Approved Professional Information for Medicines for Human Use: SISERUP

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

SISERUP 20 mg TABLETS

SISERUP 40 mg TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

SISERUP 20 mg tablets

Each tablet contains 20 mg furosemide.

SISERUP 40 mg tablets

Each tablet contains 40 mg furosemide.

Contains sugar

Each SISERUP 20 mg tablet contains 52,50 mg lactose monohydrate.

Each SISERUP 40 mg tablet contains 105,00 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

SISERUP 20 mg tablets

White or off white, circular tablets, marked with F on one side & 20

“BL” embossing on other side.

SISERUP 40 mg tablets

White or off white, circular tablets, marked with a break line which divides F & 40 on one side & BL embossing on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cardiac oedema: All forms of cardiac oedema in conjunction with adequate glycoside therapy.

Ascites due to cirrhosis of the liver, mechanical obstruction or cardiac failure.

Renal oedema in nephrotic syndrome.

Oedema occurring during the last three months of pregnancy - pre-eclamptic toxaemia and eclampsia.

As an adjunct in acute pulmonary oedema.

Cerebral oedema.

Hypertension of mild to moderate degree.

Barbiturate poisoning (using the principle of “forced diuresis”).

Burns: to reduce local oedema and to prevent oliguria from progressing to complete anuria.

4.2 Posology and method of administration

The usual dose of SISERUP is 20 mg to 80 mg per day given as a single dose, preferably in the morning. This dose may, however, be increased depending on the response of the patient.

Six hours after a 40 mg dose, 80 mg may be administered and, if necessary, after another six hours, 120 mg. After the oedema is controlled, maintenance therapy is continued at 20 mg to 40 mg daily. Daily doses exceeding 120 mg should preferably be distributed over two to three individual doses. For the

treatment of hypertension of mild or moderate degree, a daily dosage of 40 mg to 80 mg is taken orally. In combination with other hypotensive drugs, lower doses will often suffice.

Forced diuresis (e.g. management of barbiturate poisoning)
20 mg to 40 mg SISERUP is given in addition to infusion of electrolyte solution. Further treatment depends on the elimination of urine and must include substitution of the fluid and electrolyte losses. In poisoning with acid or basic substances the elimination rate can be further increased by alkalisation or acidification of the urine, respectively.

Infants and children under 15 years

Children generally receive an oral dose of 2 mg/kg body mass per day in divided doses. This may be titrated to a maximum of 6 mg/kg.

Method of administration

SISERUP is for oral administration.

4.3 Contraindications

- Hypersensitivity to furosemide or sulphonamides or to any of the excipients listed in section 6.1.
- SISERUP is contraindicated if increasing azotaemia and oliguria occur during treatment of severe progressive renal disease, anuria, hypokalaemia, hyponatraemia, hypovolaemia with or without hypotension. In hepatic coma and in states of electrolyte depletion, therapy with SISERUP should not be instituted until the basic condition is corrected or improved.

- Furosemide should not be given to lactating women (see section 4.6).
- Furosemide should not be administered during pregnancy (see section 4.6).
- Anuria and impaired renal function (creatinine clearance below 30 mL/min per 1,73 m^2 body surface area) and renal failure resulting from poisoning by nephrotoxic and/or hepatotoxic medicines.
- Electrolyte disturbances (severe hyponatraemia: severe hypokalaemia, hypovolaemia), dehydration and/or hypotension (see section 4.4).
- Concomitant potassium supplements or potassium sparing diuretics (see section 4.5).
- Pre-coma/coma associated with hepatic cirrhosis or encephalopathy Addison's disease.
- Digitalis intoxication (see also section 4.5).

4.4 Special warnings and precautions for use

Hypotension and/or hypovolaemia (see also section 4.3)

These and any acid-base disturbances should be corrected before furosemide is started. 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.

Dose titration/adjustment (see section 4.2)

- Patients with hypoproteinaemia (such as that associated with the nephrotic syndrome) require careful dose titration (reduced furosemide effect: increased risk of ototoxicity).
- In moderate liver congestion dosage adjustment may be needed.

