Baxter

SIMPLIFY
YOUR ELECTROLYTE MANAGEMENT

Baxter Renal Replacement Solutions Guide

GET STARTED

SIMPLIFY

ELECTROLYTE MANAGEMENT WITH OUR COMPREHENSIVE PORTFOLIO OF CRRT SOLUTIONS

Ready to use

Premixed solutions may help minimize preparation time, waste, and potential for medication errors[1,2]

Flexible

Available in a wide range of bicarbonate buffered solutions with various ionic formulations

Self-sealing

All solutions are packaged in two-compartment bags with self-sealing luer lock capability

Modality-specific indications

We provide a wide range of replacement solutions specifically indicated for the on label delivery of CVVH and CVVHDF modalities

PHOXILLUM

MORE INFO

Renal Replacement Solution
1.0 mmol/L phosphate

The only FDA approved CRRT replacement solution that contains phosphate in a 5L bag, available in two formulations

PRISMASOL

MORE INFO

Renal Replacement Solution

FDA-approved renal replacement solution for use in CVVH or CVVHDF therapies, available in seven formulations

REGIOCIT

MORE INFO

Sodium Chloride and Sodium Citrate Solution
CRRT Replacement Solution

For hemofiltration and regional citrate anticoagulation (RCA during continuous renal replacement therapy (CRRT)

REGIOCIT solution has been authorized by FDA for emergency use. REGIOCIT solution is not FDA-approved. REGIOCIT solution has been authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of REGIOCIT solution under section 564(b)(1) of the Act, 21 U.S.C.

§ 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

1. Culley CM, et al. Implementing a standardized safety procedure for continuous renal replacement therapy solutions. *Am J Health Syst Pharm*. 2006 Apr 15;63(8):756-63. **2.** Barletta JF. Resource utilization and total cost of commercially available versus manually compounded solutions used for dialysate in continuous renal replacement therapy. *Hospital Pharmacy*. 2008;43:29-34.

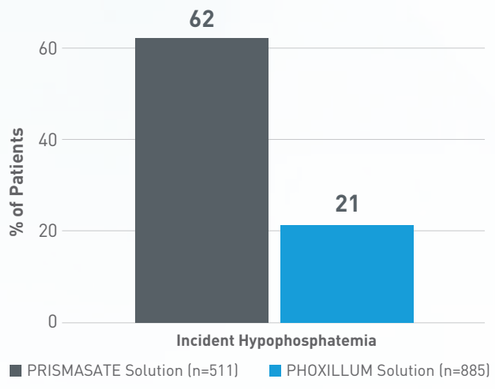
CRUSH HYPOPHOSPHATEMIA

PHOXILLUM solution is shown to reduce hypophosphatemia,[1] solution preparation time,[2,3] and potential for errors[4]* when treating acute kidney injury (AKI) patients.

REDUCE HYPOPHOSPHATEMIA WITH A PHOSPHATE-CONTAINING SOLUTION

Multiple studies around the globe have shown that phosphate-containing solutions reduce hypophosphatemia. In the largest evaluation of hypophosphatemia in critically ill patients requiring CRRT to date, data from 1,396 adult patients (single-center, retrospective, sequential period cohort) showed:[1]

- A significant and independent association between the use of a phosphate-containing solution and reduction in incident hypophosphatemia, duration of ICU stay and mechanical ventilation ($p < 0.001$)
- Use of non-phosphate solution was associated with an 8.5 fold increase in hypophosphatemia (OR 8.53, 95% CI 6.29-11.57, $p = 0.0001$)

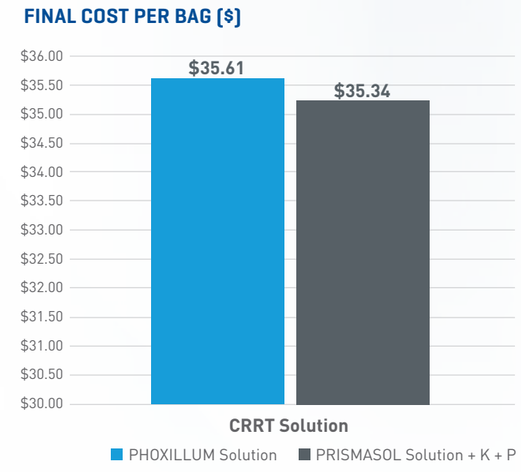


Adapted from Thompson Bastin et al. 2019;199:A5994
For more information on PRISMASATE Solution, please see enclosed IFU.

PRE-MIXED SOLUTIONS = LESS PREPARATION TIME WITHOUT NECESSARILY MORE EXPENSE

A study of CRRT solutions that included (1) PHOXILLUM solution with no electrolyte additives, (2) PHOXILLUM solution with added bicarbonate, and (3) PRISMASOL solution with added potassium chloride and sodium phosphate (control) showed:**

- **Significantly reduced average technician** time with the current PHOXILLUM bag design (45 sec. vs 179 sec with PRISMASOL solution, $p < 0.0001$ for both comparisons)[3]
- **Similar final costs** for PHOXILLUM and PRISMASOL solutions (Final costs included base solution, additives, supplies, and personnel per 5L bag)[2]



Adapted from Shaw AR, et al. *Am J Health Syst Pharm.* 2018.

Please see Important Risk Information. For more information, please see the enclosed full Prescribing Information. CLICK HERE

1. Thompson Bastin ML, Nerusu S, Adams P, Morris P, Neyra JA. Phosphorus-containing solutions reduce incident hypophosphatemia and associate with better outcomes in critically ill patients requiring continuous renal replacement therapy. *Am J Respir Crit Care Med.* 2019;199:A5994 **2.** Shaw AR, Chaijamorn W, Clark JS, Mueller BA. Preparation times and costs for various solutions used for continuous renal replacement therapy. *Am J Health Syst Pharm.* 2018;75(11):808-815. doi:10.2146/ajhp160741. **3.** Jang SM, Clark JS, Mueller BA. Update on preparation of solutions for continuous renal replacement therapy. *Am J Health Syst Pharm.* 2018;75(13):931-932. https://doi.org/10.2146/ajhp180172 **4.** Heung M, Mueller BA. Prevention of hypophosphatemia during continuous renal replacement therapy–An overlooked problem. *Semin Dial.* 2018;31(3):213-218. doi:10.1111/sdi.12677.

PHOXILLUM SOLUTION IS AVAILABLE IN TWO FORMULAS VARYING IN CALCIUM AND BICARBONATE.

		Calcium Formula	Calcium-Free Formula
	Plasma†	PHOXILLUM BK 4/2.5	PHOXILLUM B22K 4/0
Potassium K^+ (mEq/L)	3.5–5.0	4.0	4.0
Calcium Ca^{2+} (mEq/L)	2.3–2.6††	2.5	0
Magnesium Mg^{2+} (mEq/L)	1.4–2.0	1.5	1.5
Sodium Na^+ (mEq/L)	135–145	140	140
Chloride Cl^- (mEq/L)	100–108	114.5	122.0
Phosphate HPO_4^{2-} (mmol/L)	0.8-1.5	1.0	1.0
Bicarbonate HCO_3^- (mEq/L)	22–26	32	22
Lactate (mEq/L)	0.5–2.2	0	0
Dextrose (mg/dL)	70–110	0	0
Osmolarity (mOsm/L)	280–296	294	290
NDC Number		24571-116-05	24571-117-05
Catalog Number		114905	114906

†Luca, Bigatello M. et al. Critical Care Handbook of the Massachusetts General Hospital, 4th Edition, 2006.
††Ionized Calcium

*Due to manual compounding
** Please note that the only approved additives are:
PHOXILLUM Solution: phosphate up to 0.2 mmol/L sodium phosphate not to exceed 1.2 mmol/L.
PRISMASOL Solution: up to 1.2 mmol/L of phosphate added as potassium phosphate or sodium phosphate.
Total potassium should not exceed 4 mEq/L.

PHOXILLUM AND **PRISMASOL** RENAL REPLACEMENT SOLUTION

Indications and Important Risk Information

Indications

PRISMASOL and PHOXILLUM solutions are indicated in pediatric and adult patients for use as a replacement solution in Continuous Renal Replacement Therapy (CRRT) to replace plasma volume removed by ultrafiltration and to correct electrolyte and acid-base imbalances. They may also be used in case of drug poisoning when CRRT is used to remove dialyzable substances.

Important Risk Information

PHOXILLUM and PRISMASOL replacement solutions are contraindicated in patients with known hypersensitivities to these products.

- PHOXILLUM and PRISMASOL solutions can affect electrolytes and volume and may result in hyperkalemia or hyperphosphatemia. Monitor hemodynamic status and fluid inputs and outputs, potassium, phosphorous, calcium, other electrolytes and acid-base balance throughout the procedure.
- PHOXILLUM replacement solutions contain hydrogen phosphate, a weak acid that may increase the risk of metabolic acidosis.
- PRISMASOL and PHOXILLUM replacement solutions can affect blood glucose levels resulting in hypo- or hyper-glycemia depending upon the dextrose content of the replacement solution. Monitor blood glucose levels regularly.
- The following adverse reactions have been identified during post-approval use with these or other similar products and therefore may occur with use of PHOXILLUM or PRISMASOL: Metabolic acidosis, hypotension, acid-based disorders, electrolyte imbalances including calcium ionized increased, hyperphosphatemia, hypophosphatemia, fluid imbalance.

For more information, please see accompanying Full Prescribing Information for PRISMASOL and PHOXILLUM solutions or visit baxterpi.com.

