

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1. Name of the medicinal product**

Furosemide S.A.L.F 250 mg/25 ml.

### **2. Qualitative and quantitative composition:**

1 ml of solution contain 10 mg of furosemide.  
Each 25ml vial contains 250 mg of furosemide solution for infusion, at a concentration of 10 mg/ml.

#### Excipient(s) with known effect:

Sodium-17.3mg /25 ml.

For the full list of excipients, see section 6.1.

### **3. Pharmaceutical form**

Solution for infusion

Clear and colorless or slightly colorless solution, free from visible particles.

### **4. Clinical particulars**

#### **4.1 Indications**

Furosemide is a potent diuretic indicated for use when a prompt and effective diuresis is required.

Furosemide is appropriate for use in emergencies or where oral therapy is not feasible. The indications include cardiac, pulmonary, hepatic and renal oedema.

#### **4.2 Posology and method of administration**

##### **Dosage and directions for use**

Duration of the treatment will depend on usage and is determined by the doctor for each individual.

For adults, the maximum recommended dose is 1,500 mg daily, although it may reach 2,000 mg in exceptional cases.

For children, the maximum recommended daily dose of Furosemide S.A.L.F 250 mg/25 ml for parenteral administration is 1 mg of furosemide per each kilogram of body weight, up to a maximum of 20 mg.

Treatment is to be switched to the oral route as soon as possible.

Furosemide S.A.L.F 250 mg/25 ml solution for

IV infusion should be injected or infused slowly by intravenous route, at a rate not exceeding 4 mg per minute. In patients with severe kidney problems (serum creatinine >5 mg/dl), it is recommended that the rate of infusion does not exceed 2.5 mg per minute. It should not be administered in the form of intravenous bolus. It should be infused using only infusion pumps that control volume or speed in order to avoid a possible risk of accidental overdose.

Furosemide S.A.L.F 250 mg/25 ml solution for IV infusion should not be Mixed in the same syringe or infused together with other medicines.

The suitable diluent is alkaline, neutral or weakly acidic solutions with a modest buffering capacity (Ringer's lactate, glucose solution). The diluted solutions should be used immediately after preparation.

Acidic solutions, especially those with a high buffering capacity, cannot be mixed with Furosemide S.A.L.F 250 mg/25 ml (see section 6.2 incompatibilities).

The pH of the solution for infusion ready for use should not be lower than 7, because in acidic solution furosemide can precipitate.

Furosemide S.A.L.F 250 mg/25 ml should never be infused together with other medication in the same intravenous fluid.

#### **Use in children:**

Parenteral administration is contraindicated for infants and children under the age of 15; this may be carried out only in cases involving a threat to life.

#### **Elderly:**

Elimination of furosemide is generally slower in the elderly. Dosage should be titrated until the required effect is achieved.

#### **4.3 Contraindications**

- Hypersensitivity to active substance or to any of the excipients listed in section 6.1.
- Hypersensitivity to amiloride, sulphonamides or sulphonamide

derivatives.

- Hypovolemia 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).
- Anuria or renal failure with anuria not responding to furosemide, renal failure as a result of poisoning by nephrotoxic or hepatotoxic agents, renal failure associated with hepatic coma.
- Impaired renal function with a creatinine clearance below 30ml/min per 1.73 m<sup>2</sup> body surface area (see section 4.4).
- Addison's disease (see section 4.4).
- Digitalis intoxication (see section 4.5).
- Porphyria.
- Breast-feeding women (see section 4.6).

#### **4.4 Special warnings and precautions for use**

##### **Conditions requiring correction before furosemide is started (see also section 4.3)**

Hypotension.

Hypovolemia.

Severe electrolyte disturbances – particularly hypokalemia, hyponatremia and acid-base disturbances.

Furosemide is not recommended in patients at high risk for radiocontrast nephropathy - it should not be used for diuresis as part of the preventative measures against radiocontrast-induced nephropathy.

##### **Particular caution and/or dose reduction required:**

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.

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 furosemide before a glucose tolerance test).

Pregnancy (see section 4.6).

Gout (furosemide may raise uric acid levels/precipitate gout).

Patients with hepatorenal syndrome.

Impaired hepatic function (see section 4.3 and below – monitoring required).

Impaired renal function (see section 4.3 and below – monitoring required).

Adrenal disease

(see section 4.3 – contraindication in Addison's disease).

