

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

Solution, Intravenous

IV Fluid and Electrolyte Replenisher

B|BRAUN

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Lactated Ringer's Injection USP is indicated for use in adults and pediatric patients as a source of electrolytes and water for hydration.

1.1 Pediatrics

Pediatrics (<16 years of age): For considerations of the safe use in pediatric patients, see **Warnings and Precautions, Special Populations, Pediatrics.**

1.2 Geriatrics

Geriatrics (>65 years of age): For considerations of the safe use in geriatric patients, see **Warnings and Precautions, Special Populations, Geriatrics.**

2 CONTRAINDICATIONS

Lactated Ringer's Injection USP is contraindicated in patients who are hypersensitive to sodium lactate or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see the **Dosage Form, Strengths, Composition and Packaging** section of the Prescribing Information.

Lactated Ringer's Injection USP is contraindicated where the administration of sodium, potassium, calcium, lactate, or chloride could be clinically detrimental.

Lactated Ringer's Injection USP is contraindicated with concomitant use of ceftriaxone in neonates (≤ 28 days of age) whether administered via the same intravenous infusion line or when administered at different times and via different infusion lines. Fatal cases of such interactions were reported in neonates (See **Warnings and Precautions, and Postmarketing Adverse Drug Reactions**).

In patients >28 days of age, including adults, Lactated Ringer's Injection USP is contraindicated with ceftriaxone when administered simultaneously through the same infusion line (e.g., Y-connector). However, Lactated Ringer's Injection and ceftriaxone may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid (**See Warnings and Precautions, Administration, Drug Interactions, Action And Clinical Pharmacology**).

Lactate administration is contraindicated in severe metabolic acidosis or alkalosis, and in severe liver disease or anoxic states which affect lactate metabolism.

3 DOSAGE AND ADMINISTRATION

Lactated Ringer's Injection USP is for intravenous use only.

3.1 Dosing Considerations

Dosage is to be directed by a physician and is dependent upon age, weight, clinical condition of the patient and laboratory determinations. Frequent laboratory determinations and clinical evaluation are essential to monitor changes in blood glucose and electrolyte concentrations, and fluid and electrolyte balance during prolonged parenteral therapy.

3.2 Recommended Dose and Dosage Adjustment

Fluid administration should be based on calculated maintenance or replacement fluid requirements for each patient.

3.3 Administration

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

Use only if solution is clear and container and seals are intact.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Administration with Additives

The presence of calcium ions in this solution should be considered when phosphate is present in additive solutions, in order to avoid precipitation.

Some additives may be incompatible. Consult with pharmacist. When introducing additives, use aseptic technique. Mix thoroughly. **Do not store.**

Ceftriaxone must not be mixed with calcium-containing solutions, including Lactated Ringer's Injection USP, because of the risk of precipitation of ceftriaxone-calcium. In neonates (≤ 28 days of age), concomitant treatment is contraindicated whether administered via the same intravenous infusion line or when administered at different times and via different infusion lines. In patients other than neonates, ceftriaxone must not be administered simultaneously with calcium-containing intravenous solutions, including Lactated Ringer's Injection USP, through the same infusion line (e.g., Y-connector). However, ceftriaxone and Lactated Ringer's Injection may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid (See **Contraindications, Drug Interactions, Warnings and Precautions, Action and Clinical Pharmacology**).

To minimize the risk of possible incompatibilities arising from mixing this solution with other additives that may be prescribed, the final infusate should be inspected for cloudiness or precipitation immediately after mixing, prior to administration and periodically during administration.

Directions for use of Excel Container

Caution: Do not use plastic containers in series connection.

To Open

Tear overwrap down at notch and remove solution container. Check for minute leaks by squeezing solution container firmly. If leaks are found, discard solution as sterility may be impaired. If supplemental medication is desired, follow directions below before preparing for administration.

NOTE: Before use, perform the following checks:

- Inspect each container. Read the label. Ensure solution is the one ordered and is within the expiration date.

