SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE DRUG
Furosemide S.A.L.F 20mg/2ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml of solution contains Furosemide 10 mg.
Each 2 ml ampoule contains Furosemide 20 mg.

For a full list of the excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection.
clear, colourless to almost colourless solution and free of visible particles.

4. CLINICAL INFORMATION
4.1. Therapeutic indications
Furosemide S.A.L.F 20mg/2ml is a potent diuretic indicated for use when a prompt and effective diuresis is required. Furosemide S.A.L.F 20mg/2ml is appropriate for use in emergencies or when oral therapy is not feasible. The indications include cardiac, pulmonary, hepatic and renal oedema.

4.2. Posology and method of administration
Route of administration: intramuscular or intravenous use.

Adults
Intravenous furosemide must be injected or infused slowly; a rate of 4 mg per minute must not be exceeded. In patients with severe impairment of renal function (serum creatinine >5 mg/dl), it is recommended that an infusion rate of 2.5 mg per minute is not exceeded.

Intramuscular administration must be restricted to exceptional cases where neither oral nor intravenous administration is feasible. It must be noted that intramuscular injection is not suitable for the treatment of acute conditions such as pulmonary oedema.

To achieve optimum efficacy and suppress counter-regulation, a continuous furosemide infusion is generally to be preferred to repeated bolus injections. Where continuous furosemide infusion is not feasible for follow-up treatment after one or several acute bolus doses, a follow-up regimen with low doses given at short intervals (approximately four hours) is to be preferred to a regimen with higher bolus doses at longer intervals.

Doses of 20 to 50 mg intramuscularly or intravenously may be given initially. If larger doses are required, they should be given by 20 mg increments and not given more often than every two hours. If doses greater than 50 mg are required, it is recommended that they be given by slow intravenous infusion. The recommended maximum daily dose of furosemide administration is 1,500 mg.

Elderly
The dosage recommendations for adults apply, but in the elderly, furosemide is generally eliminated more slowly. Dosage should be titrated until the required response is achieved.

Children
Parenteral doses for children range from 0.5 to 1.5 mg/kg body weight daily up to a maximum total daily dose of 20 mg.

Hepatic impairment
A dosage adjustment may be necessary in patients with hepatic cirrhosis and in those with concomitant renal and hepatic impairment. The response to furosemide shall be reduced in patients with liver cirrhosis.

4.3. Contraindications
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Patients with an allergy to sulfonamides (e.g. sulfonamide antibiotics or sulfonylureas) may show a cross-sensitivity to furosemide;
- hypovolaemia or dehydration;
- anuric renal failure that does not respond to furosemide;
- hypokalemia;
- hyponatremia;
- pre-coma or coma, associated with liver encephalopathy;
- digitalis overdosing;
- first trimester of pregnancy and during breastfeeding (see section 4.6).

4.4. Special warnings and precautions for use
It is necessary to ensure the free flow of urine. The increased production of urine may cause or exacerbate disorders in patients with urinary tract obstruction (e.g. in patients with impaired bladder emptying, prostatic hyperplasia or urethral stricture). Therefore, these patients require a particularly close monitoring, especially during the initial stages of treatment.
As with all diuretics, it is recommended to start the treatment of liver cirrhosis with ascites in the hospital, in order to appropriately intervene in case tendency to hepatic coma during diuresis.
Treatment with Furosemide S.A.L.F 20mg/2ml requires regular medical tests. In particular, a careful monitoring is necessary in the following cases:
- patients with hypotension,
- patients who are particularly at risk following an excessive fall in blood pressure, e.g. patients with significant stenoses of the coronary arteries or of the blood vessels supplying the brain,
- patients with latent or manifest diabetes mellitus,
- patients with gout,
- patients with hepatorenal syndrome, e.g. with functional renal failure associated with a severe liver disease,
- patients with hypoproteinemia, e.g. associated with nephrotic syndrome (the action of furosemide may thereby be weakened and its ototoxicity enhanced). Special caution is required in determining the dosage,
- premature babies (for the possible development of nephrocalcinosis/nephrolithiasis); it is necessary to perform renal ultrasonography and monitor the renal function.