Hypoproteinemia e.g. nephritic syndrome (effect of furosemide may be impaired and its ototoxicity potentiated - cautious dose titration required).

Acute hypercalcemia (dehydration results from vomiting and diuresis-correct before giving furosemide). Treatment of hypercalcemia with a high dose of furosemide results in fluid and electrolyte depletion-meticulous fluid replacement and correction of electrolyte required.

Patients who are at risk from a pronounced fall in blood pressure.

Premature infants (possible development nephrocalcinosis/nephrolithiasis; renal function must be monitored, and renal

ultrasonography performed).

**Avoidance with other medicines (see also section 4.5 for other interactions)**

Concurrent NSAIDs should be avoided—if not possible diuretic effect of furosemide may be attenuated.

ACE-inhibitors & Angiotensin II receptor antagonists—severe hypotension may occur—dose of furosemide should be reduced/stopped (3 days) before starting or increasing the dose of these.

**Laboratory monitoring requirements:**

*Serum sodium*

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

*Serum potassium*

The possibility of hypokalemia 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 60ml/min per 1.73m<sup>2</sup> body surface area as well as in cases where furosemide is taken in combination with certain other drugs which may lead to an increase in potassium levels (see section 4.5 & refer to section 4.8 for details of electrolyte and metabolic abnormalities).

*Renal function*

Frequent BUN in 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 hypomagnesemia (as well as hypokalemia). 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 furosemide immediately.

Liver damage.

Idiosyncratic reactions.

**Other alterations in lab values**

Serum cholesterol and triglycerides may rise but usually return to normal within 6 months of starting furosemide.

*Concomitant use with risperidone*

In risperidone placebo-controlled trials in elderly people with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3%; mean age 89 years, range 75-97 years) when compared to patients treated with risperidone alone (3.1%; mean age 84 years, range 70-96 years) or furosemide alone (4.1%; mean age 80 years, range 67-90 years). 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 Contraindications).

#### **Important information about some of the ingredients:**

This product contains sodium hydroxide. Each vial of Furosemide S.A.L.F 250 mg/25 ml solution for infusion contains about 0.75 mmol (17.3 mg) of sodium; Consider this information for administration to patients with impaired renal function or patients on a controlled sodium diet.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

**General-** The dosage of concurrently administered cardiac glycosides, diuretics, anti-hypertensive agents, or other drugs with blood-pressure-lowering potential may require adjustment as a more pronounced fall in blood pressure must be anticipated if given concomitantly with furosemide.

The toxic effects of nephrotoxic drugs may be increased by concomitant administration of potent diuretics such as furosemide.

Some electrolyte disturbances (e.g., hypokalemia, hypomagnesaemia) may increase the toxicity of certain other drugs (e.g., digitalis preparations and drugs inducing QT interval prolongation syndrome).

**Antihypertensives** – enhanced hypotensive effect possible with all types. Concurrent use with ACE inhibitors or Angiotensin II receptor antagonists can result in marked falls in blood pressure, furosemide should be stopped, or the dose reduced before starting an ACE-inhibitor or Angiotensin II receptor antagonists (see

section 4.4).

**Antipsychotics** – furosemide-induced hypokalemia increases the risk of cardiac toxicity. Avoid concurrent use with pimozide. Increased risk of ventricular arrhythmias 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 Special warnings and precautions for use regarding increased mortality in elderly patients with dementia concomitantly receiving risperidone.

**Anti-arrhythmic** (including amiodarone, disopyramide, flecainide and sotalol)- risk of cardiac toxicity (because of furosemide-induced hypokalemia). The effects of lidocaine, tocainide or mexiletine may be antagonized by furosemide.

**Cardiac glycosides** – hypokalemia and electrolyte disturbances (including hypomagnesaemia) increase the risk of cardiac toxicity.

**Drugs that prolong Q-T interval** – increased risk of toxicity with furosemide-induced electrolyte disturbances.

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

**Other diuretics** – profound diuresis possible when furosemide given with metolazone. Increased risk of hypokalemia with thiazides.

**Renin inhibitors** – aliskiren reduces plasma concentrations of furosemide.

**Nitrates** – enhanced hypotensive effect.

**Lithium** – In common with other diuretics, serum lithium levels may be increased when lithium is given concomitantly with furosemide, resulting in increased lithium toxicity, including increased risk of cardiotoxic and neurotoxic effects of lithium. Therefore, it is recommended that lithium levels are carefully monitored and where necessary the lithium dosage is adjusted in patients receiving this combination.

