ZERBAXA®
ceftolozane and tazobactam
for injection (1.5 g)

Dosing and Administration Guide

Indications

- ZERBAXA is indicated for the treatment of adult patients (18 years and older) with hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP), caused by the following susceptible Gram-negative microorganisms: *Enterobacter cloacae*, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Serratia marcescens*.
- ZERBAXA is indicated for the treatment of adult and pediatric patients (birth to less than 18 years old) with complicated urinary tract infections (cUTI), including pyelonephritis, caused by the following susceptible Gram-negative microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*.
- ZERBAXA used in combination with metronidazole is indicated for the treatment of adult and pediatric patients (birth to less than 18 years old) with complicated intra-abdominal infections (cIAI) caused by the following susceptible Gram-negative and Gram-positive microorganisms: *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Bacteroides fragilis*, *Streptococcus anginosus*, *Streptococcus constellatus*, and *Streptococcus salivarius*.

Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ZERBAXA and other antibacterial drugs, ZERBAXA 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.

Important Safety Information

- **Patients with renal impairment:** Decreased efficacy of ZERBAXA has been observed in patients with baseline CrCl of 30 to ≤50 mL/min. In a clinical trial of adult patients, patients with cIAIs with CrCl >50 mL/min had a clinical cure rate of 85.2% when treated with ZERBAXA plus metronidazole vs 87.9% when treated with meropenem. In the same trial, patients with CrCl 30 to ≤50 mL/min had a clinical cure rate of 47.8% when treated with ZERBAXA plus metronidazole vs 69.2% when treated with meropenem. A similar trend was also seen in the cUTI trial. Dose adjustment is required for adult patients with CrCl 50 mL/min or less. All doses of ZERBAXA are administered over 1 hour. Monitor CrCl at least daily in patients with changing renal function and adjust the dose of ZERBAXA accordingly.

CrCl, creatinine clearance.

Please see additional Important Safety Information on the following pages and accompanying Prescribing Information.

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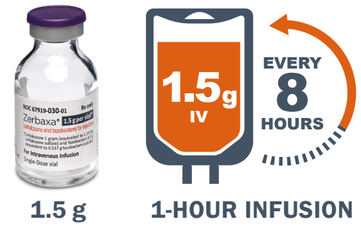
Dosage and Administration

Recommended Dosage in Adult Patients

The recommended dosage of ZERBAXA® (ceftolozane and tazobactam) in adult patients (18 years and older) with creatinine clearance (CrCl) greater than 50 mL/min is 1.5 gram (g) (ceftolozane 1 g and tazobactam 0.5 g) for cIAI and cUTI and 3 grams (ceftolozane 2 g and tazobactam 1 g) for HABP/VABP administered every 8 hours by intravenous infusion over 1 hour. The duration of therapy should be guided by the severity and site of infection and the patient's clinical and bacteriological progress, as shown below.

Dosage of ZERBAXA by Infection in Adult Patients (18 Years and Older) With CrCl[a] >50 mL/min

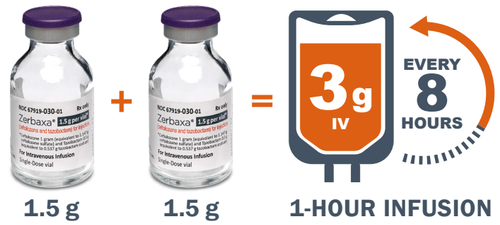
Infection	Dose	Frequency	Infusion Time	Duration of Treatment
Complicated intra-abdominal infections[b]	1.5 g	Every 8 hours	1 hour	4 to 14 days
Complicated urinary tract infections, including pyelonephritis	1.5 g	Every 8 hours	1 hour	7 days



1.5 g 1-HOUR INFUSION

Not actual size.

Infection	Dose	Frequency	Infusion Time	Duration of Treatment
Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP)	3 g	Every 8 hours	1 hour	8 to 14 days



1.5 g 1.5 g 1-HOUR INFUSION

IV, intravenous.

