

PRESCRIBING INFORMATION

**Lactated Ringer's and 5% Dextrose Injection, USP
In Viaflex Plastic Container**

Parenteral Replenisher

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Note: The proposed changes (highlighted in green) in this Prescribing Information originate from the reviewer's (Dr. Ning Dan) comments in the Clarifax dated July 4, 2014 for the PDC for Lactated Ringer's and 5% Dextrose Injection, USP in VIAFLEX Plastic Container (submission control number: 174151). In response to that Clarifax, Baxter committed to address the reviewer's comments in a separated drug submission. These changes are now included in this annotated version, except the change to the indication. Please refer to the Justification memo provided in Module 1.3.1 Product Monograph Note to Reviewer.

Lactated Ringer's and 5% Dextrose Injection, USP in VIAFLEX Plastic Container

SUMMARY PRODUCT INFORMATION

Lactated Ringer's and 5% Dextrose Injection, USP is a sterile, nonpyrogenic solution for fluid and electrolyte replenishment and caloric supply in a single dose container for intravenous administration. It contains no antimicrobial agents. This product is mildly hypertonic, containing sodium, potassium and chloride ions at concentrations similar to the corresponding value in human plasma (Table 1). This product also contains calcium ion at a concentration slightly lower than that in human plasma.

Table 1. Product Information

	Size (mL)	Composition (g/L)					Osmolarity (mOsmol/L)	pH	Ionic Concentration (mmol/L)					Caloric Content (kcal/L)
		Dextrose Hydrated, USP*	Sodium Chloride, USP	Sodium Lactate	Potassium Chloride, USP	Calcium Chloride, USP			Sodium	Potassium	Calcium	Chloride	Lactate	
Lactated Ringer's and 5% Dextrose Injection, USP	500	50	6.0	3.1	0.30	0.20	524	5.0 (4.0 – 5.5)	130	4	1.4	109	28	179

*The dextrose is purified from corn and contain fructose.

The material of the VIAFLEX plastic container is fabricated from a specially formulated polyvinyl chloride (PL 146 Plastic) with di-2-ethylhexyl phthalate (DEHP) as a plasticizer. Water in a solution in the container can permeate through the plastic wall, but in an insufficient amount to significantly affect the solution. Before the product expires, a very small amount of chemical components of the plastic can be leached into the solution container, such as up to 5 parts per million for DEHP. No safety issues of the plastic material were identified in the USP biological tests in animals as well as by tissue culture toxicity studies.

ACTIONS

Lactated Ringer's and 5% Dextrose Injection, USP has value as a source of water, electrolytes and calories. It is capable of inducing diuresis depending on the clinical conditions of the patient.

Lactated Ringer's and 5% Dextrose Injection, USP produces a metabolic alkalinizing effect. Lactate ions are metabolized ultimately to carbon dioxide and water, which requires the consumption of hydrogen cations.

INDICATIONS AND CLINICAL USE

Lactated Ringer's and 5% Dextrose Injection, USP is indicated as a source of water, electrolytes and calories or as an alkalinizing agent.

CONTRAINDICATIONS

Lactated Ringer's and 5% Dextrose Injection, USP is contraindicated in the following conditions:

- Patients with hypersensitivity to any ingredient in the formulation or component of the container. For more information, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section.
- Concomitant administration of ceftriaxone in newborns (≤ 28 days of age), even if separate infusion lines are used due to risk of fatal ceftriaxone-calcium salt precipitation in the neonate's bloodstream.
- Simultaneous administration of ceftriaxone through the same infusion line (e.g., via Y-port/Y-site) in patients older than 28 days of age. If the same infusion line is used for sequential administration, the line must be thoroughly flushed between infusions with a compatible fluid.
- Patients with known allergy to corn or corn products since dextrose in the products is purified from corn.
- Patients with hyperglycemia (glucose concentration greater than 180 mg/dL or 10 mmol/L).

WARNINGS AND PRECAUTIONS

General

Although Lactated Ringer's and 5% Dextrose 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 and 5% Dextrose Injection, USP is not for use for the treatment of lactic acidosis or severe metabolic acidosis.

WARNING: This product contains aluminum which may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

The products contain no more than 25 mcg/L of aluminum.

These products may contain fructose. Exercise caution when they are used in patients with hereditary fructose intolerance due to aldolase deficiency. In these patients, fructose may result in hypoglycemia, metabolic acidosis, liver toxicity which manifests as vomiting, nausea, sweating, jaundice, hemorrhage, seizures or coma or even death. The severity of the reactions is dependent on the amount and duration of fructose intake.

