ZEVTERA- ceftobiprole medocaril sodium injection, powder, for solution
La Jolla Pharmaceutical Company

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

ZEVTERA (ceftobiprole medocaril sodium for injection), for intravenous use
Initial U.S. Approval: 2024

INDICATIONS AND USAGE

ZEVTERA is a cephalosporin antibacterial indicated for the treatment of:

- Adult patients with *Staphylococcus aureus* bloodstream infections (bacteremia) (SAB), including those with right-sided infective endocarditis (1.1),
- Adult patients with acute bacterial skin and skin structure infections (ABSSSI) (1.2), and
- Adult and pediatric patients (3 months to less than 18 years old) with community-acquired bacterial pneumonia (CABP) (1.3).

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZEVTERA and other antibacterial drugs, ZEVTERA should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria (1.4).

DOSAGE AND ADMINISTRATION

- The recommended dosage of ZEVTERA for **adult patients** with SAB, ABSSSI and CABP is described in the table below (2.1):

Indication in Adults	Dose	Frequency
SAB	667 mg	Every 6 hours on Days 1 to 8
		Every 8 hours from Day 9
ABSSSI	667 mg	Every 8 hours
CABP	667 mg	Every 8 hours

- Duration of treatment **in adult patients** is up to 42 days for SAB and 5 days to 14 days for ABSSSI and CABP (2.1).
- Administer each prepared intravenous infusion solution of ZEVTERA over 2 hours at a concentration of 2.67 mg/mL (2.1, 2.6).
- The recommended dosage of ZEVTERA for **pediatric patients** (3 months to less than 18 years old) with CABP is described below (2.2).

Pediatric Age Group for CABP	Dose	Frequency
12 years to less than 18 years old	13.3 mg/kg (up to 667 mg/dose)	Every 8 Hours
Greater than or equal to 3 months and less than 12 years old	20 mg/kg (up to 667 mg/dose)	Every 8 Hours

- Duration of treatment **in pediatric patients** is 7 days to 14 days for CABP (2.1).
  Administer each prepared intravenous infusion solution of ZEVTERA over 2 hours at a concentration of 2.67 mg/mL for **pediatric patients** aged 12 years to less than 18 years old and at a concentration of 5.33 mg/mL for **pediatric patients** aged 3 months to less than 12 years old (2.2, 2.6).
- Reduce the dosage in **adult patients** with CL_{CR} less than 50 mL/min, including patients withCL_{CR} less than 15 mL/min on hemodialysis (2.3 and 8.6).
- Increase the dosage in **adult patients** with CL_{CR} greater than 150 mL/min (2.3).
- Reduce the dosage in **pediatric patients** aged 2 years old to less than 18 years old with eGFR less than 50 mL/min/1.73 m^2 and greater than or equal to 15 mL/min/1.73 m^2 (2.4 and 8.6).
- See Full Prescribing Information for instructions for preparation of ZEVTERA solution infusion solution (2.5).

DOSAGE FORMS AND STRENGTHS

For injection: 667 mg of ceftobiprole medocaril sodium (equivalent to 500 mg of ceftobiprole) as a

lyophilized powder for reconstitution in a single-dose vial (3).

CONTRAINDICATIONS

ZEVTERA is contraindicated in patients with a known history of severe hypersensitivity to ZEVTERA, or to other members of the cephalosporin class (4).

WARNINGS AND PRECAUTIONS

- Increased Mortality with Unapproved use in Ventilator-Associated Bacterial Pneumonia (VABP) Patients: The safety and effectiveness of ZEVTERA for the treatment of VABP has not been established and the use of ZEVTERA for VABP is not approved (5.1).
- Hypersensitivity Reactions: Discontinue ZEVTERA if a hypersensitivity reaction occurs, and institute appropriate treatment (5.2).
- Seizures and other adverse central nervous system (CNS) reactions have been associated with the use of ZEVTERA. If seizures or other CNS adverse reactions occur, evaluate patients to determine whether ZEVTERA should be discontinued (5.3).
- *Clostridioides difficile*-associated diarrhea (CDAD) has been reported with nearly all systemic antibacterial agents, including ZEVTERA. Evaluate if diarrhea occurs (5.4).

ADVERSE REACTIONS

- SAB (adult patients): The most common adverse reactions occurring in ≥ 4% of adult patients were anemia, nausea, hypokalemia, vomiting, hepatic enzyme and bilirubin increased, diarrhea, blood creatinine increased, hypertension, leukopenia, and pyrexia (6.1).
- ABSSSI (adult patients): The most common adverse reactions occurring in ≥ 2% of adult patients were nausea, diarrhea, headache, injection site reaction, hepatic enzyme increased, rash, vomiting, and dysgeusia (6.1).
- CABP (adult and pediatric patients 3 months to less than 18 years of age):
  - Adult Patients: The most common adverse reactions occurring in ≥ 2% of adult patients were nausea, hepatic enzyme increased, vomiting, diarrhea, headache, rash, insomnia, abdominal pain, phlebitis, hypertension, and dizziness (6.1).
  - Pediatric Patients: The most common adverse reactions occurring in ≥ 2% of pediatric patients were vomiting, headache, hepatic enzyme increased, diarrhea, infusion site reaction, phlebitis and pyrexia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact ISTx, LLC at 1-800-651-3861 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Organic Anion Transporting Polypeptide 1B1/1B3 (OATP1B1/OATP1B3) Substrates: ZEVTERA may increase the plasma concentrations of OATP1B1 and OATP1B3 substrates. Concomitant administration is not recommended (7.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 4/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 *Staphylococcus aureus* Bloodstream Infection (Bacteremia)

ZEVTERA is indicated for the treatment of adult patients with *Staphylococcus aureus* bloodstream infection (bacteremia) (SAB), including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates.

1.2 Acute Bacterial Skin and Skin Structure Infections

ZEVTERA is indicated for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following gram-positive and gram-negative microorganisms: *Staphylococcus aureus* (methicillin-susceptible and methicillin-resistant isolates), *Streptococcus pyogenes,* and *Klebsiella pneumoniae.*

1.3 Community-Acquired Bacterial Pneumonia

ZEVTERA is indicated for the treatment of adult and pediatric patients (3 months to less than 18 years old) with community-acquired bacterial pneumonia (CABP) caused by susceptible isolates of the following gram-positive and gram-negative microorganisms: *Staphylococcus aureus* (methicillin-susceptible isolates), *Streptococcus pneumoniae, Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Escherichia coli*, and *Klebsiella pneumoniae.*

1.4 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZEVTERA and other antibacterial drugs, ZEVTERA should be used only to treat or prevent infections that are proven, or strongly suspected, to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage and Administration for SAB, ABSSSI and CABP in Adult Patients

The recommended dosage of ZEVTERA for the treatment of adult patients with SAB, ABSSSI and CABP is described in Table 1 below. The duration of treatment in adult patients is up to 42 days for SAB and 5 days to 14 days for ABSSSI and CABP.

Administer each prepared intravenous infusion solution of ZEVTERA over 2 hours at a concentration of 2.67 mg/mL to adult patients *[see Dosage and Administration (2.5)].*

Table 1 Recommended Dosage Regimen for SAB, ABSSSI and CABP in Adult Patients

Indication*	Dose	Frequency†
SAB	667 mg‡	Every 6 hours on Days 1 to 8
		Every 8 hours from Day 9
ABSSSI	667 mg‡	Every 8 hours
CABP	667 mg‡	Every 8 hours

* Duration of treatment **in adult patients** is up to 42 days for SAB and 5 days to 14 days for ABSSSI and CABP.
† Administer each prepared intravenous infusion solution of ZEVTERA over 2 hours at a concentration of 2.67 mg/mL *[see Dosage and Administration (2.5)]*
‡ 667 mg of ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole.

2.2 Recommended Dosage and Administration for CABP in Pediatric Patients (3 months to less than 18 years old)

For treatment of pediatric patients with CABP, the recommended dosage of ZEVTERA is described in Table 2 below, based on patient age and weight *[see Clinical Pharmacology (12.3)]*. The duration of treatment for CABP in pediatric patients (3 months to less than 18 years old) is 7 days to 14 days.

Administer each prepared intravenous infusion solution of ZEVTERA over 2 hours at a concentration of 2.67 mg/mL for patients 12 years to less than 18 years old and at a concentration of 5.33 mg/mL for patients greater than or equal to 3 months to less than 12 years old *[see Dosage and Administration (2.5)].*

Table 2 Recommended Dosage Regimen in Pediatric Patients with CABP

Pediatric Age Group	Dose*	Frequency
12 years to less than 18 years old	13.3 mg/kg (up to 667 mg/dose†)	Every 8 Hours‡
3 months to less than 12 years old	20 mg/kg (up to 667 mg/dose†)	Every 8 Hours§

* Duration of treatment for CABP in **pediatric patients** is 7 days to14 days.
† 13.3 mg/kg of ceftobiprole medocaril sodium is equivalent to 10 mg/kg of ceftobiprole; 20 mg/kg ceftobiprole medocaril sodium is equivalent to 15 mg/kg of ceftobiprole. 667 mg ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole.
‡ Administer each prepared intravenous infusion solution of ZEVTERA over 2 hours at a concentration of 2.67 mg/mL for patients 12 years to less than 18 years old *[see Dosage and Administration (2.5)].*
§ Administer each prepared intravenous infusion solution of ZEVTERA over 2 hours at a concentration at a concentration of 5.33 mg/mL for patients greater than or equal to 3 months to less than 12 years old *[see Dosage and Administration (2.5)].*

2.3 Recommended Dosage Regimen in Adult Patients with Renal Impairment

The recommended ZEVTERA dosage in adult patients with renal impairment (CL_{CR} less than 50 mL/min), including patients receiving hemodialysis is shown in Table 3 below. The

duration of treatment in adult patients with renal impairment is up to 42 days for SAB and 5 days to 14 days for ABSSSI and CABP.

Administer each prepared intravenous infusion solution of ZEVTERA over 2 hours at a concentration of 2.67 mg/mL to adult patients with renal impairment *[see Dosage and Administration (2.5)].*

In adult patients with augmented renal clearance (CL_{CR} greater than 150 mL/min), increase the ZEVTERA dosage to 667 mg every 6 hours.

Table 3 ZEVTERA Recommended Dosage Regimens for SAB, ABSSSI and CABP in Adult Patients with Renal Impairment

Indication*	**Creatinine Clearance, CL_{CR} (mL/min)†**	**Dose‡**	**Frequency§**
SAB	30 to less than 50 mL/min	667 mg	Every 8 hours on Days 1 to 8
			Every 12 hours from Day 9
	15 to less than 30 mL/min	333 mg	Every 8 hours on Days 1 to 8
			Every 12 hours from Day 9
	Less than 15 mL/min, including hemodialysis¶	333 mg	Every 24 hours
ABSSSI or CABP	30 to less than 50	667 mg	Every 12 hours
	15 to less than 30	333 mg	Every 12 hours
	Less than 15 mL/min, including hemodialysis¶	333 mg	Every 24 hours

* Duration of treatment **in adult patients** is up to 42 days for SAB and 5 days to 14 days for ABSSSI and CABP.
† Based on calculated creatinine clearance *[see Use in Specific Populations (8.6)].*
‡ 667 mg ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole; 333 mg ceftobiprole medocaril sodium is equivalent to 250 mg of ceftobiprole
§ Administer each prepared intravenous infusion solution of ZEVTERA over 2 hours at a concentration of 2.67 mg/mL *[see Dosage and Administration (2.5)]*
¶ Administer ZEVTERA after intermittent hemodialysis on hemodialysis days, because ceftobiprole is removed by hemodialysis.

2.4 Recommended Dosage Regimen for CABP in Pediatric Patients (2 Years to Less than 18 Years Old) with Renal Impairment

The recommended dosage of ZEVTERA in pediatric patients (2 years to less than 18 years old) with renal impairment (with eGFR less than 50 mL/min/1.73 m^2 and greater than or equal to 15 mL/min/1.73 m^2) is shown in Table 4. The duration of treatment for CABP in pediatric patients (2 years to less than 18 years old) with renal impairment is 7 days to 14 days.

