

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CALREZDY safely and effectively. See full prescribing information for CALREZDY.

CALREZDY (calcium chloride solution), for extracorporeal use
Initial U.S. Approval: 1971

INDICATIONS AND USAGE

CALREZDY is a source of Calcium indicated for calcium substitution for regional citrate anticoagulation (RCA) during continuous venovenous hemodialysis (CVVHD) or continuous venovenous hemodiafiltration (CVVHDF) in adults and pediatric patients weighing greater than or equal to 40 kg (1)

DOSAGE AND ADMINISTRATION

- Infusion only by a dedicated pump with the extracorporeal blood purification device (2.4)
- Do not mix with any other substance or solution (2.4)
- Administer adequate amount to keep the systemic ionized calcium in desired range per RCA protocol (2.2)
- The recommended maximum dose is 3 L/day. (2.2)

- See full Prescribing Information for preparation and administration instructions.

DOSAGE FORMS AND STRENGTHS

14.7 g/L calcium chloride dihydrate (100 mmol/L calcium) provided in bag with 1,500 mL ready-to-use solution (3)

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

- Monitor systemic calcium level and adjust dose as necessary to avoid hypo/hypercalcemia. (5.1)
- Monitor for possible local clotting at calcium infusion site of the extracorporeal circuit (5.3)

ADVERSE REACTIONS

Most common adverse reactions with RCA (incidence > 5%) are hypercalcemia, hypernatremia, hypocalcemia, and metabolic alkalosis (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Medical Care Renal Therapies Group, LLC at 1-800-323-5188 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

Calrezdy is indicated for calcium substitution for regional citrate anticoagulation (RCA) during continuous venovenous hemodialysis (CVVHD) or continuous venovenous hemodiafiltration (CVVHDF) in adults and pediatric patients weighing greater than or equal to 40 kg.

2. DOSAGE AND ADMINISTRATION

2.1. General Considerations

Calrezdy should be used under the direction of a physician competent in the application of RCA and by health care professionals who are familiar with the use of the involved products.

Calrezdy should be used under close medical supervision and continuous monitoring.

Measure hemodynamic status, fluid balance, glucose level, electrolytes, acid-base balance, and coagulation parameters prior to and during administration of Calrezdy and citrate-anticoagulated CKRT.

Measure the systemic ionized calcium during and after administration of Calrezdy and citrate-anticoagulated CKRT [see *Warnings and Precautions* (5.1)].

Monitor vitals and electrocardiograph (ECG) during administration of Calrezdy and citrate-anticoagulated CKRT [see *Warnings and Precautions* (5.3)].

2.2. Recommended Dosage

Calrezdy should be administered by infusion only using a dedicated pump with the extracorporeal blood purification device, which is FDA cleared/approved for infusion of a 100 mmol/L calcium chloride solution, e.g. the multiFiltrate PRO system.

Administer Calrezdy to keep the systemic ionized calcium concentration in the desired range. When the calcium flow is below 6 mL/h, it is recommended that the users measure the systemic ionized calcium within 1 hour of starting therapy or changing dosage or blood flow and throughout treatment and adjust the flow of Calrezdy to keep the systemic ionized calcium in the desired range [see *Warnings and Precautions* (5.1)].

- Monitor systemic ionized calcium every 6-8 hours. Monitoring frequency can be increased to every 8-12 hours if the systemic ionized calcium is stable. Monitor more frequently in patients with systemic ionized calcium concentrations outside the normal range and lower weight patients.

The recommended initial dose of Calrezdy (mmol Ca infused per liter effluent) and dosage adjustments based on systemic ionized calcium are shown in Table 1.

Table 1: Recommended Dosage in RCA-CVVHD and RCA-CVVHDF

Starting dose with calcium-free dialysate*	1.7 to 1.8 mmol/L effluent
Systemic ionized calcium target range	1.12 and 1.20 mmol/L (4.48 to 4.80 mg/dL). **
Dosage adjustments	
Systemic Ionized Calcium (mmol/L)	Change of the Calrezdy dose
greater than 1.35	Decrease by 0.4 mmol/L and inform physician
1.21 – 1.35	Decrease by 0.2 mmol/L and continue monitoring
1.12 – 1.20	No change (typical target range)
1.00 – 1.11	Increase by 0.2 mmol/L and continue monitoring
less than 1.00	Increase by 0.4 mmol/L and inform physician

*Patients with hypercalcemia prior to starting treatment should be initiated on a lower starting dose and monitored closely.

