HIGHLIGHTS OF PRESCRIBING INFORMATION

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

ZERBAXA (ceftolozane/tazobactam) for Injection, for intravenous use
Initial U.S. Approval: 2014

INDICATIONS AND USAGE

ZERBAXA (ceftolozane/tazobactam) is a combination product consisting of a cephalosporin-class antibacterial drug and a beta-lactamase inhibitor indicated for the treatment of the following infections caused by designated susceptible microorganisms:

- Complicated Intra-abdominal Infections, used in combination with metronidazole (1.1)
- Complicated Urinary Tract Infections, including Pyelonephritis (1.2)

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 infections that are proven or strongly suspected to be caused by susceptible bacteria.

DOSAGE AND ADMINISTRATION

- ZERBAXA (ceftolozane/tazobactam) for Injection, 1.5 g (1 g/0.5 g) every 8 hours by intravenous infusion administered over 1 hour for patients 18 years or older with creatinine clearance (CrCl) greater than 50 mL/min. (2.1)
- Dosage in patients with impaired renal function (2.2):

Estimated CrCl (mL/min)	Recommended Dosage Regimen for ZERBAXA
30 to 50	Ceftolozane/tazobactam 750 mg (500 mg/250 mg) intravenously every 8 hours
15 to 29	Ceftolozane/tazobactam 375 mg (250 mg/125 mg) intravenously every 8 hours
End-stage renal disease (ESRD) on hemodialysis (HD)	A single loading dose of ceftolozane/tazobactam 750 mg (500 mg/250 mg) followed by a 150 mg (100 mg/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)

DOSAGE FORMS AND STRENGTHS

ZERBAXA for Injection (ceftolozane/tazobactam) 1 g/0.5 g powder for reconstitution in single-dose vials containing 1 g ceftolozane (equivalent to 1.147 g ceftolozane sulfate) and 0.5 g tazobactam (equivalent to 0.537 g tazobactam sodium) (3)

CONTRAINDICATIONS

ZERBAXA is contraindicated in patients with known serious hypersensitivity to ceftolozane/tazobactam, piperacillin/tazobactam, or other members of the beta-lactam class. (4)

WARNINGS AND PRECAUTIONS

- Decreased efficacy in patients with baseline CrCl of 30 to ≤50 mL/min. Monitor CrCl at least daily in patients with changing renal function and adjust the dose of ZERBAXA accordingly. (5.1)
- Serious hypersensitivity (anaphylactic) reactions have been reported with beta-lactam antibacterial drugs. Exercise caution in patients with known hypersensitivity to beta-lactam antibacterial drugs. (5.2)
- *Clostridium difficile*-associated diarrhea (CDAD) has been reported with nearly all systemic antibacterial agents, including ZERBAXA. Evaluate if diarrhea occurs. (5.3)

ADVERSE REACTIONS

The most common adverse reactions (≥ 5% in either indication) are nausea, diarrhea, headache and pyrexia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Cubist Pharmaceuticals at 1-877-282-4786 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

USE IN SPECIFIC POPULATIONS

- Dosage adjustment is required in patients with moderately or severely impaired renal function and in patients with end-stage renal disease on hemodialysis (HD). (2.2, 8.5, 8.6, 12.3)
- Higher incidence of adverse reactions was observed in patients age 65 years and older. In complicated intra-abdominal infections, cure rates were lower in patients age 65 years and older. (8.5)
- ZERBAXA has not been studied in pediatric patients. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZERBAXA™ (ceftolozane/tazobactam) for Injection is indicated for the treatment of patients 18 years or older with the following infections caused by designated susceptible microorganisms.

1.1 Complicated Intra-abdominal Infections

ZERBAXA used in combination with metronidazole is indicated for the treatment of complicated intra-abdominal infections (cIAI) caused by the following 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*.

1.2 Complicated Urinary Tract Infections, including Pyelonephritis

ZERBAXA is indicated for the treatment of complicated urinary tract infections (cUTI), including pyelonephritis, caused by the following Gram-negative microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*.

1.3 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 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

The recommended dosage regimen of ZERBAXA (ceftolozane/tazobactam) for Injection is 1.5 g (1 g/0.5 g) administered every 8 hours by intravenous infusion over 1 hour in patients 18 years or older and with normal renal function or mild renal impairment. The duration of therapy should be guided by the severity and site of infection and the patient's clinical and bacteriological progress (Table 1).