[a]CrCl estimated using Cockcroft-Gault formula.

[b]Used in conjunction with metronidazole 500 mg intravenously every 8 hours.

Important Safety Information *(continued)*

- **Hypersensitivity:** ZERBAXA is contraindicated in patients with known serious hypersensitivity to the components of ZERBAXA (ceftolozane/tazobactam), piperacillin/tazobactam, or other members of the beta-lactam class. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam antibacterials. Before initiating therapy with ZERBAXA, make careful inquiry about previous hypersensitivity reactions to cephalosporins, penicillins, or other beta-lactams. If an anaphylactic reaction to ZERBAXA occurs, discontinue use and institute appropriate therapy.

Please see additional Important Safety Information on the following pages and accompanying Prescribing Information.

ZERBAXA® ceftolozane and tazobactam for injection (1.5 g)

Dosage and Administration (*continued*)

Recommended Dosage in Pediatric Patients With cIAI or cUTI (Birth to Less Than 18 Years of Age)

The recommended dosage regimen of ZERBAXA® (ceftolozane and tazobactam) in pediatric patients from birth to less than 18 years of age with cIAI and cUTI with an estimated glomerular filtration rate (eGFR) greater than 50 mL/min/1.73m^2 is described below. ZERBAXA is administered every 8 hours by intravenous infusion over 1 hour. The duration of treatment should be guided by the severity and site of infection and the patient's clinical and bacteriological progress as shown below. For the treatment of cIAI, metronidazole should be given concurrently.

ZERBAXA is not recommended in pediatric patients who have an eGFR 50 mL/min/1.73m^2 or less.

There is insufficient information to recommend a dosage regimen for pediatric patients with HABP/VABP.

Dosage of ZERBAXA by Infection in Pediatric Patients (Birth to Less Than 18 Years of Age) With eGFR[a] Greater Than 50 mL/min/1.73m^2

Infection	Dose	Frequency	Infusion Time	Duration of Treatment
Complicated intra-abdominal infections[b]	30 mg/kg up to a maximum dose of 1.5 g[c]	Every 8 hours	1 hour	5 to 14 days
Complicated urinary tract infections including pyelonephritis	30 mg/kg up to a maximum dose of 1.5 g[c]	Every 8 hours	1 hour	7 to 14 days

eGFR, estimated glomerular filtration rate.

[a]Estimated GFR using an age-appropriate equation for use in the pediatric population.
[b]Used in conjunction with metronidazole.
[c]Pediatric patients weighing greater than 50 kg should not exceed a maximum dose of 1.5 g.

Important Safety Information (*continued*)

- ***Clostridioides difficile*-associated diarrhea (CDAD),** ranging from mild diarrhea to fatal colitis, has been reported with nearly all systemic antibacterial agents, including ZERBAXA. 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 confirmed, antibacterial use not directed against *C. difficile* should be discontinued, if possible.
- **Development of drug-resistant bacteria:** Prescribing ZERBAXA in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.
- **Adverse reactions in adult patients with HABP/VABP:** The most common adverse reactions occurring in ≥5% of adult patients receiving ZERBAXA in the HABP/VABP trial were hepatic transaminase increased (11.9%), renal impairment/renal failure (8.9%), and diarrhea (6.4%).

Please see additional Important Safety Information on the following pages and accompanying Prescribing Information.

ZERBAXA® ceftolozane and tazobactam for injection (1.5 g)

Dosage and Administration (*continued*)

Dosage Adjustments in Adult Patients With Renal Impairment

Dose adjustment is required for adult patients (18 years and older) with CrCl 50 mL/min or less, as shown below. All doses of ZERBAXA® (ceftolozane and tazobactam) are administered over 1 hour.

For patients with changing renal function, monitor CrCl at least daily and adjust the dosage of ZERBAXA accordingly.