- Invert container and carefully inspect the solution in good light for cloudiness, haze, or particulate matter. Any container, which is suspect, should not be used.
- Use only if solution is clear and container and seals are intact.

Preparation for Administration

1. Remove plastic protector from sterile set port at bottom of container.
2. Attach administration set. Refer to complete directions accompanying set.

To Add Medication

Warning: Some additives may be incompatible.

Addition of medication should be accomplished using complete aseptic technique.

To Add Medication before Solution Administration

1. Prepare medication site.
2. Using syringe with 18–22 gauge needle, puncture medication port and inner diaphragm and inject.
3. Squeeze and tap ports while ports are upright and mix solution and medication thoroughly.

To Add Medication during Solution Administration

1. Close clamp on the set.
2. Prepare medication site.
3. Using syringe with 18–22 gauge needle of appropriate length (at least 5/8 inch), puncture resealable medication port and inner diaphragm and inject.
4. Remove container from IV pole and/or turn to an upright position.
5. Evacuate both ports by tapping and squeezing them while container is in the upright position.
6. Mix solution and medication thoroughly.
7. Return container to in use position and continue administration.

4 OVERDOSAGE

In the event of a fluid or solute overload during parenteral therapy, re-evaluate the patient's condition and institute appropriate corrective treatment.

In the event of overdosage with potassium-containing solutions, discontinue the infusion immediately and institute corrective therapy to reduce serum potassium levels.

Treatment of hyperkalemia includes the following:

1. Dextrose Injection USP, 10% or 25%, containing 10 units of crystalline insulin per 20 grams of dextrose administered intravenously, 300 to 500 mL per hour.
2. Absorption and exchange of potassium using sodium or ammonium cycle cation exchange resin, orally and as retention enema.
3. Hemodialysis and peritoneal dialysis. The use of potassium-containing foods or medications must be eliminated. However, in cases of digitalization, too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

The composition, osmolarity, pH, and caloric content of Lactated Ringer's Injection USP are shown in **Table 1**.

Table 1: Dosage Forms, Strengths, Composition and Packaging

Lactated Ringer's Injection USP (DIN 01961636)	Package Size	Composition (g /100 mL)*				Osmolarity (mOsmol / L)	pH**	Concentration of Electrolytes (mEq / L)				
		Sodium Chloride	Sodium Lactate	Potassium Chloride	Calcium Chloride USP			Sodium	Potassium	Calcium	Chloride	Lactate (CH ₃ CH(OH)COO ⁻)
	1000 mL											
	500 mL											
	250 mL											
		0.6	0.31	0.03	0.02	275	6.2 (6.0 – 7.5)	130	4	3	110	28

* Non-medicinal ingredient = Water for Injection (qs)

**pH may be adjusted with Hydrochloric Acid NF or Sodium Hydroxide NF

Lactated Ringer's Injection USP is sterile, nonpyrogenic and contains no bacteriostatic or antimicrobial agents.

Excel Plastic Container not made with natural rubber latex, PVC or DEHP.

The plastic container is made from a multilayered film specifically developed for parenteral drugs. It contains no plasticizers and exhibits virtually no leachables. The solution contact layer is a rubberized copolymer of ethylene and propylene. The container is nontoxic and biologically inert. The container solution unit is a closed system and is not dependent upon entry of external air during administration.

The container is overwrapped to provide protection from the physical environment and to provide an additional moisture barrier when necessary.

The closure system has two ports; the one for the administration set has a tamper evident plastic protector and the other is a medication addition site. Refer to the **Directions for Use of Excel Container**.

Lactated Ringer's Injection USP is supplied in sterile and nonpyrogenic EXCEL Containers. The 1000 mL containers are packaged 12 per case; the 500 mL and 250 mL containers are packaged 24 per case.

6 WARNINGS AND PRECAUTIONS

General

The administration of intravenous solutions can cause fluid and/or solute overload resulting in dilution of serum electrolyte concentrations, overhydration, congested states or pulmonary edema. The risk of dilutional states is inversely proportional to the electrolyte concentration. The risk of solute overload causing congested states with peripheral and pulmonary edema is directly proportional to the electrolyte concentration.