Administer each prepared intravenous infusion solution of ZEVTERA over 2 hours at a concentration of 2.67 mg/mL for patients 12 years to less than 18 years old and at a concentration of 5.33 mg/mL for patients 2 years to less than 12 years old.

There is insufficient information to recommend dosage adjustments in pediatric patients 2 years of age and older with an eGFR less than 15 mL/min/1.73m^2.

There is insufficient information to recommend dosage adjustments in pediatric patients less than 2 years of age with any degree of renal impairment.

Table 4 ZEVTERA Recommended Dosage Regimens for Pediatric Patients (2 Years to less than 18 Years Old) with CABP and with Renal Impairment

Pediatric Age Group*	eGFR (mL/min/1.73 m^2)†	Dosage Regimen‡
12 years to less than 18 years old	30 to less than 50	10 mg/kg (up to 667 mg)§ every 12 hours
	15 to less than 30	10 mg/kg (up to 333 mg)§ every 12 hours
6 years to less than 12 years old	30 to less than 50	10 mg/kg (up to 667 mg)¶ every 12 hours
	15 to less than 30	10 mg/kg (up to 333 mg)¶ every 24 hours
2 years to less than 6 years old	30 to less than 50	13.3 mg/kg every 12 hours (up to 667 mg)¶
	15 to less than 30	13.3 mg/kg every 24 hours (up to 333 mg)¶

* Duration of treatment for CABP in pediatric patients (2 years to less than 18 years old) and with renal impairment is 7 days to 14 days.
† Calculate using a validated GFR estimating equation for the approved age of the pediatric population.
‡ 667 mg ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole; 333 mg ceftobiprole medocaril sodium is equivalent to 250 mg of ceftobiprole; 10 mg/kg of ceftobiprole medocaril sodium is equivalent to 7.5 mg/kg of ceftobiprole; 13.3 mg/kg ceftobiprole medocaril sodium is equivalent to 10 mg/kg of ceftobiprole
§ Administer each prepared intravenous infusion solution of ZEVTERA over 2 hours at a concentration of 2.67 mg/mL for pediatric patients 12 years to less than 18 years old *[see Dosage and Administration (2.5)].*
¶ Administer each prepared intravenous infusion solution of ZEVTERA over 2 hours at a concentration of 5.33 mg/mL for pediatric patients 2 years to less than 12 years old *[see Dosage and Administration (2.5)].*

2.5 Preparation of ZEVTERA Infusion Solution

ZEVTERA must first be reconstituted in the vial and then further diluted prior to administration by intravenous infusion over a period of 2 hours. Aseptic technique must be followed in preparing the infusion solution. See additional instructions for reconstitution and dilution below.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The

solution for infusion should be clear to slightly opalescent and yellowish in color. Discard if discoloration or visible particles are observed.

Reconstitution of ZEVTERA in the Vial

- For adult and pediatric patients 12 years of age and older, reconstitute ZEVTERA lyophilized powder in the vial with 10 mL of sterile water for injection or 10 mL of 5% dextrose injection.
- For pediatric patients aged 3 months to less than 12 years old, ZEVTERA lyophilized powder must be reconstituted with 10 mL of 5% dextrose injection.
- After reconstitution, shake the reconstituted ZEVTERA vial vigorously until dissolution is completed, which in some cases may take up to 10 minutes. The volume of the resulting reconstituted solution is approximately 10.6 mL.
- Allow any foam formed to dissipate, and then inspect the reconstituted solution visually to ensure the product is in solution and particulate matter is absent.
- The reconstituted solution contains 66.7 mg/mL of ceftobiprole medocaril sodium and must be further diluted using aseptic technique with the appropriate diluent as described below, prior to administration. If it is not possible to dilute the reconstituted solution immediately, the reconstituted solution may be stored refrigerated for up to 24 hours, and at room temperature for up to 1 hour. Discard any unused reconstituted solution *[see Dosage and Administration (2.6)]*.

Dilution of Reconstituted ZEVTERA Solution and Administration of the Diluted Product

After reconstitution with the appropriate diluent, further dilute the reconstituted ZEVETRA solution, using aseptic technique with the appropriate diluent, to the appropriate volume of ZEVTERA infusion solution as described in Table 5 below.

Table 5. Preparation of Diluted ZEVTERA Solution for Infusion

Patient Age Group	**Volume of diluent to be added to the vial**	**Volume of reconstituted solution to be withdrawn from the vial**	**Volume of Infusion solution to be administered***	**Concentration and final volume of the diluted product**
Adult (18 years of age and older)	10 mL	10 mL	250 mL 0.9% sodium chloride or 5% dextrose injection	2.67 mg/mL in a 250 mL infusion bag (667 mg/250 mL)
Adult patients with **renal Impairment** (CL_{CR} less than 30 mL/min)	10 mL	5 mL	125 mL 0.9% sodium chloride or 5% dextrose injection	2.67 mg/mL in a 125 mL infusion bag (333 mg/125 mL)
Pediatric		Refer to Table 2 for the dose to determine	The final volume to be administered should be calculated based on the patient	

Patients 12 Years of Age to Less than 18 Years of Age	10 mL	volume of reconstituted solution needed according to weight-based dosing	body weight and must not exceed a maximum of 250 mL of 0.9% sodium chloride or 5% dextrose injection (do not exceed maximum of 667 mg/250 mL dose at a concentration of 2.67 mg/mL)
Pediatric Patients 12 Years of Age to Less than 18 Years of Age with **renal Impairment**	10 mL	**Renal Impairment:** Refer to Table 4 for the dose to determine volume of reconstituted solution needed according to weight-based dosing	The final volume to be administered should be calculated based on the patient body weight and must not exceed a maximum of 250 mL of 0.9% sodium chloride or 5% dextrose injection (do not exceed maximum of 667 mg/250 mL dose at a concentration of 2.67 mg/mL)
Pediatric Patients 3 months to Less than 12 Years of Age	10 mL	Refer to Table 2 for the dose to determine the volume of reconstituted solution needed according to weight-based dosing†,‡	The final volume to be administered should be calculated based on the patient body weight and must not exceed a maximum of 125 mL of 5% dextrose injection (do not exceed maximum of 667 mg/125 mL at a concentration of 5.33 mg/mL)
Pediatric Patients **2 years** to less than 12 years of age with **renal impairment**	10 mL	**Renal Impairment:** Refer to Table 4 for the dose to determine the volume of reconstituted solution needed according to weight-based dosing†,‡	The final volume to be administered should be calculated based on the patient body weight and must not exceed a maximum of 125 mL of 5% dextrose injection (do not exceed maximum of 667 mg/125 mL at a concentration of 5.33 mg/mL)

* Gently invert 5-10 times to form a homogenous solution. Avoid vigorous agitation to prevent foaming.

† For administration via infusion bags, bottles, or syringes: For example, for a dose equal to 667 mg, withdraw 10 mL of the reconstituted solution from the vial and inject into a suitable container of 125 mL of infusion solution.

‡ For administration via a 50 mL syringe if the calculated dose does not exceed 267 mg: For example, for a dose equal to 267 mg, withdraw 4 mL of the reconstituted solution from the vial and withdraw 46 mL of the appropriate infusion solution into the syringe for infusion.

2.6 Storage of Reconstituted and Diluted Infusion Solutions

Storage of Reconstituted ZEVTERA Solution in Vials

Upon reconstitution with the appropriate diluent, the reconstituted ZEVTERA solution in the vial should be transferred and diluted into the appropriate container. If it is not possible to dilute the reconstituted ZEVTERA solution immediately, the reconstituted solution may be stored refrigerated for up to 24 hours, and at room temperature for up to 1 hour. Discard any unused reconstituted solution.

Storage of Diluted ZEVTERA Solution in Infusion Bags

ZEVTERA solutions for infusions can be stored at room temperature or refrigerated at 2 °C to 8 °C. If the infusion solution is stored in the refrigerator, it should be equilibrated to room temperature prior to administration. ZEVTERA solutions should not be exposed to direct sunlight. The infusion solution does not need to be protected from light during administration. Do not **freeze** ZEVTERA solutions for infusions.

Storage for diluted ZEVTERA infusion solutions at a concentration of 2.67 mg/mL and 5.33 mg/mL for varying storage conditions are described in Tables 6 and 7 below.

Table 6 Storage Time for Diluted ZEVTERA Infusion Solutions for Adult and Pediatric Patients 12 Years to Less than 18 Years Old (2.67 mg/mL)

Reconstitution solution diluent (vial)	**Infusion solution diluent**	**Infusion solutions stored at 25 °C NOT protected from light**	**Infusion solutions stored at 2 °C to 8 °C Protected from light**
5% Dextrose solution for injection	5% Dextrose solution for injection	6 hours	94 hours
	0.9% Sodium chloride solution for injection	4 hours	24 hours
Sterile water for injection	5% Dextrose solution for injection or 0.9% Sodium chloride solution for injection	6 hours	94 hours

Table 7 Storage Time for Diluted ZEVTERA Infusion Solutions for Pediatric Patients Less than 12 Years Old (5.33 mg/mL)

Reconstitution solution diluent (vial)	**Infusion solution diluent**	**Infusion solutions stored at 25 °C NOT protected**	**Infusion solutions stored at 2 °C to 8 °C Protected**

		from light	from light
5% Dextrose solution for injection	5% Dextrose solution for injection	6 hours	24 hours

2.7 Drug Compatibilities and Incompatibilities

ZEVTERA is compatible with 5% dextrose injection and 0.9 % sodium chloride injection *[see Dosage and Administration (2.5)]*. The compatibility of ZEVTERA with other drugs and infusion solutions other than 5% dextrose Injection or 0.9% sodium chloride Injection, has not been established.

ZEVTERA must not be mixed or administered simultaneously with calcium-containing solutions. Do **no**t mix ZEVTERA with, or co-administer through, the same intravenous line or cannula with other drug products.

3 DOSAGE FORMS AND STRENGTHS

ZEVTERA (ceftobiprole medocaril sodium for injection) is available in a single-dose vial as a white, yellowish to slightly brownish, cake to broken cake or powder containing 667 mg of ceftobiprole medocaril sodium (equivalent to 500 mg of ceftobiprole) for reconstitution.

4 CONTRAINDICATIONS

ZEVTERA is contraindicated in patients with a known history of severe hypersensitivity to ZEVTERA, or to other members of the cephalosporin class *[see Warnings and Precautions (5.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality with Unapproved Use in Ventilator-Associated Bacterial Pneumonia Patients

In Trial 4, an increase in mortality was seen in the subgroup of patients with ventilator-associated bacterial pneumonia (VABP) who were treated with ZEVTERA (35/103 [34%] versus 24/102 [24%] in comparator-treated patients) *[see Adverse Reactions (6.1)]*. The cause of this increased mortality has not been established. Generally, deaths were associated with complications of infection or underlying co-morbidities. The safety and effectiveness of ZEVTERA for the treatment of VABP has not been established and the use of ZEVTERA for VABP is not approved.

5.2 Hypersensitivity Reactions

Serious hypersensitivity reactions, including anaphylaxis, were observed in ZEVTERA-treated patients in clinical trials *[see Adverse Reactions (6.1)]*. Serious and occasionally fatal hypersensitivity reactions and serious skin reactions have been reported in patients receiving beta-lactam antibacterial drugs.

Before therapy with ZEVTERA is instituted, careful inquiry about previous

hypersensitivity reactions to other cephalosporins, penicillins, or other beta-lactam antibacterial drugs should be made. Maintain clinical supervision if this product is to be given to a penicillin- or other beta-lactam-allergic patient, because cross sensitivity among beta-lactam antibacterial agents has been established. Discontinue ZEVTERA if a hypersensitivity reaction occurs, and institute appropriate treatment.