**Chelating agents** – sucralfate may decrease the gastro-intestinal absorption of furosemide – the 2 drugs should be taken at least 2 hours apart.

**NSAIDs** – increased risk of nephrotoxicity. Indomethacin and ketorolac may antagonise the effects of furosemide (avoid, if possible, see section 4.4). NSAIDs may attenuate the action of furosemide and may cause acute renal failure in cases of pre-existing hypovolemia or dehydration.

**Salicylates** – effects may be potentiated by furosemide. Salicylic toxicity may be increased by furosemide.

**Antibiotics** – increased risk of ototoxicity with aminoglycosides, polymyxins or vancomycin - only use concurrently if compelling reasons. Increased risk of nephrotoxicity with aminoglycosides or cefaloridine. Furosemide can decrease vancomycin serum levels after cardiac surgery. Increased risk of hyponatremia 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 MAOIs. Increased risk of postural hypotension with TCAs (tricyclic antidepressants). Increased risk of hypokalemia with reboxetine.

**Antidiabetics** – hypoglycemic effects antagonised by furosemide.

**Antiepileptics** – increased risk of hyponatremia with carbamazepine. Diuretic effect reduced by phenytoin.

**Antihistamines** – hypokalemia with increased risk of cardiac toxicity.

**Antifungals** – increased risk of hypokalemia and nephrotoxicity with amphotericin.

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

**CNS stimulants (drugs used for ADHD)** – hypokalemia increases the risk of ventricular arrhythmias.

**Corticosteroids** – diuretic effect antagonized (sodium retention) and increased risk of hypokalemia.

**Glycyrrizin-** (contained in liquorice) may and increase the risk of developing hypokalemia.

**Cytotoxics** – increased risk of nephrotoxicity and ototoxicity with platinum compounds/cisplatin. Nephrotoxicity of cisplatin may be enhanced if furosemide 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 furosemide may be reduced by methotrexate and furosemide may reduce renal clearance of methotrexate.

**Dopaminergics** – enhanced hypotensive effect with levodopa.

**Immunomodulators** – enhanced hypotensive effect with aldesleukin. Increased risk of hyperkalemia with cyclosporine and tacrolimus. Increased risk of gouty arthritis with cyclosporin.

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

**Oestrogens** – diuretic effect antagonised.

**Progestogens (drospiridone)** – increased risk of hyperkalemia.

**Prostaglandins** – enhanced hypotensive effect with alprostadil.

**Sympathomimetics** – increased risk of hypokalemia with high doses of beta 2 sympathomimetics.

**Theophylline** – enhanced hypotensive effect.

**Probenecid** – effects of furosemide may be reduced by probenecid and furosemide may reduce renal clearance of probenecid.

**Anesthetic agents** – general anesthetic agents may enhance the hypotensive effects of furosemide. The effects of curare may be enhanced by furosemide.

**Alcohol** – enhanced hypotensive effect.

**Laxative abuse** - increases the risk of potassium loss.

**Others:** Concomitant administration of aminoglutethimide may increase the risk of hyponatremia.

pathological causes of oedema which are not directly or indirectly linked to the pregnancy. The treatment with diuretics of oedema and hypertension caused by pregnancy is undesirable because placental perfusion can be reduced, so, if used, monitoring of fetal growth is required. However, furosemide has been given after the first trimester of pregnancy for oedema, hypertension and toxemia of pregnancy without causing fetal or newborn adverse effects.

#### **Breast-feeding**

Furosemide is contraindicated (see section 4.3) as it passes into breast milk and may 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, operate machinery or take part in activities where these effects could put themselves or others at risk.

#### **4.8 Undesirable effects**

Undesirable effects can occur with the following frequencies: Uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), Rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), Very rare ( $< 1/10,000$ , including isolated reports), not known (cannot be estimated from the available data). The following effects have been reported and are listed below by body system:

#### **4.6 Fertility, Pregnancy and lactation**

##### **Pregnancy**

Furosemide crosses the placental barrier and should not be given during pregnancy unless there are compelling medical reasons. It should only be used for the

