

PRESCRIBING INFORMATION

Lactated Ringer's Injection, USP

Sodium chloride 6.0 g/L, Sodium lactate 3.1 g/L, Potassium chloride 0.30 g/L and Calcium chloride 0.20 g/L

Sterile solution

Parenteral Replenisher

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Lactated Ringer's Injection, USP in VIAFLEX Plastic Container

Description:

Lactated Ringer's Injection, USP is a sterile, nonpyrogenic solution for fluid and electrolyte replenishment in a single dose container for intravenous administration. It contains no antimicrobial agents. The composition, osmolarity and approx. pH are shown in Table 1.

Table 1	Size (mL)	Composition (g/L)				Osmolarity (mOsmol/L)	pH	Ionic Concentration (mmol/L)					Caloric Content (kcal/L)
		Sodium Chloride, USP	Sodium Lactate	Potassium Chloride, USP	Calcium Chloride, USP			Sodium	Potassium	Calcium	Chloride	Lactate	
Lactated Ringer's Injection, USP	250	6.0	3.1	0.30	0.20	272	6.5 (6.0 – 7.5)	130	4	1.4	109	28	9
	500												
	1000												

The VIAFLEX plastic container is fabricated from a specially formulated polyvinyl chloride (PL 146 Plastic). The amount of water that can permeate from inside the container into the overwrap is insufficient to affect the solution significantly. Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period, e.g. di-2-ethylhexyl phthalate (DEHP), up to 5 parts per million. However, the safety of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by tissue culture toxicity studies.

Clinical Pharmacology:

Lactated Ringer's Injection, USP has value as a source of water and electrolytes. It is capable of inducing diuresis depending on the clinical conditions of the patient.

Lactated Ringer's Injection, USP produces a metabolic alkalizing effect. Lactate ions are metabolized ultimately to carbon dioxide and water, which requires the consumption of hydrogen cations.

Indications:

Lactated Ringer's Injection, USP is indicated as a source of water and electrolytes or as an alkalinizing agent.

Contraindications:

As for other calcium-containing infusion solutions, concomitant administration of ceftriaxone and Lactated Ringer's Injection, USP 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).

In patients older than 28 days (including adults), ceftriaxone must not be administered simultaneously with intravenous calcium-containing solutions, including Lactated Ringer's Injection, USP, through the same infusion line (e.g., via Y-port/Y-site). If the same infusion line is used for sequential administration, the line must be thoroughly flushed between infusions with a compatible fluid.

Lactated Ringer's Injection, USP is contraindicated in patients with a known hypersensitivity to sodium lactate.

Special Warnings and Precautions for Use:

Lactated Ringer's Injection, USP is not for use in patients with hyperkalemia.

Although Lactated Ringer's Injection, USP has a potassium concentration similar to the concentration in plasma, it is insufficient to produce a useful effect in case of severe potassium deficiency; therefore, it should not be used for this purpose.

Lactated Ringer's Injection, USP is not for the treatment of lactic acidosis or severe metabolic acidosis.

Warnings and Precautions:Administration of Citrate Anticoagulated/Preserved Blood

Due to the risk of coagulation precipitated by its calcium content, Lactated Ringer's Injection, USP must not be added to or administered simultaneously through the same administration set as citrate anticoagulated/preserved blood.

Hypersensitivity Reactions

The infusion must be stopped immediately if any signs or symptoms of a suspected hypersensitivity reaction develop. Appropriate therapeutic countermeasures must be instituted as clinically indicated.

Risk of Hyponatremia

Monitoring of serum sodium is particularly important for hypotonic fluids. Lactated Ringer's Injection, USP has an osmolarity of 272 mOsmol/L

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 hyponatremia.

Acute hyponatremia can lead to acute hyponatremic encephalopathy (brain edema) characterized by headache, nausea, seizures, lethargy and vomiting. Patients with brain edema are at particular risk of severe, irreversible and life-threatening brain injury.

Risk of Fluid and/or Solute Overload and Electrolyte Disturbances

Depending on the volume and rate of infusion, intravenous administration of Lactated Ringer's Injection, USP can cause clinically relevant electrolyte disturbances and acid-base imbalance, fluid and/or solute overload resulting in dilution of serum electrolyte concentrations, overhydration and, for example, congested states, including pulmonary congestion and edema. The risk of dilutional states is inversely proportional to the electrolyte concentrations of Lactated Ringer's Injection, USP. The risk of solute overload causing congested states with peripheral and pulmonary edema is directly proportional to the electrolyte concentrations of Lactated Ringer's Injection, USP.