Solutions containing lactate are not for use in the treatment of lactic acidosis.

Solutions containing lactate should be used with great care in patients with metabolic or respiratory alkalosis, and in those conditions in which there is an increased level or an impaired utilization of lactate, such as severe hepatic insufficiency.

Solutions containing sodium ions should be used with great care, if at all, in patients with congestive heart failure, severe renal insufficiency, and in clinical states in which there is sodium retention with edema.

Solutions containing potassium ions should be used with great care, if at all, in patients with hyperkalemia, severe renal failure, and in conditions in which potassium ions retention is present.

Solutions containing calcium ions should not be administered through the same administration set as citrate anticoagulated blood because of the likelihood of coagulation.

Interaction with ceftriaxone: Calcium-containing diluents, including Lactated Ringer's Injection USP, should not be mixed with ceftriaxone because of the risk of precipitation of ceftriaxone-calcium.

In neonates (≤ 28 days of age), the concomitant treatment is contraindicated whether administered via the same infusion line or when administered at different times and via different infusion lines. Fatal cases of such interactions were reported in neonates. In patients other than neonates (> 28 days of age), ceftriaxone must not be administered simultaneously with calcium-containing intravenous solutions, including Lactated Ringer's Injection USP, through the same infusion line (e.g., Y-connector). However, ceftriaxone and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid (See **Contraindications, Postmarketing Adverse Drug Reactions, Administration, Drug Interactions**).

Lactated Ringer's Injection USP should be used with care in patients with hypervolemia, renal insufficiency, urinary tract obstruction, or impending or frank cardiac decompensation.

Extraordinary electrolytes losses such as may occur during protracted nasogastric suction, vomiting, diarrhea or gastrointestinal fistula drainage may necessitate additional electrolyte supplementation.

Additional essential electrolytes, minerals and vitamins should be supplied as needed. Sodium-containing solutions should be administered with caution to patients receiving corticosteroids or corticotropin, or to other salt-retaining patients.

Care should be exercised in administering solutions containing sodium or potassium to patients with renal or cardiovascular insufficiency, with or without congestive heart failure, particularly if they are postoperative or elderly.

Potassium therapy should be guided primarily by serial electrocardiograms, especially in patients receiving digitalis. Serum potassium levels are not necessarily indicative of tissue potassium levels.

Solutions containing calcium should be used with caution in the presence of cardiac disease, particularly when accompanied by renal disease. Parenteral calcium should be administered with extreme caution to patients receiving digitalis preparations.

Solutions containing lactate should be used with caution. Excess administration may result in metabolic alkalosis.

The conversion of lactate to bicarbonate is markedly delayed in the presence of tissue anoxia and reduced capacity of the liver to metabolize lactate. This may occur under conditions such as metabolic acidosis associated with circulatory insufficiency, extracorporeal circulation, hypothermia, glycogen storage disease, liver dysfunction, respiratory alkalosis, shock or cardiac decompensation.

Do not use plastic containers in series connection.

If administration is controlled by a pumping device, care must be taken to discontinue pumping action before the container runs dry or air embolism may result. If administration is not controlled by a pumping device, refrain from applying excessive pressure (>300mmHg) causing distortion to the container such as wringing or twisting. Such handling could result in breakage of the container.

Carcinogenesis and Mutagenesis

Studies with Lactated Ringer's Injection USP have not been performed to evaluate carcinogenic or mutagenic potential.

Monitoring and Laboratory Tests

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 warrants such evaluation. Significant deviations from normal concentrations may require tailoring of the electrolyte pattern, in this or an alternative solution.

Renal

In patients with diminished renal function, administration of solutions containing sodium or potassium ions may result in sodium or potassium retention.

Sexual Health

Reproduction

Studies with Lactated Ringer's Injection USP have not been performed to evaluate effects on fertility.