Dosage of ZERBAXA in Adult Patients (18 Years and Older) With Renal Impairment (CrCl ≤50 mL/min)

Estimated CrCl (mL/min)[a]	Complicated Intra-abdominal Infections and Complicated Urinary Tract Infections, Including Pyelonephritis	Hospital-acquired Bacterial Pneumonia and Ventilator-associated Bacterial Pneumonia
30 to 50	750 mg (500 mg and 250 mg) intravenously every 8 hours	1.5 g (1 g and 0.5 g) intravenously every 8 hours
15 to 29	375 mg (250 mg and 125 mg) intravenously every 8 hours	750 mg (500 mg and 250 mg) intravenously every 8 hours
End-stage renal disease (ESRD) on hemodialysis (HD)	A single loading dose of 750 mg (500 mg and 250 mg) followed by a 150 mg (100 mg and 50 mg) maintenance dose administered intravenously every 8 hours for the remainder of the treatment period (on hemodialysis days, administer the dose at the earliest possible time following completion of dialysis)	A single loading dose of 2.25 g (1.5 g and 0.75 g) followed by a 450 mg (300 mg and 150 mg) maintenance dose administered intravenously every 8 hours for the remainder of the treatment period (on hemodialysis days, administer the dose at the earliest possible time following completion of dialysis)

CrCl, creatinine clearance.

[a]CrCl estimated using Cockcroft-Gault formula.

Dosage Adjustments in Pediatric Patients With Renal Impairment

Dosage adjustment of ZERBAXA in pediatric patients (birth to less than 18 years of age) with eGFR 50 mL/min/1.73 m^2 or less has not been determined.

ZERBAXA is not recommended in pediatric patients who have an eGFR 50 mL/min/1.73m^2 or less.

Important Safety Information (*continued*)

- **Adverse reactions in adult patients with cIAI or cUTI:** The most common adverse reactions occurring in ≥5% of adult patients receiving ZERBAXA in the cUTI and cIAI trials were headache (5.8%) in the cUTI trial, and nausea (7.9%), diarrhea (6.2%), and pyrexia (5.6%) in the cIAI trial.
- **Adverse reactions in pediatric patients with cIAI or cUTI:** The most common adverse reactions occurring in ≥7% of pediatric patients receiving ZERBAXA in the cIAI trial were diarrhea (17%), thrombocytosis (16%), pyrexia (13%), abdominal pain (11%), vomiting (10%), increased aspartate aminotransferase (7%), and anemia (7%). The most common adverse reactions occurring in ≥7% of pediatric patients receiving ZERBAXA in the cUTI trial were thrombocytosis (9%), leukopenia (8%), diarrhea (7%), and pyrexia (7%).

Please see additional Important Safety Information on the following pages and accompanying Prescribing Information.

ZERBAXA® ceftolozane and tazobactam for injection (1.5 g)

Preparation of Solutions

ZERBAXA® (ceftolozane and tazobactam) does not contain a bacteriostatic preservative. Aseptic technique must be followed in preparing the infusion solution.

STEP 1

Constitute each vial with 10 mL of sterile water for injection or 0.9% Sodium Chloride for Injection, USP

STEP 2

Gently shake to dissolve

- The final volume is approximately 11.4 mL per vial
- **CAUTION: THE CONSTITUTED SOLUTION IS NOT FOR DIRECT INJECTION**

STEP 3

To prepare the required dose, **withdraw** the appropriate volume determined from the table below from the reconstituted vial(s)

STEP 4

Add the withdrawn volume to an infusion bag containing 100 mL of 0.9% Sodium Chloride for Injection, USP or 5% Dextrose Injection, USP

STEP 5

For doses above 1.5 g:

- **Reconstitute** a second vial in the same manner as the first one
- **Withdraw** an appropriate volume, as shown in the table below
- **Add** to the same infusion bag