<b>MedDRA system organ class database</b>	<b>Frequency</b>	<b>Undesirable effects</b>
Blood and lymphatic system disorders	Uncommon	Thrombocytopenia
	Rare	Eosinophilia, Leukopenia, Bone marrow depression (necessitates withdrawal of treatment). The haemopoietic status should therefore be regularly monitored.
	Very Rare	Aplastic anemia or hemolytic anemia, Agranulocytosis
Nervous system disorders	Rare	Paresthesia, Hyperosmolar coma
	Not known	Dizziness, syncope and loss of consciousness (caused by symptomatic hypotension).
Eye disorders	Uncommon	Visual disturbance
Ear and labyrinth disorders	Uncommon	Deafness (sometimes irreversible)
	Rare	Hearing disorders and tinnitus <sup>1</sup>
Cardiac arrhythmias	Uncommon	Cardiac arrhythmias
Hepatobiliary disorders	Not known	Cholestasis Intrahepatic (In isolated cases), Hepatic encephalopathy in patients with hepatocellular insufficiency may occur (see Section 4.3).
Vascular Disorder	Uncommon	Hypotension <sup>2</sup>
	Rare	Vasculitis
	Not Known	Thrombosis <sup>8</sup>
Skin and subcutaneous tissue disorders	Uncommon	Photosensitivity
	Rare	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 generalized exanthematous pustulosis) and DRESS (Drug rash with eosinophilia and systemic symptoms).
	Not Known	Bullous Pemphigoid

Metabolism and nutrition disorders	Not Known	Symptomatic electrolyte disturbances and Metabolic alkalosis <sup>3</sup> , Metabolic acidosis <sup>4</sup> , Hyponatremia <sup>5</sup> , Hypokalemia <sup>6</sup> , Reduction of serum HDL- cholesterol, elevation of serum LDL-cholesterol and elevation of serum triglycerides. During long term therapy they will usually return to normal within six months Hypocalcemia and hypomagnesemia <sup>7</sup> , Hypovolemia and dehydration <sup>8</sup> .
Psychiatric disorders	Rare	Mental disorder
Congenital, familial and genetic disorders	Not Known	Patent ductus arteriosus <sup>9</sup>
General disorders and administration site conditions	Uncommon	Fatigue
	Rare	Severe anaphylactic or anaphylactoid reactions (e.g., with shock) occurs rarely. Fever, Malaise.
Gastrointestinal disorders	Uncommon	Dry mouth, thirst, nausea, bowel motility disturbances, vomiting, diarrhea, constipation <sup>10</sup>
	Rare	Acute Pancreatitis
Renal and urinary disorders	Rare	Interstitial nephritis, Acute renal failure, Increased urine production, Urinary incontinence and urinary obstruction <sup>11</sup> , Acute urine retention. <sup>12</sup>
	Not known	Nephrocalcinosis/Nephrolithiasis has been reported in premature infants.
Investigations	Uncommon	Blood creatinine increased and Blood urea increased <sup>13</sup> .
	Not known	Transaminases increased (In isolated cases), Glucose tolerance decreased. <sup>14</sup>

<sup>1</sup> Although usually transitory, may occur in rare cases, particularly in patients with renal failure, hypoproteinemia (e.g., in nephritic syndrome) and/or when intravenous furosemide has been given too rapidly.

<sup>2</sup> Furosemide 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, orthostatic intolerance.

<sup>3</sup> As with other diuretics, electrolytes and water balance may be disturbed as a result of diuresis after prolonged therapy. Furosemide leads to increased excretion of sodium and chloride and consequently increase excretion of water. In addition, excretion of other electrolytes (in particular potassium, calcium and magnesium) is increased. Symptomatic electrolyte disturbances and metabolic alkalosis may develop in the form of a gradually increasing electrolyte deficit or e.g., where higher furosemide doses are administered to patients with normal renal function, acute severe electrolyte losses.

<sup>4</sup> The risk of this abnormality increases at higher dosages and is influenced by the underlying disorder (e.g., cirrhosis of the liver, heart failure), concomitant medication (see section 4.5) and diet.

<sup>5</sup> Sodium deficiency can occur; this can manifest itself in the form of confusion, muscle cramps, muscle weakness, loss of appetite, dizziness, drowsiness and vomiting.

<sup>6</sup> Potassium deficiency manifests itself in neuromuscular symptoms (muscular weakness, paralysis), intestinal symptoms (vomiting, constipation, meteorism), renal symptoms (polyuria) or cardiac symptoms. Severe potassium depletion can result in paralytic ileus or confusion, which can result in coma.

<sup>7</sup> Magnesium and calcium deficiency result very rarely in tetany and heart rhythm disturbances. Serum calcium levels may be reduced; in very rare cases tetany has been observed.