Caution must be exercised in the administration of parenteral fluids to patients receiving corticosteroids or corticotropin. (See DRUG INTERACTIONS).

Administration of Citrate Anticoagulated/Preserved Blood

Due to the risk of coagulation precipitated by its calcium content, Lactated Ringer's and 5% Dextrose Injection, USP must not be added to or administered simultaneously through the same administration set as citrate anticoagulated/preserved blood.

Hypersensitivity Reactions

Hypersensitivity/infusion reactions, including anaphylactic/anaphylactoid reactions, have been reported with Lactated Ringer's and 5% Dextrose Injection, USP.

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 Fluid and/or Solute Overload and Electrolyte Disturbances

Depending on the volume and rate of infusion, intravenous administration of Lactated Ringer's and 5% Dextrose 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 and 5% Dextrose 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 and 5% Dextrose 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 and 5% Dextrose 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 and 5% Dextrose 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 and 5% Dextrose Injection, USP should be administered with particular caution, if at all, to hypervolemic or overhydrated patients.

Lactated Ringer's and 5% Dextrose 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 and 5% Dextrose 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 and 5% Dextrose Injection, USP may result in sodium and/or potassium retention.

Use in Patients with or at Risk of Hyponatremia

Glucose intravenous infusions are usually isotonic solutions. In the body, however, glucose containing fluids can become extremely physiologically hypotonic due to rapid glucose metabolization.

Monitoring of serum sodium is particularly important for hypotonic fluids. Lactated Ringer's and 5% Dextrose Injection, USP has an osmolarity of 525 mOsm/L.

Depending on the tonicity of the solution, the volume and rate of infusion and depending on a patient's underlying clinical condition and capability to metabolize glucose, intravenous administration of glucose can cause electrolyte disturbances, most importantly hypo- or hyperosmotic hyponatremia.

High volume of 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 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 Hyperglycemia

Solutions containing dextrose should be used with caution in patients with impaired glucose tolerance or diabetes mellitus. Lactate is a substrate for gluconeogenesis. This should be taken into account when Lactated Ringer's and 5% Dextrose Injection, USP is used in patients with type 2 diabetes.

Because Lactated Ringer's and 5% Dextrose Injection, USP contains dextrose and lactate (which is metabolized to glucose), administration that exceeds the metabolic capacity for glucose may lead to hyperglycemia.

Hyperglycemia has been implicated in increasing cerebral ischemic brain damage and impairing recovery after acute ischemic strokes. Caution is recommended in using dextrose-containing solutions in such patients.

Early hyperglycemia has been associated with poor outcomes in patients with severe traumatic brain injury. Dextrose-containing solutions should, therefore, be used with caution in patients with head injury, in particular during the first 24 hours following the trauma.

Newborns – especially those born premature and with low birth weight - are at increased risk of developing hypo- or hyperglycemia and therefore need close monitoring during treatment with intravenous glucose solutions to ensure adequate glycemic control in order to avoid potential long term adverse effects. (see SPECIAL POPULATIONS - PEDIATRICS)

If hyperglycemia occurs, the rate of dextrose administration should be reduced and/or insulin administered, or the insulin dose adjusted.

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

Lactated Ringer's and 5% Dextrose 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 and 5% Dextrose Injection, USP may not produce its alkalizing 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.

Osmolarity

The addition of 5% dextrose to the electrolyte solution renders Lactated Ringer's and 5% Dextrose Injection, USP hypertonic, having an osmolarity of 524 mOsmol/L. The normal physiologic serum osmolarity range is approximately 280 to 310 mOsmol/L. Administration of substantially hypertonic solutions may cause venous irritation, including phlebitis. Hyperosmolar solutions should be administered with caution, if at all, to patients with hyperosmolar states.

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.

Special Populations

Pediatrics

Safety and effectiveness of Lactated Ringer's and 5% Dextrose 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.

The infusion rate and volume depends on the age, weight, clinical and metabolic conditions of the patient, concomitant therapy and should be determined by the consulting physician experienced in pediatric intravenous fluid therapy.

Newborns – especially those born premature and with low birth weight - are at increased risk of developing hypo- or hyperglycemia and therefore need close monitoring during treatment with intravenous glucose solutions to ensure adequate glycemic control in order to avoid potential long term adverse effects. Hypoglycemia in the newborn can cause prolonged seizures, coma and brain damage. Hyperglycemia has been associated with intraventricular hemorrhage, late onset bacterial and fungal infection, retinopathy of prematurity, necrotizing enterocolitis, bronchopulmonary dysplasia, prolonged length of hospital stay, and death.