In general, during a furosemide therapy a regular monitoring of serum sodium, potassium and creatinine is recommended; in particular, a strict monitoring is required for patients at high risk of electrolyte imbalance or when there is a further

significant fluid removal (e.g. due to vomiting, diarrhea, or heavy sweating). Although the use of Furosemide S.A.L.F 20mg/2ml only rarely leads to hypokalemia, a potassium-rich diet is recommended (potatoes, bananas, oranges, tomatoes, spinach and dried fruits). Sometimes an adequate pharmacological correction may also be necessary.
In particular, states predisposing to potassium deficiency, such as liver cirrhosis, chronic diarrhea, prolonged use of laxatives, low potassium diet, concomitant use of mineralocorticoid, require appropriate checks and additions.
Hypovolaemia, dehydration, and any significant alteration of electrolyte and acid-base balance must be adjusted. This may require a temporary suspension of the administration of furosemide.
It is also advisable to carry out regular checks of blood glucose, urinary glucose and, where necessary, of uric acid metabolism.
Furosemide S.A.L.F 20mg/2ml does not change pressure values in normotensive patients, while it is hypotensive in hypertensive patients; in severe forms of hypertension this treatment is recommended in combination with other medical devices.
Concomitant use with risperidone
In placebo-controlled studies on risperidone in elderly patients with dementia, there was a higher incidence of mortality in patients treated with furosemide plus risperidone (7.3%, mean age 89 years, range 75-97 years) than in patients treated with risperidone alone (3.1%, mean age 80 years, range 70-96 years) or furosemide alone (4.1%, mean age 80 years, range 67-90 years). A concomitant use of risperidone with other diuretics (mainly thiazide diuretics at low dosage) was not associated with such an event.
No patho-physiological mechanism has been identified to explain this finding and there was no pattern correlated to the cause of death. However, before deciding on the use of such a combination, caution should be used and the risks and benefits of this combination or co-administration with other strong diuretics should be taken into account. There was no increased incidence of mortality in patients taking other diuretics concomitantly with risperidone. Regardless of treatment, dehydration was an overall risk factor for mortality and should therefore be avoided in elderly patients with dementia (see section 4.5).

Special precautions and/or dose reduction
In patients treated with furosemide, particularly in the elderly, in patients treated with other medicines that may induce hypotension and in patients with other clinical disorders involving risks of hypotension, there may be cases of symptomatic hypotension resulting in dizziness, fainting or loss of consciousness.

Important information about some of the ingredients:
This product contains sodium hydroxide.
Each ampoule of Furosemide S.A.L.F 20mg/ml contains less than 1 mmol sodium (23 mg) per ampoule, that is to say essentially 'sodium-free'.

4.5. Interaction with other medicinal products and other forms of interaction

Non-recommended combinations
Chloral hydrate: in isolated cases, intravenous administration of furosemide within 24 hours after taking chloral hydrate may cause skin redness, sudden sweating, shaking, nausea, increased blood pressure and tachycardia. Therefore, a concomitant administration of furosemide and chloral hydrate is not recommended.
Aminoglycoside antibiotics: Furosemide may potentiate the ototoxicity of aminoglycoside antibiotics and other ototoxic drugs. Since this can cause the onset of irreversible damage, these drugs can be used in combination with furosemide only in case of evident clinical need.

Precautions for use
Cisplatin. A simultaneous administration of furosemide and cisplatin can lead to ototoxic effects. Furthermore, the nephrotoxicity of cisplatin may be enhanced, if furosemide is not administered at low doses (e.g. 40 mg to patients with normal renal function) and in the presence of a positive fluid balance, when furosemide is used to obtain a forced diuresis during a treatment with cisplatin.
Lithium salts. Furosemide reduces the elimination of lithium salts and can cause an increase in serum concentration, resulting in an increased risk of toxicity, including an increased risk of lithium cardiotoxic and neurotoxic effects. Therefore, a careful monitoring of lithium concentrations in patients, who will receive this association, is recommended.
ACE inhibitors / angiotensin II receptor antagonists. Patients receiving a diuretic therapy may experience severe hypotension and renal impairment, including cases of renal failure, particularly in conjunction with the first dose of an ACE inhibitor or an angiotensin II receptor antagonist or the first time that the dosage is increased. You must take into consideration the possibility of temporarily suspending the administration of furosemide or, at least, of reducing the dose 3 days before starting the treatment with an ACE inhibitor or an angiotensin II receptor antagonist or before increasing the dose.
Risperidone. You should take caution and consider the risks and benefits of the combination or co-treatment with furosemide or with other strong diuretics, before deciding to use such a combination.
See section 4.4 for the increased mortality in elderly patients with dementia co-treated with risperidone.