For full Prescribing Information CLICK HERE

THE POWER OF 7

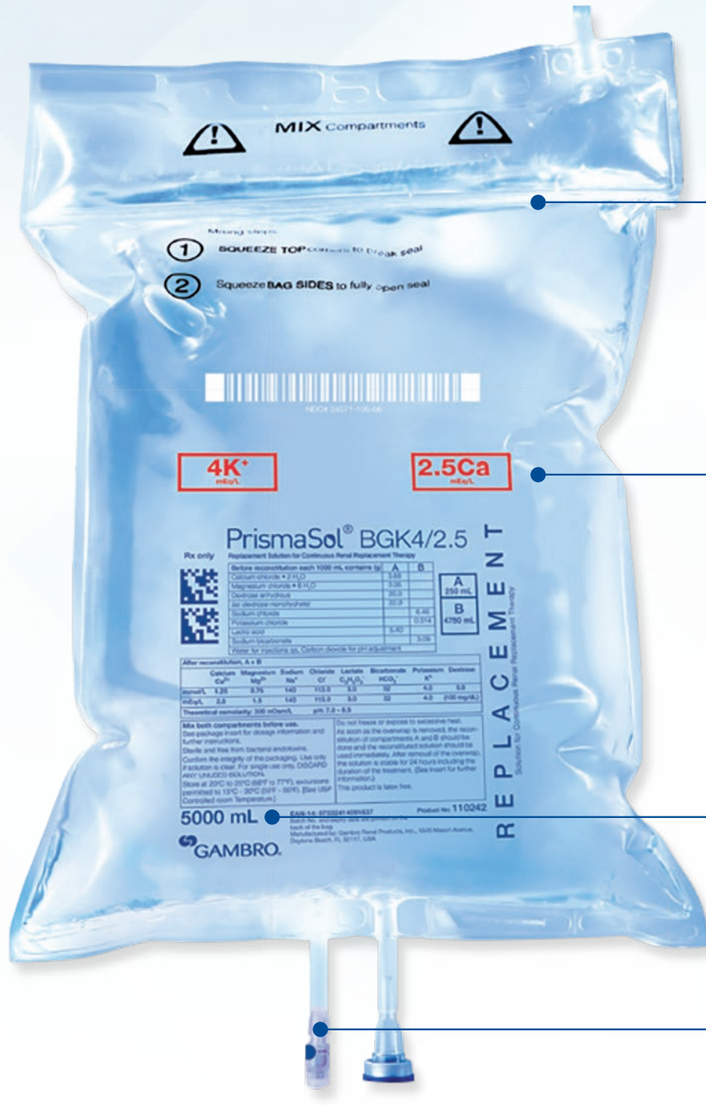
PRISMASOL SOLUTION IS AVAILABLE IN SEVEN FORMULATIONS FOR INDIVIDUALIZED PATIENT THERAPY

Provides the physician with a range of choices in response to each patient's specific condition.

Designed to correct acid-base imbalances with pre-mixed formula selections varying in calcium, potassium, bicarbonate and dextrose levels, including calcium and calcium-free formulas.

MAY REDUCE THE NEED FOR SOME ELECTROLYTE/ADDITIVE REPLACEMENTS:

- Bicarbonate
- Sodium
- Magnesium
- Dextrose
- Chloride
- Calcium
- Potassium



Press seal for easier mixing

Enhanced labeling for easy identification

Available as a 5 Liter bag that may help reduce downtime

Luer lock

Please see Important Risk Information. For more information, please see the enclosed full Prescribing Information. CLICK HERE

1000 ML OF THE RECONSTITUTED PRISMASOL SOLUTION CONTAINS (IN MEQ/L EXCEPT WHERE NOTED):

		Calcium Formula			Calcium-Free Formula			Dextrose-Free
	Plasma*	PRISMASOL BGK 4/2.5	PRISMASOL BGK 2/3.5	PRISMASOL BGK 0/2.5	PRISMASOL BGK 4/0/1.2	PRISMASOL BGK 2/0	PRISMASOL B22GK 4/0	PRISMASOL BK 0/0/1.2
Potassium K^+ (mEq/L)	3.5–5.0	4	2	0	4	2	4	0
Calcium Ca^{2+} (mEq/L)	2.3–2.6†	2.5	3.5	2.5	0	0	0	0
Magnesium Mg^{2+} (mEq/L)	1.4–2.0	1.5	1	1.5	1.2	1	1.5	1.2
Sodium Na^+ (mEq/L)	135–145	140	140	140	140	140	140	140
Chloride Cl^- (mEq/L)	100–108	113	111.5	109	110.2	108	120.5	106.2
Bicarbonate HCO_3^- (mEq/L)	22–26	32	32	32	32	32	22	32
Lactate (mEq/L)	0.5–2.2	3	3	3	3	3	3	3
Dextrose (mg/dL)	70–110	100	100	100	100	100	100	0
Osmolarity (mOsm/L)	280–296	300	296	292	295	291	296	282
NDC Number		24571-105-06	24571-103-06	24571-108-06	24571-114-06	24571-102-06	24571-111-06	24571-113-06
Catalog Number		110242	110243	110240	110241	110244	115001	110239

* Luca, Bigatello M. et al. Critical Care Handbook of the Massachusetts General Hospital, 4th Edition, 2006.
†Ionized Calcium

PHOXILLUM AND **PRISMASOL** RENAL REPLACEMENT SOLUTION

Indications and Important Risk Information

Indications

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- PHOXILLUM and PRISMASOL solutions can affect electrolytes and volume and may result in hyperkalemia or hyperphosphatemia. Monitor hemodynamic status and fluid inputs and outputs, potassium, phosphorous, calcium, other electrolytes and acid-base balance throughout the procedure.
- PHOXILLUM replacement solutions contain hydrogen phosphate, a weak acid that may increase the risk of metabolic acidosis.
- PRISMASOL and PHOXILLUM replacement solutions can affect blood glucose levels resulting in hypo- or hyper-glycemia depending upon the dextrose content of the replacement solution. Monitor blood glucose levels regularly.
- The following adverse reactions have been identified during post-approval use with these or other similar products and therefore may occur with use of PHOXILLUM or PRISMASOL: Metabolic acidosis, hypotension, acid-based disorders, electrolyte imbalances including calcium ionized increased, hyperphosphatemia, hypophosphatemia, fluid imbalance.

For more information, please see accompanying Full Prescribing Information for PRISMASOL and PHOXILLUM solutions or visit baxterpi.com.

For full Prescribing Information CLICK HERE

EMERGENCY USE AUTHORIZATION GRANTED FOR

REGIOCIT SOLUTION

REGIOCIT (sodium chloride and sodium citrate) solution is indicated for use as replacement solution for regional citrate anticoagulation (RCA) of the extracorporeal circuit in patients treated with continuous renal replacement therapy (CRRT), particularly when systemic anticoagulation with heparin is contraindicated, e.g., in patients with increased bleeding risks.

Available as a 5 Liter bag that may help reduce downtime

valve and spike connector options

"We are very excited to offer REGIOCIT to our patients, especially during the coronavirus pandemic. REGIOCIT could be a contributor to helping to improve continuous dialysis, known as Continuous Renal Replacement Therapy (CRRT), for COVID-19 patients. These patients often have high inflammatory syndrome with Cytokine storm leading to continual filter clogging. REGIOCIT is a dilute citrate commercial solution which provides regional anticoagulation (to CRRT machine) without causing systemic bleeding complications to a patient. With anticoagulation limited to the circuit specifically, we hope to see improvements in circuit life and overall treatment duration in patients with coagulation abnormalities such as what has been seen in COVID-19 patients. This can possibly extend 'continual therapy' time and could impact filter life and staff time. REGIOCIT has undergone rigorous study abroad, and will allow us more options to provide care for our patients requiring continuous dialysis (CRRT)."

Ashita Tolwani, MD

Professor, Division of Nephrology at the University of Alabama at Birmingham School of Medicine, who first developed the solution in 2004.

REGIOCIT has been authorized by FDA for emergency use. REGIOCIT is not FDA-approved. REGIOCIT is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of REGIOCIT under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner. The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product, REGIOCIT: a replacement solution that contains citrate for Regional Citrate Anticoagulation (RCA) of the extracorporeal circuit. REGIOCIT has been authorized for emergency use as a replacement solution in adult patients treated with Continuous Renal Replacement Therapy (CRRT), and for whom RCA is appropriate, during the COVID-19 pandemic. REGIOCIT is intended for use in a critical care setting. REGIOCIT is intended to be used in continuous venovenous hemofiltration (CVVH) and continuous venovenous hemodiafiltration (CVVHDF) modalities. Use of REGIOCIT is limited to healthcare providers and/or institutions that Baxter has qualified to administer REGIOCIT for these emergency uses.

Please see Important Risk Information. For more information, please see the enclosed full Prescribing Information. CLICK HERE