Clinical evaluation and periodic laboratory determinations are 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.

Use in Patients with or at Risk for Hyperkalemia

Lactated Ringer's Injection, USP should be administered with particular caution, if at all, to patients with hyperkalemia or conditions predisposing to hyperkalemia (such as severe renal impairment or adrenocortical insufficiency, acute dehydration, or extensive tissue injury or burns) and in patients with cardiac disease.

Use in Patients with or at Risk for Alkalosis

Lactated Ringer's Injection, USP should be administered with particular caution, if at all, to patients with alkalosis or at risk for alkalosis. Because lactate is metabolized to bicarbonate, administration may result in, or worsen, metabolic alkalosis.

Use in Patients with Hypervolemia or Overhydration, or Conditions that Cause Sodium Retention and Edema

Lactated Ringer's Injection, USP should be administered with particular caution, if at all, to hypervolemic or overhydrated patients.

Lactated Ringer's Injection, USP should be administered with particular caution, if at all, to patients with conditions that may cause sodium retention, fluid overload and edema, such as patients with primary hyperaldosteronism, secondary hyperaldosteronism (associated with, e.g., hypertension, congestive heart failure, renal artery stenosis, or nephrosclerosis), or preeclampsia.

Use in Patients with Severe Renal Impairment

Lactated Ringer's Injection, USP should be administered with particular caution, if at all, to patients with severe renal impairment. In such patients, administration of Lactated Ringer's Injection, USP may result in sodium and/or potassium retention.

Risk of Air Embolism

Do not connect flexible plastic containers in series connections. Such use could result in air embolism due to residual air (approximately 15 mL) being drawn from the primary container before administration of the fluid from the secondary container is completed.

Pressurizing intravenous solutions contained in flexible plastic containers to increase flow rates can result in air embolism if the residual air in the container is not fully evacuated prior to administration.

Use of a vented intravenous administration set with the vent in the open position could result in air embolism. Vented intravenous administration sets with the vent in the open position should not be used with flexible plastic containers.

Use in Patients with or at Risk for Increased Lactate Levels or with Impaired Lactate Utilization

Lactated Ringer's Injection, USP should be administered with particular caution, if at all, to patients with conditions associated with increased lactate levels or impaired lactate utilization, such as severe hepatic insufficiency. Hyperlactatemia (i.e., high lactate levels) can develop in

patients with severe hepatic insufficiency, since lactate metabolism may be impaired. In addition, Lactated Ringer's Injection, USP may not produce its alkalinizing action in patients with severe hepatic insufficiency, since lactate metabolism may be impaired.

Lactate-containing solutions should be administered with particular caution to neonates and infants less than 6 months of age.

Use in Patients with or at Risk for Hypercalcemia

Solutions containing calcium salts should be used with caution in patients with

- hypercalcemia or conditions predisposing to hypercalcemia, such as patients with severe renal impairment and granulomatous diseases associated with increased calcitriol synthesis such as sarcoidosis.
- calcium renal calculi or a history of such calculi.

Use in Patients with Type 2 Diabetes

Lactate is a substrate for gluconeogenesis. This should be taken into account when Lactated Ringer's Injection, USP is used in patients with type 2 diabetes.

Use in Pediatric Patients

Safety and effectiveness of Lactated Ringer's Injection, USP in children have not been established by adequate and well-controlled trials; however, the use of electrolyte solutions in the pediatric population is referenced in the medical literature.

Lactate-containing solutions should be administered with particular caution to neonates and infants less than 6 months of age.

Use in Geriatric Patients

When selecting the type of infusion solution and the volume/rate of infusion for a geriatric patient, consider that geriatric patients are generally more likely to have cardiac, renal, hepatic, and other diseases or concomitant drug therapy.