** Physician may alter the range based on patient needs.

Do not set the target systemic ionized calcium value below 0.9 mmol/L (3.6 mg/dL).

The recommended maximum volume is 3 L/day (derived based on 75 L/day use of dialysis fluid and a high Calrezdy dose of 3 mmol/L).

2.3. Preparation Instructions

1. Before opening, check the overwrap for damage. Discard bags with damaged overwrapping.
 - a. Remove the overwrap immediately before administration.
2. Check the label and the expiration date on the solution bag.
3. Visually inspect the bag and solution before use. Check that the solution is clear and colorless and that the bag and connector are undamaged. Discard bag if there is any damage.
4. Put the bag on the dedicated attachment by its hanger hole.
5. Remove the protection cap from the connector with its white ring.
 - a. Do not touch any inner parts; especially do not touch on top of the connector. The inner part of the connector is delivered sterile and is not intended to be further treated with chemical disinfectants.

6. Connect the white connector with a twisting motion to the white calcium tubing line connector, overcoming a guarding force until a “click” is audible and connection is established.
7. Locate the cone (frangible) above the bag connector.
8. Bend the line at the cone (frangible) back and forth multiple times in different directions to fully break open the cone (frangible), allowing fluid to flow freely during use.
9. Proceed with further steps as indicated in the device instructions.

For further instructions on storage, handling, and disposal, see *How Supplied/Storage and Handling (16)*.

2.4. Administration Instructions

Calrezdy should be administered by infusion only using a dedicated pump with an extracorporeal blood purification device, that is FDA cleared/approved for infusion of a 100 mmol/L calcium chloride solution, e.g. the multiFiltrate PRO system.

- Adhere to the manufacturer’s handling instructions for the extracorporeal blood purification device and the tubing line.
- Calrezdy is for infusion only into the extracorporeal blood circuit
- Calrezdy is not intended for intramuscular, subcutaneous use, or peripheral intravenous infusion.

Visually inspect Calrezdy for particulate matter and discoloration prior to administration. Use only if solution is clear and colorless, and the bag and connector are undamaged.

- Use aseptic technique throughout administration to the patient. Use the solution immediately after opening.
- Do not add other substances or solutions to Calrezdy.

3. DOSAGE FORMS AND STRENGTHS

Solution for infusion: 1,500 mL of clear, colorless solution supplied in a single-dose bag.

Each 1,000 mL of the ready-to-use solution contains:

Calcium chloride dihydrate	14.7 g
Calcium ²⁺	100 mmol
Chloride ⁻	200 mmol

4. CONTRAINDICATIONS

None

5. WARNINGS AND PRECAUTIONS

5.1. Hyper/Hypocalcemia

Hypocalcemia and hypercalcemia can occur in patients receiving Calrezdy for RCA during CKRT [see *Adverse Reactions* (6.1)]. Excess dosing with Calrezdy may result in hypercalcemia and insufficient dosing may result in hypocalcemia.

Hypocalcemia should be corrected prior to starting treatment. Patients with hypercalcemia prior to starting treatment should be initiated on a lower starting dose and monitored closely [see *Dosage and Administration* (2.2, 2.4)].

During Calrezdy infusion, regularly check the systemic ionized calcium concentration and increase or decrease the dose as required [see *Dosage and Administration* (2.2, 2.4)].

The full effect of calcium dose changes, including calcium released from calcium-citrate chelate complexes, can lead to ionized hypercalcemia up to 12 hours or longer after treatment [see *Dosage and Administration* (2.2, 2.4)].

In patients with comorbidities affecting calcium metabolism or excretion (such as but not limited to nephrocalcinosis, hypercalciuria and overdose of vitamin D), monitor blood calcium levels more closely before, during, and after treatment.

Drug interactions may increase the risk of hypercalcemia [see *Drug Interactions* (7.3)].

5.2. Arrhythmias and Hypotension

Calrezdy infusion during RCA may cause cardiac arrhythmias and decreased blood pressure. ECG monitoring during administration with Calrezdy is recommended.

