

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

CIENBY (sodium citrate solution), for extracorporeal use

Initial U.S. Approval: 1980

INDICATIONS AND USAGE

CIENBY is an anticoagulant indicated 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)
- Adjust application volume to reduce ionized calcium per applied RCA protocol (2.2)
- The recommended maximum dose is 10.4 L/day (2.2)
- See full Prescribing Information for preparation and administration instructions.

DOSAGE FORMS AND STRENGTHS

40 g/L trisodium citrate dihydrate (136 mmol/L citrate) provided in bag with 1,500 mL clear, colorless solution (3)

CONTRAINDICATIONS

- Known hypersensitivity to active substance (4)
- Severely impaired citrate metabolism (4)

WARNINGS AND PRECAUTIONS

- Electrolyte and acid-base imbalances can occur. Monitor for calcium, magnesium, sodium, bicarbonate, and pH changes (5.1, 5.2, 5.3, 5.4)
- Citrate accumulation may occur with use of Cienby (5.4)

ADVERSE REACTIONS

The most common adverse reactions with Cienby (incidence > 5%) were hypercalcemia, hyponatremia, 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.

Revised: 10/2026

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

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

Cienby is indicated 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

Cienby 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.

Cienby 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 administration of Cienby.

Monitor and adjust the electrolyte and acid-base balance regularly during and after citrate-anticoagulated extracorporeal blood purification treatments. Frequency of monitoring should be determined by the treating physician and status of the patient.

A separate infusion of calcium in the post-filter (return) bloodline of the extracorporeal circuit is required during CVVHD or CVVHDF with Cienby due to calcium loss in the effluent [*see Warnings and Precautions (5.1)*].

Consider calcium-free, low sodium and low hydrogen carbonate dialysis fluids in view of Cienby-associated sodium and buffer supply.

2.2. Recommended Dosage

Cienby should be used in accordance with the instructions for use accompanying an extracorporeal blood purification device that has been FDA-cleared/approved for the infusion of a concentrated citrate solution, e.g. the multiFiltratePRO system.

The Cienby flow is dependent on the blood flow as prescribed by the physician and set on the extracorporeal blood purification device as Cienby dose in mmol/L, i.e., mmol citrate infused per liter treated blood. To calculate the corresponding Cienby flow (in mL/min):

Multiply the intended Cienby dose (in mmol/L) by the blood flow (in mL/min) and divide by 136 mmol/L (citrate concentration in Cienby).

Titrate the Cienby dose to achieve a sufficient suppression of ionized calcium of the blood within the filter, assessed by measuring postfilter ionized calcium levels. In general, the postfilter ionized calcium should be checked 5 to 10 minutes after the treatment start and then every 6 to 8 hours or as clinically required, 8 to 12 hours under stable conditions, and if the citrate anticoagulation is

turned off. The recommended initial dose, postfilter ionized calcium target range and recommended dosage adjustment are presented in [Table 1](#) for RCA-CVVHD and [Table 2](#) for RCA-CVVHDF below.

Table 1: RCA-CVVHD Recommended Dosage

Starting Dose	4 mmol/L
Postfilter ionized calcium target range	0.25 to 0.34 mmol/L
Dosage Adjustments	
Postfilter ionized calcium (mmol/L)	Change of the Cienby dose
greater than 0.4	Increase by 0.2 mmol/L and inform physician
0.35 – 0.4	Increase by 0.1 mmol/L and continue monitoring
0.25 – 0.34	No change (typical target range)
0.2 – 0.24	Decrease by 0.1 mmol/L and continue monitoring
less than 0.2	Decrease by 0.2 mmol/L and inform physician

Table 2: RCA-CVVHDF Recommended Dosage

Starting Dose	5 mmol/L
Postfilter ionized calcium target range	0.2 to 0.29 mmol/L
Dosage Adjustments	
Postfilter ionized calcium (mmol/L)	Change of the Cienby dose
Greater than 0.35	Increase by 0.2 mmol/L and inform physician
0.3 – 0.35	Increase by 0.1 mmol/L and continue monitoring
0.2 – 0.29	No change (typical target range)
Less than 0.2	Decrease by 0.1 mmol/L and inform physician

Set the citrate dose within a range of 3 to 5.5 mmol/L of treated blood depending on patient status and chosen treatment mode. For further treatment mode-specific dosing guidance (CVVHD vs. CVVHDF), see the manual for the extracorporeal blood purification device.