5.3 Seizures and Other Central Nervous System Reactions

Seizures and other adverse central nervous system (CNS) reactions have been reported during treatment with ZEVTERA and other cephalosporins *[see Adverse Reactions (6.1)]*.

Nonconvulsive status epilepticus (NCSE), encephalopathy, coma, asterixis, neuromuscular excitability, and myoclonia have been reported with cephalopsorins particularly in patients with a history of epilepsy or when recommended dosages of cephalosporins were exceeded due to renal impairment. Adjust ZEVTERA dosing based on creatinine clearance *[see Dosage and Administration (2.3, 2.4)]*.

Anticonvulsant therapy should be continued in patients with known seizure disorders. If CNS adverse reactions, including seizures, occur, patients should undergo a neurological evaluation to determine whether ZEVTERA should be discontinued.

5.4 *Clostridioides difficile*-Associated Diarrhea

Clostridioides difficile-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including ZEVTERA, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antibacterial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* should be discontinued, if possible. Manage fluid and electrolyte levels as appropriate, supplement protein intake, monitor antibacterial treatment of *C. difficile*, and institute surgical evaluation as clinically indicated.

5.5 Development of Drug-Resistant Bacteria

Prescribing ZEVTERA in the absence of a proven or strongly-suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in the Warnings and Precautions section:

- Increased Mortality in Ventilator-Associated Bacterial Pneumonia Patients [*see Warnings and Precautions (5.1)*]
- Hypersensitivity Reactions *[see Contraindications (4) and Warning and Precautions*

(5.2)]
- Seizures and Other Central Nervous System Reactions *[see Warnings and Precautions (5.3)]*
- *Clostridioides difficile*-Associated Diarrhea *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, 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.

Overview of the Safety Evaluation of ZEVTERA

ZEVTERA was evaluated in four controlled comparative phase 3 clinical trials (TRIALS 1 through 4) which included 1221 adult patients treated with ZEVTERA 667 mg (equivalent to 500 mg of ceftobiprole) administered by IV infusion over 2 hours every 6 to 8 hours and 1248 patients treated with comparator for a treatment period up to 42 days. The median age of patients treated with ZEVTERA was 56 years, ranging between 18 and 95 years old. Patients treated with ZEVTERA were predominantly male (64%) and White (82%).

ZEVTERA was also evaluated in a controlled phase 3 clinical trial (TRIAL 5) which included 138 pediatric patients aged from 3 months to less than 18 years with CABP and hospital-acquired bacterial pneumonia (HABP) requiring hospitalization. Although HABP was included in the safety data, the safety and effectiveness of ZEVTERA for the treatment of HABP has not been established and ZEVTERA is not approved for the treatment of HABP.

Adult Patients

Clinical Trials Experience in Adult Patients with Staphylococcus aureus Bloodstream Infection (Bacteremia)

ZEVTERA was evaluated in an active-controlled randomized, double-blind, multicenter phase 3 trial (TRIAL 1) in patients with *Staphylococcus aureus* bloodstream infection (bacteremia) (SAB) including right-sided infective endocarditis. In TRIAL 1, 191 patients received ZEVTERA 667 mg (equivalent to 500 mg of ceftobiprole) administered as a 2-hour IV infusion every 6 hours from Day 1 to Day 8, and ZEVTERA 667 mg every 8 hours from Day 9 onwards, and 198 patients were treated with a comparator (daptomycin administered as an IV 0.5 hour infusion, 6 mg/kg up to 10 mg/kg every 24 hours, with optional aztreonam). The dose of study drugs were adjusted based on renal function.

The median age of patients treated with ZEVTERA was 57 years, ranging between 20-89 years old with approximately 30% aged greater than or equal to 65 years. Patients treated with ZEVTERA were predominantly male (68%), White (95%), and from Europe (93%). The median duration of treatment was 21 days in both treatment arms.

Serious Adverse Reactions and Adverse Reactions Leading to Discontinuation

In TRIAL 1, a total of 36/191 (18.8%) patients with SAB treated with ZEVTERA and 45/198 (22.7%) of patients with SAB treated with daptomycin ± aztreonam experienced serious adverse reactions. Discontinuation of treatment due to any adverse reaction occurred in 18/191 (9.4%) of patients treated with ZEVTERA, and 18/198 (9.1%) of patients treated with daptomycin ± aztreonam. In patients treated with ZEVTERA, the

most common adverse reactions leading to discontinuation were nausea, vomiting, rash, and urticaria, each occurring in 2/191 (1%). Deaths occurred in 17/191 (8.9%) patients treated with ZEVTERA and 18/198 (9.1%) patients treated with daptomycin ± aztreonam.

Common Adverse Reactions

Table 8 lists the most common selected adverse reactions occurring in ≥ 2% of SAB patients receiving ZEVTERA in TRIAL 1.

Table 8 Selected Adverse Reactions Occurring in ≥ 2% of SAB Adult Patients Receiving ZEVTERA in TRIAL 1*

Adverse Reaction	ZEVTERA† N = 191	Daptomycin‡ ± Aztreonam N = 198
Anemia§	12%	13%
Nausea	10%	4%
Hypokalemia¶	9%	3%
Vomiting	8%	2%
Hepatic enzyme and bilirubin increased#	8%	10%
Diarrhea	7%	3%
Blood creatinine increasedÞ	7%	5%
Hypertensionß	5%	2%
Leukopeniaà	4%	3%
Pyrexiaè	4%	3%
Abdominal painð	3%	1%
Fungal infectionø	3%	2%
Headache	3%	3%
Dyspneaý	2%	1%

SAB = *Staphylococcus aureus* bacteremia.

* Trial 1 was not designed to evaluate meaningful comparisons of the incidence of adverse reactions in the ZEVTERA and the daptomycin plus or minus aztreonam treatment groups.

† ZEVTERA 667 mg IV over 2-hours every 6 hours from Day 1 to Day 8, and every 8 hours from Day 9 onwards, with dosing adjustment based on renal function. 667 mg ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole

‡ Daptomycin 6 mg/kg up to 10 mg/kg IV over 0.5 hours every 24 hours, with dosing adjustment based on renal function.

§ Anemia includes: Anemia, Hemoglobin decreased, Hypochromic anemia, Normochromic normocytic anemia

¶ Hypokalemia replaces: Blood potassium decreased

\# Hepatic enzyme increased includes: Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Gamma-glutamyltransferase increased, blood bilirubin increased, hyperbilirubinemia

Þ Blood creatinine increased includes: Acute kidney injury, Blood creatinine increased, Creatinine renal clearance decreased, Oliguria, Renal impairment

ß Hypertension includes: Hypertension, Blood pressure increased, Hypertensive crisis

à Leukopenia includes: Leukopenia, Lymphocyte count decreased, Lymphopenia, Neutropenia, Neutrophil count decreased, White blood cell count decreased
è Pyrexia includes Hyperthermia, Pyrexia
ð Abdominal pain includes: Abdominal pain upper, Abdominal tenderness
ø Fungal infection includes: *Candida* infection, *Candida* sepsis, Fungal test positive, Oral candidiasis , Vulvovaginal candidiasis, Tinea pedis
ý Dyspnea includes: Dyspnea, Respiratory distress

Clinical Trials Experience in Adult Patients with Acute Bacterial Skin And Skin Structure Infections

ZEVTERA was evaluated in an active-controlled, randomized, double-blind, multicenter phase 3 trial (TRIAL 2) in patients with acute bacterial skin and skin structure infections (ABSSSI).

In TRIAL 2, 334 patients received ZEVTERA 667 mg (equivalent to 500 mg of ceftobiprole) administered as a 2-hour IV infusion every 8 hours, and 342 patients were treated with vancomycin plus aztreonam. The daily dose of vancomycin was 2 grams, as a 1 gram fixed dose or 15 mg/kg, administered as a 2-hour IV infusion every 12 hours. Aztreonam was administered as a 1 gram fixed dose as a 0.5-hour IV infusion every 12 hours and the requirement for aztreonam therapy was reassessed at the 72-hour study visit. The dose of study drugs was adjusted based on renal function.

The median age of patients treated with ZEVTERA was 51 years ranging from 18–89 years old with approximately 12% aged greater than or equal to 65 years. Patients treated with ZEVTERA were mostly male (59%), White (95%), and from the United States (60%). Patients across treatment arms received treatment for a median duration of 6 days.

Serious Adverse Reactions and Adverse Reactions Leading to Discontinuation

In TRIAL 2, a total of 6/334 (1.8%) ABSSSI patients treated with ZEVTERA and 12/342 (3.5%) of ABSSSI patients treated with vancomycin plus aztreonam experienced serious adverse reactions. Discontinuation of treatment due to any adverse reaction occurred in 6/334 (1.8%) of patients treated with ZEVTERA, and 10/342 (2.9%) of patients treated with vancomycin plus aztreonam. In patients treated with ZEVTERA, the most common adverse reactions leading to discontinuation were dysgeusia and both pruritus and rash, occurring in 1/334 (0.3%). Deaths occurred in 1/334 (0.3%) patients treated with ZEVTERA and 2/342 (0.6%) patients treated with vancomycin plus aztreonam.

Common Adverse Reactions

Table 9 lists the most common selected adverse reactions occurring in ≥ 2% of ABSSSI patients receiving ZEVTERA in TRIAL 2.

Table 9 Selected Adverse Reactions Occurring in ≥ 2% of ABSSSI Adult Patients Receiving ZEVTERA in TRIAL 2[*]

Adverse Reaction	ZEVTERA[†] N = 334	Vancomycin plus Aztreonam[‡] N = 342
Nausea	11%	6%
Diarrhea	6%	5%

Headache	6%	7%
Injection site reaction§	2%	3%
Hepatic enzyme increased¶	2%	3%
Rash#	2%	3%
Vomiting	2%	2%
Dysgeusia	2%	0%

ABSSSI = Acute Bacterial Skin and Skin Structure Infections.

* Trial 2 was not designed to evaluate meaningful comparisons of the incidence of adverse reactions in the ZEVTERA and the vancomycin plus or minus aztreonam treatment groups.
† ZEVTERA 667 mg IV over 2-hours every 8 hours with dosing adjustment based on renal function. 667 mg ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole
‡ Vancomycin IV, as fixed 1 gram or 15 mg/kg, administered over hours every 12 hours with dosing adjustment based on renal function; aztreonam IV 1 gram over 0.5 hours every 12 hours with dosing adjustment based on renal function.
§ Infusion site reaction includes: Injection site reaction, Infusion related reaction
¶ Hepatic enzyme increased includes: Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Gamma-glutamyltransferase increased
# Rash includes Rash, Drug eruption, Dermatitis

Clinical Trials Experience in Adult Patients with Community-Acquired Bacterial Pneumonia

ZEVTERA was evaluated in an active-controlled, randomized, double-blind, multicenter phase 3 study in adult patients with community-acquired bacterial pneumonia (CABP).

In TRIAL 3, 310 patients received ZEVTERA 667 mg (equivalent to 500 mg of ceftobiprole) every 8 hours as a 2-hour IV infusion, and 322 patients were treated with ceftriaxone 2 grams as a 0.5 hour IV infusion with or without linezolid 600 mg every 12 hours as a 60-minute IV infusion. The dose of ZEVTERA was adjusted based on renal function.

The median age of patients treated with ZEVTERA was 56 years, ranging from 18–90 with approximately 36% aged greater or equal to 65 years. Approximately 62% of patients were White, 45% were from outside Europe or the United States, and 57% were male. Patients across treatment arms received treatment for a median duration of 9 days.

