic group: High-ceiling diuretic sulphonamides, loop diuretics.

ATC code: C03CA01.

Mechanism of action:

The principal renal action of furosemide is to inhibit active chloride transport in the thick ascending limb.

Re-absorption of sodium and chloride from the nephron is reduced, and a hypotonic or isotonic urine produced.

Furosemide is a high-ceiling diuretic acting primarily by inhibiting electrolyte re-absorption in the thick ascending limb of Henle, but also in the proximal tubule. Blood-flow is diverted from the juxta-medullary region to the outer cortex.

It has been established that prostaglandin (PG) biosynthesis and the renin-angiotensin system are affected by furosemide administration and that furosemide alters the renal permeability of the glomerulus to serum proteins.

5.2 Pharmacokinetic properties

Absorption:

Approximately 65 % of the dose is absorbed after oral administration. The plasma half-life is biphasic with a terminal elimination phase of about 1½ hours.

Furosemide is a weak carboxylic acid which exists mainly in the dissociated form in the gastrointestinal tract. Furosemide is rapidly but incompletely absorbed (60 – 70 %) on oral administration and its effect is largely over within 4 hours. The optimal absorption site is the upper duodenum at pH 5,0.

Distribution:

Furosemide is approximately 99 % bound to plasma albumin.

Biotransformation:

Furosemide is bound to plasma albumin and little biotransformation takes place.

Elimination:

Regardless of route of administration 69 – 97 % of activity from a radio-labelled dose is excreted in the first 4 hours after furosemide is given. Furosemide is mainly eliminated via the kidneys (80 – 90 %) mainly excreted in the urine, largely unchanged; but also excreted in the

bile, non-renal elimination being considerably increased in renal failure. Furosemide crosses the placental barrier and is excreted in the milk.

A small fraction of the dose undergoes biliary elimination and 10 – 15 % of the activity can be recovered from the faeces.

In renal/hepatic impairment:

Where liver disease is present, biliary elimination is reduced up to 50 %. Renal impairment has little effect on the elimination rate of furosemide, but less than 20 % residual renal function increases the elimination time.

Elderly patients:

The elimination of furosemide is delayed in elderly patients where a certain degree of renal impairment is present.

Newborn patients:

A sustained diuretic effect is seen in the newborn, possibly due to immature tubular function.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid (37 % solution) (pH adjuster)

Sodium chloride (adjust isotonicity)

Sodium hydroxide (solubiliser)

Water for injection (vehicle).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Protect from light.

Store at or below 30 °C.

6.5 Nature and contents of container

25 ml amber type I glass ampoules packed in boxes of 10.

6.6 Special precautions for disposal and other handling

Any unused medicine should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi Manufacturing SA (Pty) Ltd

6 Gibaud Road

Korsten, 6020

Gqeberha

South Africa

8. REGISTRATION NUMBER

Z/18.1/139

9. DATE OF FIRST AUTHORISATION

11 May 1992

10. DATE OF REVISION OF THE TEXT

16 July 2024