When used in combination with a calcium-free dialysis solution for CVVHD or CVVHDF having a sodium content of 133 mmol/L and bicarbonate content of 20 mmol/L, target the citrate amount added to the blood before entering the dialysis filter within a range of 3 to 5 mmol/L of treated blood during CVVHD and within a range of 3 to 5.5 mmol/L of treated blood during CVVHDF treatment modes.

Maintain an extracorporeal blood flow sufficient to reach the therapy targets, but low enough to avoid unnecessary citrate infusion and promote clearance of citrate within the applied filter. Higher blood flows in combination with a lower dosing of Cienby may reduce efficacy.

Maintain the patient's systemic ionized calcium concentration in the normal physiologic range, which commonly requires calcium supplementation. [see *Warnings and Precautions* (5.1)].

The recommended maximum daily application volume is 10.4 L/day. This volume has been derived based on a maximal daily dialysis fluid volume of 75 L/day used with CVVHD or CVVHDF, the correspondent blood flow per recommended protocol and a Cienby dose of 6 mmol/L.

2.3. Preparation Instructions

1. Before opening, check the overwrap for damage. Discard bags with damaged overwrapping.
 - a. Remove the overwrap only 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 green 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 green connector with a twisting motion to the green citrate 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* (16.1).

2.4. Administration Instructions

Cienby is to be administered by infusion only by a dedicated pump and an extracorporeal blood purification device that is FDA-cleared/approved for the infusion of a concentrated citrate solution in the pre-pump segment of the access tubing system (“blood access line”), e.g. the multiFiltratePRO system. The device must also remove the volume provided by Cienby with the effluent, to prevent fluid overload.

Use aseptic technique throughout administration to the patient. Use the solution immediately after opening.

Do not add another substance or solution to Cienby.

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:

Trisodium citrate dihydrate	40 g
Na ⁺	408 mmol
Citrate ³⁻	136 mmol

4. CONTRAINDICATIONS

Cienby solutions are contraindicated in patients with:

- Known hypersensitivity to the active substance
- Severely impaired citrate metabolism [see *Warnings and Precautions* (5.4)]

5. WARNINGS AND PRECAUTIONS

5.1. Hypocalcemia/Hypercalcemia

Due to its mechanism of action, Cienby causes hypocalcemia [see *Adverse Reactions* (6.1), *Clinical Pharmacology* (12.1)]. Severe hypocalcemia can lead to serious and life-threatening consequences including arrhythmia, cardiac arrest, seizure, and coma.

Correct pre-existing hypocalcemia before initiating treatment with Cienby to reduce the risk of clinically relevant hypocalcemia.

To prevent depletion of the patient's calcium stores due to calcium loss in the continuous kidney replacement therapy (CKRT) effluent fluid, a separate infusion of calcium in the post-filter (return) bloodline of the extracorporeal circuit is required during CKRT with Cienby [see *Dosage and Administration* (2.2, 2.4)]

Hypercalcemia can occur in patients treated with Cienby and calcium replacement infusion [see *Adverse Reactions* (6.1)]. Adjust calcium replacement infusion rates and CKRT settings as clinically indicated to maintain electrolytes within target ranges.

In patients undergoing prolonged RCA-CKRT, a decrease in calcium infusion requirements may indicate bone demineralization and PTH levels and bone turnover markers should be monitored to prevent spontaneous fractures.

5.2. Hypernatremia

Cienby is hypernatremic and can cause hypernatremia. Use in combination with low-sodium fluids [see *Dosage and Administration* (2.2), *Adverse Reactions* (6.1), and *Drug Interactions* (7.1)]. Monitor serum sodium concentrations regularly during and after use of Cienby [see *Dosage and Administration* (2.2, 2.4)].

For patients with pre-existing severe hypo/hyponatremia, slowly correct serum sodium concentration according to physician discretion prior to treatment with Cienby and consider an anticoagulation method other than RCA.

5.3. Hypomagnesemia

Cienby chelates magnesium ions which can cause hypomagnesemia. Monitor serum magnesium levels regularly during and after use of Cienby [see *Dosage and Administration* (2.2, 2.4)].

Supplementation with magnesium may be necessary.