6.1 Special Populations

6.1.1 Pregnant Women

There are no adequate data from the use of Lactated Ringer's Injection USP in pregnant women. Animal reproduction studies have not been conducted with Lactated Ringer's Injection USP. It is not known whether Lactated Ringer's Injection USP can affect reproduction capacity or cause fetal harm when given to pregnant women. Healthcare practitioners should carefully consider the potential risks and benefits for each specific patient before administration of Lactated Ringer's Injection USP.

As reported in the literature, Lactated Ringer's Injection USP has been administered during labor and delivery. Caution should be exercised, and the fluid balance, glucose and electrolyte concentrations, and acid-base balance, of both mother and fetus should be evaluated periodically or whenever warranted by the condition of the patient or fetus.

6.1.2 Breast-feeding

There are no adequate data from the use of Lactated Ringer's Injection USP in lactating women. Because many drugs are excreted in human milk, caution should be exercised when Lactated Ringer's Injection USP is administered with any other additives to a nursing woman.

6.1.3 Pediatrics

Safety and effectiveness of Lactated Ringer's Injection USP in pediatric patients 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. The warnings, precautions, and adverse reactions identified in the label copy should be observed in the pediatric population.

6.1.4 Geriatrics

Clinical studies of Lactated Ringer's Injection USP did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

7 ADVERSE REACTIONS

7.1 Post-Market Adverse Drug Reactions

The following adverse reactions have been reported in the post-marketing experience.

Allergic reactions or anaphylactoid symptoms such as localized or generalized urticaria and pruritus; periorbital, facial, and/or laryngeal edema; coughing, sneezing, and/or difficulty with breathing have been reported during administration of Lactated Ringer's Injection USP. The reporting frequency of these signs and symptoms is higher in women during pregnancy.

Reactions which may occur because of the solution or the technique of administration include febrile response, infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection, extravasation and hypervolemia.

Symptoms may result from an excess or deficit of one or more of the ions present in the solution; therefore, frequent monitoring of electrolyte levels is essential.

Hypertremia may be associated with edema and exacerbation of congestive heart failure due to the retention of water, resulting in an expanded extracellular fluid volume.

Reactions reported with the use of potassium-containing solutions include nausea, vomiting, abdominal pain and diarrhea. The signs and symptoms of potassium intoxication include paresthesias of the extremities, areflexia, muscular or respiratory paralysis, mental confusion, weakness, hypotension, cardiac arrhythmias, heart block, electrocardiographic abnormalities and cardiac arrest. Potassium deficits result in disruption of neuromuscular function, and intestinal ileus and dilatation.

If infused in large amounts, chloride ions may cause a loss of bicarbonate ions, resulting in an acidifying effect.

Abnormally high plasma levels of calcium can result in depression, amnesia, headaches, drowsiness, disorientation, syncope, hallucinations, hypotonia of both skeletal and smooth muscles, dysphagia, arrhythmias and coma. Calcium deficits can result in neuromuscular hyperexcitability, including cramps and convulsions.

Although the metabolism of lactate to bicarbonate is a relatively slow process, aggressive administration of sodium lactate may result in metabolic alkalosis. Careful monitoring of blood acid-base balance is essential during the administration of sodium lactate.

The physician should also be alert to the possibility of adverse reactions to drug additives. Prescribing information for drug additives to be administered in this manner should be consulted.

A small number of cases with fatal outcomes in which a crystalline material was observed in the lungs and kidneys at autopsy have been reported in neonates receiving ceftriaxone sodium and calcium-containing fluids. In some of these cases, the same intravenous infusion line was used for both ceftriaxone sodium and calcium-containing fluids, and in some, a precipitate was observed in the intravenous infusion line. At least one fatality has been reported in a neonate in whom ceftriaxone sodium and calcium-containing fluids were administered at different time points via different intravenous lines; no crystalline material was observed at autopsy in this neonate. There have been no similar reports in patients other than neonates (See **Contraindications, Warnings And Precautions, Administration, and Drug Interactions**).

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

8 DRUG INTERACTIONS

Some additives may be incompatible. Consult with pharmacist.