Interactions with Other Medicinal Products and Other Forms of Interaction:

- Ceftriaxone: See Contraindications.
- Caution is advised when administering Lactated Ringer's Injection, USP to patients treated with drugs leading to an increased vasopressin effect. The below listed drugs increase the vasopressin effect, leading to reduced renal electrolyte free water excretion and may increase

the risk of hyponatremia following treatment with IV fluids. (See Special Warnings and Precautions for Use and Adverse Reactions).

- Drugs stimulating vasopressin release such as chlorpropamide, clofibrate, carbamazepine, vincristine, selective serotonin reuptake inhibitors (SSRIs), 3,4-methylenedioxy-N-methamphetamine, ifosfamide, antipsychotics, opioids.
- Drugs potentiating vasopressin action such as chlorpropamide, non steroidal anti-inflammatories (NSAIDs), cyclophosphamide.
- Vasopressin analogues such as desmopressin, oxytocin, vasopressin, terlipressin.
- Caution is advised when administering Lactated Ringer's Injection, USP to patients treated with drugs that may increase the risk of hyponatremia, such as diuretics and antiepileptics (e.g., oxcarbazepine).
- Caution must be exercised in the administration of Lactated Ringer's Injection, USP to patients treated with drugs that may increase the risk of sodium and fluid retention, such as corticosteroids, corticotrophin and carbenoxolone.
- Caution is advised when administering Lactated Ringer's Injection, USP to patients treated with drugs for which renal elimination is pH dependent. Due to the alkalinizing action of lactate (formation of bicarbonate), Lactated Ringer's Injection, USP may interfere with the elimination of such drugs.
 - Renal clearance of acidic drugs such as salicylates, barbiturates, and lithium may be increased.
 - Renal clearance of alkaline drugs, such as sympathomimetics (e.g., ephedrine, pseudoephedrine), dextroamphetamine (dexamphetamine) sulfate, and fenfluramine (phenfluramine) hydrochloride may be decreased.
- Because of its potassium content, Lactated Ringer's Injection, USP should be administered with caution in patients treated with agents or products that can cause hyperkalemia or increase the risk of hyperkalemia, such as potassium sparing diuretics (amiloride, spironolactone, triamterene), with ACE inhibitors, angiotensin II receptor antagonists, or the immunosuppressants tacrolimus and cyclosporine. Administration of potassium in patients treated with such medications can produce severe and potentially fatal hyperkalemia, particularly in patients with severe renal insufficiency.
- Administration of calcium may increase the effects of digitalis and lead to serious or fatal cardiac arrhythmia. Therefore, larger volumes or faster infusion rates should be used with caution in patients treated with digitalis glycosides.
- Caution is advised when administering Lactated Ringer's Injection, USP to patients treated with thiazide diuretics or vitamin D, as these can increase the risk of hypercalcemia.

Pregnancy and Lactation:

There are no adequate data from the use of Lactated Ringer's Injection, USP in pregnant or lactating women. The potential risks and benefits for each specific patient should be carefully considered before using Lactated Ringer's Injection, USP in pregnant or lactating women.

Pregnancy Category C. Animal reproduction studies have not been conducted with Lactated Ringer's Injection, USP. It is also not known whether Lactated Ringer's Injection, USP can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Lactated Ringer's Injection, USP should be given to pregnant woman only if clearly needed.

Adverse Reactions:

Adverse Reactions from Clinical Trials

There are no data available on adverse reactions from Baxter-sponsored clinical trials conducted with Lactated Ringer's Injection, USP.

Post-Marketing Adverse Reactions

The following adverse reactions have been reported in the post-marketing experience, listed by MedDRA System Organ Class (SOC), then by Preferred Term in order of severity, where feasible.

IMMUNE SYSTEM DISORDERS: Hypersensitivity/infusion reactions, including Anaphylactic/Anaphylactoid reactions, and the following manifestations: Angioedema, Chest pain, Chest discomfort, Decreased heart rate, Tachycardia, Blood pressure decreased, Respiratory distress, Bronchospasm, Dyspnea, Cough, Urticaria, Rash, Pruritus, Erythema, Flushing, Throat irritation, Paresthesias, Hypoesthesia oral, Dysgeusia, Nausea, Anxiety, Pyrexia, Headache

METABOLISM AND NUTRITION DISORDERS: Hyperkalemia

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Infusion site reactions, including Phlebitis, Infusion site inflammation, Infusion site swelling, Infusion site rash, Infusion site pruritus, Infusion site erythema, Infusion site pain, Infusion site burning

Class Reactions

Other adverse reactions reported with Lactated Ringer's Injection, USP and similar products are: Hyponatremia, Hyponatremic encephalopathy, Infusion site anesthesia (numbness) (reported with Lactated Ringer's and 5% Dextrose Injection)

If any adverse reaction does occur, discontinue the infusion, evaluate the patient, institute appropriate therapeutic countermeasures, and save the remainder of the fluid and administration set for examination if deemed necessary.