Caution required:

Caution needed in the following circumstances

- impaired hepatic function (see sections 4.2 & 4.3 and below – monitoring required),
- impaired renal function and hepato-renal syndrome (see section 4.3 and below –monitoring required),
- diabetes mellitus (latent diabetes may become overt: insulin requirements in established diabetes may increase),
- elderly patients,
- difficulty with micturition/potential obstruction in the urinary tract including prostatic hypertrophy (increased risk of acute retention),
- gout (increased risk of hyperuricaemia),
- patients at risk of pronounced falls in blood pressure.

Renal disorders

SISERUP should be used with care in patients with prostatic hyperplasia or impairment of micturition since it can precipitate acute urinary retention.

Clinical monitoring requirements (see also section 4.8):

Regular monitoring for

- blood dyscrasias. If these occur, stop furosemide immediately,
- liver damage,
- idiosyncratic reactions.

In premature infants there is a risk of development of nephrocalcinosis /nephrolithiasis. Renal function must be monitored, and renal ultrasonography performed.

Laboratory monitoring requirements:

- frequent blood urea nitrogen (BUN) in first few months of treatment, periodically thereafter,
- serum electrolytes with replacement as appropriate.

Other alterations in lab values

- Serum creatinine and urea levels tend to rise during treatment.
- Serum cholesterol and triglycerides may rise but usually return to normal within 6 months of starting furosemide.
- Furosemide should be discontinued before a glucose tolerance test.

Excipient lactose

This medicine contains lactose:

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Excipient sodium

SISERUP 20 mg contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

SISERUP 40 mg contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Angiotensin-converting enzyme (ACE) inhibitors

Enhanced hypotensive effect when given with diuretics. A marked fall in blood pressure and deterioration in renal function may be seen when ACE inhibitors are added to furosemide therapy. The dose of furosemide should be reduced

for at least three days, or the medicine stopped, before initiating the ACE inhibitor or increasing the dose of an ACE inhibitor.

Alpha-blockers

Enhanced hypotensive effect when diuretics are given with alpha-blockers, also increased risk of first dose hypotension with post-synaptic alpha-blockers such as prazosin.

Antipsychotics

Hypokalaemia caused by diuretics increase the risk of ventricular arrhythmias with amisulpiride or sertindole. An enhanced hypotensive effect may be seen when diuretics are given with phenothiazines. Hypokalaemia caused by diuretics increases risk of ventricular arrhythmias with pimozide (avoid

Antidepressants

Possible increase of hypokalaemia when loop diuretics are given with reboxetine. There is an enhanced hypotensive effect when diuretics are given with Monoamine oxidase inhibitors (MAOIs). There is an increased risk of postural hypotension when diuretics are given with tricyclic antidepressants.

Anti-dysrhythmics

Hypokalaemia caused by loop diuretics increases cardiac toxicity with amiodarone, disopyramide, flecainide, and antagonises the action of lidocaine and mexiletine.

Analgesics

Diuretics can increase the risk of nephrotoxicity of non-steroidal anti-inflammatory drugs (NSAIDs), also antagonism of diuretic effect. Antagonism of diuretic effect (especially with indomethacin and ketorolac). Salicylic toxicity may be increased by furosemide.

Angiotensin –II receptor antagonists

Enhanced hypotensive effect when diuretics given with angiotensin-II receptor antagonists.

Antibacterials

Avoid the use of diuretics in lymecycline treatment. There is an increased risk of ototoxicity when loop diuretics are given with aminoglycosides, polymyxins or vancomycin. Since this may lead to irreversible damage, these medicines must only be used with furosemide if there are compelling medical reasons. Impairment of renal function may develop in patients receiving concurrent treatment with furosemide and high doses of certain cephalosporins.

Antiepileptics

There is an increased risk of hyponatraemia when diuretics are given with carbamazepine. The effects of furosemide are antagonised by phenytoin.

Antifungals

There is an increased risk of hypokalaemia when loop diuretics are given with amphotericin.

Antivirals

Plasma concentration of diuretics may be increased by nelfinavir, ritonavir or saquinavir.

Atomoxetine

Hypokalaemia caused by diuretics increases the risk of ventricular dysrhythmias with atomoxetine.

Barbiturates

Plasma concentrations of diuretics may be decreased. There may be an increased risk of osteomalacia when diuretics are taken in combination with phenobarbital.

Beta-blockers

There is an enhanced hypotensive effect when diuretics are given with beta-blockers. Hypokalaemia caused by loop diuretics increases the risk of ventricular dysrhythmias with sotalol.

