Approved Professional Information for Ringer-Lactate Solution Fresenius

SCHEDULING STATUS **S3**

1. NAME OF THE MEDICINE

Ringer-Lactate Solution Fresenius solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 000 ml contains:

Calcium chloride hexahydrate	0,4 g
Or Calcium chloride dihydrate	0,268 g
Potassium chloride	0,4 g
Sodium chloride	6,0 g
Sodium lactate	3,25 g

Electrolytes:

Na^+	131 mmol/l
K^+	5,4 mmol/l
Ca^{2+}	1,8 mmol/l
Cl^-	112 mmol/l
Lactate	29 mmol/l.

Sugar free.

Excipients with known effect

Each ml Ringer-Lactate Solution Fresenius contains 0,0021 g sodium, equivalent to 2,1 g sodium per 1 000 ml solution.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

Clear, colourless solution in water for injection.

Theoretical osmolarity: 278 mOsm/l

pH value: 6,0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reduced plasma volume resulting from burns, trauma, severe diarrhoea and surgery.

Reduced blood volumes resulting from haemorrhage.

4.2 Posology and method of administration

Posology

Infuse as prescribed, taking into consideration central venous pressure and blood pressure.

Fluid balance, serum electrolytes and acid-base balance may need to be monitored before and during administration, with particular attention to serum sodium in patients with increased non-osmotic vasopressin release (syndrome of inappropriate antidiuretic hormone secretion, SIADH) and in patients co-medicated with vasopressin agonist medicines, due to the risk of hospital-acquired hyponatraemia (see sections 4.4, 4.5 and 4.8). Monitoring of serum sodium is particularly important for hypotonic fluids.

Ringer-Lactate Solution Fresenius has a tonicity of 278 mOsm/l.

The infusion rate and volume depend on the age, weight, clinical condition (e.g. burns, surgery, head-injury, infections), and concomitant therapy should be determined by the consulting doctor experienced in paediatric intravenous fluid therapy (see sections 4.4. and 4.8).

Method of administration

Intravenous infusion.

4.3 Contraindications

- Known hypersensitivity to any active substance listed in section 2.
- Concomitant administration of ceftriaxone and Ringer-Lactate Solution Fresenius is contraindicated in newborns (≤ 28 days of age), even if separate infusion lines are used (risk of fatal ceftriaxone-calcium salt precipitation in the neonate's bloodstream). For patients over 28 days of age please see section 4.4.
- Renal insufficiency, oliguria or anuria.
- Crush syndrome.
- Severe haemolytic reactions.
- Adrenocortical insufficiency.
- Hyperkalaemia.
- Early postoperative oliguria, except when gastrointestinal drainage is being done.
- Hypernatraemia.
- Extracellular hyperhydration or hypervolaemia.
- Uncompensated cardiac failure.
- Hypercalcaemia.
- Metabolic alkalosis.
- Ascitic cirrhosis.
- Severe metabolic acidosis.
- Conditions associated with increased lactate levels (hyperlactataemia) including lactic acidosis, or impaired lactate utilisation, such as severe hepatic insufficiency.
- Concomitant use of digoxin (see section 4.5).

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Ringer-Lactate Solution Fresenius must be stopped immediately if any signs or symptoms of a suspected hypersensitivity reaction develop. Appropriate therapeutic countermeasures must be instituted as clinically indicated.

Incompatibilities

Ceftriaxone

In patients older than 28 days (including adults), ceftriaxone must not be administered simultaneously with intravenous calcium-containing solutions, including Ringer-Lactate Solution Fresenius, through the same infusion line. If the same infusion line is used for sequential administration, the line must be thoroughly flushed between infusions with a compatible fluid. For patients under 28 days please see section 4.3.

Electrolyte balance

Hypernatraemia

Ringer-Lactate Solution Fresenius is contraindicated in hypernatraemia (see section 4.3).
Monitoring of plasma sodium and volume status during treatment is recommended.
Ringer-Lactate Solution Fresenius should be administered with particular caution in patients with conditions predisposing to hypernatraemia (such as adrenocortical insufficiency, diabetes insipidus or extensive tissue injury) and in patients with cardiac disease.

Hyperchloraemia

Ringer-Lactate Solution Fresenius should only be administered to patients with hyperchloraemia after careful consideration of the underlying cause and alternative intravenous fluids. Monitoring of plasma chloride and acid-base balance during treatment is recommended.

Ringer-Lactate Solution Fresenius should be administered with particular caution to patients with conditions predisposing to hyperchloraemia (such as renal failure and renal tubular acidosis, diabetes insipidus), and patients with urinary diversion or patients taking certain diuretics (carbonic anhydrase inhibitors e.g. acetazolamide) or steroids (androgens, estrogens or corticosteroids) and in patients with severe dehydration.

