FACT SHEET FOR HEALHCARE PROVIDERS

# REGIOCIT

**(Sodium Chloride and Sodium Citrate Renal Replacement and Regional Anticoagulant solution)**

For continuous renal replacement therapy

For extracorporeal use only

**Emergency Use Authorization for the United States**

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.

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 scope of the EUA is as follows:

- REGIOCIT will be used as a replacement solution only in adult patients being treated with CRRT and for whom RCA is appropriate.
- REGIOCIT will be administered only by a licensed healthcare provider in a critical care setting.
- REGIOCIT will available for use only in facilities that Baxter Healthcare Corporation has qualified and provided appropriate training on the use of REGIOCIT.

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## Product Description

REGIOCIT is a sterile, replacement solution intended for use in adult patients being treated with CRRT and for whom RCA is appropriate. REGIOCIT, contains physiological concentrations of sodium (140 mmol/l), chloride (86 mmol/l), and a low concentration of citrate (18 mmol/L).

**IMPORTANT ADMINISTRATION INSTRUCTIONS:**

- **A separate systemic infusion of calcium must be administered during use of REGIOCIT to prevent or treat hypocalcemia. Blood calcium concentrations (ionized and total) must be monitored throughout CRRT.**
- **REGIOCIT solution 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 and in combination with other replacement and/or dialysate solution to provide the recommended dose of CRRT.**
- **REGIOCIT may only be administered by health care providers/institutions that have been qualified by Baxter to administer the product.**

**Instructions for Use**

**1. DOSAGE AND ADMINISTRATION**

1.1 Administration Instructions

Renal Replacement Solution: Not for direct intravenous infusion.

The recommended effluent volume for patients receiving CRRT for acute kidney injury (AKI) is 20 to 25 mL/kg/h. This usually requires a higher prescription of effluent volume. The prescription of REGIOCIT solution 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.

The mode of therapy, solute formulations, flow rates and length of therapy should be selected by the physician responsible for managing treatment depending on the clinical condition of the patient as well as the patient's fluid, electrolyte, acid base and glucose balance.

Dialysate and replacement fluid formulations and flow rates are prescribed in accordance with the patient's clinical needs. The use of a calcium-containing dialysate or replacement fluid is not recommended, since the calcium provided by these solutions may counteract the anticoagulant effect of citrate in the circuit.

1.2 Suggested Dosing

The rate at which REGIOCIT solution is administered depends on the targeted citrate dose and the prescribed blood flow rate. The pre-filter infusion rate of REGIOCIT solution is indexed to the blood flow rate to achieve a target blood citrate concentration of 3 mmol/L of blood (See Table 1). Flow rate for anticoagulation of the extracorporeal circuit should be titrated to achieve a post-filter concentration of ionized calcium in the range of 0.25 to 0.35 mmol/L.

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**Table 1: REGIOCIT Solution Flow Rates to Achieve Citrate Dose of 3 mmol/L of Blood**

| Blood flow rate (mL/min) | REGIOCIT solution flow rate (mL/h) |
|---|---|
| 100 | 1000 |
| 110 | 1100 |
| 120 | 1200 |
| 130 | 1300 |
| 140 | 1400 |
| 150 | 1500 |
| 160 | 1600 |
| 170 | 1700 |
| 180 | 1800 |
| 190 | 1900 |
| 200 | 2000 |

Prior to initiating therapy, the patient's systemic ionized calcium concentration should be within the normal physiologic range (1.0 to 1.2 mmol/L) by adjustment of calcium supplementation. A separate infusion of calcium is always required during use of REGIOCIT, due to loss in the effluent. Calcium solution infusion is commenced at the rate of 4 mmol/h, when commencing therapy (see Table 4). Adjust or stop calcium infusion according to physician's prescription when REGIOCIT is stopped.

Citrate also acts as a buffer source (due to conversion to bicarbonate); the infusion rate of REGIOCIT solution must be considered in relation to the rate at which buffer administration occurs from other sources (e.g., dialysate and/or replacement fluid). REGIOCIT solution must be used together with a dialysis solution/replacement solution with appropriate bicarbonate concentration.

## 1.3 Laboratory Monitoring

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 such as acid-base balance and serum electrolytes are essential to guide appropriate REGIOCIT solution dosage based on the desired level of anticoagulation. Levels should be taken at baseline, 1 hour after initiation (or adjustment), and every 6 hours (See Table 2). Rapidly decreasing systemic ionized calcium levels are an early indicator of citrate accumulation.