Cardiac glycosides

Hypokalaemia caused by loop diuretics increases cardiac toxicity with cardiac glycosides.

Ciclosporin

There is an increased risk of nephrotoxicity and possibly hypermagnesemia when diuretics are given with ciclosporin.

Cisplatin

There is a risk of increased ototoxic effects if cisplatin and furosemide are given concomitantly. In addition, 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.

Corticosteroids

The diuretic effect of diuretics is antagonized by corticosteroids. There is an increased risk of hypokalaemia when loop diuretics are given with corticosteroids.

Other diuretics

There is an increased risk of hypokalaemia when loop diuretics are given with acetazolamide. Profound diuresis is possible when metolazone is given with furosemide. There is an increased risk of hypokalaemia when loop diuretics are given with thiazides and related diuretics.

Lithium

Loop diuretics reduce the excretion of lithium, which may lead to increased plasma concentrations and a risk of toxicity. Therefore, it is recommended that lithium levels are carefully monitored and where necessary the lithium dosage is adjusted in patients receiving this combination.

Potassium salts

There is an increased risk of hyperkalaemia when given with potassium salts.

Sucralfate

Furosemide and sucralfate must not be taken within 2 hours of each other as sucralfate decreases the absorption of furosemide from the intestine and so reduces its effect.

Sympathomimetics, beta-2

There is an increased risk of hypokalaemia when loop diuretics are given with high doses of beta-2 sympathomimetics.

Tacrolimus

There is an increased risk of hypokalaemia when given with tacrolimus.

Theophylline

There is an increased risk of hypokalaemia when loop diuretics are given with theophylline.

Carbenoxolone, prolonged use of laxatives, liquorice

May increase the risk of developing hypokalaemia.

Warfarin and clofibrate

Warfarin and clofibrate compete with furosemide in the binding to serum albumin.

This may have clinical significance in patients with low serum albumin levels (e.g., in nephrotic syndrome). Furosemide does not change the pharmacokinetics of warfarin to a significant extent, but a strong diuresis with associated dehydration may weaken the antithrombotic effect of warfarin.

Probenecid, methotrexate and other medicines which, like furosemide, undergo significant renal tubular secretion may reduce the effect of furosemide. Conversely, furosemide may decrease renal elimination of these medicines. In case of high-dose treatment (in particular, of both furosemide and the other medicines), this may lead to increased serum levels and an increased risk of adverse effects due to furosemide or the concomitant medication.

Risperidone

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.

Electrolyte imbalances

Although administration of furosemide only rarely leads to hypokalaemia, a potassium rich diet is advisable. Treatment with potassium containing or potassium sparing preparations may be indicated.

4.6 Fertility, pregnancy and lactation

SISERUP should not be given during pregnancy only if strictly indicated, and then only for short periods of time (see section 4.3).

Breastfeeding

Furosemide passes into breast milk and may inhibit lactation. Women must not breastfeed if they are treated with furosemide (see section 4.3).

Fertility

No human data on the effect of furosemide on fertility are available**.**

4.7 Effects on ability to drive and use machines

Reduced mental alertness and rarely dizziness and blurred vision have been reported. Patients so affected should not drive or operate machinery.

4.8 Undesirable effects

a) Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and post market spontaneous reports with furosemide.

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**
Blood and lymphatic system disorders		Aplastic anaemia Bone marrow depression (necessitates withdrawal of treatment), eosinophilia, leukopenia. Haemolytic anaemia, agranulocytosis, thrombocytopenia~~,~~ vasculitis.	

Metabolism and nutritional disorders	Dehydration, hyponatraemia, hypochloremic metabolic alkalosis, hypocalcaemia, hypomagnesemia (incidences of the last three are reduced by triamterene), nephrocalcinosis in infants. Hypovolaemia, hypochloraemia.	Impaired glucose tolerance (by hypokalaemia) hyperuricaemia, gout, reduction of serum HDL-cholesterol, elevation of serum LDL-cholesterol, elevation of serum triglycerides, hyperglycaemia, tetany.	aggravated pre-existing metabolic alkalosis (in decompensated cirrhosis of the liver), fluid and electrolyte disturbances, hyperglycaemia.
Psychiatric disorder		Psychiatric disorder	
Nervous system disorders		Paraesthesia, confusion, headache, dizziness, tetany.	
Eye disorders:		Visual disturbance, blurred vision, yellow vision.	
Ear and labyrinth disorders		Tinnitus and reversible or irreversible loss of hearing (although usually transitory,	

		particularly in patients with renal failure, hypoproteinaemia (e.g. in nephritic syndrome).	
Cardiac disorders		Orthostatic intolerance, cardiac dysrhythmias, increased risk or persistence of patent ductus arteriosus in premature infants.	
Vascular disorders	Decreased 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,	Hypotension, hypovolaemia Vasculitis, thrombosis, shock.	