Serious Adverse Reactions and Adverse Reactions Leading to Discontinuation in Adult Patients

In TRIAL 3, a total of 35/310 (11.3%) patients with CABP treated with ZEVTERA and 37/322 (11.5%) patients with CABP treated with ceftriaxone ± linezolid experienced serious adverse reactions. Discontinuation of treatment due to any adverse reaction occurred in 18/310 (5.8%) of patients treated with ZEVTERA, and 12/322 (3.7%) of patients treated with ceftriaxone ± linezolid. The most common adverse reaction leading to discontinuation in patients treated with ZEVTERA was vomiting, occurring in 4/310 (1.3%). Deaths occurred in 9/310 (2.9%) patients treated with ZEVTERA and 9/322 (2.8%) in patients treated with ceftriaxone ± linezolid.

Common Adverse Reactions in Adult Patients

Table 10 lists the most common selected adverse reactions occurring in ≥ 2% of CABP patients receiving ZEVTERA in TRIAL 3.

Table 10 Selected Adverse Reactions Occurring in ≥ 2% of CABP Adult Patients Receiving ZEVTERA in Safety Analysis Set in TRIAL 3

Adverse Reaction	ZEVTERA* N = 310	Ceftriaxone† ± linezolid N = 322
Nausea	10%	4%
Hepatic enzyme increased‡	10%	11%
Vomiting	9%	3%
Diarrhea	7%	9%
Headache	7%	7%
Rash§	5%	2%
Insomnia	5%	4%
Abdominal pain¶	4%	3%
Phlebitis#	4%	2%
Hypertensionᵖ	4%	4%
Dizziness	3%	2%

CABP = Community-Acquired Bacterial Pneumonia.

* ZEVTERA 667 mg IV over 2-hours every 8 hours with dosing adjustment based on renal function. 667 mg ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole

† Ceftriaxone 2 grams IV over 0.5 hours every 24 hours, with or without linezolid 600 mg IV over 1 hour every 12 hours

‡ Hepatic enzyme increased includes: Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Blood alkaline phosphatase increased, Alanine aminotransferase increased, Hepatic enzyme increased, Transaminases increased, Alanine aminotransferase, Liver function test increased.

§ Rash includes: Dermatitis contact, Dermatitis allergic, Rash, Rash pruritic

¶ Abdominal pain includes: Abdominal discomfort, Abdominal pain, Abdominal pain upper

\# Phlebitis includes: Phlebitis, Injection site phlebitis

ᵖ Hypertension includes: Hypertension, Blood pressure increased, Hypertensive Crisis

Clinical Trials Experience in Adult Patients with Unapproved Use of Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia

ZEVTERA was evaluated in an active-controlled, randomized, double-blind, multicenter, phase 3 trial in patients with hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP) [TRIAL 4]. Although HABP/VABP are included in the safety data, the safety and effectiveness of ZEVTERA for the treatment of HABP/VABP have not been established and ZEVTERA is not approved for HABP or VABP.

In TRIAL 4, 386 patients received ZEVTERA 667 mg (equivalent to 500 mg of

ceftobiprole) every 8 hours as a 2-hour IV infusion, and 386 patients were treated with ceftazidime 2 grams every 8 hours as a 2-hour IV infusion with or without linezolid 600 mg every 12 hours as a 1-hr infusion. The dose of ZEVTERA and ceftazidime were adjusted based on renal function.

The median age of patients treated with ZEVTERA was 62.5 years (range 18 - 95) with approximately 47% aged 65 years or older. Approximately 81% of the patients were White, most were outside of the United States (88%) and 72% were male. Patients across treatment arms received treatment for a median duration of 8 days.

Serious Adverse Reactions and Adverse Reactions Leading to Discontinuation in Adult Patients

In TRIAL 4, a total of 140/386 (36.3%) HABP/VABP patients treated with ZEVTERA and 123/386 (31.9%) HABP/VABP patients treated with ceftazidime ± linezolid experienced serious adverse reactions. Discontinuation of treatment due to any adverse reaction occurred in 54/386 (14%) of patients treated with ZEVTERA, and 40/386 (10.4%) of patients treated with ceftazidime ± linezolid. Deaths occurred in 88/386 patients (22.8%) treated with ZEVTERA and 84/386 patients (21.8%) treated with ceftazidime ± linezolid. In the subgroup of patients with VABP, 35/103 patients treated with ZEVTERA died (34.0%) versus 24/102 (23.5%) of the patients treated with ceftazidime ± linezolid. In the subgroup of patients with HABP, 53/283 patients treated with ZEVTERA died (18.7%) versus 60/284 patients treated with ceftazidime ± linezolid (21.1%).

Common Adverse Reactions in Adult Patients

Common adverse reactions occurring in >2% of HABP/VABP patients who received ceftobiprole in TRIAL 4 include diarrhea, hypokalemia, hyponatremia, hepatic enzyme increased, vomiting, anemia, rash, phlebitis, nausea, abdominal pain, and seizures.

Selected Adverse Reactions of ZEVTERA in Adult Patients

The following selected adverse reactions were reported in ZEVTERA-treated adult patients at a rate of less than 2% in Trials 1, 2, 3 and 4.

Blood and lymphatic system disorders:	Thrombocytosis, Thrombocytopenia
Gastrointestinal disorders:	Dyspepsia, Dysphagia
General disorders and administration site conditions:	Fatigue, Chills, Facial swelling, Infusion site pain
Immune system disorders:	Hypersensitivity, Angioedema, Anaphylactic shock
Infections and infestations:	Mucocutaneous fungal infections
Investigations:	Blood lactate dehydrogenase increased, Blood triglycerides increased, Prothrombin time prolonged
Psychiatric disorders:	Anxiety, Irritability,
Renal and urinary disorders:	Pollakiuria
Respiratory, thoracic and mediastinal disorders:	Bronchospasm, Wheezing
Skin and subcutaneous tissue	Pruritus

disorders:	Pruritus
Vascular disorders:	Thrombosis

Pediatric Patients

Clinical Trials Experience in Pediatric Patients with Community-Acquired Bacterial Pneumonia

ZEVTERA was evaluated in an active-controlled, randomized, investigator-blind, multicenter phase 3 study in pediatric patients aged from 3 months to less than 18 years with HABP or CABP requiring hospitalization. Although patients with HABP are included in the safety data, the safety and effectiveness of ZEVTERA for the treatment of HABP has not been established and ZEVTERA is not approved for HABP.

In TRIAL 5, 94 patients received ZEVTERA 13.3 mg/kg (equivalent to 10 mg/kg of ceftobiprole) to 26.7 mg/kg (equivalent to 20 mg/kg of ceftobiprole – higher than the recommended approved dose) *[see Dosage and Administration (2.2, 2.4)].* ZEVTERA was administered by intravenous infusion every 8 hours, age-adjusted for dose and infusion duration (2-hour or 4-hour infusion). In the comparator arm, 44 patients received either ceftriaxone 50-80 mg/kg IV as a single daily dose (maximum 2 grams/day) for CABP or ceftazidime 50 mg/kg IV every 8 hours (maximum 6 grams/day) for HABP, with or without vancomycin 10-15 mg/kg IV every 6 hours (maximum 2 grams/day). The median age of study patients was 5 years, ranging from 0.6 to 17 years. All patients were from Europe, 100% were classified as White and 56% of patients were male.

Serious Adverse Reactions and Adverse Reactions Leading to Discontinuation in Pediatric Patients

In TRIAL 5, a total of 7/94 (7.4%) pediatric patients treated with ZEVTERA and 2/44 (4.5%) patients in the comparator group experienced serious adverse reactions. Discontinuation of treatment due to any adverse reaction occurred in 4/94 (4.3%) of patients treated with ZEVTERA and 0/44 patients treated in the comparator group. Specific adverse reactions leading to treatment discontinuation in patients who received ZEVTERA included aggravated pneumonia, pleuritis, urticaria, and hypersensitivity, each occurring in 1/94 (1.1%). There were no deaths in either arm of the pediatric study.

The most common selected adverse reactions, occurring in ≥ 2% of pediatric patients treated with ceftobiprole, were vomiting (7.4%) headache (3.2%), hepatic enzyme increased (including alanine aminotransferase increased and aspartate aminotransferase increased) (3.2%), diarrhea, infusion site reaction, phlebitis, and pyrexia (all 2.1%).

6.2 Postmarketing Experience

The following adverse reactions and altered laboratory tests have been identified during post-approval use of ZEVTERA and ceftobiprole outside of the United States, or other cephalosporin-class antibacterial drugs. 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.

Altered Laboratory Tests: Positive direct Coombs' test, false-positive test for urinary glucose.
Blood and lymphatic system disorders: Agranulocytosis, aplastic anemia.

Hepatobiliary disorders: Hepatic dysfunction including cholestasis
Immune system disorders: Drug fever, serum sickness-like reaction
Nervous system disorders: Myoclonus
Renal and urinary disorders: Renal dysfunction, toxic nephropathy
Vascular disorders: Hemorrhage, hypertension

7 DRUG INTERACTIONS

7.1 Organic Anion Transporting Polypeptide 1B1/1B3 (OATP1B1/OATP1B3) Substrates

ZEVTERA may increase the plasma concentrations of OATP1B1 and OATP1B3 substrates. Concomitant administration is not recommended *[see Clinical Pharmacology (12.3)].*

7.2 Drug-Laboratory Test Interactions

Dipstick Tests

ZEVTERA may result in false-positive results in dipstick tests (urine protein, ketones, or occult blood). Use alternate clinical laboratory methods of testing to confirm positive tests.

Serological Testing

Treatment with ZEVTERA has the potential to interfere with serological testing, such as the Coombs test. In clinical studies there was no evidence of hemolytic anemia in adults or children. However, the possibility that hemolytic anemia may occur cannot be ruled out. Patients experiencing anemia during or after treatment should be investigated for this possibility.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data with use of ZEVTERA in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. Available data from published observational studies and case reports over several decades with cephalosporin use in pregnant women have not established drug-associated risks of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Available studies have methodologic limitations, including small sample size, retrospective data collection, and inconsistent comparator groups, and cannot definitely establish the absence of risk.

Intravenous administration of ceftobiprole medocaril to pregnant rats and monkeys during organogenesis showed no evidence of adverse fetal developmental outcomes at doses approximately 1.4 times and 0.9 times, respectively, the maximum recommended human dose (MRHD). Some evidence of maternal toxicity (slight reduction in body weight and food consumption) was noted in pregnant monkeys at 0.9 times the MRHD. Intravenous administration of ceftobiprole medocaril to rats 2-weeks prior to mating,

during organogenesis, and through lactation resulted in no adverse fertility or fetal development effects in offspring at doses approximately 1.4 times the MRHD (*see Data*).

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

Data

Animal Data

Pregnant rats administered ceftobiprole medocaril intravenously at doses up to 360 mg/kg/day (approximately 1.4 times the MRHD based on total body surface area (BSA)-normalized comparisons) during organogenesis on gestation days (GD) 6 to 17 showed no adverse fetal development effects. Maternal body weight gain and food consumption were slightly decreased at 360 mg/kg/day.

Pregnant cynomolgus monkeys were administered ceftobiprole medocaril intravenously at doses up to 120 mg/kg/day (approximately 0.9 times the MRHD based on BSA comparison) during organogenesis (GD 20 to 50). Maternal body weight gain and food consumption were slightly reduced at 120 mg/kg/day. This dose was associated with a slight increase in abortion rate (approximately 10% above historical controls). No other fetal development adverse effects (i.e., no fetal malformations) were observed at the high dose.

In a pre- and post-natal development toxicity study, ceftobiprole medocaril was administered intravenously to pregnant rats during organogenesis starting at GD 6 and continuing to lactation day 21 (L21) at doses up to 360 mg/kg (approximately 1.4 times the MRHD based on BSA comparisons). Maternal toxicity (mortality, reduced food consumption and body weight gain in surviving females during gestation) was observed at the high dose. Effects in the offspring were also observed at the high dose during the post-natal pre-weaning period (decrease in the number of pups born per litter and decreased postnatal survival up to day 4 after birth). No adverse effects were observed in surviving pups during the postnatal postweaning development period (days 5-22) at doses up to 360 mg/kg.