Indication and Important Risk Information

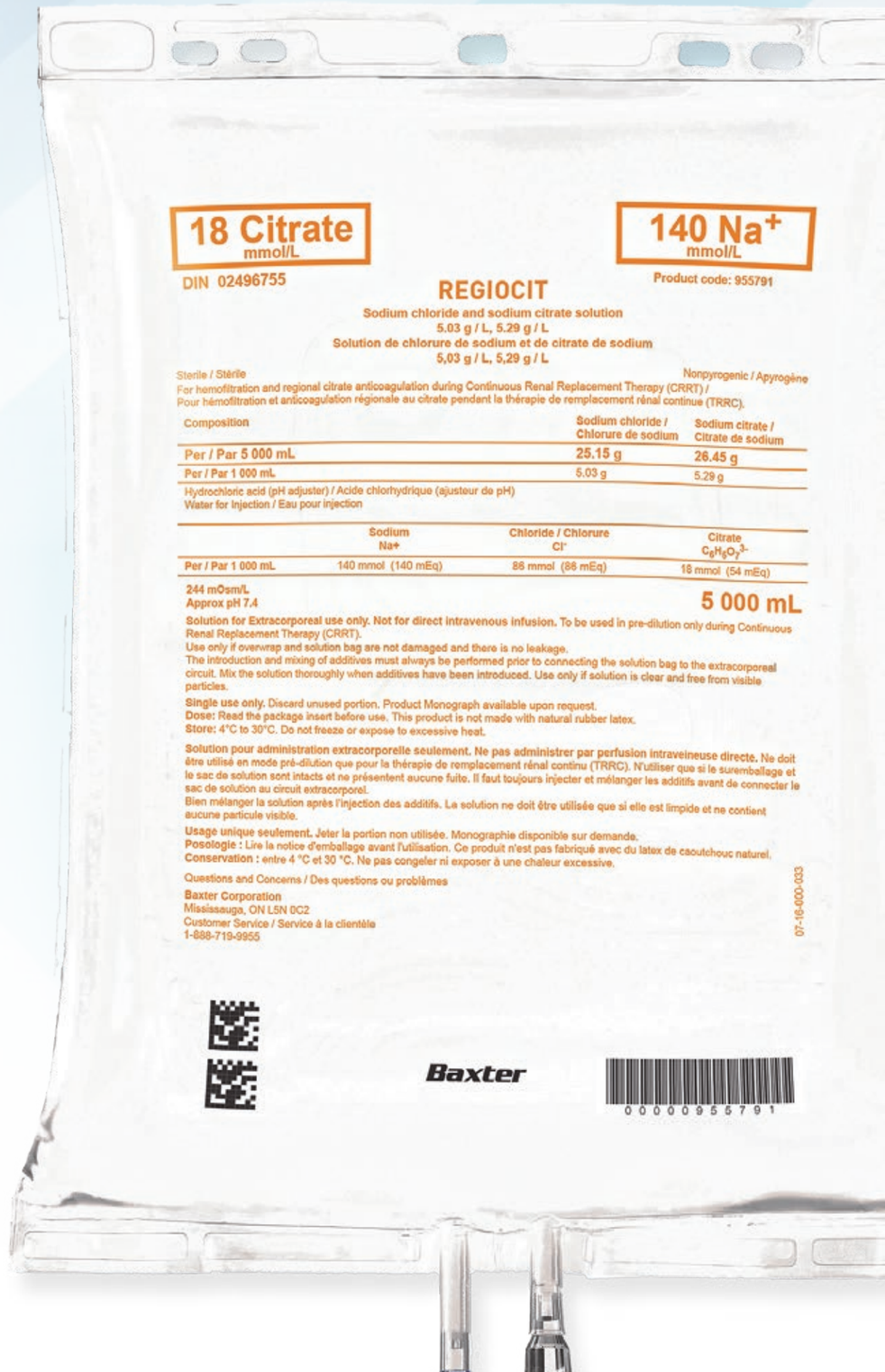
INDICATIONS

REGIOCIT (sodium chloride and sodium citrate) solution is indicated for use as replacement solution for regional citrate anticoagulation (RCA) of the extracorporeal circuit in adults treated with continuous renal replacement therapy (CRRT), particularly when systemic anticoagulation with heparin is contraindicated, e.g., in patients with increased bleeding risks.

IMPORTANT RISK INFORMATION

- REGIOCIT solution is contraindicated in patients with severe liver failure, shock with muscle hypoperfusion and those who are hypersensitive to this drug, any ingredients (including non-medicinal ingredients), formulation or component of the container.
- **There have been reports of system failure due to apparent operator error during administration of CRRT with REGIOCIT solution, leading to serious adverse events, including life-threatening hypocalcemia. Plasma electrolyte and acid-base parameters should be closely monitored during CRRT.**
- Special attention is required in patients with liver failure, including hepatic cirrhosis or acute hepatic failure, or in shock, as patients may be exposed to citrate accumulation. Systemic metabolism of citrate to bicarbonate may be impaired in patients with hepatic impairment and can result in metabolic acidosis and ionized hypocalcemia.
- Medicinal products containing calcium used for maintenance of calcium homeostasis in CRRT patients can increase the risk of hypercalcemia and can result in a reduced anticoagulation effect.
- Use of the REGIOCIT solution may result in hypomagnesemia due to CRRT effluent losses, hypoglycemia, or hypokalemia.
- Additional sodium bicarbonate (or buffer source) contained in the CRRT fluids or in other fluids administered during therapy may increase the risk of metabolic alkalosis. Metabolic acidosis may occur if metabolic clearance of citrate by the liver or skeletal muscle is impaired.
- REGIOCIT solution should be used with caution in patients with traumatic brain injury, cerebral edema, or increased intracranial pressure.
- Plasma electrolyte and acid-base parameters should be closely monitored during CRRT. Closely monitor sodium, magnesium, potassium, phosphate, calcium, blood glucose levels, hematocrit, hemodynamic status and fluid balance, pH, bicarbonate, total-to-ionized calcium ratio, and systemic ionized calcium. Infusion of electrolytes may be needed to supplement any loss.
- Adverse Reactions - Hypotension, hypocalcemia, other electrolyte imbalances (hypomagnesemia, hypokalemia, hypophosphatemia), acid base balance disorders (including metabolic alkalosis, metabolic acidosis), hypoglycemia, fluid imbalance

For full Prescribing Information CLICK HERE



HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PRISMASOL and PHOXILLUM safely and effectively.
See full prescribing information for PRISMASOL and PHOXILLUM.

PRISMASOL renal replacement solution
PRISMASOL Initial U.S. Approval: 2006

PHOXILLUM renal replacement solution
PHOXILLUM Initial U.S. Approval: 2015

----------INDICATIONS AND USAGE----------
PRISMASOL and PHOXILLUM solutions are indicated:

- As a replacement solution in Continuous Renal Replacement Therapy (CRRT) and in case of drug poisoning when CRRT is used to remove dialyzable substances (1)

----------DOSAGE AND ADMINISTRATION----------

- Therapy must be individualized based on the patient's clinical condition, fluid, electrolyte, acid-base and glucose balance (2.2)
- Solution must be mixed prior to use (2.2)
- Use only with extracorporeal dialysis equipment appropriate for CRRT (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
PRISMASOL and PHOXILLUM are available in multiple combinations of ingredients and in multiple variations of strengths. See full Prescribing Information for detailed descriptions of each formulation. (2, 3, 11)

----------CONTRAINDICATIONS----------

- Known hypersensitivities to PRISMASOL and PHOXILLUM solutions (4)

---------- WARNINGS AND PRECAUTIONS----------

- Monitor hemodynamic status and fluid inputs and outputs, potassium, phosphorus, other electrolytes and acid-base balance. Abnormalities may be corrected by the use of appropriate formulations and dosage of PRISMASOL and PHOXILLUM solutions (5.1)
- Treatment may affect glucose levels. Monitor blood glucose levels. Antidiabetic therapy adjustment or other corrective measures may be required during treatment (5.2)

To report SUSPECTED ADVERSE REACTIONS, contact Baxter Healthcare Corporation at 1-866-888-2472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

Revised: 11/2018

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

PRISMASOL and PHOXILLUM solutions are indicated in pediatric and adult patients for use as a replacement solution in Continuous Renal Replacement Therapy (CRRT) to replace plasma volume removed by ultrafiltration and to correct electrolyte and acid-base imbalances. They may also be used in case of drug poisoning when CRRT is used to remove dialyzable substances.

2 DOSAGE AND ADMINISTRATION

2.1 Administration Instructions

Visually inspect PRISMASOL and PHOXILLUM for particulate matter and discoloration prior to administration.

Administration should only be under the direction of a physician competent in intensive care treatment including CRRT. Use only with extracorporeal dialysis equipment appropriate for CRRT.

The prepared solution is for single patient use only.

Aseptic technique should be used throughout administration to the patient.

Discard any unused solution.

2.2 Dosing Considerations

PRISMASOL replacement solutions contain 4 different combinations of active ingredients (7 different products with varying ingredient amounts). PHOXILLUM replacement solutions contain 2 different combinations of active ingredients (2 different products with varying ingredient amounts). PRISMASOL and PHOXILLUM are supplied in a two-compartment bag that must be mixed immediately prior to use *[see Dosage and Administration (2.3)]:*

- Small compartment A (250 mL) containing an electrolyte solution, and
- Large compartment B (4750 mL) containing the buffer solution.

See **Table 1** for the concentrations of the active ingredients (after mixing) in these 9 different replacement solutions (total volume is 5 Liters).

Table 1: Concentrations of Active Ingredients in the 7 PRISMASOL and 2 PHOXILLUM Replacement Solutions after Mixing

	Ca^{2+} mEq/L	HCO_3^- mEq/L	K^+ mEq/L	Mg^{2+} mEq/L	Na^+ mEq/L	HPO_4^{2-} mmol/L	Cl^- mEq/L	Lactate mEq/L	Dextrose mg/dL	Osmolarity mOsm/L
PRISMASOL Replacement Solutions										
BGK0/2.5	2.5	32	0	1.5	140	0	109	3	100	292
BGK4/2.5	2.5	32	4	1.5	140	0	113	3	100	300
BGK2/3.5	3.5	32	2	1	140	0	111.5	3	100	296
BGK2/0	0	32	2	1	140	0	108	3	100	291
B22GK4/0	0	22	4	1.5	140	0	120.5	3	100	296
BGK4/0/1.2	0	32	4	1.2	140	0	110.2	3	100	295
BK0/0/1.2	0	32	0	1.2	140	0	106.2	3	0	282
PHOXILLUM Replacement Solutions										
BK4/2.5	2.5	32	4	1.5	140	1	114.5	0	0	294
B22K4/0	0	22	4	1.5	140	1	122	0	0	290

Ca^{2+} = calcium, HCO_3^- = bicarbonate, K^+ = potassium, Mg^{2+} = magnesium, Na^+ = sodium, HPO_4^{2-} = phosphate, Cl- = chloride; osmolarity is estimated

The mode of therapy, solute formulation, flow rates, and length of PRISMASOL and PHOXILLUM replacement therapy in CRRT should be established by a physician based on the patient's clinical condition, blood concentration of phosphate and other electrolytes, acid-base and glucose balance. Administer either PRISMASOL or PHOXILLUM into the extracorporeal circuit:

- Before (pre-dilution) the hemofilter or hemodiafilter,
- After (post-dilution) the hemofilter or hemodiafilter, or
- Before and after the hemofilter or hemodiafilter.

2.3 Preparing the Solution

Use only if the overwrap is not damaged, all seals are intact, peel seal is not broken, and the solution is clear.