Use in patients with potassium deficiency

Although Ringer-Lactate Solution Fresenius has a potassium concentration similar to the concentration in plasma, it is insufficient to produce a useful effect in case of severe potassium insufficiency and therefore it should not be used for this purpose.

Use in patients at risk for hyperkalaemia

Ringer-Lactate Solution Fresenius should be administered with particular caution to patients with conditions predisposing to hyperkalaemia (such as severe renal impairment or adrenocortical insufficiency, acute dehydration, or extensive tissue injury or burns) and in patients with cardiac disease. The plasma potassium level of the patient must be particularly closely monitored in patients at risk of hyperkalaemia.

Use in patients at risk for hypercalcaemia

Calcium chloride is an irritant; therefore, care should be taken to prevent extravasation during intravenous injection and intramuscular injection must be avoided. Ringer-Lactate Solution Fresenius should be used with caution in patients with conditions predisposing to hypercalcaemia, such as patients with renal impairment and granulomatous diseases associated with increased calcitriol synthesis such as sarcoidosis, calcium renal calculi or a history of such calculi.

Fluid balance/renal function

Use in patients with renal impairment

Ringer-Lactate Solution Fresenius should be administered with particular caution to patients with renal impairment. In such patients, administration of Ringer-Lactate Solution Fresenius may result in sodium and/or potassium retention.

Risk of fluid and/or solute overload and electrolyte disturbances

Depending on the volume and rate of infusion, intravenous administration of Ringer-Lactate Solution Fresenius can cause:

- fluid and/or solute overload resulting in overhydration and, for example, congested states, including pulmonary congestion and oedema
- clinically relevant electrolyte disturbances and acid-base imbalance.

Clinical evaluation and periodic laboratory determinations may be necessary to monitor changes in fluid balance, electrolyte concentrations and acid-base balance during prolonged parenteral therapy or whenever the condition of the patient or the rate of administration warrants such evaluation.

High volume infusion must be used under specific monitoring in patients with cardiac or pulmonary failure and in patients with non-osmotic vasopressin release (including SIADH), due to the risk of hospital-acquired hyponatraemia (see below).

Hyponatraemia

Patients with non-osmotic vasopressin release (e.g. in acute illness, pain, post-operative stress, infections, burns and central nervous system (CNS) diseases), patients with heart-, liver- and kidney diseases and patients exposed to vasopressin agonists (see section 4.5) are at particular risk of acute hyponatraemia upon infusion of hypotonic fluids.

Acute hyponatraemia can lead to acute hyponatraemic encephalopathy (cerebral oedema) characterised by headache, nausea, seizures, lethargy and vomiting. Patients with cerebral oedema are at particular risk of severe, irreversible and life-threatening brain injury.

Children, women of child-bearing potential and patients with reduced cerebral compliance (e.g. meningitis, intracranial bleeding, cerebral contusion and brain oedema) are at particular risk of the severe and life-threatening brain swelling caused by acute hyponatraemia.

Use in patients with hypervolaemia, overhydration or conditions causing sodium retention and oedema

Ringer-Lactate Solution Fresenius should be administered with particular caution to hypervolaemic or overhydrated patients.

Due to the sodium chloride content, Ringer-Lactate Solution Fresenius solution should be administered with particular caution to patients with conditions that may cause sodium retention, fluid overload and oedema, such as patients with primary hyperaldosteronism, secondary hyperaldosteronism (associated with, e.g. hypertension, congestive heart failure, renal artery stenosis or nephrosclerosis), or preeclampsia (see section 4.5).

Acid-base balance

Use in patients at risk for alkalosis

Ringer-Lactate Solution Fresenius should be administered with particular caution to patients at risk for alkalosis. Because lactate is metabolised to bicarbonate, administration may result in, or worsen, metabolic alkalosis. Seizure may be precipitated by the alkalosis induced by lactate, but this is uncommon.

Other warnings

Administration of citrate anticoagulated/preserved blood

Due to the risk of coagulation precipitated by its calcium content, Ringer-Lactate Solution Fresenius must not be added to or administered simultaneously through the same tubing with citrate anticoagulated/preserved blood.

Use in patients with type 2 diabetes

Lactate is a substrate for gluconeogenesis. Therefore, glucose levels should be carefully monitored in patients receiving Ringer-Lactate Solution Fresenius.

Administration

Adding other medicine or using an incorrect administration technique might cause the appearance of fever reactions due to the possible introduction of pyrogens. In such case the infusion must be stopped immediately.

During long term parenteral treatment, a convenient nutritive supply must be given to the patient.

4.5 Interaction with other medicines and other forms of interaction

Ceftriaxone: See sections 4.3 and 4.4 for more information.