8.2 Lactation

Risk Summary

There are no data on the presence of ceftobiprole in human milk, the effects of ceftobiprole on the breastfed infant, or the effects of ceftobiprole on milk production. Animal studies have shown that ceftobiprole was excreted in milk of lactating rats at low concentrations *(see Data)*. When a drug is present in animal milk, it is likely the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZEVTERA and any potential adverse effects on the breastfed child from ZEVTERA or from the underlying maternal conditions.

Data

During pregnancy, rats were administered ceftobiprole at doses of 175, 250, and 360 mg/kg/day from 14-days pre-mating through lactation/postpartum day 21. Ceftobiprole

was detected in the milk of lactating rats 2 hours post-dose on lactation day 20 at levels approximately 20% of the corresponding maternal plasma ceftobiprole levels. The concentration of ceftobiprole in animal milk does not necessarily predict the concentration of drug in human milk.

8.4 Pediatric Use

The safety and effectiveness of ZEVTERA have been established for the treatment of CABP in pediatric patients 3 months to less than 18 years. Use of ZEVTERA in this age group is supported by evidence from an adequate and well-controlled trial of ZEVTERA in adults, with additional pharmacokinetic, safety and efficacy data from pediatric trials *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.3)]*.

The safety and effectiveness of ZEVTERA have not been established for the treatment of CABP in pediatric patients less than 3 months of age.

The safety and effectiveness of ZEVTERA have not been established for the treatment of ABSSSI and SAB in pediatric patients.

8.5 Geriatric Use

Of the 835 adult CABP, ABSSSI, and SAB patients treated with ZEVTERA in the Trials 1, 2 and 3, 210 patients (25%) were 65 years of age and older, including 85 patients (10%) 75 years of age and older. No overall differences in safety or effectiveness of ZEVTERA were observed between patients 65 years of age and older and younger adult patients.

No clinically significant changes in the pharmacokinetics of ZEVTERA were observed in patients 65 years of age and older compared to younger adult patients *[*see *Clinical Pharmacology (12.3)]*. Dosage adjustment for geriatric patients should be based on renal function *[see Dosage and Administration (2.3), Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

Adult Patients

The ZEVTERA dosage is reduced in adult patients with CL_{CR} < 50 mL/min, including patients with a CL_{CR} < 15 mL/min either receiving or not receiving hemodialysis *[see Dosage and Administration (2.3)]*.

Renal impairment (CL_{CR} < 50 mL/min) increases ceftobiprole AUC in adult patients *[see Clinical Pharmacology (12.3)]*, which may increase the risk of ZEVTERA adverse reactions.

ZEVTERA is removed by hemodialysis; thus, ZEVTERA should be administered after intermittent hemodialysis on hemodialysis days *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].*

Pediatric Patients

The ZEVTERA dosage is reduced in pediatric patients 2 years to less than 18 years old with renal impairment (eGFR 15 to < 50 mL/min/1.73 m^2) *[see Dosage and Administration (2.4)].*

Use in pediatric patients 2 years to less than 18 years old with renal impairment (eGFR 15 to < 50 mL/min/1.73 m^2) is predicted to increases ceftobiprole AUC *[see Clinical*

Pharmacology (12.3)], which may increase the risk of ZEVTERA adverse reactions. The effect of any degree of renal impairment in pediatric patients younger than 2 years of age or in pediatric patients 2 years to less than 18 years old with an eGFR < 15 mL/min/1.73 m^2 either receiving or not receiving hemodialysis on ceftobiprole pharmacokinetics is unknown.

Augmented Renal Clearance

Increase the ZEVTERA dosing frequency in adult patients with augmented renal clearance (CL_{CR} > 150 mL/min).

Use in adult patients with augmented renal clearance (CL_{CR} > 150 mL/min) is predicted to decrease ceftobiprole exposure *[see Clinical Pharmacology (12.3)]*, which may reduce ZEVTERA efficacy. The effect of augmented renal clearance function (CL_{CR} > 150 mL/min) on ceftobiprole pharmacokinetics in pediatric patients is unknown.

10 OVERDOSAGE

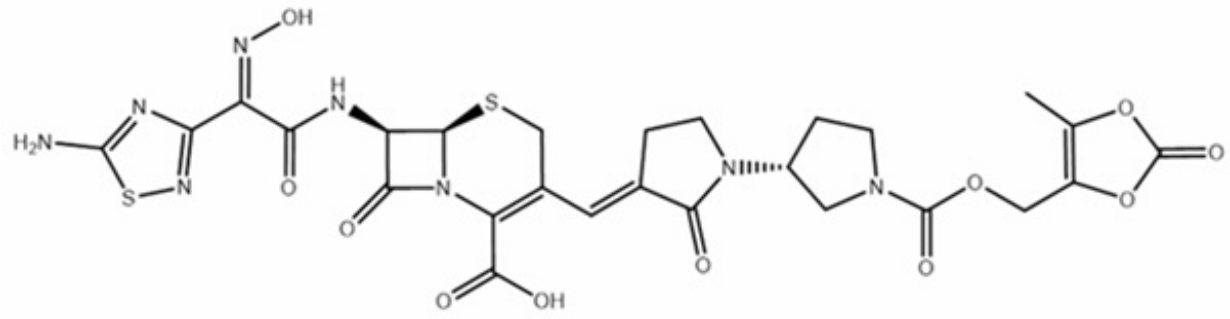
There is no information on clinical signs and symptoms associated with an overdose of ZEVTERA. For patients who receive doses greater than the recommended dosage regimen and have unexpected adverse reactions associated with ZEVTERA, discontinue ZEVTERA, treat symptomatically, and institute general supportive treatment.

ZEVTERA can be removed by hemodialysis. However, no information is available on the use of hemodialysis to treat overdose *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

ZEVTERA (ceftobiprole medocaril sodium for injection) contains sodium salt of ceftobiprole medocaril, a, semisynthetic, cephalosporin antibacterial, for intravenous use. Chemically, ceftobiprole medocaril is (6*R*,7*R*)-7-[[(2*Z*)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-hydroxyiminoacetyl]amino]-3-[(*E*)-[1-[(3*R*)-1-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxycarbonyl]pyrrolidin-3-yl]-2-oxopyrrolidin-3-ylidene]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid. Its molecular weight is 690.6 g/mol. The empirical formula is $C_{26}H_{25}N_8NaO_{11}S_2$.

Figure 1 Chemical Structure of ceftobiprole medocaril



ZEVTERA vials contain 667 mg of ceftobiprole medocaril sodium (equivalent to 500 mg of ceftobiprole). The powder for injection is a white, yellowish to slightly brownish sterile

powder. Each vial includes inactive ingredient citric acid monohydrate (26.3 mg/vial) as a buffer component and sodium hydroxide (q.s.) as a pH adjustment agent. Each vial of ZEVTERA contains approximately 32 mg of sodium.

The pH of the reconstituted solution is 4.5–5.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ZEVTERA is an antibacterial drug *[see Microbiology (12.4)]*

12.2 Pharmacodynamics

Ceftobiprole exposure-response relationships and the time course of pharmacodynamic response are unknown.

Time Above the Minimum Inhibitory Concentration (MIC)

The time that the unbound plasma concentration of ceftobiprole exceeds the MIC of *Staphylococcus aureus* , *Streptococcus pneumoniae*, and species of Enterobacterales correlates with efficacy in a neutropenic murine thigh infection model *[see Clinical Pharmacology (12.4)]*.

Cardiac Electrophysiology

At a dose 1 to 2 times the maximum recommended dose, ZEVTERA does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Ceftobiprole medocaril is the prodrug of the active moiety ceftobiprole. No clinically significant differences in the pharmacokinetics of ceftobiprole were observed with ZEVTERA following single or multiple dose administration. Ceftobiprole exhibits linear and time-independent pharmacokinetics. The C_{max} and AUC increase proportionally with the dose over a range of 125 to 1000 mg (0.25 to 2 times the highest approved recommended adult dosage).

The pharmacokinetic properties of ceftobiprole are summarized in Table 11.

The mean pharmacokinetic parameters of ceftobiprole in healthy adults with normal renal function after single and multiple 2-hour IV infusions of ZEVTERA 667 mg (equivalent to 500 mg of ceftobiprole) administered every 8 hours are summarized in Table 11. Pharmacokinetic parameters were similar for single and multiple dose administrations.

Table 11 Mean (Standard Deviation) Pharmacokinetic Parameters of ZEVTERA in Healthy Adults

Parameter	**Multiple doses administered every 8 hours as a 2-hour infusion (n = 27)**
C_{max} (µg/mL)	33.0 (4.83)
AUC_{0-8h} (µg.h/mL)	102 (11.9)
Distribution	

% Bound to human plasma protein	16
% ELF/unbound plasma	15-19
Vss (L)	18
Metabolism	
	Minimally Metabolized
$t_{1/2}$ (h)	3.3 (0.3)
CL (L/h)	4.98 (0.582)
Excretion	
Major route of elimination	Renal
% excreted unchanged in urine	83

C_{max} = Maximum plasma concentration; $AUC_{0\text{-}8h}$ = Area under the plasma concentration-time curve from 0 to 8 h; V_{ss} = Volume of distribution at steady state; CL = Clearance.

Specific Populations

No clinically significant differences in the pharmacokinetics of ceftobiprole were observed in adults based on age (18 to 91 years), gender (36% female), or race/ethnicity (88% white, 3% Black, 5% Asian). The effect of hepatic impairment on ceftobiprole pharmacokinetics is unknown.

Patients with Renal Impairment

No clinically significant differences in the pharmacokinetics of ceftobiprole were observed in adult subjects and subjects with mild renal impairment (CL_{CR} 50 to 80 mL/min). Ceftobiprole AUC increased 2.5-fold in adult subjects with moderate renal impairment (CL_{CR} 30 to < 50 mL/min) and 3.3-fold in severe renal impairment (CL_{CR} < 30 mL/min). The effect of any degree of renal impairment in pediatric patients less than 2 years of age or in pediatric patients with CL_{CR} < 15 mL/min/1.73 m^2 on ceftobiprole pharmacokinetics is unknown.

End-stage Renal Disease Requiring Dialysis

No clinically significant difference in the pharmacokinetics of ceftobiprole were observed in adult patients with ESRD (CL_{CR} < 15 mL/min) compared to healthy adult subjects based on limited PK data and pharmacokinetic modeling and simulation. Ceftobiprole was demonstrated to be removed by hemodialysis in patients receiving ZEVTERA.

Patients with Augmented Renal Clearance

A clinically significant reduction in ceftobiprole exposure is predicted in adult patients with augmented renal clearance (CL_{CR} > 150 mL/min) based upon a mechanistic understanding of this drug. The effect of augmented renal clearance (CL_{CR} > 150 mL/min) on ceftobiprole pharmacokinetics in pediatric patients is unknown.

Pediatric Use

No clinically significant differences in the pharmacokinetics of ceftobiprole were observed between pediatric patients from birth to < 18 years with normal renal function following administration of an intravenous dose of ZEVTERA. ZEVTERA is not approved for use in pediatric patients less than 3 months of age *[see Use in Specific Populations*

(8.4)].

Drug Interaction Studies

In Vitro Studies

Ceftobiprole does inhibit or induce CYP450 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5.

Transporter Systems: Ceftobiprole is an inhibitor of OATP1B1, OATP1B3, MRP2 and BSEP but is not an inhibitor of P-glycoprotein, BCRP, OAT1, OAT3, OCT1, OCT2, or MATE1.

12.4 Microbiology

Mechanism of Action

Ceftobiprole is a cephalosporin with bactericidal activity by inhibition of bacterial cell wall synthesis. Ceftobiprole has *in vitro* activity against gram-positive and gram-negative bacteria, including methicillin-resistant and susceptible *Staphylococcus aureus*. Bactericidal activity is mediated through binding to essential penicillin-binding proteins (PBPs) and inhibiting their transpeptidase activity, which is essential for the synthesis of the peptidoglycan layer of the bacterial cell wall. Ceftobiprole has a high affinity for *S. aureus* PBPs 1 – 4, including PBP2a in methicillin-resistant *Staphylococcus aureus*, and PBP2x and PBP2b in penicillin-resistant *Streptococcus pneumoniae*.