Patients with pre-existing magnesium deficiency or those receiving medications known to lower magnesium levels (e.g., proton pump inhibitors) may be at increased risk for hypomagnesemia with Cienby.

5.4. Metabolic and Acid-Base Disturbances, including Citrate Accumulation

Cienby can cause metabolic alkalosis or metabolic acidosis, depending on citrate accumulation or citrate insufficiency.

Metabolic acidosis

In patients with hepatic impairment, shock, or other conditions associated with reduced citrate metabolism, citrate accumulation may occur, which can present as a progressive increase in the ratio of total calcium to ionized calcium, accompanied by metabolic acidosis and ionized hypocalcemia [see *Contraindications* (4)].

Monitor acid-base status and calcium parameters frequently during Cienby administration, especially in patients with hepatic impairment, shock, or other conditions associated with reduced citrate metabolism. Use the total calcium to ionized calcium ratio as a surrogate marker for citrate accumulation. Adjust citrate infusion rates and CKRT settings as clinically indicated based on ongoing monitoring [see *Dosage and Administration* (2.2, 2.4)].

Metabolic alkalosis

Metabolic alkalosis has been reported in patients receiving Cienby [see *Adverse Reactions* (6.1)]. Metabolic alkalosis may result from excessive conversion of citrate to bicarbonate in the liver. Use in combination with low-bicarbonate fluids [see *Dosage and Administration* (2.2, 2.4)].

6. ADVERSE REACTIONS

The following adverse reactions are described elsewhere in the labeling:

- Hypocalcemia/Hypercalcemia [see *Warnings and Precautions* (5.1)]
- Hyponatremia [see *Warnings and Precautions* (5.2)]
- Hypomagnesemia [see *Warnings and Precautions* (5.3)]
- Metabolic and Acid-Base Disturbances including Citrate Accumulation [see *Warnings and Precautions* (5.4)]

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 Cienby was evaluated in an open-label, prospective, single-arm, multicenter study (SARCA) [NCT# 05339139] conducted at 10 sites in the United States. 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 (twenty-four) or CVVHDF (seven) per investigator discretion. Patients received CKRT using RCA with Cienby and a separate calcium chloride solution administered via the multiFiltratePRO system, an extracorporeal blood purification device. Patients were dosed according to the instructions for use of the multiFiltratePRO system [see *Dosage and Administration* (2.2, 2.4)].

The mean duration of treatment exposure was 62 hours (range: 8-412 hours).

The most common adverse reactions reported in adults are provided in Table 3. Most reactions were mild to moderate severity. Adverse reactions leading to treatment discontinuation included hypernatremia, metabolic alkalosis, and hemorrhage.

Table 3: Adverse Reactions Reported in 5% or More of Subjects receiving CKRT using RCA with Cienby and calcium chloride solution administered via an extracorporeal blood purification device

	Cienby and calcium chloride solution N = 31 (%)
Hypercalcemia	3 (9.7)
Hypernatremia	3 (9.7)
Hypocalcemia	3 (9.7)
Metabolic alkalosis	3 (9.7)
Hyperglycemia	2 (6.5)
Hyperkalemia	2 (6.5)

7. DRUG INTERACTIONS

7.1. Calcium Containing Solutions

Avoid administration of calcium-containing solutions upstream of the filter as they may reduce the effect of Cienby.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary

There are no available data on the use of Cienby during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Animal reproduction studies were not conducted with extracorporeal administration of trisodium citrate. Systemic exposure to trisodium citrate is not expected following maternal Cienby extracorporeal administration [see *Clinical Pharmacology* (12.3)]. No direct effects on embryofetal development are expected with the indicated use. There are risks to the mother and fetus associated with acute kidney injury requiring CKRT during pregnancy (see *Clinical Considerations*).

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

There are no available data on the presence of trisodium citrate in human milk, the effects on the breastfed infant, or the effects on milk production. However, breastfeeding is not expected to result in exposure of the infant to trisodium citrate following maternal Cienby extracorporeal administration [see *Clinical Pharmacology* (12.3)]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Cienby and any potential adverse effects on the breastfed infant from Cienby or from the underlying maternal condition.