	drowsiness, weakness, disorders of vision, dry mouth, orthostatic intolerance).		
Gastrointestinal disorders		Dry mouth, thirst, nausea, bowel motility disturbances, vomiting, diarrhoea, constipation, acute pancreatitis (in long-term diuretic treatment, including furosemide).	
Hepatobiliary disorders		Pure intrahepatic cholestasis (jaundice), hepatic function abnormal.	
Skin and subcutaneous tissue disorders		Rash, pruritus, photosensitivity, toxic epidermal necrolysis.	Urticaria, erythema multiforme, purpura, exfoliative dermatitis, itching, allergic

			reactions, such as skin rashes, various forms of dermatitis including urticaria, bullous lesions, when these occur treatment should be withdrawn.
Musculoskeletal and connective tissue disorders		Muscle cramps, muscle weakness	
Renal and urinary disorders		Reduced diuresis, urinary incontinence, urinary obstruction (in patients with hyperplasia of the prostate, bladder inability to empty, urethral stricture unspecified).	

		Nephrocalcinosis (in pre-term infants treated with furosemide), interstitial nephritis, acute renal failure.	
Congenital, familial and genetic disorders		Patent ductus arteriosus	
General disorders and administration site conditions:		Fatigue, malaise, fever, severe anaphylactoid or anaphylactic reactions (e.g. with shock).	
Investigations	Creatinine increased; blood urea increased		

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions

to SAHPRA 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

Fluid, electrolyte depletion and dehydration are the most common symptoms in over dosage.

The guiding principal of treatment is water and electrolyte replacement in accordance with urine output. If difficulty in micturition is proved or suspected, as in cases of prostatic hypertrophy or impairment of consciousness, care must be taken to ensure a free outflow of urine from the bladder. Other than the above, treatment is supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A18.1. Diuretics.

Pharmacotherapeutic group: 3.4.1.2 - Cardiovascular apparatus.

Antihypertensives. Diuretics, Diuretics of loop

ATC Code: C03CA01

The primary action is to inhibit sodium and chloride absorption in the ascending part of the Henle loop. Inhibition of electrolyte reabsorption in the proximal tube has been observed. The increase in potassium excretion occurs as a result of the distal secretion and is more or less proportional to the flow speed in this segment. It is often possible, in situations where other methods of treatment fail to induce diuresis, to increase the excretion of sodium and water with SISERUP tablet, even when glomerular filtration rate is markedly impaired.

Phosphaturic response varies. SISERUP lowers pathologically raised blood pressure, but does not affect normal levels.

5.2 Pharmacokinetic properties

Furosemide is a diuretic which is incompletely absorbed from the gastrointestinal tract. It is generally bound to plasma protein. It is excreted by glomerular filtration and tubular excretion. With oral administration, the onset of action is rapid usually within half an hour. Peak action is usually achieved after two hours and the duration of action is 4 to 5 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose (lactose monohydrate)

Magnesium stearate

Maize starch

Pregelatinised starch (Starch 1500)

Purified water

Sodium starch glycollate (Primogel)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

48 Months

6.4 Special precautions for storage

Store at or below 25 °C.

Keep blister packs in carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

SISERUP 20 mg and 40 mg are available in white opaque PVDC coated PVC / Aluminium blisters in pack sizes of 28's, 30's 56's 84's or 112's.

SISERUP 20 mg and 40 mg are available in white HDPE jars in pack sizes of 250's, 500's and 1000's.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Dezzo Trading 392 (Pty) Ltd

Jespan Centre,

Corner Garrick & Flagtail Street, Extension 8,

Lenasia, 1821, South Africa

Tel: +27 87 405 9660

8. REGISTRATION NUMBERS

SISERUP 20 mg: 56/18.1/1244

SISERUP 40 mg: 56/18.1/1245

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05 September 2023

10. DATE OF REVISION OF THE TEXT