Table 1: Dosage of ZERBAXA by Infection in Patients with Creatinine Clearance (CrCl) Greater than 50 mL/min

Infection	Dose	Frequency	Infusion Time (hours)	Duration of Treatment
Complicated Intra-abdominal Infections*	1.5 g (1 g/0.5 g)	Every 8 Hours	1	4-14 days
Complicated Urinary Tract Infections, including Pyelonephritis	1.5 g (1 g/0.5 g)	Every 8 Hours	1	7 days

*Used in conjunction with metronidazole 500 mg intravenously every 8 hours

2.2 Patients with Renal Impairment

Dose adjustment is required for patients whose creatinine clearance is 50 mL/min or less. Renal dose adjustments are listed in Table 2. For patients with changing renal function, monitor CrCl at least daily and adjust the dosage of ZERBAXA accordingly [*see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

Table 2: Dosage of ZERBAXA in Patients with Renal Impairment

Estimated CrCl (mL/min)*	Recommended Dosage Regimen for ZERBAXA**
30 to 50	Ceftolozane/tazobactam 750 mg (500 mg/250 mg) intravenously every 8 hours
15 to 29	Ceftolozane/tazobactam 375 mg (250 mg/125 mg) intravenously every 8 hours
End-stage renal disease (ESRD) on hemodialysis (HD)	A single loading dose of ceftolozane/tazobactam 750 mg (500 mg/250 mg) followed by a 150 mg (100 mg/50 mg) maintenance dose administered 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 estimated using Cockcroft-Gault formula
**All doses of ZERBAXA are administered over 1 hour.

2.3 Preparation of Solutions

ZERBAXA does not contain a bacteriostatic preservative. Aseptic technique must be followed in preparing the infusion solution.

Preparation of doses:

Constitute the vial with 10 mL of sterile water for injection or 0.9% Sodium Chloride for Injection, USP and gently shake to dissolve. The final volume is approximately 11.4 mL. Caution: The constituted solution is not for direct injection.

To prepare the required dose, withdraw the appropriate volume determined from Table 3 from the reconstituted vial. Add the withdrawn volume to an infusion bag containing 100 mL of 0.9% Sodium Chloride for Injection, USP or 5% Dextrose Injection, USP.

Table 3: Preparation of Doses

Ceftolozane/Tazobactam Dose	Volume to Withdraw from Reconstituted Vial
1.5 g (1 g/0.5 g)	11.4 mL (entire contents)
750 mg (500 mg/250 mg)	5.7 mL
375 mg (250 mg/125 mg)	2.9 mL
150 mg (100 mg/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.

2.4 Compatibility

Compatibility of ZERBAXA with other drugs has not been established. ZERBAXA should not be mixed with other drugs or physically added to solutions containing other drugs.

2.5 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 to 8°C (36 to 46°F).

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

3 DOSAGE FORMS AND STRENGTHS

ZERBAXA (ceftolozane/tazobactam) for Injection is supplied as a white to yellow sterile powder for reconstitution in single-use vials; each vial contains 1 g ceftolozane (equivalent to 1.147 g of ceftolozane sulfate) and 0.5 g tazobactam (equivalent to 0.537 g of tazobactam sodium).

4 CONTRAINDICATIONS

ZERBAXA is contraindicated in patients with known serious hypersensitivity to ceftolozane/tazobactam, piperacillin/tazobactam, or other members of the beta-lactam class.

5 WARNINGS AND PRECAUTIONS

5.1 Decreased Efficacy in Patients with Baseline Creatinine Clearance of 30 to ≤50 mL/min

In a subgroup analysis of a Phase 3 cIAI trial, clinical cure rates were lower in patients with baseline creatinine clearance (CrCl) of 30 to ≤50 mL/min compared to those with CrCl ≥50 mL/min (Table 4). The reduction in clinical cure rates was more marked in the ZERBAXA plus metronidazole arm compared to the meropenem arm. A similar trend was also seen in the cUTI trial. Monitor CrCl at least daily in patients with changing renal function and adjust the dosage of ZERBAXA accordingly [*see Dosage and Administration (2.2)*].