Resistance

Ceftobiprole is not active against gram-negative bacteria producing extended-spectrum β-lactamases (ESBLs) from the TEM, SHV or CTX-M families, serine carbapenemases (such as KPC), class B metallo-β-lactamases, class C (AmpC cephalosporinases) if expressed at high levels), and Ambler class D β-lactamases including carbapenemases.

No cross-resistance with other classes of antimicrobials has been identified. Although cross-resistance may occur, some isolates resistant to other cephalosporins may be susceptible to ceftobiprole.

Interaction with Other Antimicrobials

In vitro studies have not demonstrated any antagonism between ceftobiprole and other commonly-used antibacterial agents (e.g., gentamicin, vancomycin, daptomycin, rifampicin) against strains of *Staphylococcus aureus*. Against *Escherchia coli*, no antagonism was observed between ceftobiprole and doripenem or levofloxacin.

Activity against Bacteria in Animal Infection Models

Ceftobiprole demonstrated activity in a neutropenic murine thigh infection model reducing tissue counts of MRSA. Ceftobiprole was effective in treating experimental murine septicemia for strains of MSSA, MRSA, *S. pneumoniae* (including strains of penicillin-resistant *S. pneumoniae* [PRSP]), *E. coli* expressing TEM-1 and Act-1 AmpC cephalosporinase, *K. pneumoniae*, *C. freundii*, *S. marcescens*, and *P. mirabilis*. In an acute mouse model of pneumonia ceftobiprole was effective against *S. pneumoniae* (ceftobiprole MICs < 0.5 µg/mL)including a strain of PRSP). In a rabbit model of meningitis ceftobiprole was effective at clearing strains of *E. coli*, *K. pneumoniae* and β-lactamase positive and negative *H. influenzae*. In both a rat and rabbit model of endocarditis, ceftobiprole did not sterilize but was effective in reducing cardiac vegetations of MRSA including a vancomycin intermediate strain (ceftobiprole MIC ≤ 2

µg/mL). Similarly in both a rat and rabbit model of osteomyelitis, ceftobiprole was effective in clearing MRSA infection (ceftobiprole MIC ≤ 1µg/mL). The clinical significance of the above findings in animal infection models is not known.

Antimicrobial Activity

ZEVTERA has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections *[see Indications and Usage (1.3)].*

SAB

Gram-positive bacteria
- *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant isolates)

ABSSSI

Gram-positive bacteria
- *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant isolates)
- *Streptococcus pyogenes*

Gram-negative bacteria
- *Klebsiella pneumoniae*

CABP

Gram-positive bacteria
- *Staphylococcus aureus* (including methicillin-susceptible isolates)
- *Streptococcus pneumoniae*

Gram-negative bacteria
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Haemophilus influenzae*
- *Haemophilus parainfluenzae*

The following *in vitro* data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for ZEVTERA against isolates of similar genus or organism group. However, the efficacy of ZEVTERA in treating clinical infections caused by these bacteria has not been established in adequate and well-controlled clinical trials.

Gram-positive bacteria
- *Staphylococcus epidermidis*
- *Staphylococcus hominis*
- *Staphylococcus lugdunensis*
- *Streptococcus agalactiae*
- *Streptococcus mitis group*
- *Streptococcus dysgalactiae*
- *Streptococcus anginosus group*

Gram-negative bacteria

- *Citrobacter koseri*
- *Enterobacter cloacae*
- *Klebsiella aerogenes*
- *Moraxella catarrhalis*
- *Morganella morganii*
- *Proteus mirabilis*

Susceptibility Test Methods

For specific information regarding susceptibility testing methods, interpretive criteria, and associated test methods and quality control standards recognized by FDA for ZEVTERA, see: https://www.fda.gov/STIC.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No animal studies have been performed to evaluate the carcinogenic potential of ZEVTERA as none were warranted.

Mutagenesis

Ceftobiprole medocaril was negative in a standard bacterial reverse mutation test, however, the test was limited by bactericidal activity. Further genetic toxicology studies performed in vitro in mammalian cells showed that both ceftobiprole medocaril (pro-drug) and ceftobiprole (active metabolite) induced mutations at the TK locus in mouse lymphoma L5178Y TK+/- cells, however the pro-drug did not induce mutations in an in vitro HPRT forward mutation assay in CHO cells.

Ceftobiprole medocaril was positive for structural chromosome aberrations in human peripheral blood lymphocytes. When administered intravenously, ceftobiprole medocaril was negative for clastogenic effects in the in vivo mouse bone marrow micronucleus assay.

Impairment of Fertility

Administration of repeated doses of intravenous ceftobiprole medocaril at doses up to 360 mg/kg (approximately 1.4 times the MRHD based on BSA comparisons) to male and female rats starting approximately 2 weeks prior to mating, during mating and continuing through implantation (up to GD 7) were without effect on fertility or early fetal development.

13.2 Animal Toxicology and/or Pharmacology

Both rats and marmosets showed convulsions and thrombi and/or emboli with dosing durations greater than one month. In the 13-week intravenous rat study, clonic convulsions were noted at 500 mg/kg/day (2 times the MRHD based on BSA comparisons) with early deaths seen at 250 mg/kg in the males (1 time the MRHD based on BSA comparison). In the 13-week intravenous marmoset study, convulsions and thrombi were noted at multiple sites distal to the injection site (i.e., lung, and heart) at

doses ≥ 50 mg/kg/day (0.1 times the MRHD, based on BSA comparisons). While dogs did not show convulsions in a 13-week toxicology study, catheter patency could only be maintained between 4 to 11 weeks in most animals at doses up to 32 mg/kg/day (0.4 times the MRHD based on BSA comparisons). Fibrin, erythrocytes and inflammatory cells within the lumens of the catheters were noted in the 13-week dog study, while thrombi were observed at the injection site in all species tested. Kidney findings were also noted in the 13-week studies in rats (tubular/duct eosinophilic bodies and presence of foreign material) at 1 times the MRHD.

14 CLINICAL STUDIES

14.1 *Staphylococcus aureus* Bloodstream Infection (Bacteremia)

Adult Patients

Trial design

The efficacy of ZEVTERA in the treatment of adult patients with SAB, including right-sided infective endocarditis, was demonstrated in a randomized, controlled, double-blind, multinational, multicenter trial (Trial 1) (NCT03138733). In this trial, adult patients were randomized to either ZEVTERA 667 mg (equivalent to 500 mg of ceftobiprole) IV every 6 hours from study Day 1 to Day 8, and 667 mg IV every 8 hours from study Day 9 onwards) or daptomycin (6 mg/kg up to 10 mg/kg IV every 24 hours) plus optional aztreonam for coverage of gram-negative co-infections (the comparator). Randomization was stratified by study site, dialysis status, and use of prior antibacterial drugs.The study was performed in two cohorts based on findings in animal studies *[see Nonclinical Toxicology (13.2)]*. The initial cohort was enrolled to receive a maximum treatment duration of 28 days. Based on a safety evaluation of cohort 1, patients could be enrolled in cohort 2 to receive a treatment duration of up to 42 days. The duration of study treatment was based on the investigator's clinical evaluation.

Study patients were required to have at least one positive blood culture for *S. aureus* obtained within 72 hours prior to randomization, signs and symptoms of bacteremia (fever, elevated white blood cell count or immature neutrophils, tachycardia, or hypotension), and at least one of the following conditions of complicated *S. aureus* bacteremia: chronic dialysis, persistent SAB, acute bacterial skin and skin structure infection, metastatic infections of native tissue, osteomyelitis, epidural or cerebral abscess, or definite native-valve right-sided infective endocarditis by Modified Duke's Criteria. Patients with uncomplicated *S. aureus* bacteremia, left-sided infective endocarditis, prosthetic heart valves, foreign body material that could not be removed, severe neutropenia, or pneumonia, were excluded from the study.

Upon entry, patients were classified for likelihood of endocarditis using the modified Duke's criteria (definite, possible, or rejected). Echocardiography, including a transesophageal echocardiogram, was to be performed during screening or within 7 days following study enrollment. Final diagnoses were to be made by the study investigators within 7 days of randomization. The final diagnosis for persistent *S. aureus* bacteremia was made by an independent treatment-blinded Data Review Committee (DRC).

Baseline Demographic and Disease Characteristics

A total of 390 patients (192 ZEVTERA, 198 daptomycin) with SAB were randomized from 60 centers in the USA, Europe, Latin America, and South Africa. The modified ITT (mITT) population was used for the primary efficacy analysis, comprising 387 patients (189 ZEVTERA, 198 daptomycin ± aztreonam) who received study drugs and had a baseline blood culture positive for *S. aureus*.

Patient demographic and baseline characteristics were balanced between the treatment groups. The median age among the 387 patients in the mITT population was 58 years, ranging from 19 to91 years), with 31% aged ≥ 65 years, 69% of patients were male, and 96% were White.

Frequent conditions of complicated SAB included acute bacterial skin and skin structure infections (61%), intra-abdominal abscesses (14%), osteoarticular infections (13%), and patients on chronic dialysis (13%). A total of 6.5% of patients had definite right-sided infective endocarditis. A total of 24% had bacteremia caused by methicillin-resistant *S. aureus* (MRSA).

Efficacy Results

The primary efficacy outcome in the study was overall success at the post-treatment evaluation (PTE) visit at 70 days post-randomization in the mITT population, as assessed by the independent DRC.

Overall success required survival, symptom improvement, *S. aureus* bacteremia bloodstream clearance, no new *S. aureus* bacteremia complications, and no use of other potentially effective antibacterial drugs.

Overall success rates at the PTE visit in the mITT population were 69.8% (132/189) in patients treated with ZEVTERA and 68.7% (136/198) in patients treated withthe comparator. The overall primary study outcome and in pre-defined subgroups in the mITT population is shown in Table 12.

Table 12 Data Review Committee Overall Success Rate at the PTE Visit in the mITT Population from the Adult SAB Patients in Trial 1

Group/Subgroup	**ZEVTERA n/N (%)**	**Daptomycin ± aztreonam n/N (%)**	**Between-group Difference (%) (2-sided 95% CI)***
Overall	132/189 (69.8)	136/198 (68.7)	2.0 (−7.1, 11.1)
MSSA (methicillin-susceptible)	100/141 (70.9)	97/146 (66.4)	4.8 (−5.9, 15.5)
MRSA (methicillin-resistant)	31/45 (68.9)	38/49 (77.6)	−8.3 (−25.3, 8.6)
ABSSSI	81/116 (69.8)	80/121 (66.1)	4.5 (−7.3, 16.3)
Definite right-sided infective endocarditis	10/15 (66.7)	7/10 (70.0)	−6.6 (−40.1, 27.0)

* Between-group difference of ceftobiprole minus daptomycin ± aztreonam using Cochran-Mantel-Haenszel weights method adjusted for actual stratum (dialysis status and prior antibacterial treatment use).

For patients enrolled in Ukraine, overall success rates at the PTE visit in the mITT population were 77/84 (84.1%) in patients treated with ZEVTERA and 82/92 (89.1%) in patients treated with the comparator. For patients enrolled outside Ukraine, overall success rates at the PTE visit in the mITT population were 58/101 (57.4%) in patients treated with ZEVTERA and 54/106 (50.9%) in patients treated with the comparator.

All-cause mortality between randomization and the PTE visit was observed in 17/189 (9.0%) patients treated with ZEVTERA, and 18/198 (9.1%) patients treated with the comparator. Other key secondary efficacy outcomes included microbiological eradication at the PTE visit in the mITT population, which was achieved in 82% of patients treated with ZEVTERA and 77% of patients treated with the comparator, and the development of new *S. aureus* bacteremia complications, which occurred in 6% of patients treated with ZEVTERA and 6% of patients treated with the comparator. *S. aureus* bloodstream clearance, defined as 2 consecutive study days with negative blood cultures for *S. aureus* with no subsequent *S. aureus* relapse or reinfection, was achieved after a median of 4 days in each treatment group.