The solution may be warmed to 37°C/98.6°F prior to removing the overwrap to enhance patient comfort. However, only dry heat should be used. Solutions should not be heated in water or in a microwave oven. After heating, verify that the solution remains clear and contains no particulate matter.

The solutions are supplied in two different two-compartment bags made of polyolefin with a peel seal separating compartment A and B (**see Figure 1**).

Follow the instructions below when connecting the solution bags for correct use of the access ports.

Instructions for preparing solutions supplied in a two-compartment, polyolefin bag with a peel seal:

Figure 1

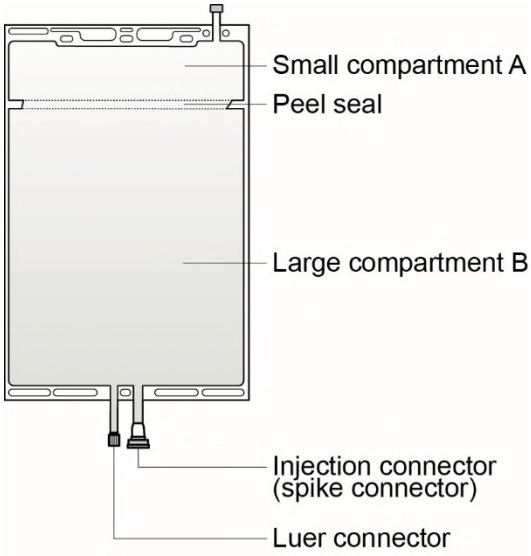


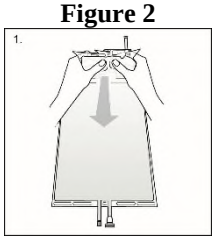
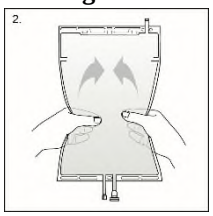
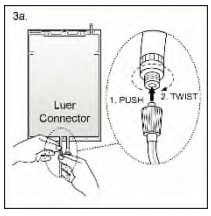
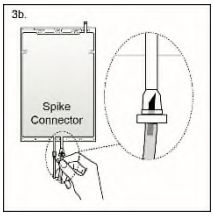
Figure 2 	**Step 1** Immediately before use, remove the overwrap from the bag and mix the solutions in the two different compartments. After removing the overwrap, inspect the bag for leakage by pressing firmly on the bag. Discard the bag if any leakage is detected since sterility cannot be assured. As soon as the overwrap is removed, the reconstitution of compartments A and B should be done and the mixed solution should be used immediately. After removal of the overwrap, the solution is stable for 24 hours including the duration of the treatment. Hold the small compartment with both hands and squeeze it until an opening is created in the peel seal. (See **Figure 2** beside)
Figure 3 	**Step 2** Squeeze with both hands on the large compartment until the peel seal between the two compartments is entirely open. Shake gently to mix. (See **Figure 3** beside) The solution is now ready to use and the bag can be hung on the equipment.
Figure 4a 	**Step 3** The replacement line may be connected to the bag through either of the luer connector or the injection connector (spike connector). **Step 3a** The luer connector is a needle-less and swabbable connector. Remove the cap with a twist and pull motion, and connect the male luer lock on the replacement line to the female luer receptor on the bag. (See **Figure 4a** beside) Ensure that the connection is fully seated and tighten. The connector is now open. Verify that the fluid is flowing freely during use. When the replacement line is disconnected from the luer connector, the connector will close and the flow of the solution will stop.

Figure 4b	
	**Step 3b** If the injection connector (spike connector) is used, first remove the snap-off cap. Then introduce the replacement line spike through the rubber septum of the bag connector. (See **Figure 4b** beside) Ensure that the spike is fully inserted and verify that the fluid is flowing freely during use.

2.4 Adding Drugs to the Solutions

After mixing, additional drugs may be added to the bag via injection connector (spike connector) in large compartment B. In general, administer drugs other than phosphate through a different access line.

When introducing drugs, use aseptic techniques and mix thoroughly prior to connecting the solution bag to the extracorporeal circuit.

Do not use if there is a color change and/or the appearance of precipitates, insoluble complexes or crystals after addition of medication.

Phosphate: Up to 1.2 mmol/L of phosphate can be added to the bag as potassium phosphate or sodium phosphate. The total potassium concentration of PRISMASOL solution should not exceed 4 mEq/L. Use sodium phosphate to add phosphate if the total potassium concentration in PRISMASOL solution is 4 mEq/L.

PHOXILLUM Solutions:
Phosphate: Phosphate up to 0.2 mmol/L may be added to the solution. Use sodium phosphate if adding phosphate to bag. The total phosphate concentration should not exceed 1.2 mmol/L.

3 DOSAGE FORMS AND STRENGTHS

See **Table 1** for the concentrations of the active ingredients (after mixing) in these 9 different replacement solutions *[see Dosage and Administration (2.2)]***.**

4 CONTRAINDICATIONS

PHOXILLUM and PRISMASOL replacement solutions are contraindicated in patients with known hypersensitivities to these products.

5 WARNINGS AND PRECAUTIONS

5.1 Electrolyte and Volume Abnormalities

PHOXILLUM and PRISMASOL solutions can affect electrolytes and volume and may result in hyperkalemia or hyperphosphatemia. Monitor hemodynamic status and fluid inputs and outputs, potassium, phosphorous, calcium, other electrolytes and acid-base balance throughout the procedure. Abnormalities may be corrected by changing the formulation of replacement solution and/or dialysate, supplementation, or adjusting flow rates appropriately [*see Dosage and Administration (2)*].

PHOXILLUM replacement solutions contain hydrogen phosphate, a weak acid that may increase the risk of metabolic acidosis.

5.2 Blood Glucose Abnormalities

The use of PRISMASOL and PHOXILLUM replacement solutions can affect blood glucose levels resulting in hypo- or hyper-glycemia depending upon the dextrose content of the replacement solution. Monitor blood glucose levels regularly. Patients may require initiation of or modification of antidiabetic therapy or othercorrective measures during treatment.

6 ADVERSE REACTIONS

The following adverse reactions have been identified during postapproval use with these or other similar products and therefore may occur with use of PHOXILLUM or PRISMASOL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Metabolic acidosis
- Hypotension
- Acid-base disorders
- Electrolyte imbalance including calcium ionized increased (reported in PRISMASOL solutions containing calcium), hyperphosphatemia, and hypophosphatemia
- Fluid imbalance

7 DRUG INTERACTIONS

As with the use of other replacement solutions, blood concentrations of dialyzable drugs may be reduced by CRRT due to their removal by the hemofilter or hemodiafilter. The blood concentrations of certain drugs may need to be monitored and appropriate therapy implemented to correct for removal during treatment.

7.1 Citrate

When used as an anticoagulant, citrate contributes to the overall buffer load and can reduce plasma calcium levels. Select the PRISMASOL/PHOXILLUM formulation(s) accordingly.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

PRISMASOL and PHOXILLUM are pharmacologically inactive solutions. While there are no adequate and well controlled studies in pregnant women, appropriate administration of PRISMASOL and PHOXILLUM solutions with monitoring of fluid, electrolyte, acid-base and glucose balance, is not expected to cause fetal harm. Animal reproduction studies have not been conducted with PRISMASOL and PHOXILLUM solutions.

The estimated background risk of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Maintenance of normal acid-base balance is important for fetal well-being.

8.2 Lactation

Risk Summary

The components of PRISMASOL and PHOXILLUM solutions are excreted in human milk. Appropriate administration of PRISMASOL and PHOXILLUM solutions with monitoring of fluid, electrolyte, acid-base and glucose balance, is not expected to harm a nursing infant.

8.4 Pediatric Use

Safety and effectiveness have been established based on published clinical data of CRRT replacement solutions with compositions similar to PRISMASOL and PHOXILLUM used in adults and two hemofiltration studies in pediatric patients, including a study of newborns to 17 years old.

8.5 Geriatric Use

The experience with PRISMASOL and PHOXILLUM solutions in geriatric patients has not identified novel concerns.

11 DESCRIPTION

PRISMASOL and PHOXILLUM solutions are clear, sterile, free of bacterial endotoxins and contain no bacteriostatic or antimicrobial agents. These solutions are used in Continuous Renal Replacement Therapies (CRRT) as a replacement solution in hemofiltration and hemodiafiltration. Depending on the product (see **Table 2**), the two compartments contain:

Calcium chloride, USP, is chemically designated calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$).
Magnesium chloride, USP, is chemically designated magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$).
Sodium chloride, USP, is chemically designated NaCl.
Potassium chloride, USP, is chemically designated KCl.
Sodium bicarbonate, USP, is chemically designated $NaHCO_3$.
Dextrose, USP, is chemically designated D-Glucose anhydrous ($C_6H_{12}O_6$) or D-Glucose monohydrate ($C_6H_{12}O_6 \cdot H_2O$).
Lactic acid, USP, is chemically designated $CH_3CH(OH)COOH$.
Dibasic sodium phosphate, USP, is chemically designated as disodium hydrogen phosphate, dihydrate ($Na_2HPO_4 \cdot 2H_2O$)

Table 2 – Compartment Composition (Before Mixing)

	Compartment A (g/L)				Compartment B (g/L)			
	Calcium Chloride • $2H_2O$	**Magnesium Chloride • $6H_2O$**	**Dextrose anhydrous (as monohydrate)**	**Lactic Acid**	**Sodium Chloride**	**Sodium bicarbonate**	**Potassium Chloride**	**Sodium Phosphate • $2H_2O$**
PRISMASOL SOLUTIONS								
BGK 0/2.5	3.68	3.05	20 (22)	5.40	6.46	3.09	0	0
BGK 4/2.5	3.68	3.05	20 (22)	5.40	6.46	3.09	0.314	0
BGK 2/3.5	5.15	2.03	20 (22)	5.40	6.46	3.09	0.157	0
BGK 2/0	0	2.03	20 (22)	5.40	6.46	3.09	0.157	0
B22GK 4/0	0	3.05	20 (22)	5.40	7.07	2.21	0.314	0
BK 0/0/1.2	0	2.44	0 (0)	5.40	6.46	3.09	0	0
BGK 4/0/1.2	0	2.44	20 (22)	5.40	6.46	3.09	0.314	0
PHOXILLUM SOLUTIONS								
BK 4/2.5	3.68	3.05	0 (0)	0	6.34	3.09	0.314	0.187
B22K 4/0	0	3.05	0 (0)	0	6.95	2.21	0.314	0.187

The pH of the final solution is in the range of 7.0 to 8.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

PRISMASOL and PHOXILLUM solutions are pharmacologically inactive. The electrolyte concentrations in the solutions are chosen to restore plasma levels to clinically desired concentrations or maintain plasma

levels at the desired concentrations.