To be carefully considered
Non-steroidal anti-inflammatory drugs. Concomitant administration of NSAIDs, including acetylsalicylic acid, can reduce the effect of furosemide. In patients with dehydration or hypovolaemia, non-steroidal anti-inflammatory drugs can cause acute renal failure. Furosemide may increase the toxicity of salicylates.
Phenytoin. The reduction of the effect of furosemide may occur in the case of co-administration of phenytoin.
The damaging effects of **nephrotoxic drugs** may be increased.
The administration of **corticosteroids, carbenoxolone and high doses of liquorice**, as well as the prolonged use of **laxatives**, may increase the risk of hypokalemia.
Certain electrolyte disturbances (e.g. hypokalemia, hypomagnesaemia) may increase the toxicity of certain drugs (e.g. **digital preparations and drugs that induce long QT syndrome**).
In case of concomitant administration of furosemide and **antihypertensive drugs, diuretics or other drugs with potentially antihypertensive effect**, a more pronounced fall in blood pressure should be expected.

Probenecid, methotrexate and other drugs, that, like furosemide, are mainly excreted by the kidney, may reduce the effect of furosemide. On the contrary, furosemide may reduce the renal elimination of these substances. In the case of treatment with high doses (both of furosemide and of other drugs) an increase in serum concentrations of both may occur. Consequently, the risk of adverse events due to furosemide or other concomitant therapies increases.
The effects of **antidiabetic and sympathomimetic drugs** (e.g. epinephrine, norepinephrine) can be decreased. The effects of the **curare-like muscle relaxants** or **theophylline** may be increased.
A renal impairment may develop in patients receiving a concomitant therapy with furosemide and high doses of certain **cephalosporins**.
A concomitant use of **cyclosporine A** and furosemide is associated with an increased risk of secondary gouty arthritis, hyperuricemia due to furosemide and a reduction of urate excretion induced by cyclosporine.
Patients at high risk of radiocontrast nephropathy treated with furosemide have experienced a higher incidence of renal function deterioration after contrast medium administration than high-risk patients who have received intravenous hydration only prior to contrast medium administration.

4.6. Pregnancy and breastfeeding
Pregnancy
Furosemide crosses the placental barrier.
In the first trimester of pregnancy *Furosemide S.A.L.F 20mg/2ml* should not be administered.
In the second and third trimesters of pregnancy *Furosemide S.A.L.F 20mg/2ml* can be used, but only if clearly needed. A treatment during the last two trimesters of pregnancy requires the monitoring of the foetus growth.
Breastfeeding
Furosemide passes into breast milk and may inhibit lactation, therefore, breastfeeding should be discontinued during a treatment with furosemide.

4.7. Effects on ability to drive and use machines
Some adverse events (e.g. an unexpected and serious decrease in blood pressure) may impair the ability of concentration and reaction of the patient and, therefore, constitute a risk in situations where these abilities are of particular importance (e.g. by driving or using machines).

4.8. Side effects
Here below are the possible side effects of furosemide.
The frequency of side effects is reported according to what follows:
Very common: ≥ 1/10; Common: ≥1/100 to <1/10; Uncommon: ≥ 1/1,000 to <1/100; Rare: ≥ 1/10,000 to <1/1,000; Very rare: <1/10,000; Unknown (frequency cannot be estimated from the available data).

System/Organ Classification	Frequency	Side effects
Cardiac disorders	uncommon	Cardiac arrhythmias
Blood and lymphatic system disorders	common	Haemoconcentration
	uncommon	Thrombocytopenia
	rare	Leukopenia, eosinophilia
	very rare	Aplastic anemia, agranulocytosis, haemolytic anaemia
Nervous system disorders	common	Hepatic encephalopathy in patients with hepatocellular insufficiency
	uncommon	Drowsiness, headache, dizziness, confusion
	rare	Paraesthesia
	unknown	Dizziness, fainting and loss of consciousness (due to symptomatic hypotension)
Eye disorders	uncommon	Visual disorders
Ear and labyrinth disorders	uncommon	Usually transient hearing disorders, especially in patients with renal failure, hypoproteinemia (e.g. in the nephrotic syndrome) and / or in the event of too rapid intravenous administration. Deafness (sometimes irreversible)
	very rare	Tinnitus
Gastrointestinal disorders	uncommon	Dry mouth, nausea, intestinal motility disorders
	uncommon	Vomiting, diarrhoea
	very rare	Acute pancreatitis
Renal and urinary disorders	common	Polyuria
	rare	Interstitial nephritis
	unknown	Increased sodium in the urine, increased chlorine in the urine, urinary retention (in patients with prostatic hypertrophy, urethral stricture or difficulty in emptying the bladder), nephrocalcinosis / nephrolithiasis (in pre-term infants treated with furosemide); kidney failure