S. aureus bloodstream clearance in patients with MSSA was achieved after a median of 3 days in patients treated with ZEVTERA and after a median of 4 days in patients treated with the comparator.

S. aureus bloodstream clearance in patients with MRSA was achieved after a median of 5 days in each treatment group.

Failure of treatment due to relapse of *S. aureus* bacteremia was assessed by the DRC in two patients (1%) treated with ZEVTERA, and in four patients (2%) treated in the comparator arm. No increase in ceftobiprole MIC was observed for the two isolates from the ZEVTERA treated patients.

14.2 Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

Adult Patients

Trial Design

The efficacy of ZEVTERA in the treatment of adult patients with ABSSSI was demonstrated in a randomized, controlled, double-blind, multinational, multicenter trial (Trial 2) (NCT03137173). Patients were randomized to either ZEVTERA 667 mg (equivalent to 500 mg of ceftobiprole) IV every 8 hours or vancomycin plus aztreonam (vancomycin 1 gram or 15 mg/kg IV every 12 hours, aztreonam 1 gram IV every 12 hours). Randomization was stratified by study site and type of ABSSSI. Treatment duration was 5 to 14 days. Patients could receive concomitant metronidazole for suspected anaerobic infection. A switch to oral therapy was not allowed.

The study enrolled adult patients with ABSSSI (cellulitis/erysipelas, major cutaneous abscess, wound infection) with a lesion area of at least 75 cm^2, systemic or regional signs of infection, and a requirement for IV antibiotic treatment. Patients with other forms of ABSSSI, uncomplicated skin and skin structure infections, or infections related to prosthetic devices, were excluded.

The ITT primary analysis population comprised all patients randomized.

The primary endpoint, assessed in the ITT population, was early clinical response 48–72 hours after start of treatment. Early clinical response required a reduction of the primary skin lesion by at least 20%, survival for at least 72 hours, and the absence of concomitant antibacterial treatment or additional unplanned surgery.

The main secondary endpoint was investigator-assessed clinical success at the test-of-cure (TOC) visit 15 to 22 days after randomization and at least 5 days after the end-of-treatment.

A total of 679 patients (335 ZEVTERA, 344 vancomycin plus aztreonam) were randomized from 32 centers in the USA and Europe. The microbiological ITT (mITT) population included 506 patients with at least one valid baseline pathogen.

Baseline Demographic and Disease Characteristics

Patient demographic and baseline characteristics in the ITT population were balanced between the treatment groups. Approximately 95% of patients were classified as White, 59% were male, the median age was 50 years (range: 18 to 89), and the mean body mass index was 28 kg/m^2, 62% of patients were enrolled in the USA, and 38% in Europe. A history of diabetes was present in 11% of patients and current injection drug use was reported in 33% of patients. The types of ABSSSI included cellulitis/erysipelas (33%), wound infection (39%), and major cutaneous abscesses (28%). The median area of the primary skin infection was 259 cm^2.

Efficacy Results

The primary and main secondary outcomes are shown in Table 13.

Table 13 Primary and Main Secondary Efficacy Outcomes from the Adult Patients with ABSSSI in Trial 2

	ZEVTERA n/N (%)	**Vancomycin plus aztreonam n/N (%)**	**Between-group Difference (%) (2-sided 95% CI)***
Primary endpoint analyses†			
Early clinical response at 48–72 hours after start of treatment (ITT)	306/335 (91.3)	303/344 (88.1)	3.3 (−1.2, 7.8)
Main secondary endpoint analysis‡			
Investigator-assessed clinical success at the TOC visit (ITT)	302/335 (90.1)	306/344 (89.0)	1.0 (−3.5, 5.6)

* Between-group difference of ceftobiprole minus vancomycin plus aztreonam, using Cochran-Mantel-Haenszel weights method adjusted for geographical region and actual type of ABSSSI.

† Early clinical response based on at least 20% reduction from baseline in the area of the primary lesion, survival for ≥ 72 hours from the time of administration of the first dose of study drug, no use of concomitant systemic antibacterial treatments or topical antibacterial administration on the primary

lesion, and no additional unplanned surgical procedure for the ABSSSI after the start of study treatment.

‡ Clinical success was defined as complete (cured) or nearly complete (improved) resolution of baseline signs and symptoms of the primary infection, such that no further antibacterial treatment was needed.

Clinical response rates at TOC by the most common baseline pathogens in the microbiological ITT (mITT) population, defined as all randomized patients with a baseline pathogen, are presented in Table 14.

Table 14 Primary Efficacy Outcome by Pathogen from the Adult Patients with ABSSSI in Trial 2

	Early clinical response at 48–72 hours after start of treatment* (mITT)		**Investigator-assessed clinical success at the TOC visit† (mITT)**	
Pathogen	**ZEVTERA n/N (%)**	**Vancomycin plus aztreonam n/N (%)**	**ZEVTERA n/N (%)**	**Vancomycin plus aztreonam n/N (%)**
Any gram-positive pathogen	213/228 (93.4)	220/244 (90.2)	203/228 (89.0)	217/244 (88.9)
Staphylococcus aureus	186/197 (94.4)	185/205 (90.2)	174/197 (88.3)	180/205 (87.8)
Methicillin-susceptible	102/108 (94.4)	112/124 (90.3)	95/108 (88.0)	107/124 (86.3)
Methicillin-resistant	81/86 (94.2)	67/73 (91.8)	76/86 (88.4)	66/73 (90.4)
Streptococcus pyogenes	17/20 (85.0)	23/24 (95.8)	17/20 (85.0)	22/24 (91.7)
Any gram-negative pathogen	26/27 (96.3)	33/37 (89.2)	24/27 (88.9)	34/37 (91.9)
Enterobacterales	16/16 (100.0)	24/27 (88.9)	15/16 (93.8)	25/27 (92.6)
Klebsiella pneumoniae	8/8 (100.0)	5/5 (100.0)	7/8 (87.5)	5/5 (100.0)

* Early clinical response based on at least a 20% reduction from baseline in the area of the primary lesion, survival for ≥ 72 hours from the time of administration of the first dose of study drug, no use of concomitant systemic antibacterial treatments, or topical antibacterial administration on the primary lesion and no additional unplanned surgical procedure for the ABSSSI after the start of study treatment.

† Clinical success was defined as complete (cured) or nearly complete (improved) resolution of baseline signs and symptoms of the primary infection such that no further antibacterial treatment was needed.

14.3 Community-Acquired Bacterial Pneumonia

Adult Patients

Trial Design

The efficacy of ZEVTERA in the treatment of adult patients with community-acquired bacterial pneumonia (CABP) was demonstrated in a randomized, controlled, double-blind, multinational, multicenter study (Trial 3) (NCT00326287). 638 adults hospitalized with CABP and requiring IV antibacterial treatment for at least 3 days were included in the intent-to-treat (ITT) population, comparing ZEVTERA 667 mg (equivalent to 500 mg of ceftobiprole) IV every 8 hours to ceftriaxone (2 grams IV every 24 hours) with optional linezolid (600 mg IV every 12 hours) for the coverage of resistant gram-positive pathogens, including methicillin-resistant *S. aureus* (MRSA). Randomization was stratified by Pneumonia Outcomes Research Team (PORT) classification I to III versus IV to V, and by the need for adjunctive treatment with linezolid or matching placebo. The treatment duration was 5–14 days. No adjunctive macrolide therapy was allowed. A switch to oral cefuroxime (500 mg every 12 hours) was allowed after at least 72 hours of IV study treatment for patients who met stringent protocol-specified criteria for improvement and were candidates for hospital discharge.

The study enrolled adult patients hospitalized with CABP based on clinical signs and symptoms, fever and/or leukocytosis/leukopenia, and new radiographic evidence of pulmonary infiltrates. Patients with known bronchial obstruction, pulmonary malignancies, cystic fibrosis, lung abscess, pleural effusion as the primary source of infection, active tuberculosis, or pneumonia known or suspected to be caused by atypical bacteria, were excluded from study participation, as were patients with known or suspected extrapulmonary complications such as concomitant meningitis, endocarditis, septic arthritis, or osteomyelitis.

The ITT primary analysis population comprised all patients randomized. The clinically evaluable (CE) population comprised patients in the ITT population who received at least 48 hours of study medication and met protocol-defined criteria regarding clinical evaluability.

The protocol-specified primary efficacy analyses included clinical cure rates at TOC visit, 7 to 14 days after the end-of-treatment (EOT) in the co-primary ITT and CE populations. The ITT population comprised 638 patients (314 ZEVTERA, 324 ceftriaxone ± linezolid), in 103 centers in the USA, Asia, Europe, and Latin America. The CE population comprised 469 patients, and the microbiological ITT (mITT) population comprised 184 patients with at least one valid baseline pathogen.

Baseline Demographic and Disease Characteristics

Patient demographic and baseline characteristics in the ITT population were balanced between the treatment groups. Approximately 62% of patients were classified as White, and 57% were male. The median age was 56 years (range 18–94). 48% of patients were categorized at baseline as PORT classification III to V, and 22% of patients as PORT classification IV or V. 40% of patients did not receive any prior antibacterial drugs within 30 days of randomization. 12% of patients in the ceftriaxone arm received adjunctive linezolid, and 52% of patients in the ITT population switched to oral antibacterial therapy after at least 72 hours of IV study treatment.

Efficacy Results

The results for clinical cure at the test-of-cure visit at Day 7 to 14 after end of treatment are shown in Table 15.

Table 15 Clinical Cure at Test of Cure visit, 7 to 14 days After End-of-Treatment, in Adult Patients with CABP in Trial 3

	ZEVTERA n/N (%)	Ceftriaxone ± Linezolid n/N (%)	Between-group Difference (%) (two-sided 95% CI)*
Clinical cure† at TOC visit (ITT)	240/314 (76.4)	257/324 (79.3)	−2.9 (−9.3, 3.6)
Clinical cure† at TOC visit (CE)	200/231 (86.6)	208/238 (87.4)	−0.8 (−6.9, 5.3)

* Between-group difference of ceftobiprole minus ceftriaxone ± linezolid. Two-sided 95% CI is based on the Normal approximation to the difference of the two proportions.

† Clinical cure was defined as survival with resolution of signs and symptoms of the infection or improvement to such an extent that no further antimicrobial therapy was necessary; improvement or stabilization of chest X-ray findings and no receipt of non-study antibacterial treatment for CABP.

The 30-day all-cause mortality rates in the ITT population were 5/314 (1.6%) for patients treated with ZEVTERA, and 8/324 (2.5%) for patients treated with ceftriaxone ± linezolid group.

As this study was designed prior to the current regulatory guidelines, post-hoc re-analyses were conducted to determine the consistency of study results with these guidelines. These post-hoc analyses considered an earlier timepoint of clinical success at Day 3 in patients in the ITT population, based on survival and the improvement in at least two, and no worsening in any, of the following symptoms: pleuritic chest pain, cough, purulent sputum production or respiratory secretion, tachypnea.

Clinical success at Day 3 was also evaluated in the following analysis populations which were also defined post-hoc:

The Day 3-ITT population included 97% (618 of 638) of ITT patients who had at least two of the following symptoms at baseline: difficulty breathing, cough, production of purulent sputum, or chest pain.

The Day 3-modified ITT population included Day 3-ITT patients with baseline PORT classification of PORT Risk Class ≥ III, at least two of fever, hypothermia, hypotension, tachycardia, and tachypnea, as well as, at least one of new-onset hypoxemia, rales or pulmonary consolidation, and leukocytosis or leukopenia and new radiographic infiltrates (not related to another disease process) consistent with the diagnosis of bacterial pneumonia.