STEP 6

Discard unused portion

Preparation of Doses

ZERBAXA® (ceftolozane and tazobactam) Dose	Volume to Withdraw From Reconstituted Vial(s)
3 g (2 g and 1 g)	Two vials of 11.4 mL each (entire contents from two vials)
2.25 g (1.5 g and 0.75 g)	11.4 mL from one vial (entire contents) and 5.7 mL from a second vial
1.5 g (1 g and 0.5 g)	11.4 mL (entire contents from one vial)
750 mg (500 mg and 250 mg)	5.7 mL
450 mg (300 mg and 150 mg)	3.5 mL
375 mg (250 mg and 125 mg)	2.9 mL
150 mg (100 mg and 50 mg)	1.2 mL

Inspect drug products visually for particulate matter and discoloration prior to use. ZERBAXA infusions range from clear, colorless solutions to solutions that are clear and slightly yellow. Variations in color within this range do not affect the potency of the product.

Important Safety Information *(continued)*

- **Pediatric Use:** There is insufficient information to recommend dosage adjustment for pediatric patients younger than 18 years of age with cIAI and cUTI with eGFR 50 mL/min/1.73m^2 or less. ZERBAXA is not recommended in pediatric patients who have an eGFR 50 mL/min/1.73m^2 or less. Pediatric patients born at term or pre-term may not have an eGFR of 50 mL/min/1.73m^2 or greater at birth or within the first few months of life.

Please see additional Important Safety Information on the following pages and accompanying Prescribing Information.

ZERBAXA® ceftolozane and tazobactam for injection (1.5 g)

Preparation of Solutions (*continued*)

Compatibility

Compatibility of ZERBAXA® (ceftolozane and tazobactam) with other drugs has not been established. ZERBAXA should not be mixed with other drugs or physically added to solutions containing other drugs.

Storage of Constituted Solutions

Upon constitution with sterile water for injection or 0.9% sodium chloride injection, reconstituted ZERBAXA solution may be held for 1 hour prior to transfer and dilution in a suitable infusion bag.

Following dilution of the solution with 0.9% sodium chloride or 5% dextrose, ZERBAXA is stable for 24 hours when stored at room temperature or 7 days when stored under refrigeration at 2°C to 8°C (36°F to 46°F). Discard unused portion.

24 HOURS

Room temperature stability of ZERBAXA in a suitable infusion bag

7 DAYS

Stability under refrigeration of ZERBAXA in a suitable infusion bag: 2°C to 8°C (36°F to 46°F)

Constituted ZERBAXA solution or diluted ZERBAXA infusion should not be frozen.

Important Safety Information

- **Patients with renal impairment:** Decreased efficacy of ZERBAXA has been observed in patients with baseline CrCl of 30 to ≤50 mL/min. In a clinical trial of adult patients, patients with cIAIs with CrCl >50 mL/min had a clinical cure rate of 85.2% when treated with ZERBAXA plus metronidazole vs 87.9% when treated with meropenem. In the same trial, patients with CrCl 30 to ≤50 mL/min had a clinical cure rate of 47.8% when treated with ZERBAXA plus metronidazole vs 69.2% when treated with meropenem. A similar trend was also seen in the cUTI trial. Dose adjustment is required for adult patients with CrCl 50 mL/min or less. All doses of ZERBAXA are administered over 1 hour. Monitor CrCl at least daily in patients with changing renal function and adjust the dose of ZERBAXA accordingly.
- **Hypersensitivity:** ZERBAXA is contraindicated in patients with known serious hypersensitivity to the components of ZERBAXA (ceftolozane/tazobactam), piperacillin/tazobactam, or other members of the beta-lactam class. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam antibacterials. Before initiating therapy with ZERBAXA, make careful inquiry about previous hypersensitivity reactions to cephalosporins, penicillins, or other beta-lactams. If an anaphylactic reaction to ZERBAXA occurs, discontinue use and institute appropriate therapy.