<sup>8</sup> The diuretic action of furosemide may lead to or contribute to hypovolemia and dehydration, especially in elderly patients. Severe fluid depletion may lead to hemoconcentration with a tendency for thromboses to develop.

<sup>9</sup> If furosemide is administered to premature infants (including those with respiratory distress syndrome) during the first weeks of life, it may increase the risk of persistent patent ductus arteriosus.

<sup>10</sup> Gastro-intestinal disorder such as nausea, malaise or gastric upset (vomiting or diarrhea) and constipation may occur, but not usually severe enough to necessitate withdrawal of treatment.

<sup>11</sup> Increased urine production, urinary incontinence, can be caused or symptoms can be exacerbated in patients with urinary tract obstruction.

<sup>12</sup> Acute urine retention, possibly accompanied by complications, can occur for example in patients with bladder disorders, prostatic hyperplasia or narrowing of the urethra.

<sup>13</sup> As with other diuretics, treatment with furosemide may lead to transitory increase in blood creatinine and urea levels. Serum levels of uric acid may increase, and attacks of gout may occur.

<sup>14</sup> Glucose tolerance may decrease with furosemide. 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.

**Special population:****Patients with hepatic impairment.**

Pre-existing metabolic alkalosis (e.g., in decompensated cirrhosis of the liver) may be aggravated by furosemide treatment.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse event should be reported to the Ministry of Health according to the National Regulation by using an online form

<https://sideeffects.health.gov.il/>

**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).

**Management**

Benefits of gastric decontamination are uncertain. In patients presenting within 1 hour of ingestion, consider activated charcoal (50g for adults: 1g/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 ECG in patients with significant electrolyte disturbances.

**5. Pharmacological Properties****5.1 Pharmacodynamic properties:**

Pharmacotherapeutic Group: High-ceiling diuretic sulfonamides, loop diuretics; ATC code: C03CA01.

**Mechanism of action:**

The principle renal action of furosemide is to inhibit active chloride transport in the thick

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

**Pharmacodynamic effects:**

The evidence from many experimental studies suggests that furosemide acts along the entire nephron with the exception of the distal exchange site. The main effect is on the ascending limb of the loop of Henley with a complex effect on renal circulation. 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 up to 99% bound to plasma proteins.

**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 the drug 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.

#### Hepatic impairment

Where liver disease is present, biliary elimination is reduced up to 50%.

#### Renal impairment

Renal impairment has little effect on the elimination rate of furosemide, but less than 20% residual renal function increases the elimination time.

#### Elderly

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

#### Pediatric population

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

### **5.3 Preclinical safety data**

No further information other than that which is contained in other sections of the Summary of Product Characteristics.

## **6. Pharmaceutical particulars**

### **6.1 List of excipients**

Sodium Hydroxide,  
Water for Injections.

### **6.2 Incompatibilities**

Furosemide, as an anthranilic acid derivative, dissolves in an alkaline environment with salt formation. The solution has a pH of about 9 and does not have a buffering effect; below pH 7 the active ingredient precipitates. Therefore, you should consider that Furosemide S.A.L.F 250 mg/25 ml can be mixed with alkaline, neutral or weakly acidic solutions with a modest buffering capacity (Ringer's lactate,

glucose solution).

Acidic solutions, especially those with a high buffering capacity, cannot be mixed with Furosemide S.A.L.F 250mg/25ml.

However, Furosemide S.A.L.F 250mg/25ml should not be combined with other drugs in the same syringe.

### **6.3 Shelf life**

The expiry date of the product is indicated on the packaging materials.

For shelf life after dilution see clause 6.6.

### **6.4 Special precautions for storage**

Store below 25°C. Store in its original package tightly closed, in order to protect it from light.

Keep out of sight and reach of children.

### **6.5 Nature and contents of container**

Type I glass vial of 25 ml.

Each box contains 5 vials of 25 ml.

### **6.6 Special precautions for disposal and other handling**

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

The diluted solutions should be used immediately after preparation.

## **7. Manufacturer**

S.A.L.F. S.p.A. Laboratorio Farmacologico -  
Cenate Sotto (Bergamo), Italy.

## **8. Marketing authorization holder**

RAZ PHARMACEUTICS LTD.,  
31 Gesher Haetz, Industrial Park Emek Hefer,  
Israel

## **9. Registration Number**

166-77-35843-00

Revised in April 2023 according to MOHs guidelines.

RAZS0181-01