Measurement of total calcium and assessment of total-to-ionized calcium ratio is necessary. Citrate accumulation causes systemic ionized calcium levels to drop and the ratio of total-to-ionized calcium increases (total-to-ionized calcium ratio > 2.5). In the presence of impaired citrate metabolism, a progressively higher calcium infusion rate is required to maintain the systemic ionized calcium concentration within the intended target. When a total-to-ionized-calcium ratio > 2.5 is recorded, any one of the following abnormalities reported concurrently increases the likelihood of citrate accumulation:

- A rapid decline in systemic iCa concentration despite adequate calcium compensation
- A rapid decrease in pH or a decrease in base excess
- A rapid increase in anion gap

In order to avoid metabolic alkalosis, acid-base balance and systemic ionized calcium can be measured using blood gas analysis. If metabolic alkalosis or citrate accumulation is suspected, decrease the citrate dose while tolerating a post-filter ionized calcium of < 0.5 mmol/L. This can be achieved by either decreasing the blood flow rate to decrease the overall citrate load, increasing the dialysate/replacement flow rate (when applicable) to increase the citrate removal, or decreasing the citrate flow to decrease the citrate dose. Dialysate solutions contain bicarbonate below or above physiological range of 22 to 26 mmol/L, and increasing or decreasing the flow rates of the dialysate solutions can impact the acid-base status of the patient.

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

Table 2 provides a summary of the most important parameters to be monitored during RCA therapy, as well as options for adjustment.

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**Table 2: Monitoring and Adjustment During RCA Therapy**

| Parameter | Recommended Monitoring | Aim and significance | Options for Adjustment |
|---|---|---|---|
| Post-filter ionized calcium | Baseline<br><br>Within 1 hour of initiation or dose adjustment until stable and then at least every 6 hours | To monitor the anticoagulation effect and adjust citrate dose as necessary. | Increase the citrate dose by 0.5 mmol/L of blood if post-filter iCa is ≥ 0.35 mmol/L (see Table 3)<br><br>Decrease the citrate dose by 0.5 mmol/L of blood if post-filter iCa ≤ 0.25 mmol/L (see Table 3) |
| Systemic Ionized Calcium | | To adjust calcium compensation<br><br>To early detect systemic ionized hypocalcemia due to the lack of calcium release from calcium-citrate complexes because of impaired citrate metabolism (after excluding inappropriate calcium replacement). | Adjust calcium infusion according to Table 4 below to maintain patient $Ca^{2+}$ in the 1.0 to 1.2 mmol/L range |
| Systemic Total Calcium | Every 12 to 24 hours. Monitor more frequently if citrate accumulation is suspected | To detect systemic hyper and hypocalcemia<br><br>To calculate the calcium ratio (total-to-ionized systemic calcium) as an indirect index of citrate accumulation (> 2.5) | *See Total-to-Ionized Calcium Ratio* |
| Total-to-Ionized Calcium Ratio | Every 12 to 24 hours. Monitor more frequently if citrate accumulation is | An indirect index of citrate accumulation (> 2.5) | Notify the prescribing clinician if ratio is > 2.5.<br>• Decrease the citrate |

| | | | |
|---|---|---|---|
| | suspected | | dose, or<br>• Decrease the blood flow rate, and/or<br>• Increase the dialysate/replacement flow rate, when applicable<br>Monitor patient status – if improvement does not occur within 2 hours, discontinue citrate infusion. |

Table 3 provides the REGIOCIT solution flow rate adjustment based on a citrate dose adjustment of 0.5 mmol/L.

**Table 3: REGIOCIT Solution Flowrate Adjustment Based on a Citrate Dose Adjustment of 0.5 mmol/L**

| | **Blood Flow Rate (mL/min)** | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **100** | **110** | **120** | **130** | **140** | **150** | **160** | **170** | **180** | **190** | **200** |
| REGIOCIT solution rate increase for an increase of citrate dose by 0.5 mmol/L | + 150 mL/h | + 200 mL/h | + 200 mL/h | + 200 mL/h | + 250 mL/h | + 250 mL/h | + 250 mL/h | + 300 mL/h | + 300 mL/h | + 300 mL/h | + 350 mL/h |
| REGIOCIT solution rate decrease for a decrease of citrate dose by 0.5 mmol/L | - 150 mL/h | - 200 mL/h | - 200 mL/h | - 200 mL/h | - 250 mL/h | - 250 mL/h | - 250 mL/h | - 300 mL/h | - 300 mL/h | - 300 mL/h | - 350 mL/h |
| Example: At a blood flow rate of 150 mL/min, an increase of the citrate dose by 0.5 mmol/L of blood corresponds to an increase of REGIOCIT solution flowrate by 250 mL/h. | | | | | | | | | | | |

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Table 4 provides recommendations to maintain a systemic ionized calcium level between 1.0 mmol/L and 1.2 mmol/L.