Synergistic arrhythmias may occur if calcium and cardiac glycosides are administered together [see *Drug Interactions* (7.1)].

5.3. Local Clotting of Extracorporeal Circuit

When infused into the extracorporeal circuit, the site of Calrezdy infusion must regularly be inspected for signs of locally developing clotting. If observed, consider changing the extracorporeal circuit.

6. ADVERSE REACTIONS

The following potential adverse reactions are described elsewhere in the labeling:

- Hyper/Hypocalcemia [see *Warnings and Precautions* (5.1)]
- Arrhythmias and Hypotension [see *Warnings and Precautions* (5.2)]
- Local Clotting of Extracorporeal Circuit [see *Warnings and Precautions* (5.3)]

6.1. Clinical Trials Experience

Clinical trials are conducted under widely varying conditions, and as such, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of Calrezdy was evaluated in an open-label, prospective, single-arm, multicenter study (SARCA) [NCT# 05339139] conducted at 10 sites in the U.S. The study enrolled 31 adult patients (median age 69 years; range 42-85) with a primary diagnosis of acute kidney injury (87%) or end-stage kidney disease (3.2%) who required CKRT. The study excluded patients with metabolic alkalosis (defined by serum bicarbonate greater than 30 mmol/L and arterial pH greater than 7.55) and inability to tolerate citrate therapy, defined as severe liver disease, shock with muscle hypoperfusion, or known hypersensitivity to citrate. Enrolled patients were assigned to either CVVHD or CVVHDF per investigator discretion. Patients received CKRT using RCA with sodium citrate solution and Calrezdy administered via the multiFiltratePRO system, an extracorporeal blood purification device. Patients were dosed with Calrezdy according to the instructions for use of the multiFiltratePRO system [*see Dosage and Administration (2.2)*].

In the SARCA study, the mean duration of treatment exposure was 62 hours (range: 8-412 hours). The most common adverse reactions reported in adults related to Calrezdy with RCA during CKRT were hypocalcemia and hypercalcemia, each occurring in 3 patients (9.7%).

7. DRUG INTERACTIONS

7.1. Cardiac Glycosides

Avoid coadministration of Calrezdy in patients receiving cardiac glycosides. Synergistic arrhythmias may occur with concomitant use. The use of calcium chloride may result in hypercalcemia which increases the risk of digoxin toxicity. If concomitant use is unavoidable, monitor ECG closely during administration of Calrezdy.

7.2. Calcium Channel Blockers

Administration of calcium may reduce the response to calcium channel blockers.

7.3. Drugs That Increase the Risk of Hypercalcemia

Increase frequency of monitoring of calcium concentrations in patients taking concomitant drugs that increase the risk of hypercalcemia (e.g., calcipotriene, estrogen, teriparatide, Vitamin A, and Vitamin D).

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary

Administration of Calrezdy for calcium substitution during continuous kidney replacement therapy (CKRT) with RCA is not expected to cause major birth defects, miscarriage, or other adverse maternal or fetal outcomes when calcium levels are maintained within the desired range. There are risks to the mother and fetus associated with acute kidney injury requiring CKRT during pregnancy (*see Clinical Considerations*). Multiple, published, *in vivo* animal studies demonstrated no adverse reproductive or teratogenic effects at clinically relevant doses when calcium levels were maintained with the desired range.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defects, loss, and 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

Disease-Associated Maternal and/or Fetal Risk

Acute kidney injury requiring CKRT during pregnancy increases the risk for maternal mortality, stillbirth, perinatal death, preterm birth, low birth weight, and neonatal ICU admissions.

8.2. Lactation

Risk Summary

Calcium is present in human milk. Administration of calcium chloride dihydrate solution for calcium substitution during CKRT with RCA is not expected to cause harm to a breastfed infant. There are no available data on the effects of calcium chloride dihydrate solution on the breastfed infant or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Calrezdy and any potential adverse effects on the breastfed infant from Calrezdy or from the underlying maternal condition.