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

Geriatrics

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.

Pregnant or Nursing Women

Animal reproduction studies have not been conducted with Lactated Ringer's and 5% Dextrose Injection, USP. It is also not known whether Lactated Ringer's and 5% Dextrose Injection, USP can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Lactated Ringer's and 5% Dextrose 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 and 5% Dextrose 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, Bronchospasm, Dyspnea, Cough, Urticaria, Rash, Pruritus, Erythema, Nausea, Pyrexia

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Infusion site reactions, including Infusion site pruritus, Infusion site erythema, Infusion site anesthesia (numbness)

Other Reactions

Other adverse reactions reported with Lactated Ringer's Injection and Sodium Lactate Injection are:

- Other manifestations of hypersensitivity/infusion reactions: Decreased heart rate, Tachycardia, Blood pressure decreased, Respiratory distress, Flushing, Throat irritation, Paresthesias, Hypoesthesia oral, Dysgeusia, Anxiety, Headache
- Hyperkalemia

- Other infusion site reactions: Phlebitis, Infusion site inflammation, Infusion site swelling, Infusion site rash, Infusion site pain, Infusion site burning
- Other adverse reactions reported with other similar products are: hyponatremia, hyponatremic encephalopathy

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.

DRUG INTERACTIONS

Co-administration of this product and ceftriaxone increase the risk of ceftriaxone-calcium salt precipitation in the body which may result in serious clinical outcomes (see CONTRAINDICATIONS).

Caution must be exercised in the administration of Lactated Ringer's and 5% Dextrose 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 and 5% Dextrose 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 and 5% Dextrose 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 and 5% Dextrose 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 a faster infusion rates should be used with caution in patients treated with digitalis glycosides. Caution is advised when administering Lactated Ringer's and 5% Dextrose Injection, USP to patients treated with thiazide diuretics or vitamin D, as these can increase the risk of hypercalcemia.

Caution is advised when administering Lactated Ringer's and 5% Dextrose Injection, USP to patients treated with drug 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 intravenous fluids. (See Warnings and Precautions and Adverse Reactions).

Drugs stimulating vasopressin release such as chlorpropamide, clofibrate, carbazepine, 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 and 5% Dextrose Injection, USP to patients treated with drugs that may increase the risk of hyponatremia, such as diuretics and antiepileptics (e.g., oxcarbazepine).

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 and 5% Dextrose Injection, USP is intended for intravenous administration using sterile and nonpyrogenic equipment. It is recommended that intravenous administration apparatus be replaced at least once every 24 hours. The infusion rate should not exceed the patient's ability to utilize glucose in order to avoid hyperglycemia. The infusion rate of intravenous solutions containing dextrose should be selected with caution in children (See SPECIAL POPULATIONS – PEDIATRICS).

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 and 5% Dextrose Injection, USP, aseptic technique must be used. Mix the solution thoroughly when additives have been introduced. Do not store solutions containing additives.

Ceftriaxone must not be mixed with calcium-containing solutions including Lactated Ringer's and 5% Dextrose Injection, USP. See also DRUG INTERACTIONS.

Additives may be incompatible with Lactated Ringer's and 5% Dextrose Injection, USP. Complete information is not available. Those additives known to be incompatible should 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. Before adding a substance or medication, verify that it is soluble and/or stable in water and that the pH range of Lactated Ringer's and 5% Dextrose Injection, USP is appropriate. After addition, check for a possible color change and/or the appearance of precipitates, particulate matter or crystals.

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.

OVERDOSAGE

An excessive volume or too high a rate of administration of Lactated Ringer's and 5% Dextrose 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.

Excessive administration of a dextrose-containing solution may lead to hyperglycemia, hyperosmolarity, osmotic diuresis, and dehydration.

When assessing overdose, any additives in the solution must also be considered.

Interventions include discontinuation of Lactated Ringer's and 5% Dextrose Injection, USP administration, dose reduction, administration of insulin and other measures as indicated for the specific clinical constellation.

Clinically significant overdose of Lactated Ringer's and 5% Dextrose Injection, USP may, therefore, constitute a medical emergency.

Dosage Form, Composition and Packaging

How Supplied

See Summary Product Information, Table 1 which shows the ionic composition, osmolarity, approximate pH and volume of Lactated Ringers and 5% Dextrose Injection, USP. The presence of the catalogue code number indicates that the injection is available in that size.

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.

Storage

Store between 15°C and 25°C.

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