Skin and subcutaneous tissue disorders	rare or very rare	Urticaria, pruritus, purpura, bullous dermatitis, erythema multiforme, pemphigoid, exfoliative dermatitis, photosensitivity reactions
	unknown	Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS syndrome)
Metabolism and nutrition disorders	very common	Electrolyte disorders (including symptomatic ones); dehydration and hypovolemia, especially in elderly patients, increased creatinine and triglycerides in the blood
	common	Hyponatremia, hypochloraemia, hypokalemia, increased cholesterol, hyperuricaemia and gout
	uncommon	Impaired glucose tolerance. Clinical manifestations of latent diabetes mellitus
	unknown	Hypocalcaemia, hypomagnesaemia, metabolic alkalosis, increased urea. Pseudo-Bartter syndrome in the context of abuse and / or a long-term use of furosemide
Vascular disorders	very common (for i.v. infusion)	Reduction in blood pressure, including orthostatic hypotension
	rare	Vasculitis
	unknown	Hypovolaemia, thrombosis
Musculoskeletal and connective tissue disorders	uncommon	Muscle cramps, tetany, myasthenia
General disorders and administration site conditions	uncommon	Fatigue
	rare	Fever
	unknown	Local reactions
Hepato-biliary disorders	very rare	Intrahepatic cholestasis, increased liver transaminase
Congenital, familial and genetic diseases	unknown	Increased risk of persistence of patent ductus arteriosus when furosemide is administered to premature infants during the first weeks of life
Immune system disorders	rare	Severe anaphylactic or anaphylactoid reactions (e.g. with shock)

Reporting of suspected adverse reactions

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

The clinical picture after an acute or chronic overdose primarily depends on the size and the consequences of the loss of fluids, e.g. hypovolaemia, dehydration, haemoconcentration, cardiac arrhythmias (including AV block and ventricular fibrillation). The symptoms of these disorders consist of severe hypotension (up to the shock), acute renal failure thrombosis, delirious states, flaccid paralysis, apathy and confusion.

There is no known specific antidote to furosemide. If this drug has just been administered, you can try to limit the systemic absorption of the active ingredient through measures such as a gastric lavage or by decreasing its absorption (e.g. activated charcoal).

Clinically relevant imbalances of the electrolyte balance should be adjusted.

In conjunction with the prevention and the treatment of both severe complications arising from these imbalances and other effects on the body, the corrective action may require a more intensive monitoring of the clinical conditions, as well as appropriate therapeutic measures.

In the case of patients with micturition disorders, such as prostatic hypertrophy or unconsciousness, it is necessary to restore the free flow of urine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diuretics with a major diuretic action. ATC code: C03CA01

Furosemide, a synthesis saluretic agent, causes an increase in the water and sodium elimination, even in cases in which the glomerular filtration is very limited.

The natriuretic effect is dose-dependent, therefore, furosemide allows to obtain a guided diuresis; the urinary excretion of potassium is, instead, significantly limited. As a result, the sodium-potassium ratio is extremely favourable.

The diuretic effect following an oral administration begins within the first hour and lasts 4-6 hours; by intravenous administration the effect occurs within few minutes and lasts for about 2 hours, while by intramuscular administration the

effect occurs a few minutes later, but the duration of the action is longer.

5.2. Pharmacokinetic properties

Furosemide is rapidly absorbed from the gastrointestinal tract. The t_{max} for the tablets is about 1-1.5 hours, while for the oral solution is 0.6 hours. The absorption of the drug shows a marked inter- and intra-individual variability.

The bioavailability in healthy volunteers is approximately 50 % - 70 % for tablets and about 80 % for the oral solution. In patients, the bioavailability of the drug is affected by various factors including the underlying pathologies and it can be reduced to 30% (e.g. nephrotic syndrome).

Furosemide has a high plasma protein binding (98%), mainly to albumin.

Furosemide is mainly excreted in an unchanged form, through secretion in the proximal tubule. After intravenous administration, approximately 60% - 70 % of the drug is eliminated by this route. There is a metabolite glucuronized for about 10-20% of the total amount excreted in the urine. The remaining amount is excreted in the faeces, probably due to biliary secretion. The terminal half-life of furosemide after intravenous administration is approximately 1 - 1.5 hours.

Furosemide is excreted in breast milk. In addition, it crosses the placental barrier and passes slowly to the fetus. In the fetus and newborn infant it reaches the same concentrations found in the mother.

Renal disorders

The elimination of furosemide is slowed in patients with impaired renal function and its half-life is prolonged up to 24 hours in patients with severe renal insufficiency.