Overdose:

- An excessive volume or too high a rate of administration of Lactated Ringer's Injection, USP may lead to fluid and sodium overload with a risk of edema (peripheral and/or pulmonary), particularly when renal sodium excretion is impaired.
- Excessive administration of lactate may lead to metabolic alkalosis. Metabolic alkalosis may be accompanied by hypokalemia.
- Excessive administration of potassium may lead to the development of hyperkalemia, especially in patients with severe renal impairment.
- Excessive administration of calcium salts may lead to hypercalcemia.
- When assessing an overdose, any additives in the solution must also be considered.
- The effects of an overdose may require immediate medical attention and treatment.

Incompatibilities:

Ceftriaxone must not be mixed with calcium-containing solutions including Lactated Ringer's Injection, USP. See also Contraindications.

Additives may be incompatible with Lactated Ringer's Injection, USP. Complete information is not available. Those additives known or determined to be incompatible must not be used. If in the informed judgment of the physician it is deemed advisable to introduce additives, use aseptic technique.

As with all parenteral solutions, compatibility of the additives with the solution must be assessed before addition, by checking for a possible color change and/or the appearance of precipitates, insoluble complexes or crystals. Before adding substance or medication, verify that it is soluble and/or stable in water and that the pH range of Lactated Ringer's Injection, USP is appropriate.

Thorough and careful mixing of any additive is mandatory. Do not store solutions containing additives. The instructions for use of the medication to be added and other relevant literature must be consulted.

Dosage and Administration:

As directed by a physician. Dosage, rate, and duration of administration are to be individualized and depend upon the indication for use, the patient's age, weight, clinical condition, and concomitant treatment, and on the patient's clinical as well as laboratory response to treatment.

Lactated Ringer's Injection, USP is intended for intravenous administration using sterile and nonpyrogenic equipment. It is recommended that the intravenous administration apparatus be replaced at least once every 24 hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not administer unless the solution is clear and the seal is intact.

When making additions to Lactated Ringer's Injection, USP, aseptic technique must be used. Mix the solution thoroughly when additives have been introduced. Do not store solutions containing additives (see Incompatibilities).

How Supplied:

Lactated Ringer's Injection, USP in VIAFLEX plastic container is available as shown in Table

1. Store between 15°C and 25°C.

Directions for use of VIAFLEX Plastic Container:

WARNING: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air (approximately 15 mL) being drawn from the primary container before administration of the fluid from the secondary container is completed. Do not remove unit from overwrap until ready to use.

After opening the container, the contents should be used immediately and should not be stored for a subsequent infusion. Do not reconnect any partially used containers.

To Open:

Tear overwrap down side at slit and remove solution container. Visually inspect the container. If the outlet port protector is damaged, detached, or not present, discard container as solution path sterility may be impaired. If supplemental medication is desired, follow directions below before preparing administration. Some opacity of the plastic due to moisture absorption during sterilization process may be observed. This is normal and does not affect the solution quality and safety. The opacity will diminish gradually. Check for leaks by squeezing inner bag firmly. If leaks are found discard solution as sterility may be impaired.

Preparation for Administration:

1. Suspend container from eyelet support.
2. Remove plastic protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

To Add Medication:

1. Prepare medication site.
2. Using a syringe and a 20 – 22 gauge needle, puncture resealable rubber plug at target area and inject. Multiple additions may be made in this manner.
3. Mix solution and medication thoroughly. For high density medications such as potassium chloride, squeeze ports while ports are upright and mix thoroughly.

*Normal physiologic isotonicity range is approximately 280 – 310 mOsmol/liter. Administration of substantially hypotonic solutions may cause hemolysis and administration of substantially hypertonic solutions may cause vein damage.