**Table 4: Sliding Scale of Calcium Infusion**

| **Measured Arterial Ionized Calcium (mmol/L)** | **Changes in Calcium Solution Infusion Rate** |
|---|---|
| > 1.40 | Decrease by 1 mmol/h and monitor in 1 hour and inform the physician. |
| 1.21 to 1.40 | Decrease by 0.5 mmol/h and monitor in 1 hour |
| 1.00 to 1.20 | No change, monitor in 6 hours |
| 0.91 to 1.00 | Increase by 0.5 mmol/h and monitor in 1 hour |
| < 0.9 | A slow bolus of calcium chloride or gluconate (10 mmol over 10 minutes) and inform the physician. |

Calcium solution infusion is commenced at the rate of 4 mmol/h, when commencing therapy. Arterial ionized calcium is evaluated 1 hour later.

## 2. WARNINGS AND PRECAUTIONS

### 2.1 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. Calcium

reinfusion is required during use of REGIOCIT and blood calcium concentrations (ionized and total) must be monitored.

2.3 Hypomagnesemia

REGIOCIT solution contains no magnesium. Use of the REGIOCIT solution may result in hypomagnesemia due to CRRT effluent losses. Magnesium levels must be monitored as infusion of magnesium may be necessary.

2.4 Hypoglycemia

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

2.5 Hypokalemia

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

2.6 Metabolic Alkalosis

REGIOCIT solution contains citrate, which contributes to the overall buffer load. Metabolization of 1 mol of citrate generates 3 mol of bicarbonate. 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/replacement flow rate (when applicable) or change the composition of the CRRT solution.

2.7 Metabolic Acidosis

Metabolic acidosis may occur if metabolic clearance of citrate by the liver or skeletal muscle is impaired. If citrate accumulation develops and/or metabolic acidosis develops or worsens during therapy with REGIOCIT solution, the infusion rate may need to be decreased or its administration stopped.

2.8 Use in Patients with Mild to Moderate Hepatic Impairment

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.

2.9 Hypoosmolarity/Hypotonicity

REGIOCIT solution is hypoosmolar/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.

3. CONTRAINDICATIONS

Contraindications for the use of REGIOCIT include:
- Severe liver failure
- Shock with muscle hypoperfusion
- Known hypersensitivity to any component of REGIOCIT

***Adverse Event Reporting***

Report adverse events or quality problems experienced with the use of this product.

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Healthcare facilities and prescribing health care providers or their designee receiving REGIOCIT will track all medication errors associated with the use of and all serious adverse events that are considered to be potentially attributable to REGIOCIT use and must report these to FDA using one of the following methods:

• Complete and submit a MedWatch form online (www.fda.gov/medwatch/report.htm)
• Complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178) (this form can be found via link above).

Call 1-800-FDA-1088 for questions. Submitted reports should state, “use of REGIOCIT was under an EUA” at the beginning of the question “Describe Event” for further analysis.

Contact Baxter Healthcare Corporation at 1-866-888-2472 or
global_pharmacovigilance_deerfield@baxter.com

**What is an EUA?**

The United States FDA has made REGIOCIT available to treat patients in an ICU during the COVID-19 pandemic under an emergency access mechanism called an Emergency Use Authorization (EUA). The EUA is supported by a Secretary of Health and Human Service (HHS) declaration that circumstances exist to justify the emergency use of drugs and biological products during the COVID-19 pandemic.

REGIOCIT made available under an EUA have not undergone the same type of review as an FDA-approved product. FDA may issue an EUA when certain criteria are met, which includes that there are no adequate, approved, available alternatives. In addition, the FDA decision is based on the totality of scientific evidence available showing that it is reasonable to believe that REGIOCIT may be effective for use as a replacement solution in adult patients treated with Continuous Renal Replacement Therapy (CRRT) and requiring regional citrate anticoagulation (RCA) of the extracorporeal circuit in an ICU setting during the Coronavirus Disease 2019 (COVID-19) pandemic and that the known and potential benefits of REGIOCIT for such use outweigh the known and potential risks of REGIOCIT.

This EUA for REGIOCIT is in effect for the duration of the COVID-19 declaration justifying emergency use of the products, unless terminated or revoked (after which the products may no longer be needed). The EUA will end when the declaration is terminated or revoked or when there is a change in the approval status of the product such that an EUA is no longer needed.

This communication and product information is available on Baxter Healthcare’s website:
To access COVID-19 Resources, product details, product use information, and the comprehensive Prismaflex Control Unit Operator’s Manual and PrisMax Control Unit Operator’s Manual please visit the Baxter Healthcare Acute Therapies website at http://www.renalacute.com

FDA’s webpage also includes links to patient fact sheet and manufacturer’s instructions
https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#covidtherapeutics.

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