Ceftriaxone must not be mixed with calcium-containing solutions, including Lactated Ringer's Injection USP. In vitro studies using adult and neonatal plasma from umbilical cord blood

demonstrated that neonates have an increased risk of precipitation of ceftriaxone-calcium (See **Action And Clinical Pharmacology**).

In neonates (≤ 28 days of age), concomitant treatment is contraindicated whether administered via the same intravenous infusion line or when administered at different times and via different infusion lines. In patients other than neonates, ceftriaxone must not be administered simultaneously with calcium-containing intravenous solutions, including Lactated Ringer's Injection USP, through the same infusion line (e.g., Y-connector). However, ceftriaxone and Lactated Ringer's Injection may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid (See **Contraindications, Administration, Warnings and Precautions, Postmarketing Adverse Drug Reactions**).

9 ACTION AND CLINICAL PHARMACOLOGY

Lactated Ringer's Injection USP provides electrolytes and is a source of water for hydration. It is capable of inducing diuresis depending on the clinical condition of the patient. This solution also contains lactate which produces a metabolic alkalizing effect.

Sodium, the major cation of the extracellular fluid, functions primarily in the control of water distribution, fluid balance, and osmotic pressure of body fluids. Sodium is also associated with chloride and bicarbonate in the regulation of the acid-base equilibrium of body fluid. Potassium, the principal cation of intracellular fluid, participates in carbohydrate utilization and protein synthesis, and is critical in the regulation of nerve conduction and muscle contraction, particularly in the heart.

Chloride, the major extracellular anion, closely follows the metabolism of sodium, and changes in the acid-base balance of the body are reflected by changes in the chloride concentration. Calcium, an important cation, provides the framework of bones and teeth in the form of calcium phosphate and calcium carbonate. In the ionized form, calcium is essential for the functional mechanism of the clotting of blood, normal cardiac function, and regulation of neuromuscular irritability.

Sodium lactate is a racemic salt containing both the levo form, which is oxidized by the liver to bicarbonate, and the dextro form, which is converted to glycogen. Lactate is slowly metabolized to carbon dioxide and water, accepting one hydrogen ion and resulting in the formation of bicarbonate for the lactate consumed. These reactions depend on oxidative cellular activity.

In Vitro interaction of ceftriaxone and calcium: Two in vitro studies, one using adult plasma and the other neonatal plasma from umbilical cord blood, were carried out to assess the interaction of ceftriaxone and calcium. Ceftriaxone concentrations of 0.1 – 1 mM (55 – 555 mcg/mL) were incubated for 2 hours with calcium concentrations of 2 – 12 mM (80 – 480 mcg/mL). Recovery of ceftriaxone from plasma was statistically significantly reduced at calcium concentrations of 6 mM (240 mcg/mL) or higher in adult plasma and 4 mM (160 mcg/mL) or higher in neonatal plasma. These measures included total free and protein bound ceftriaxone and calcium. The difference observed in the assays may be reflective of ceftriaxone-calcium precipitations (See **Contraindications, Administration, Warnings and Precautions, Drug Interactions**).

10 STORAGE, STABILITY AND DISPOSAL

Exposure of pharmaceutical products to heat should be minimized.

Avoid excessive heat. Protect from freezing. It is recommended that the product be stored at room temperature (25°C); however, brief exposure up to 40°C does not adversely affect the product.

11 SPECIAL HANDLING INSTRUCTIONS

This product is intended for intravenous administration in a single dose container.

Discard any unused portion.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name	Chemical name	Molecular formula and molecular mass	Structural formula
Sodium Chloride USP	Sodium Chloride	NaCl; 58,44	Na - Cl
Sodium Lactate USP	Sodium Lactate	CH ₃ CH(OH)COONa; 112.06	
Potassium Chloride USP	Potassium Chloride	KCl; 74,55	K—Cl
Calcium Chloride Dihydrate USP	Calcium Chloride Dihydrate	CaCl ₂ •2H ₂ O; 147,02	

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