Table 4: Clinical Cure Rates in a Phase 3 Trial of cIAI by Baseline Renal Function (MITT Population)

Baseline Renal Function	ZERBAXA plus metronidazole n/N (%)	Meropenem n/N (%)
Normal/mild impairment (CrCl ≥50 mL/min)	312/366 (85.2)	355/404 (87.9)
Moderate impairment (CrCl 30 to ≤50 mL/min)	11/23 (47.8)	9/13 (69.2)

5.2 Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving beta-lactam antibacterial drugs.

Before initiating therapy with ZERBAXA, make careful inquiry about previous hypersensitivity reactions to other cephalosporins, penicillins, or other beta-lactams. If this product is to be given to a patient with a cephalosporin, penicillin, or other beta-lactam allergy, exercise caution because cross sensitivity has been established. If an anaphylactic reaction to ZERBAXA occurs, discontinue the drug and institute appropriate therapy.

5.3 *Clostridium difficile*-associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including ZERBAXA, 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. 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 confirmed, discontinue antibacterials not directed against *C. difficile*, 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.

5.4 Development of Drug-Resistant Bacteria

Prescribing ZERBAXA in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

6 ADVERSE REACTIONS

The following serious reactions are described in greater detail in the Warnings and Precautions section:

- Hypersensitivity reactions [*see Warnings and Precautions (5.2)*]
- *Clostridium difficile*-associated diarrhea [*see Warnings and Precautions (5.3)*]

6.1 Clinical Trial 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 also may not reflect rates observed in practice.

ZERBAXA was evaluated in Phase 3 comparator-controlled clinical trials of cIAI and cUTI, which included a total of 1015 patients treated with ZERBAXA and 1032 patients treated with comparator (levofloxacin 750 mg daily in cUTI or meropenem 1 g every 8 hours in cIAI) for up to 14 days. The mean age of treated patients was 48 to 50 years (range 18 to 92 years), across treatment arms and indications. In both indications, about 25% of the subjects were 65 years of age or older. Most patients (75%) enrolled in the cUTI trial were female, and most patients (58%) enrolled in the cIAI trial were male. Most patients (>70%) in both trials were enrolled in Eastern Europe and were White.

The most common adverse reactions (5% or greater in either indication) occurring in patients receiving ZERBAXA were nausea, diarrhea, headache, and pyrexia. Table 5 lists adverse reactions occurring in 1% or greater of patients receiving ZERBAXA in Phase 3 clinical trials.

Table 5: Adverse Reactions Occurring in 1% or Greater of Patients Receiving ZERBAXA in Phase 3 Clinical Trials

Preferred Term	Complicated Intra-abdominal Infections		Complicated Urinary Tract Infections, Including Pyelonephritis	
	ZERBAXA[a] (N=482)	Meropenem (N=497)	ZERBAXA[a] (N=533)	Levofloxacin (N=535)
Nausea	38 (7.9)	29 (5.8)	15 (2.8)	9 (1.7)
Headache	12 (2.5)	9 (1.8)	31 (5.8)	26 (4.9)
Diarrhea	30 (6.2)	25 (5)	10 (1.9)	23 (4.3)
Pyrexia	27 (5.6)	20 (4)	9 (1.7)	5 (0.9)
Constipation	9 (1.9)	6 (1.2)	21 (3.9)	17 (3.2)
Insomnia	17 (3.5)	11 (2.2)	7 (1.3)	14 (2.6)
Vomiting	16 (3.3)	20 (4)	6 (1.1)	6 (1.1)
Hypokalemia	16 (3.3)	10 (2)	4 (0.8)	2 (0.4)
ALT increased	7 (1.5)	5 (1)	9 (1.7)	5 (0.9)
AST increased	5 (1)	3 (0.6)	9 (1.7)	5 (0.9)
Anemia	7 (1.5)	5 (1)	2 (0.4)	5 (0.9)
Thrombocytosis	9 (1.9)	5 (1)	2 (0.4)	2 (0.4)
Abdominal pain	6 (1.2)	2 (0.4)	4 (0.8)	2 (0.4)
Anxiety	9 (1.9)	7 (1.4)	1 (0.2)	4 (0.7)
Dizziness	4 (0.8)	5 (1)	6 (1.1)	1 (0.2)
Hypotension	8 (1.7)	4 (0.8)	2 (0.4)	1 (0.2)
Atrial fibrillation	6 (1.2)	3 (0.6)	1 (0.2)	0
Rash	8 (1.7)	7 (1.4)	5 (0.9)	2 (0.4)

[a] The ZERBAXA (ceftolozane/tazobactam) for Injection dose was 1 g/0.5 g intravenously every 8 hours, adjusted to match renal function where appropriate. In the cIAI trials, ZERBAXA was given in conjunction with metronidazole.