PRISMASOL and PHOXILLUM solutions are used as replacement solution to replace water and electrolytes removed during hemofiltration and hemodiafiltration. Bicarbonate (or precursor lactate) in the solution is used as an alkalinizing buffer to restore acid-base balance to a clinically desirable level.

12.3 Pharmacokinetics

The distribution of electrolytes, bicarbonate, and dextrose is determined by the patient's clinical condition, metabolic status, and residual renal function.

The elimination and replacement of water, electrolytes and buffer depend on the patient's electrolyte and acid-base balance, metabolic status, residual renal function and ongoing physiologic losses through intestinal, respiratory and cutaneous routes.

16 HOW SUPPLIED/STORAGE AND HANDLING

PRISMASOL and PHOXILLUM solutions are supplied in a two-compartment bag made of polyolefin. The 5000 mL bag is composed of a small compartment (250 mL) and a large compartment (4750 mL). The two compartments are separated by a peel seal.

The bag is overwrapped with a transparent overwrap. See **Table 2** for the concentrations of the active ingredients in each compartment for each product *[see Description (11)]*.

Container	Fill Volume	NDC
PRISMASOL Solutions		
PRISMASOL BGK0/2.5	5000 mL	24571-108-06
PRISMASOL BGK4/2.5	5000 mL	24571-105-06
PRISMASOL BGK2/3.5	5000 mL	24571-103-06
PRISMASOL BGK2/0	5000 mL	24571-102-06
PRISMASOL B22GK4/0	5000 mL	24571-111-06
PRISMASOL BK0/0/1.2	5000 mL	24571-113-06
PRISMASOL BGK4/0/1.2	5000 mL	24571-114-06
PHOXILLUM Solutions		
PHOXILLUM BK4/2.5	5000 mL	24571-116-06
PHOXILLUM B22K4/0	5000 mL	24571-117-06

Not all formulations may be marketed.

Storage conditions

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15ºC to 30ºC (59ºF to 86ºF). *[See USP Controlled Room Temperature]*
Do not freeze or expose to excessive heat. Do not use if precipitate has formed or if container seals have been damaged.

Manufactured for:
Baxter Healthcare Corporation
One Baxter Parkway
Deerfield, Illinois 60015

07-19-00-0408

PrismaSATE®

PRISMASATE® DIALYSIS SOLUTION FOR CONTINUOUS RENAL REPLACEMENT THERAPY

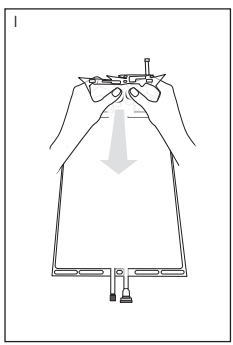
READ ALL OF THIS LEAFLET CAREFULLY BEFORE YOU START USING THIS SOLUTION

Keep this leaflet. You may need to read it again.

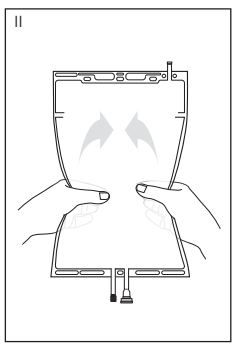
INSTRUCTION FOR USE / HANDLING:

The product is presented in a two-compartment bag separated by a peel seal. Aseptic technique should be used throughout the administration to the patient. Use only if the solution is clear, all seals are intact and the overwrap is undamaged. All seals, including the peel seal between the two compartments must be intact. If leakage is discovered, discard the solution immediately since sterility can no longer be assured. Not for direct infusion.

MIXING

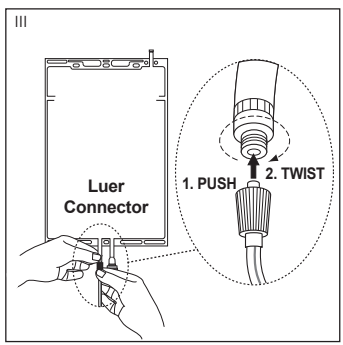


I Immediately before use, remove the overwrap from the bag and mix the solutions in the two different compartments. Hold the small compartment with both hands and squeeze it until an opening is created in the peel seal.



II Squeeze with both hands on the large compartment until the peel seal between the two compartments is entirely open. Shake gently to mix.
The solution is now ready for use and can be hung on the equipment.

CONNECTING



The dialysate line may be connected to bag through either the luer or the spike connector.

III The **luer connector** is a needle-less and swabbable connector.

Remove the cap with a twist and pull motion, and connect the male luer lock on the dialysate line to the female luer receptor on the bag. Ensure that the connection is fully seated and tighten. The connector is now open. Verify that the fluid is flowing freely during use.
When the dialysate line is disconnected from the luer connector, the connector will close and the flow of the solution will stop.

If the **spike connector** is used, first remove the snap-off cap. Then introduce the dialysate line spike through the rubber septum of the bag connector. Ensure that the spike is fully inserted and verify that the fluid is flowing freely.

The reconstituted solution should be used up within 24 hours of removing the overwrap. The reconstituted solution is for single use only. Discard any unused solution immediately after use.
During treatment, hemodynamic status, fluid balance, electrolyte and acid-base balance should be closely monitored throughout the procedure.

WHAT DOES PRISMASATE SOLUTION CONTAIN?

The product is presented in a two compartment bag containing in the smaller compartment A, an electrolyte solution, and in the larger compartment B, a buffer solution. Solution formulations for each compartment are listed on the bag.

The final reconstituted solution is obtained after breaking the peel seal between the two compartments and mixing both solutions. Refer to bag labeling for composition of the final reconstituted solution.

PACKAGING:

2 bags at 5000 mL each per case.

WHAT IS PRISMASATE SOLUTION AND WHAT IS IT USED FOR?

The product is a sterile dialysis solution intended for treatment of acute kidney disease (renal failure) using Continuous Renal Replacement Therapies, such as continuous hemodialysis and hemodiafiltration aimed at normalizing the composition of the blood.

The product is a sterile solution packaged in a two-compartment bag. The electrolyte solution (in the small compartment A) must be mixed with the buffer solution (in the large compartment B) before use to obtain the final solution suitable for the treatment.

The product may also be used in case of drug poisoning with dialyzable or filterable substances.

The product should only be used by or under the prescription and direction of a physician competent in intensive care treatment using Continuous Renal Replacement Therapy.

Federal Law (USA) restricts this device to sale by or on the order of a physician.

WHAT SIDE EFFECTS CAN PRISMASATE SOLUTION CAUSE?

When continuous hemodialysis and hemodiafiltration are performed correctly, side effects are uncommon.

Some side effects may occur, including nausea, vomiting, muscle cramps and low blood pressure (hypotension).

STORAGE AND EXPIRY DATE

Do not store below +4°C/39°F.

Do not use after the expiry date shown on the label and the packaging.

From a chemical point of view, once the overwrap is removed, the product should be used immediately. Stability of the product after removal of the overwrap is 24 hours including the time of treatment. Other in-use storage times and conditions are the responsibility of the user.

This product is not made with natural rubber latex.

Date of issue: 2015-11-05

GAMBRO®

Baxter Healthcare Corporation, One Baxter Parkway, Deerfield, IL, 60015, United States of America

PrismaSATE®

PRISMASATE® SOLUCIÓN DE DIÁLISIS PARA LA TERAPIA DE SUSTITUCIÓN RENAL CONTINUA

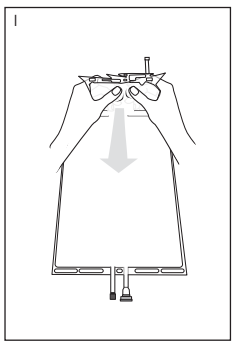
LEA DETENIDAMENTE TODO EL FOLLETO ANTES DE USAR LA SOLUCIÓN

Conserve este folleto ya que es posible que necesite repasarlo.

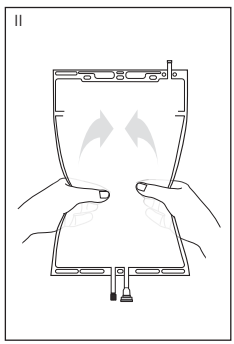
MODO DE EMPLEO Y MANIPULACIÓN DEL PRODUCTO:

El producto se ofrece en una bolsa de doble compartimento separado por un sello adhesivo. Una técnica aséptica deber ser utilizada durante la administración de la solución al paciente. Utilizar sólo si la solución es transparente, todos los sellos están intactos y la envoltura está intacta. Todos los sellos incluyendo el sello adhesivo entre los dos compartimentos deben estar intactos. Si descubriera alguna fuga, deseche la solución de inmediato, dado que, en ese caso, la esterilidad de la solución no estaría asegurada. No es para infusion directa.

MEZCLANDO

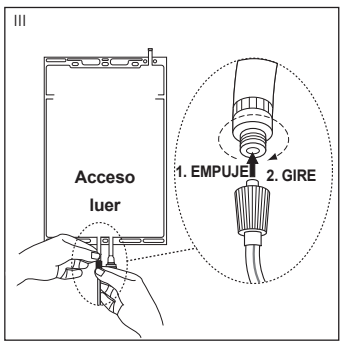


I Quite la envoltura externa de la bolsa inmediatamente antes de usarla y mezcle las soluciones de los dos compartimentos. Sostenga el compartimento pequeño con ambas manos y oprima las esquinas hasta que una abertura se haya formado en el sello adhesivo.