Medicines leading to an increased vasopressin effect:

The below listed medicines increase the vasopressin effect, leading to reduced renal electrolyte free water excretion and may increase the risk of hospital-acquired hyponatraemia following inappropriately balanced treatment with IV fluids (see sections 4.2, 4.4 and 4.8):

- Medicines stimulating vasopressin release include:
  Chlorpropamide, clofibrate, carbamazepine, vincristine, selective serotonin reuptake inhibitors, 3,4-methylenedioxy-*N*-methamphetamine, ifosfamide, antipsychotics, narcotics.
- Medicines potentiating vasopressin action include:

Chlorpropamide, NSAIDs, cyclophosphamide.

- Vasopressin analogues include:

  Desmopressin, oxytocin, vasopressin, terlipressin.
- Other medicines increasing the risk of hyponatraemia include:Diuretics in general and antiepileptics such as oxcarbazepine.

Interaction related to the presence of sodium:

Caution is advised when administering Ringer-Lactate Solution Fresenius to patients treated with medicines that may increase the risk of sodium and fluid retention (with oedema and hypertension), such as corticosteroids.

Interaction related to the presence of potassium:

Because of its potassium content, Ringer-Lactate Solution Fresenius should be administered with caution in patients treated with medicines or products that can cause hyperkalaemia or increase the risk of hyperkalaemia, such as:

- Potassium-sparing diuretics (amiloride, spironolactone, triamterene, alone or in association).
- Angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists.
- Tacrolimus, ciclosporin.

Administration of potassium in patients treated with such medicines can produce severe and potentially fatal hyperkalaemia, particularly in patients with severe renal insufficiency.

Interaction related to the presence of calcium:

Administration of calcium may increase the effects of digoxin and lead to serious or fatal cardiac dysrhythmia. Therefore, larger volumes or a faster infusion rate should be used with caution in patients treated with digoxin.

- Caution is advised when administering Ringer-Lactate Solution Fresenius to patients

treated with thiazide diuretics or vitamin D, as these can increase the risk of hypercalcaemia.

- Bisphosphonates, fluoride, some fluoroquinolones and tetracyclines which are less absorbed (lower availability) when administered with calcium.

Interaction related to the presence of lactate (which is metabolised into bicarbonate):

Caution is advised when administering Ringer-Lactate Solution Fresenius to patients treated with medicines for which renal elimination is pH dependent. Due to the alkalinising action of lactate (formation of bicarbonate), Ringer-Lactate Solution Fresenius may interfere with the elimination of such medicines.

- Renal clearance of acidic medicines such as salicylates, barbiturates and lithium may be increased because of the alkalinisation of urine by the bicarbonate resulting from lactate metabolism.
- Renal clearance of alkaline medicines, such as sympathomimetics (e.g. ephedrine, pseudoephedrine) and stimulants (e.g. dexamphetamine sulphate, fenfluramine hydrochloride) may be decreased.

4.6 Fertility, pregnancy and lactation

The safety of this preparation in pregnancy and lactation has not been established.

Ringer-Lactate Solution Fresenius should be administrated with special caution to pregnant women during labour particularly as to serum-sodium if administered in combination with oxytocin (see sections 4.4, 4.5 and 4.8).

4.7 Effects on ability to drive and use machines

There is no information of the effects of Ringer-Lactate Solution Fresenius on the ability to operate any task requiring attention.

4.8 Undesirable effects

The following adverse reactions (listed by MedDRA System Organ Class) have been reported spontaneously during the post-market experience.

Immune system disorders

Frequency unknown:

Hypersensitivity/infusion reactions including anaphylactic/ anaphylactoid reaction, possibly manifested by one or more of the following symptoms: angioedema, chest pain, chest discomfort, decreased heart rate, tachycardia, decreased blood pressure, respiratory distress, bronchospasm, dyspnoea, cough, urticaria, rash, pruritus, erythema, flushing, throat irritation, paraesthesia, oral hypoesthesia, dysgeusia, nausea, anxiety, pyrexia, headache.

Metabolism and nutrition disorders

Frequency unknown:

Hyperkalaemia, hospital-acquired hyponatraemia*.

Nervous system disorders

Frequency unknown:

Acute hyponatraemic encephalopathy*.

General disorders and administration site conditions

Frequency unknown:

Excessive infusion of Ringer-Lactate Solution Fresenius can lead to sodium overload and peripheral oedema. Infusion site reactions manifested by one or more of the following symptoms: Phlebitis, infusion site inflammation, infusion site swelling, infusion site rash, infusion site pruritus, infusion site erythema, infusion site pain, infusion site burning.