The Day 3-micro ITT population was the subset of the Day 3-ITT patients who had a valid pathogen at baseline.

Results of early clinical success at Day 3 in the Day 3-ITT and Day 3- modified ITT populations are shown in Table 16 below:

Table 16 Early Clinical Success at Day 3 in Adult Patients with

CABP Based on a Post-hoc Analysis of Trial 3

	ZEVTERA n/N (%)	Ceftriaxone ± linezolid n/N (%)	Between-group Difference (%) (two-sided 95% CI)*
Day-3 ITT Population			
Clinical Success at Day 3†	218/307 (71.0)	221/311 (71.1)	-0.1% (-7.2, 7.1)
Day-3 modified ITT Population			
Clinical Success at Day 3	69/97 (71.1)	60/90 (66.7))	4.5% (−8.8, 17.7))

* Between-group difference of ceftobiprole minus ceftriaxone ± linezolid. Two-sided 95% CI is based on the Normal approximation to the difference of the two proportions.

† Clinical success based on improvement in at least two, with no worsening in any, of the following symptoms: pleuritic chest pain, cough, purulent sputum production or respiratory secretion, tachypnea. Seven patients in the ZEVTERA arm and 13 patients in the comparator arm did not report any of these symptoms, and were therefore not included in the ITT population for the analysis evaluating early clinical success at Day 3.

Clinical response rates at TOC by most common baseline pathogen in the mITT population, defined as all randomized patients with a baseline pathogen, are presented in Table 17.

Table 17 Clinical Cure at Test of Cure Visit and Post-hoc Outcome of Early Clinical Success at Day 3 by Pathogen in Adult CABP Patients in Trial 3

	Clinical Cure at the TOC visit* (micro-ITT)		Early Clinical Success at Day 3† (Day 3 micro-ITT)	
Pathogen	**ZEVTERA n/N (%)**	**Ceftriaxone ± linezolid n/N (%)**	**ZEVTERA n/N (%)**	**Ceftriaxone ± linezolid n/N (%)**
Any gram-positive pathogen	37/48 (77.1)	40/53 (75.5)	36/46 (78.3)	35/52 (67.3)
Staphylococcus aureus	10/14 (71.4)	6/10 (60.0)	10/14 (71.4)	7/10 (70.0)
Methicillin-susceptible	9/12 (75.0)	6/10 (60.0)	8/12 (66.7)	7/10 (70.0)
Streptococcus pneumoniae	29/35 (82.9)	33/41 (80.5)	27/33 (81.8)	27/41 (65.9)
Any gram-negative pathogen	39/49 (79.6)	43/51 (84.3)	35/49 (71.4)	40/51 (78.4)
Enterobacterales spp	14/18	11/16 (68.8)	14/18	13/16 (81.3)

Enterobacterales spp.	(77.8)	11/16 (68.8)	(77.8)	13/16 (81.3)
Escherichia coli	6/6 (100.0)	1/4 (25.0)	6/6 (100.0)	2/4 (50.0)
Klebsiella pneumoniae	6/8 (75.0)	7/8 (87.5)	7/8 (87.5)	7/8 (87.5)
Haemophilus influenzae	9/10 (90.0)	15/16 (93.8)	4/10 (40.0)	11/16 (68.8)
Haemophilus parainfluenzae	6/9 (66.7)	7/8 (87.5)	8/9 (88.9)	8/8 (100.0)

* Clinical cure was defined as resolution of signs and symptoms of the infection or improvement to such an extent that no further antimicrobial therapy was necessary; and improvement or stabilization of chest X-ray findings.
† Clinical success based on improvement in at least two, with no worsening in any, of the following symptoms: pleuritic chest pain, cough, purulent sputum production or respiratory secretion, tachypnea.

Pediatric Patients (3 months to < 18 Years of Age) with CABP

The pediatric pneumonia phase 3 study was a randomized, investigator-blind, active-controlled study in pediatric patients 3 months to < 18 years of age with CABP or hospital-acquired bacterial pneumonia (HABP) requiring IV antibacterial drug treatment (Trial 5) (NCT03439124). Although patients with HABP were included in the study, the safety and effectiveness of ZEVTERA for the treatment of HABP have not been established and ZEVTERA is not approved for the treatment of HABP.

138 pediatric patients were randomized in a 2:1 ratio to ZEVTERA 13.3 mg/kg (equivalent to 10 mg/kg of ceftobiprole) to 26.7 mg/kg (equivalent to 20 mg/kg of ceftobiprole - higher than the recommended approved dose) *[see Dosage and Administration (2.2, 2.4)].* ZEVTERA was administered by intravenous infusion every 8 hours based on age with a maximum dose of ZEVTERA 667 mg (equivalent to 500 mg of ceftobiprole) (n = 94) or a standard-of-care cephalosporin antibacterial drug (n = 44) for a treatment duration of 7 to 14 days. A switch to an age-appropriate oral antibacterial drug after study Day 3 was allowed.

The primary objective of this study was to evaluate the safety of ZEVTERA. The study was not powered for comparative inferential efficacy analysis, and no efficacy endpoint was identified as primary.

The numbers of patients in the age groups evaluated in the ZEVTERA arm were as follows: 18 pediatric patients aged 12 to < 18 years, 27 pediatric patients aged 6 to < 12 years, 37 pediatric patients aged 2 to < 6 years, and 12 pediatric patients (infants) aged 3 months to < 2 years.

Of the 138 pediatric patients enrolled in the ITT/Safety population, 94% had CABP requiring hospitalization, and 6% had HABP. Patients with ventilator-associated HABP were excluded from the study.

The median treatment duration with ZEVTERA was 6.0 days; 88% of patients treated with ZEVTERA switched to oral antibacterial drugs to complete treatment.

The clinical response was determined at study Day 4, the EOT visit, and at the TOC visit 7 to 14 days after the EOT visit. The ITT population included all patients randomized.

In the ITT population, the clinical response rates in the ZEVTERA and comparator arms were, respectively, 95.7% and 93.2% on Day 4 (between-group difference 2.6% [95% confidence interval (CI): -5.5, 14.7]), 96.8% and 100% at the EOT visit (between-group difference -3.2% [95% CI: -9.1, 5.5]), and 90.4% and 97.7% at the TOC visit (between-group difference -7.3% [95% CI: -15.7, 3.6]).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ZEVTERA (ceftobiprole medocaril sodium for injection), a white, yellowish to slightly brownish sterile powder for reconstitution, supplied in a single-dose clear glass vial (NDC# 68547-578-01) sealed with a rubber stopper (not made with natural rubber latex) and an aluminum seal with a flip-off cap. Each vial contains 667 mg ceftobiprole medocaril sodium (equivalent to 500 mg of ceftobiprole) and is supplied in a carton containing 10 single-dose vials (NDC# 68547-578-10).

16.2 Storage and Handling

Store ZEVTERA vials refrigerated at 2 °C to 8 °C (36 °F to 46 °F) protected from light. Store in carton until time of use.

ZEVTERA must be reconstituted and then further diluted prior to administration by intravenous infusion. Store reconstituted and diluted solution of ZEVTERA as described elsewhere in the labeling *[see Dosage and Administration (2.7)].*

17 PATIENT COUNSELING INFORMATION

Serious Allergic Reactions

Advise patients (or caregiver) that hypersensitivity reactions were reported with the use of ZEVTERA and that serious and occasionally fatal serious allergic reactions could occur and require immediate treatment. Advise patients to discontinue ZEVTERA if a hypersensitivity reaction occurs and inform their healthcare provider about any previous hypersensitivity reactions to ZEVTERA, other beta-lactams (including cephalosporins), or other allergens *[see Warnings and Precautions (5.2)].*

Seizures and Central Nervous System Adverse Reactions

Advise patients (or caregiver) that seizures and other adverse central nervous system (CNS) reactions have been reported during treatment with ZEVTERA. If CNS adverse reactions, including seizures, occur, advise patients to inform their healthcare provider to determine whether ZEVTERA should be discontinued *[see Warnings and Precautions (5.3)].*

Potentially Serious Diarrhea

Advise patients (or caregiver) that diarrhea is a common problem caused by antibacterial drugs, including ZEVTERA. Sometimes, frequent watery or bloody diarrhea may occur and may be a sign of a more serious intestinal infection. If severe watery or bloody diarrhea develops, instruct patients to contact their healthcare provider *[see Warnings and Precautions (5.4)].*

Antibacterial Resistance

Patients should be counseled that antibacterial drugs, including ZEVTERA, should be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). Patients should be told that the medication should be administered exactly as directed *[see Warnings and Precautions (5.5)].*

Manufactured for:
ISTx, LLC

Distributed by:
La Jolla Pharmaceutical Company, Waltham, MA 02451

Product of Japan.

ZEVTERA is a trademark of Basilea Pharmaceutica International Ltd., Allschwil.
Exclusively licensed by Basilea to ISTx, LLC in the USA

PRINCIPAL DISPLAY PANEL - 667 mg Vial Box

NDC# 68547-578-10

Rx Only
10 single-dose vials

ZEVTERA® 667 mg/vial*
(ceftobiprole medocaril sodium for injection)
*equivalent to 500 mg ceftobiprole

For intravenous use only.
Reconstitute and further dilute before use.
Single-dose vial. Discard unused portion.

F50000402486

NDC# 68547-578-10

Rx Only
10 single-dose vials

ZEVTERA® 667 mg/vial*

(ceftobiprole medocaril sodium for injection)

*equivalent to 500 mg ceftobiprole

For intravenous use only.
Reconstitute and further dilute before use.
Single-dose vial. Discard unused portion.

ZEVTERA® 667 mg/vial*
(ceftobiprole medocaril sodium for injection)

*equivalent to 500 mg ceftobiprole

Inactive ingredients: Citric acid monohydrate 26.3 mg/vial, sodium hydroxide to adjust pH

Product of Japan.

NDC# 68547-578-10

ZEVTERA® 667 mg/vial*
(ceftobiprole medocaril sodium for injection)

*equivalent to 500 mg ceftobiprole

For intravenous infusion. Reconstitute and further dilute before use.
Single-dose vials. Discard unused portion.

Rx Only
10 single-dose vials

GTIN 00368547578100

LOT:
EXP:
SN:

Storage: Store refrigerated at 2°C to 8°C (36°F to 46°F). Protect from light. Store vials in carton until time of use.

Dosage and Administration: See prescribing information. Reconstitute each single-dose vial with 10 ml of diluent as specified in the prescribing information to obtain a concentration of 66.7 mg/ml ceftobiprole medocaril sodium. Shake vigorously until dissolution is complete. The reconstituted solution in a vial can be stored for up to 1 hour at room temperature. Further dilute into an appropriate container prior to administration per prescribing information.

F50000402486

Distributed by:
La Jolla Pharmaceutical Company,
Waltham, MA 02451
For product complaints or questions, please call
1-800-651-3861

GTIN# 00368547578100

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ZEVTERA® 667 mg/vial*
(ceftobiprole medocaril sodium for injection)

*equivalent to 500 mg ceftobiprole

Inactive ingredients: Citric acid monohydrate 26.3 mg/vial, sodium hydroxide to adjust pH

P

ZEVTERA

ceftobiprole medocaril sodium injection, powder, for solution

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:68547-578
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
ceftobiprole medocaril sodium (UNII: N99027V28J) (ceftobiprole - UNII:5T97333YZK)	ceftobiprole medocaril sodium	667 mg

Inactive Ingredients	
Ingredient Name	**Strength**
citric acid monohydrate (UNII: 2968PHW8QP)	
sodium hydroxide (UNII: 55X04QC32I)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68547-578-10	10 in 1 BOX	04/01/2025	
1	NDC:68547-578-01	1 in 1 VIAL, GLASS; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA218275	04/01/2025	

Labeler - La Jolla Pharmaceutical Company (613541192)

Registrant - ISTx, LLC (119446715)

Revised: 3/2025 La Jolla Pharmaceutical Company