II Oprima con ambas manos en el compartimento grande hasta que el sello adhesivo entre los dos compartimentos se abra completamente. Agite delicadamente para mezclar la solución de ambos compartimentos. La solución esta lista para ser utilizada y puede colgarse del equipo.

CONECTANDO



La línea de dializado puede ser conectada a la bolsa a través del acceso luer o el conector de inyección.

III El **acceso luer** es un conector sin aguja y limpiable.

Gire y jale el tapón para retirarlo, y conecte el conector masculino de la vía de dializado al conector hembra en la bolsa. Confirme que la conexión este asegurada. El conector estará abierto. Verifique que la solución fluya libremente.

Cuando la línea de dializado es desconectada del acceso luer, el acceso se cerrara y el flujo de la solución parará.

Si el **puerto de inyección** es utilizado, primero remueva el tapón. Introduzca la punta a través del diafragma de goma del conector. Asegúrese que la punta este completamente insertada y verifique que la solución fluya libremente.

La solución reconstituida debe ser utilizada hasta 24 horas después de haber removido la envoltura externa. La solución reconstituida se puede utilizar una sola vez. Deseche el resto de la solución inmediatamente después de haberla utilizado.

Durante el tratamiento, se debe monitorear constantemente el estado hemodinámico del paciente, así como el equilibrio de líquidos y el equilibrio ácido-base y electrolítico.

¿QUÉ CONTIENE LA SOLUCIÓN PRISMASATE?

El producto se ofrece en una bolsa doble que contiene una solución electrolítica (bolsa A de menor tamaño) y otra amortiguadora (bolsa B de mayor tamaño). El contenido de cada solución se señala en la bolsa correspondiente.

La solución final reconstituida se obtiene después de abrir el sello adhesivo y mezclar ambas soluciones. Consulte la tabla de composición de la solución reconstituida en la etiqueta de la bolsa.

EMPAQUE:

2 bolsas (5000 mL) por paquete.

¿QUÉ ES LA SOLUCIÓN PRISMASATE Y PARA QUÉ SE USA?

El producto es una solución estéril indicada como dializado para la terapia de sustitución renal continua, como hemodiálisis continua y hemodiafiltración, tendente a normalizar la composición de la sangre.

El producto es una solución estéril que se ofrece en una bolsa doble.

La solución electrolítica (contenida en la bolsa A de menor tamaño) se debe mezclar con la solución amortiguadora (en la bolsa de B de mayor tamaño) antes de usar el producto a fin de obtener la solución final para el tratamiento.

El producto también podrá ser utilizado en casos de intoxicación farmacológica para sustancias dializables o filtrables.

El producto se debe usar exclusivamente por prescripción médica o bajo la supervisión de un médico capacitado en terapia intensiva para la terapia de sustitución renal por hemodiafiltración.

Las leyes federales de los Estados Unidos restringen la venta de este producto al médico o por prescripción médica.

¿QUÉ EFECTOS COLATERALES TIENE LA SOLUCIÓN PRISMASATE?

Cuando la hemodiálisis o hemodiafiltración continua se realiza correctamente, los efectos colaterales son poco comunes.

Es posible que se presenten algunos efectos colaterales.

Entre los efectos colaterales más comunes se encuentran náusea, vómito, calambres abdominales y baja presión arterial (hipotensión).

ALMACENAMIENTO Y FECHA DE CADUCIDAD

No almacene el producto a temperaturas inferiores a +4°C/39°F.

No use el producto después de la fecha de caducidad que aparece en la etiqueta y el empaque.

Desde el punto de vista químico, una vez que se ha quitado la envoltura externa, la solución debe usarse de inmediato.

En la práctica, el producto tiene una estabilidad comprobada de 24 horas después de quitar la envoltura externa y subsiguentemente reconstituir el producto, incluyendo la duración del tratamiento.

El almacenawmiento por períodos distintos y en condiciones diferentes a las especificadas es responsabilidad del usuario.

Este producto no es fabricado con resina de látex natural.

Fecha de emisión: 2015-11-05

GAMBRO®

Baxter Healthcare Corporation, One Baxter Parkway, Deerfield, IL, 60015, United States of America

Baxter

REGIOCIT

Package Insert for Emergency Use Authorization

REGIOCIT has been authorized by FDA for emergency use. REGIOCIT is not FDA-approved.

REGIOCIT is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of REGIOCIT under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

Sodium chloride and sodium citrate solution /
Solution de chlorure de sodium et de citrate de sodium

for hemofiltration and regional citrate anticoagulation during Continuous Renal Replacement Therapy (CRRT) /
pour hémofiltration et anticoagulation régionale au citrate pendant la thérapie de remplacement rénal continue (TRRC)

Sodium chloride 5.03 g/L, sodium citrate 5.29 g/L
chlorure de sodium 5,03 g/L, citrate de sodium 5,29 g/L

Solution for Extracorporeal use only. Not for direct intravenous infusion /
Solution pour administration extracoporelle seulement. N'est pas destinée à la perfusion intraveineuse directe

REGIOCIT

Sodium chloride and sodium citrate solution
or hemofiltration and regional citrate anticoagulation
during Continuous Renal Replacement Therapy (CRRT)

sodium chloride 5.03 g/L, sodium citrate 5.29 g/L

Solution for Extracorporeal use only, Not for direct intravenous infusion

INDICATIONS

REGIOCIT (sodium chloride and sodium citrate) solution is indicated for use as replacement solution for regional citrate anticoagulation (RCA) of the extracorporeal circuit in patients treated with continuous renal replacement therapy (CRRT), particularly when systemic anticoagulation with heparin is contraindicated, e.g., in patients with increased bleeding risks.

REGIOCIT should be administered only under the supervision of a physician experienced in the use of CRRT.

Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

Geriatrics

Geriatrics (> 65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is not associated with differences in safety or effectiveness.

CONTRAINDICATIONS

REGIOCIT solution is contraindicated in:

- patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.
- severe liver failure
- shock with muscle hypoperfusion

DOSAGE AND ADMINISTRATION

For Extracorporeal use only. Not for direct intravenous infusion.

REGIOCIT solution is used as a renal replacement solution. The product has an osmolarity of 244 mOsm/L and a pH of approximately 7.4.

Dosing Considerations

Dosing considerations of the drug:

- REGIOCIT solution should not be used for direct intravenous infusion. The product must be used in pre-dilution mode only, with appropriate extracorporeal renal replacement equipment intended for CRRT, using an integrated pre-blood pump for RCA.

- In addition to providing anticoagulation to the extracorporeal circuit and hemofilters, citrate also acts as a buffer source due to its metabolic conversion to bicarbonate systemically. Thus, the infusion rate of REGIOCIT solution to be administered should take into account the rate at which buffer administration occurs from other sources, e.g., dialysate and/or replacement fluid. The product must be used together with a dialysis/replacement solution at an appropriate bicarbonate concentration.
- Dose reduction may be needed in patients with mild to moderate hepatic impairment. In these patients, more frequent monitoring of citrate accumulation is advised. REGIOCIT solution should not be administered to patients with reduced liver and muscle perfusion, e.g., during conditions such as septic shock and lactic acidosis, or in patients with severe hepatic impairment, due to limited citrate metabolism (see CONTRAINDICATIONS).
- **A separate systemic infusion of calcium is always required to prevent or treat hypocalcemia. Adjust calcium infusion depending on measured serum total-to-ionized calcium ratio and ionized calcium levels, to maintain values in the physiologic range. Adjust or stop calcium infusion according to the direction of the attending physician when REGIOCIT solution has been stopped.**
- **Magnesium may need to be supplemented intravenously, based on systemic serum magnesium levels.**

Recommended Dose and Dosage Adjustment

The rate at which REGIOCIT solution is administered depends on the targeted citrate dose and the prescribed blood flow rate (BFR). The prescription of the product must consider the flow rates of the effluent and other therapeutic fluids, the patient's fluid removal requirements, additional fluid inputs and outputs, and the desired acid-base and electrolyte balance.

REGIOCIT solution should be prescribed and its administration (dose, infusion rate, and cumulative volume) established only by critical care or nephrology physicians experienced in administration of CRRT.

The pre-filter infusion rate of REGIOCIT solution (based on its concentration) is indexed to the blood flow rate to achieve a target blood citrate concentration of 3 to 4 mmol/L in the blood. Flow rate for anticoagulation of the extracorporeal circuit should be titrated to achieve a post-filter concentration of ionized calcium in the range 0.25 to 0.35 mmol/L. The patient's systemic ionized calcium concentration should be maintained in the normal physiologic range by adjustment of calcium supplementation.

Administration

Monitoring of the post-filter blood ionized calcium (iCa), systemic blood iCa, and total blood calcium levels in conjunction with other laboratory and clinical parameters is essential to guide appropriate REGIOCIT solution dosage based on the desired level of anticoagulation (see WARNINGS AND PRECAUTIONS).

Plasma levels of sodium, magnesium, potassium, and phosphate should also be monitored regularly and these electrolytes supplemented as needed.

REGIOCIT solution may be warmed to 37°C to enhance patient comfort. Warming of the product prior to use should be done with dry heat only. Solution should not be heated in water or in a microwave oven due to the potential for patient injury or discomfort.

REGIOCIT solution 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.

OVERDOSAGE

Electrolyte imbalance and acid–base balance abnormalities, e.g., hypocalcemia, metabolic alkalosis, etc. may occur in the event of an overdose. Stop administration promptly (see WARNINGS AND PRECAUTIONS).

In patients with impaired citrate metabolism, e.g., liver failure, circulatory shock etc, overdosage with REGIOCIT solution may be manifested as citrate accumulation, metabolic acidosis, systemic total hypercalcemia and ionized hypocalcemia along with increased total calcium/ionized calcium ratio (see CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS).