8.4. Pediatric Use

The safety and effectiveness of Calrezdy have been established for calcium substitution in pediatric patients weighing greater than or equal 40 kg undergoing CVVHD or CVVHDF with RCA. Use of Calrezdy for this indication is supported by evidence from three published studies. These consisted of a meta-analysis evaluating efficacy and safety outcomes in critically ill pediatric patients who required CKRT, a prospective crossover study in critically ill pediatric patients requiring CVVHD who received RCA with the multiFiltratePRO system, and a retrospective comparative cohort study in critically ill pediatric patients requiring CKRT who received RCA with the multiFiltratePRO system. In all three studies, pediatric patients received other calcium replacement products. Calrezdy is expected to perform similarly based on the established physiological effect of intravenous calcium administration in preventing citrate-induced hypocalcemia. The safety findings from these studies were similar to those observed in adults [*see Clinical Trials Experience (6.1)*].

The safety and effectiveness of Calrezdy have not been established for calcium substitution in pediatric patients weighing less than 40 kg undergoing CVVHD or CVVHDF with RCA.

8.5. Geriatric Use

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

10. OVERDOSAGE

Overdosage of Calrezdy may lead to hypercalcemia. Symptoms of hypercalcemia typically develop when the total serum calcium concentration is > 3 mmol/L [12 mg/dL] or ionized calcium > 1.2 mmol/L [4.8 mg/dL], and include shortening of QT interval, bradycardia, hypertension, anorexia, nausea, vomiting, bowel hypomotility and constipation, muscle weakness, bone pain, decreased concentration, depression, weakness, fatigue, confusion, hallucinations, disorientation, hypotonicity, seizures, and coma. Hypercalcemia effects on kidney include diminished ability to concentrate urine and diuresis.

In the event of overdosage, promptly discontinue Calrezdy, and institute appropriate countermeasures.

11. DESCRIPTION

Calrezdy solution for infusion is a source of calcium for extracorporeal use. Calrezdy contains calcium chloride dihydrate, which has a molecular formula of $\text{CaCl}_2 \cdot 2 \text{H}_2\text{O}$ and a molecular weight of 147.02 g/mol.

Calrezdy is a sterile solution of calcium chloride dihydrate in water for injection. Each ready-to-use bag of Calrezdy contains 1500 mL of a 14.7 g/L solution of calcium chloride dihydrate in sterile water for injection (q.s.). The pH of Calrezdy is 5.0 – 7.0 and it has a theoretical osmolarity of 300 mOsm/L.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

Calcium is removed by the dialyzer during CVVHD and CVVHDF. In addition, when using RCA, calcium is chelated by citrate and removed as calcium-citrate complexes into the effluent. These processes reduce the calcium concentration in the blood returning to the patient. Calrezdy is administered to compensate for such calcium losses.

12.3. Pharmacokinetics

Absorption

Calrezdy is 100% bioavailable following intravenous injection.

Distribution

Calcium in the body is distributed mainly in skeleton (99%), with 1% distributed within the extracellular fluids and soft tissues. About 50% of total serum calcium is in the ionized form and represents the biologically active part; 8% to 10% serum calcium is bound to organic and inorganic acid, respectively; and approximately 40% is protein bound (primarily to albumin).

Elimination

Metabolism

Calcium itself does not undergo direct metabolism.

Excretion

Calcium is excreted by the kidney through a combination of glomerular filtration and tubular reabsorption. In patients with kidney failure undergoing CVVHD and CVVHDF with RCA, calcium is removed by the dialyzer as calcium-citrate complexes into the effluent, resulting in reduced calcium levels in the blood returned to the patient.

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1. How Supplied

Calrezdy is a clear, colorless solution supplied in a bag equipped with connective tubing and a connector. The solution bag is covered by an overwrap.

For concentration of active ingredients, see *Dosage Forms and Strengths* (3).

Pack size: Nine 1,500 mL bags per box

NDC: 46163-200-15

16.2. Storage Conditions

- Store at 20 °C to 25 °C (68 °F to 77 °F); excursions permitted to 15 °C to 30 °C (59 °F to 86 °F) [*see USP Controlled Room Temperature*]
- Do not refrigerate or freeze.

16.3. Disposal

Calrezdy is provided in a single-dose container. Discard any unused portion. Any unused product or waste material shall be disposed of in accordance with local requirements, and in accordance with local requirements for potentially contaminated materials.

For additional handling instructions, see *Dosage and Administration* (2).

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