8.4. Pediatric Use

The safety and effectiveness of Cienby have been established for RCA during CVVHD or CVVHDF in pediatric patients weighing greater than or equal to 40 kg. Use of Cienby 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 and received various citrate formulations for RCA, a prospective crossover study in critically ill pediatric patients requiring continuous venovenous hemodialysis who received RCA with Cienby and the multiFiltrate system, and a retrospective comparative cohort study in critically ill pediatric patients requiring CRKT who received RCA with Cienby and the multiFiltrate system. The safety findings from these studies were similar to those observed in adults see [Clinical Trials Experience (6.1)].

The safety and effectiveness of Cienby have not been established for RCA during CVVHD or CVVHDF in pediatric patients weighing less than 40 kg.

8.5. Geriatric Use

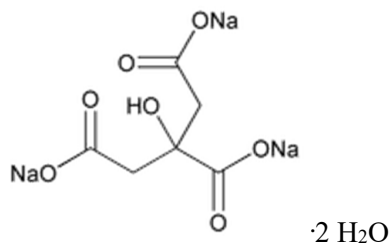
Elderly patients may be at risk of impaired citrate metabolism. No dose reduction is required. Frequent monitoring to detect citrate accumulation is recommended [see *Warnings and Precautions* (5.4)].

10. OVERDOSAGE

Excessive infusion causes acute hypocalcemia that may expose the patient to neurological and cardiac complications. In addition, metabolic alkalosis and hyponatremia could also occur due to an excessive amount of Cienby. Immediately discontinue or lower the dose of Cienby and administer intravenous calcium in patients with an overdose.

11. DESCRIPTION

Cienby solution for infusion is an anticoagulant for extracorporeal use only. Cienby contains trisodium citrate dihydrate, which has a molecular formula of $\text{Na}_3\text{C}_6\text{H}_5\text{O}_7 \cdot 2 \text{H}_2\text{O}$ and a molecular weight of 294.1 g/mol. The structure of trisodium citrate dihydrate is shown below.



Cienby is a sterile solution of sodium citrate in water for injection. Each ready-to-use bag of Cienby contains 1500 mL of a 40 g/L solution of trisodium citrate dihydrate in Water for Injection (q.s.). Hydrochloric acid is added for pH adjustment. The pH of Cienby is 7.1 to 7.5 and it has a theoretical osmolarity of 544 mOsm/L.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

Citrate acts as a regional anticoagulant within the CKRT extracorporeal circuit by binding free ionized calcium in the blood. Calcium is a necessary co-factor in several steps of the coagulation cascade. By binding ionized calcium, citrate reduces thrombin generation and clot formation within the circuit. In vitro data indicates that an ionized calcium concentration of $<0.33 \text{ mmol/L}$ is needed to prevent coagulation.

12.3. Pharmacokinetics

Distribution

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

Elimination

Metabolism

Citrate is an endogenous intermediate in the Krebs cycle. Citrate is rapidly metabolized in the liver, skeletal muscle and kidney.

Following discontinuation of RCA, citrate metabolism continues, and calcium released from calcium-citrate chelate complexes dissociate.

Excretion

A substantial portion of the infused citrate is removed by the effluent. Direct renal excretion is negligible in patients with severe impaired kidney.

14. CLINICAL STUDIES

The efficacy of Cienby as an anticoagulant during CKRT is supported by published studies in critically ill adult and pediatric patients requiring CKRT and in vitro data on the efficacy of citrate as an anticoagulant [see *Adverse Reactions* (6.1), *Use in Specific Populations* (8.4), and *Clinical Pharmacology* (12.1)]. In these published clinical studies, RCA (including Cienby) prolonged filter and/or circuit lifespan.

16. HOW SUPPLIED/STORAGE AND HANDLING

16.1. How Supplied

Cienby is a clear, colorless solution supplied in a bag equipped with connective tubing and a connector. The solution bag is covered by overwraps.

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

Pack size: Nine 1500 mL bags per box

NDC: 46163-100-15

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.
- Keep the bags in the outer carton in order to protect from light.

16.3. Disposal

Cienby 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).

Manufactured by:

Fresenius Medical Care de Mexico, S.A. de C.V.

Paseo del Norte No. 5300, Zapopan, Jalisco 45010, Mexico (MEX)

Manufactured for:

Fresenius Medical Care

Renal Therapies Group, LLC

350 Merrimack Street

Lawrence, MA 01843

1-800-323-5188