Careful calcium supplementation can reverse the effects of an overdose. The risk can be minimized by close monitoring during treatment.

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

DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength / Composition	Non-medicinal Ingredients
Extracorporeal	Sodium chloride 5.03 g/L, sodium citrate 5.29 g/L solution for hemofiltration and regional citrate anticoagulation (RCA)	Hydrochloric acid, water

Table 2 – Electrolyte Concentrations from the Medicinal Ingredients

Component	mmol/L
Citrate, $C_6H_5O_7^{3-}$	18
Sodium, Na^+	140
Chloride, Cl^-	86

REGIOCIT (sodium chloride and sodium citrate) solution is available in a 5 000 mL bag, with a luer connector valve and a spike connector. The bag is made of a multilayer film containing polyolefins and elastomers.

This product is not made with natural rubber latex.

WARNINGS AND PRECAUTIONS

There have been reports of system failure due to apparent operator error during administration of CRRT with REGIOCIT solution, leading to serious adverse events, including life-threatening hypocalcemia. Plasma electrolyte and acid-base parameters should be closely monitored during CRRT, and appropriate action taken if imbalances of electrolytes or acid-base balance are detected. Instructions for use of REGIOCIT and CRRT must be strictly followed.

Cautionary statements are provided in WARNINGS AND PRECAUTIONS, Endocrine and Metabolism, Hematologic, Hepatic / Biliary / Pancreatic, and Monitoring and Laboratory Tests, and in DRUG INTERACTIONS to avoid the following when performing the CRRT procedure:

- Hypercalcemia
- Hyponatremia
- Fluid retention, dehydration
- Nausea, vomiting
- Muscle spasms

Citrate Accumulation

Special attention is required in patients with liver failure, including hepatic cirrhosis or acute hepatic failure, or in shock, since metabolism of citrate may be markedly reduced and patients may be thus exposed to citrate accumulation. In these circumstances, more frequent monitoring of citrate accumulation should be undertaken. With systemic citrate accumulation, metabolic acidosis and ionized hypocalcemia may ensue, and the ratio of total to ionized calcium in the blood rises. If total/ionized calcium ratio rises above 2.3, REGIOCIT infusion should be reduced or stopped. CRRT may then be continued without anticoagulation, or by using other means of anticoagulation.

REGIOCIT is contraindicated in patients with severe hepatic impairment or in circulatory shock with muscle hypoperfusion (see ONTRAINDICATIONS).

Excessive infusion of citrate can lead to acute hypocalcemia and metabolic alkalosis, with neurologic and cardiac complications. Treatment consists of discontinuation of the citrate infusion and infusion of calcium.

Endocrine and Metabolism

Hypocalcemia

REGIOCIT solution contains no calcium, and may lead to systemic ionized hypocalcemia, due to loss of calcium bound to citrate in the effluent and/or in the case of systemic citrate accumulation (see DOSAGE AND ADMINISTRATION, Administration).

Electrolyte and Acid–Base Balance

REGIOCIT solution contains citrate, which can influence the patient’s electrolyte and acid–base balance. Plasma electrolyte and acid–base parameters should be closely monitored during CRRT. Closely monitor sodium, magnesium, potassium, phosphate, and calcium. Infusion of electrolytes may be needed to supplement any loss.

Hypercalcemia

Medicinal products containing calcium used for maintenance of calcium homeostasis in CRRT patients can increase the risk of hypercalcemia, and can result in a reduced anticoagulation effect. Care should be taken to avoid excessive titration in administering calcium as this can lead to hypercalcemia. Frequent monitoring of pH, electrolytes, total-to-ionized calcium ratio, and systemic ionized calcium is important to avoid electrolyte and/or acid-base imbalance.

Hypomagnesemia

REGIOCIT solution contains no magnesium. Use of the REGIOCIT solution may result in hypomagnesemia due to CRRT effluent losses (see DOSAGE AND ADMINISTRATION, Administration).

Hypoglycemia

REGIOCIT solution contains no dextrose. Administration of REGIOCIT solution may lead to hypoglycemia. Blood glucose levels should be monitored regularly.

Hypokalemia

REGIOCIT solution contains no potassium. The serum potassium concentration must be monitored before and during CRRT.

Metabolic Alkalosis

REGIOCIT solution contains citrate, which contributes to the overall buffer load. Additional sodium bicarbonate (or buffer source) contained in the CRRT fluids or in other fluids administered during therapy may increase the risk of metabolic alkalosis. Metabolic alkalosis may occur if the net citrate administration rate exceeds that which is necessary to maintain acid–base balance.

If metabolic alkalosis occurs, decrease the citrate dose, and/or increase the dialysate flow rate or change the composition of the CRRT solution.

Blood calcium levels, pH and bicarbonate should be monitored regularly in patients with metabolic alkalosis since this condition may potentiate hypocalcemia.

Metabolic Acidosis

Metabolic acidosis may occur if metabolic clearance of citrate by the liver or skeletal muscle is impaired (see CONTRAINDICATIONS).

If citrate accumulation develops and/or metabolic acidosis develops or worsens during therapy with REGIOCIT, the infusion rate may need to be decreased or its administration stopped.

Hypo-osmolarity/Hypotonicity

REGIOCIT solution is hypo-osmolar/hypotonic relative to standard CRRT replacement fluids and should be used with caution in patients with traumatic brain injury, cerebral edema, or increased intracranial pressure.

Instructions for use of REGIOCIT must be strictly followed. Incorrect use of the access ports or other restrictions to fluid flow may lead to incorrect patient weight loss and may result in machine alarms being set off. Continuing treatment without resolving the originating cause may lead to patient injury or death.

Careful ongoing assessment is required of all solutions infused during REGIOCIT

administration, whether related to CRRT dialysis fluids or to other solutions infused systemically.

REGIOCIT has a physiological sodium level of 140 mmol/L. However, sodium losses occurring during CRRT must be balanced as part of overall fluid and electrolyte management to avoid a drop in blood sodium level leading to systemic hyponatremia.

Hematologic

Hemodynamic Status and Fluid Balance

The patient's hematocrit, hemodynamic status and fluid balance should be monitored throughout the procedure.

- In case of hypervolemia, the net ultrafiltration rate prescribed for the CRRT device can be increased, and/or the rate of administration of solutions other than replacement fluid and/or dialysate can be reduced.
- In case of hypovolemia, the net ultrafiltration rate prescribed for the CRRT device can be reduced, and/or the rate of administration of solutions other than replacement fluid and/or dialysate can be increased.

Hepatic/Biliary/Pancreatic

Use in Patients with Mild to Moderate Hepatic Impairment

Systemic metabolism of citrate to bicarbonate may be impaired in patients with hepatic impairment, resulting in accumulation of citrate. If REGIOCIT solution is administered to patients with mild to moderate hepatic impairment, frequent monitoring of pH, electrolytes, total-to-ionized calcium ratio, and systemic ionized calcium is important to avoid electrolyte and/or acid–base imbalance (see CONTRAINDICATIONS).

Monitoring and Laboratory Tests

Plasma electrolyte and acid–base parameters should be closely monitored during CRRT. Closely monitor sodium, magnesium, potassium, phosphate, calcium, blood glucose levels, hematocrit, hemodynamic status and fluid balance, pH, bicarbonate, total-to-ionized calcium ratio, and systemic ionized calcium. Infusion of electrolytes may be needed to supplement any loss.

Special Populations

Pregnant Women

There are no adequate data from the use of REGIOCIT solution in pregnant women.

Physicians should carefully consider the potential risks and benefits for each specific patient before administering REGIOCIT solution.

Breast-feeding

There are no adequate data from the use of REGIOCIT solution in lactating women.

Physicians should carefully consider the potential risks and benefits for each specific patient before administering REGIOCIT solution.

It is unknown if the drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised.

Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

Geriatrics

Geriatrics (> 65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is not associated with differences in safety or effectiveness.

ADVERSE REACTIONS

Adverse Reaction Overview

The following adverse reactions represent those adverse reactions that are thought to have an association with the use of REGIOCIT solution or that may occur in conjunction with performing the CRRT procedure:

Adverse reactions reported with other CRRT products include:

- Hypotension
- Hypocalcemia (due to excessive and uncorrected effect of citrate in the body)
- Other electrolyte imbalances (hypomagnesemia, hypokalemia, hypophosphatemia)
- Acid–base balance disorders (including metabolic alkalosis, metabolic acidosis)
- Hypoglycemia
- Fluid imbalance

Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In an open-label randomised study, 54 patients were administered RCA with an equimolar solution of citrate, sodium and chloride, as contained in REGIOCIT solution, and 49 received systemic anticoagulation with unfractionated heparin (UFH) while undergoing CRRT using continuous venovenous hemodiafiltration. Adverse events related to metabolic disorders occurred in 26% of patients in the RCA-treated group, compared to 28% of patients in the UFH-treated group. These adverse events were generally transient and reversible. Metabolic alkalosis was seen in 6% of patients treated with RCA, compared to none treated with UFH, and metabolic acidosis was reported in 6% and 2% of patients in the RCA and UFH groups, respectively. Six patients treated with RCA experienced severe hypocalcemia, compared to one patient treated with UFH.

In a second hemodiafiltration trial which evaluated 19 patients randomised to an equimolar solution of citrate, sodium and chloride, as contained in REGIOCIT solution, and 11 patients randomised to UFH anticoagulation, Hypocalcemia requiring intervention was reported in 3 patients treated with RCA, with 2 of these

patients requiring treatment interruption of RCA.

Post-Market Adverse Reactions

To date, adverse events reported in the post-marketing setting for REGIOCIT appear to be consistent with those listed above in Adverse Reaction Overview.

DRUG INTERACTIONS

Overview

The blood concentration of filterable/dialyzable drugs may be reduced during treatment due to their removal by the extracorporeal filter. Corresponding corrective therapy should be instituted if necessary to establish the desired blood concentrations for drugs removed during treatment. Patient monitoring at an appropriate frequency is required.