*Hospital-acquired hyponatraemia may cause irreversible brain injury and death, due to development of acute hyponatraemic encephalopathy, frequency unknown (see sections 4.2, 4.4, 4.5).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of Ringer-Lactate Solution Fresenius is important. It allows continued monitoring of the benefit/risk balance of Ringer-Lactate Solution 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.

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 medicines regulatory authority in the country where the product is marketed.

4.9 Overdose

See section 4.8 above.

An excessive volume or too high a rate of administration of Ringer-Lactate Solution Fresenius may lead to fluid and sodium overload with a risk of oedema (peripheral and/or pulmonary), particularly when renal sodium excretion is impaired. In this case extra renal dialysis may be necessary.

Excessive administration of potassium may lead to the development of hyperkalaemia, especially in patients with renal impairment. Symptoms include paraesthesia of the extremities, muscle weakness, paralysis, cardiac dysrhythmias, heart block, cardiac arrest and mental confusion.

Excessive administration of calcium salts may lead to hypercalcaemia. Symptoms of hypercalcaemia may include anorexia, nausea, vomiting, constipation, abdominal pain, muscle weakness, mental disturbances, polydipsia, polyuria, nephrocalcinosis, renal calculi, and, in severe cases, cardiac dysrhythmias and coma. Too rapid intravenous injection of calcium salts may also lead to many of the symptoms of hypercalcaemia as well as to a chalky taste, hot flushes, and peripheral vasodilatation. Mild asymptomatic hypercalcaemia will usually resolve on stopping administration of calcium and other contributory medicines such as vitamin D. If hypercalcaemia is severe, urgent treatment (such as loop diuretics, haemodialysis, calcitonin, bisphosphonates, trisodium edetate) is required.

Excessive administration of lactate may lead to metabolic alkalosis. Metabolic alkalosis may be accompanied by hypokalaemia, Symptoms may include mood changes, tiredness, shortness of breath, muscle weakness and irregular heartbeat. Muscle hypertonicity, twitching and tetany may develop, especially in hypocalcaemic patients. Treatment of metabolic alkalosis due to bicarbonate overdose consists mainly of appropriate correction of fluid and electrolyte balance. Replacement of calcium, chloride, and potassium may be of particular importance.

5. PHARMACOLOGICAL PROPERTIES

Category and class: A 24 Mineral substitutes, electrolytes and trace elements.

Pharmacotherapeutic group: Electrolytes, ATC code: B05BB01.

5.1 Pharmacodynamic properties

Sodium lactate in this electrolyte-containing solution is metabolised along two pathways. The dextro moiety is converted to liver glycogen, this contributing to the alleviation of diabetic ketoacidosis by sparing β oxidative fat breakdown. The laevorotatory component is converted to bicarbonate.

Ringer-Lactate Solution Fresenius is an isotonic solution of electrolytes. The constituents of Ringer-Lactate Solution Fresenius and their concentrations are designed to match those of plasma.

The pharmacological properties of this solution are those of its components (calcium, chloride, lactate, potassium and sodium). The main effect of Ringer-Lactate Solution Fresenius is the expansion of the extracellular compartment including both the interstitial and intravascular fluids.

The lactate is metabolised into bicarbonate, mainly in the liver, and produces an alkalinising effect on the plasma.

In healthy volunteers receiving Ringer-Lactate Solution Fresenius, central venous pressure changes were associated with a secretion of atrial natriuretic peptide.

In healthy volunteers, Ringer-Lactate Solution Fresenius decreased serum osmolality, increased blood pH, and the time until first urination was shorter than that with normal saline.
There is no significant change in glucagon, norepinephrine, epinephrine, blood glucose and insulin levels in aortic surgery patients receiving Ringer-Lactate Solution Fresenius.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of Ringer-Lactate Solution Fresenius are those of the ions its composition includes (calcium, chloride, lactate, potassium and sodium).

Infusion of Ringer-Lactate Solution Fresenius in normal haemodynamically stable adults does not increase circulating lactate concentrations.

The pharmacokinetics of D-lactate and L-lactate are similar. The lactate in Ringer-Lactate Solution Fresenius is metabolised by both oxidation and gluconeogenesis, predominantly in the liver and bicarbonate is generated by both processes over 1 – 2 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injection.

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from light.

6.5 Nature and contents of container

30 or 40 x 200 ml in **free***flex*® or PVC bags

10, 18 or 20 x 500 ml in **free***flex*® or PVC bags

12 x 1 000 ml in **free***flex*® or PVC bags

4 x 3 000 ml in PVC bags.

Not all container types and pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Discard after single use.

Discard any unused portion.

Do not reconnect partially used bags.

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

C/24/218

9. DATE OF FIRST AUTHORISATION

01 August 1982

10. DATE OF REVISION OF THE TEXT

14 April 2022