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ZERBAXA® ceftolozane and tazobactam for injection (1.5 g)

How ZERBAXA® (ceftolozane and tazobactam) Is Supplied

ZERBAXA 1.5 g for injection is supplied in single-dose vials containing 1 g ceftolozane (equivalent to 1.147 g of ceftolozane sulfate) and 0.5 g tazobactam (equivalent to 0.537 g of tazobactam sodium) per vial, in a carton containing 10 vials.

Storage and Handling

ZERBAXA vials should be stored refrigerated at 2°C to 8°C (36°F to 46°F) and protected from light.

Package Size and Dimensions

Item Weight (Ounces per Vial)	Sales Package Size (Carton)	Carton Dimensions (L x H x W) (Inches)
13.2 oz	Ten (10) single-dose vials	6 5/16” x 2 11/16” x 2 9/16”

1.5 g

Ordering

National Drug Code for ZERBAXA IV Vials (10-ct)	67919-030-01

ZERBAXA is available for purchase by all Merck Authorized Distributors, including, but not limited to, the distributors listed below. Contact your supplier for availability.

Wholesaler	Order Entry Number
Cencora (formerly known as AmerisourceBergen Corporation)	10237721
Capital Wholesale Drug Co.	190030
Cardinal Health (includes Harvard Drug)	5045810
DMS Pharmaceutical Group	583420
McKesson Corporation	3971686
Morris & Dickson Co.	31179
NC Mutual	160648
Pharmacy Buying Association, Inc.	67919003001
Prescription Supply Inc.	855700
Smith Drug Company (Includes Burlington Drug Company)	737924
Value Drug	159049

Merck does not recommend the use of one authorized distributor over another. Merck does not make any warranty as to the services offered by any particular authorized distributor.

Important Safety Information *(continued)*

- ***Clostridioides difficile*-associated diarrhea (CDAD),** ranging from mild diarrhea to fatal colitis, has been reported with nearly all systemic antibacterial agents, including ZERBAXA. 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 confirmed, antibacterial use not directed against *C. difficile* should be discontinued, if possible.

Please see additional Important Safety Information on the following pages and accompanying Prescribing Information.

ZERBAXA® ceftolozane and tazobactam for injection (1.5 g)

ZERBAXA®
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Important Safety Information (*continued*)

- **Development of drug-resistant bacteria:** Prescribing ZERBAXA in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.
- **Adverse reactions in adult patients with HABP/VABP:** The most common adverse reactions occurring in ≥5% of adult patients receiving ZERBAXA in the HABP/VABP trial were hepatic transaminase increased (11.9%), renal impairment/renal failure (8.9%), and diarrhea (6.4%).
- **Adverse reactions in adult patients with cIAI or cUTI:** The most common adverse reactions occurring in ≥5% of adult patients receiving ZERBAXA in the cUTI and cIAI trials were headache (5.8%) in the cUTI trial, and nausea (7.9%), diarrhea (6.2%), and pyrexia (5.6%) in the cIAI trial.
- **Adverse reactions in pediatric patients with cIAI or cUTI:** The most common adverse reactions occurring in ≥7% of pediatric patients receiving ZERBAXA in the cIAI trial were diarrhea (17%), thrombocytosis (16%), pyrexia (13%), abdominal pain (11%), vomiting (10%), increased aspartate aminotransferase (7%), and anemia (7%). The most common adverse reactions occurring in ≥7% of pediatric patients receiving ZERBAXA in the cUTI trial were thrombocytosis (9%), leukopenia (8%), diarrhea (7%), and pyrexia (7%).
- **Pediatric Use:** There is insufficient information to recommend dosage adjustment for pediatric patients younger than 18 years of age with cIAI and cUTI with eGFR 50 mL/min/1.73m^2 or less. ZERBAXA is not recommended in pediatric patients who have an eGFR 50 mL/min/1.73m^2 or less. Pediatric patients born at term or pre-term may not have an eGFR of 50 mL/min/1.73m^2 or greater at birth or within the first few months of life.

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