When prescribing REGIOCIT, the physician needs to consider the use of other anticoagulants along with other buffer-containing and electrolyte solutions (including CRRT replacement fluid and dialysate).

Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction case studies or clinical trials, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3 - Established or Potential Drug-Drug Interactions

Proper/ Common name	Source of Evidence	Effect	Clinical comment
Calcium (e.g. calcium chloride or calcium gluconate)	C, CT	Increase the risk of hypercalcemia, and can result in a reduced anticoagulation effect	Such drugs are used for maintenance of calcium homeostasis in CRRT patients receiving citrate anticoagulation.
Vitamin D and Vitamin D analogues	C, CT	Increase the risk of hypercalcemia, and can result in a reduced anticoagulation effect	-
Sodium bicarbonate		May increase the risk of high concentrations of bicarbonate in blood, leading to metabolic alkalosis	Blood calcium levels should be monitored regularly in patients with metabolic alkalosis since this condition may potentiate hypocalcaemia.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Citrate provides regional anticoagulation of blood in the continuous renal replacement therapy (CRRT) extracorporeal circuit by binding calcium and rendering calcium unavailable to the clotting cascade. Several steps of the clotting cascade are dependent on calcium and the absence of calcium prevents clotting in the circuit.

uring CRRT, pre-dilution infusion of citrate into the access line of the extracorporeal circuit provides only regional extracorporeal anticoagulation (and thus avoids systemic anticoagulation of the patient) for two reasons. First, once blood from the extracorporeal circuit is returned to the patient, it mixes with the central venous blood which contains calcium. The second way in which a systemic anticoagulant effect is avoided is by infusion of calcium in the post-filter (return) bloodline of the extracorporeal circuit.

This procedure not only helps neutralize citrate's anticoagulant effect in the patient's blood, but also prevents any depletion of the patient's calcium stores which may result from the loss of calcium (bound to citrate) in the CRRT effluent fluid.

Pharmacodynamics

Citrate provides anticoagulation by its ability to form complexes with ionized calcium, making it unavailable to the clotting cascade. In REGIOCIT, sodium concentration has been set to 140 mmol/l as critically ill patients may develop severe hyponatremia. Chloride is set to the level required to balance cations as the solution is hydrogen carbonate free. Sodium and chloride are normal constituents of the human body and are considered to be pharmacologically inactive. Citrate is a normal metabolite in the human body that acts as a first intermediate substance in the Krebs cycle. REGIOCIT does not contain potassium or glucose.

Two studies provide information on the dose/response relationship between citrate concentration and anticoagulation. In one study, *ex-vivo* anticoagulation with anticoagulant citrate dextrose formula A (ACD-A) in blood collected from six healthy volunteers was studied. The study concluded that the clinically relevant effects of citrate anticoagulation rely solely on the disturbed formation of the calcium-dependent coagulation factors complexes. In this study, the anticoagulation effects of citrate were monitored either by methods that quantify clot formation (i.e., activated clotting time) or by direct assessment of ionized calcium levels.

The correlation between concentrations of ionized calcium and clotting times revealed almost no anticoagulant effect when ionized calcium levels were up to or above 0.50 mmol/L, while clotting times showed a steep increase when calcium levels were decreased below 0.50 mmol/L. With respect to maximum effect, 5.65 mmol/L citrate induced clotting times of infinity in all samples.

Pharmacokinetics

Citrate is a normal metabolite in the human body and an intermediate substance in the Krebs cycle. This physiological pathway is capable of processing high amounts of citric acid as long as it occurs at low concentrations. The Krebs cycle takes place in the mitochondria, and all cells that contain these cellular organelles can

metabolize citrate. Tissues rich in mitochondria such as liver, skeletal muscles, and kidney therefore have a higher capacity for citrate generation and elimination.

Absorption: Absorption of sodium and chloride is determined by the patient's clinical condition, metabolic status, and residual renal function.

Distribution: Extracellular citrate can be transported from the blood across the plasma membrane by a group of proteins i.e. the plasma membrane citrate transporters (PMCTs) into the cells and then metabolized in various organs and tissues.

Metabolism: Citrate is an intermediate in the central metabolic pathway called Krebs cycle as mentioned above. Citrate is rapidly metabolized mainly in the liver, but can also be metabolized by other organs/tissues.

Elimination: Any excess of circulating citrate is normally excreted via the kidneys.

Special Populations and Conditions

Hepatic Insufficiency:

When treating decompensated cirrhosis patients, one should also consider:

- Impairment of citrate metabolism due to failure of microcirculation and oxidative metabolism (lactic acidosis and/or shock),
- Impaired muscular utilization of citrate (cachexia, high doses of vasopressors),
- Citrate load associated with blood products.

STORAGE, STABILITY AND DISPOSAL

Store at 4 °C to 30 °C. Do not freeze or expose to excessive heat.

SPECIAL HANDLING INSTRUCTIONS

Aseptic technique should be used throughout the handling and administration to the patient.

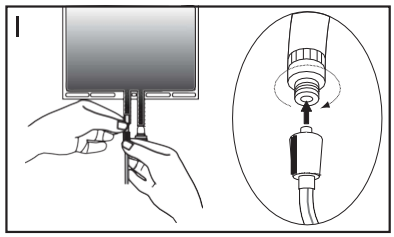
Remove the overwrap from the bag immediately before use.

Use only if the overwrap is not damaged, all seals are intact, and the solution is clear. Press bag firmly to test for any leakage. If leakage is discovered, discard the solution immediately since sterility can no longer be assured.

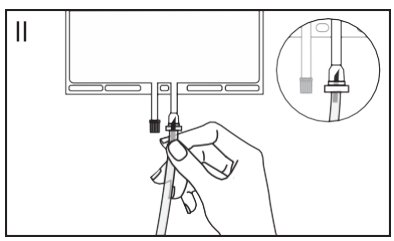
Follow the instructions below when connecting the solution bags for correct use of the access ports.

- If the luer connector is used, remove the cap with a twist and pull motion. Connect the male luer lock on the pre-blood pump line to the female luer connector on the bag using a push and twist motion. Ensure that the connection is fully sealed and tighten (see Figure I). The connector is now open. Verify that the fluid is flowing freely.

  When the pre-blood pump line is disconnected from the luer connector, the connector will close and the flow of the solution will stop. The luer is a needle-less port.



- If the injection connector (or spike connector) is used, remove the snap-off cap. Introduce the spike through the rubber septum (see Figure II). Verify that the fluid is flowing freely.



- Before adding a substance or medication, verify that it is soluble and stable in REGIOCIT, and that the pH range of REGIOCIT is appropriate.
- Additives known or determined to be incompatible should not be added.
- The instructions for use of the medication to be added and other relevant literature must be consulted.
- After addition, if there is a discoloration and/or the appearance of precipitates, insoluble complexes, or crystals, do not use.
- Mix the solution thoroughly when additives have been introduced. The introduction and mixing of additives must always be performed prior to connecting the solution bag to the extracorporeal circuit.
- The solution is for single use only.
- Discard any unused portion.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE PATIENT MEDICATION INFORMATION

REGIOCIT

Sodium chloride and sodium citrate solution

Read this carefully before you start taking REGIOCIT solution and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about REGIOCIT solution.

What is REGIOCIT solution used for?

- Is a solution for hemofiltration and prevents blood clotting during continuous renal replacement therapy (CRRT), which is a form or dialysis treatment. This medicine is used for critically ill patients particularly when other medicine used to prevent blood clotting is not an appropriate choice.

How does REGIOCIT solution work?

This medicine is to be administered into the blood circuit outside of your body when you have CRRT. This medicine is to be used in hospitals and administered by medical professionals only.

What are the ingredients in REGIOCIT solution?

Medicinal ingredients: sodium chloride and sodium citrate

Non-medicinal ingredients: hydrochloric acid, water

REGIOCIT solution comes in the following dosage forms:

Solution with 5.03 g/L of sodium chloride and 5.29 g/L of sodium citrate

Do not use REGIOCIT solution if:

- You are allergic to any ingredients (See What are the ingredients in REGIOCIT solution).
- Severely impaired liver function
- Severely decreased blood flow in the muscles

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take REGIOCIT solution. Talk about any health conditions or problems you may have, including if you:

- have diabetes
- have been treated for chronic kidney disease
- have a history of liver disease

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines. The following may interact with REGIOCIT solution:

- Medicinal products that contain calcium, sodium bicarbonate, or any form of vitamin D.

How to take REGIOCIT solution:

Your healthcare professional will prescribe and administer the product.

Overdose:

If you think you have taken too much REGIOCIT solution, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using REGIOCIT solution?

These are not all the possible side effects you may feel when taking REGIOCIT solution. If you experience any side effects, contact your healthcare professional.

The following side effects have been associated with other CRRT products:

- Low Blood Pressure **(Hypotension)**
- Low blood calcium, due to excessive and uncorrected effect of citrate in the body **(Hypocalcemia)**
- Having an imbalance in your body where you do not have enough magnesium, potassium or phosphate **(Electrolyte imbalances, including hypomagnesemia, hypokalemia, hypophosphatemia)**
- Disorder where the pH in your body is not balanced **(Acid-base disorders, including metabolic acidosis, metabolic alkalosis)**
- Low Blood Sugar **(Hypoglycemia)**
- Having an imbalance in the fluids in your body **(Fluid imbalance)**

The possible side effects can be resulted from your CRRT procedure:

- Having an imbalance in your body where you have too much calcium
- **(Hypercalcemia)**, or do not have enough sodium (Hyponatremia)
- Having too much fluids **(Fluid retention)** or not enough fluids in your body **(Dehydration)**
- Nausea and vomiting
- Muscle Spasms

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at 4 °C to 30 °C. Do not freeze or expose to excessive heat. Keep out of reach and sight of children.

If you want more information about REGIOCIT solution:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website (http://baxter.ca), or by calling 1-888-719-9955.

This leaflet was prepared by Baxter Corporation, Mississauga, Ontario L5N 0C2, Canada.

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANNA J PARK
08/17/2020 11:00:17 AM
see final signature on page 7 of the letter