In the nephrotic syndrome the reduced concentrations of plasma proteins lead to a higher concentration of free furosemide (unbound). On the other hand, however, the effectiveness of furosemide is reduced in these patients because of the intratubular albumin binding and the reduced tubular secretion.

Furosemide is poorly removed by haemodialysis in patients undergoing haemodialysis, peritoneal dialysis and CAPD.

Hepatic failure

In patients with hepatic failure, the half-life of furosemide is increased from 30% to 90 %, primarily due to a larger volume of distribution. Moreover, in these patients there is a wide variation in all pharmacokinetic parameters.

5.3. Preclinical safety data

Acute toxicity

Studies carried out on various species of rodents and dogs, by administering furosemide orally and intravenously, revealed a low acute toxicity. The DL50 of furosemide by oral administration in mice and rats is between 1050 mg/kg and 4600 mg/kg of body weight, while in the guinea pig it is 243 mg/kg. In dogs, the DL50 is around 2000 mg/kg by oral administration and it is more than 400 mg/kg of body weight by intravenous administration.

Chronic toxicity

With administration of furosemide for 6 and 12 months, renal abnormalities (including focal fibrosis, calcification) were found in rats and dogs at high doses (10 to 20 times the human therapeutic dose).

Ototoxicity

Furosemide may interfere with the mechanisms of transport in the inner ear vascular streak, which may result in hearing disorders that are usually reversible.

Carcinogenesis

Furosemide at doses of about 200 mg/kg of body weight/day (14,000 ppm) was administered in the diet to mice and rats for a period of 2 years. An increased incidence of mammary adenocarcinomas was found in mice, but not in rats. This dose is considerably higher than the therapeutic dose administered to human beings. In addition, these tumours were morphologically identical to tumors of spontaneous nature observed in 2% - 8% of the tests.

Therefore, it seems unlikely that the incidence of tumours is important in the treatment of human beings. In fact, there is no evidence of an increased incidence of mammary adenocarcinomas following an administration of furosemide. On the basis of epidemiologic studies, a classification for carcinogenicity of furosemide in humans does not appear possible.

In a carcinogenicity study in rats, doses of furosemide of 15 and 30 mg/kg of body weight were administered daily. In male rats at the dose of 15 mg/kg, but not at the dose of 30 mg/kg, there was a marginal increase of uncommon cancers. These results are considered to be random.

In rats, studies of bladder carcinogenesis induced by nitrosamine revealed no evidence that furosemide may act as a promoting factor.

Mutagenesis

In in-vitro studies on bacterial and mammalian cells, there were both positive and negative results. However, there was an induction of genetic and chromosomal mutations only when furosemide reached cytotoxic concentrations.

Reproductive toxicology

Furosemide did not impair fertility in male and female rats at daily doses of 90 mg/kg of body weight and in male and female mice at daily doses of 200 mg/kg orally.

There were no significant embryotoxic or teratogenic effects in several mammalian species including mice, rats, cats, rabbits and dogs following a treatment with furosemide. A delay in renal maturation - reduction in the number of differentiated glomeruli - was observed in the offspring of rats treated with doses of 75 mg/kg of furosemide on days 7-11 and 14-18 of pregnancy.

Furosemide crosses the placenta and in the umbilical cord it reaches concentrations equal to 100% of the serum concentration in the mother. To date, no malformations have been detected in the human being that can be linked to the exposure to furosemide.

However, no sufficient experience has been obtained to enable the formulation of a final assessment on the possible harmful effects on the embryo/fetus. The urinary output in the foetus can be stimulated in utero.

Nephrolithiasis and nephrocalcinosis have been observed in premature infants treated with furosemide.

No studies have been conducted to evaluate the effects of furosemide ingested with breast milk on the infant.

6. PHARMACEUTICAL INFORMATION

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.

Acidic solutions, especially those with a high buffering capacity, cannot be mixed with Furosemide S.A.L.F 20mg/2ml.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

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 the original container tightly closed in order to protect from light.

6.5. Nature and contents of container

Yellow type I glass ampoule.

Each pack contains 5 ampoules of 2ml solution.

6.6 Special precautions for disposal and other handling

Furosemide S.A.L.F 20mg/2ml can be diluted with Glucose 5%, Sodium chloride 0.9% or Ringer lactate solutions.

In case of dilution: Do not freeze. The product is stable for 8 hours with no special storage conditions, but from a microbiological point of view, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user.

For single use only.

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

7. Manufacturer

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

8. Marketing authorisation holder

RAZ PHARMACEUTICS LTD, 31 Gesher Haetz ST., Industrial park Emek hefer, Israel.

9. MARKETING AUTHORIZATION NUMBER

159-12-34330-00.

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