Treatment discontinuation due to adverse events occurred in 2.0% (20/1015) of patients receiving ZERBAXA and 1.9% (20/1032) of patients receiving comparator drugs. Renal impairment (including the terms renal impairment, renal failure, and renal failure acute) led to discontinuation of treatment in 5/1015 (0.5%) subjects receiving ZERBAXA and none in the comparator arms.

Increased Mortality

In the cIAI trials (Phase 2 and 3), death occurred in 2.5% (14/564) of patients receiving ZERBAXA and in 1.5% (8/536) of patients receiving meropenem. The causes of death varied and included worsening and/or complications of infection, surgery and underlying conditions.

Less Common Adverse Reactions

The following selected adverse reactions were reported in ZERBAXA-treated subjects at a rate of less than 1%:

Cardiac disorders: tachycardia, angina pectoris

Gastrointestinal disorders: ileus, gastritis, abdominal distension, dyspepsia, flatulence, ileus paralytic

General disorders and administration site conditions: infusion site reactions

Infections and infestations: candidiasis, oropharyngeal, fungal urinary tract infection

Investigations: increased serum gamma-glutamyl transpeptidase (GGT), increased serum alkaline phosphatase, positive Coombs test

Metabolism and nutrition disorders: hyperglycemia, hypomagnesemia, hypophosphatemia

Nervous system disorders: ischemic stroke

Renal and urinary system: renal impairment, renal failure

Respiratory, thoracic and mediastinal disorders: dyspnea

Skin and subcutaneous tissue disorders: urticaria

Vascular disorders: venous thrombosis

7 DRUG INTERACTIONS

No significant drug-drug interactions are anticipated between ZERBAXA and substrates, inhibitors, and inducers of cytochrome P450 enzymes (CYPs) [*see Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B.

There are no adequate and well-controlled trials in pregnant women with either ceftolozane or tazobactam. Because animal reproduction studies are not always predictive of human response, ZERBAXA should be used during pregnancy only if the potential benefit outweighs the possible risk.

Embryo-fetal development studies performed with intravenous ceftolozane in mice and rats with doses up to 2000 and 1000 mg/kg/day, respectively, revealed no evidence of harm to the fetus. The mean plasma exposure (AUC) values associated with these doses are approximately 7 (mice) and 4 (rats) times the mean daily human ceftolozane exposure in healthy adults at the clinical dose of 1 gram thrice-daily. It is not known if ceftolozane crosses the placenta in animals.

In a pre-postnatal study in rats, intravenous ceftolozane administered during pregnancy and lactation (Gestation Day 6 through Lactation Day 20) was associated with a decrease in auditory startle response in postnatal Day 60 male pups at maternal doses of greater than or equal to 300 mg/kg/day. The plasma exposure (AUC) associated with the NOAEL dose of 100 mg/kg/day in rats is approximately 0.4 fold of the mean daily human ceftolozane exposure in healthy adults at the clinical dose of 1 gram thrice-daily.

In an embryo-fetal study in rats, tazobactam administered intravenously at doses up to 3000 mg/kg/day (approximately 19 times the recommended human dose based on body surface area comparison) produced maternal toxicity (decreased food consumption and body weight gain) but was not associated with fetal toxicity. In rats, tazobactam was shown to cross the placenta. Concentrations in the fetus were less than or equal to 10% of those found in maternal plasma.

In a pre-postnatal study in rats, tazobactam administered intraperitoneally twice daily at the end of gestation and during lactation (Gestation Day 17 through Lactation Day 21) produced decreased maternal food consumption and body weight gain at the end of gestation and significantly more stillbirths with a tazobactam dose of 1280 mg/kg/day (approximately 8 times the recommended human dose based on body surface area comparison). No effects on the development, function, learning or fertility of F1 pups were noted, but postnatal body weights for F1 pups delivered to dams receiving 320 and 1280 mg/kg/day tazobactam were significantly reduced 21 days after delivery. F2-generation fetuses were normal for all doses of tazobactam. The NOAEL for reduced F1 body weights was considered to be 40 mg/kg/day (approximately 0.3 times the recommended human dose based on body surface area comparison).

8.3 Nursing Mothers

It is not known whether ceftolozane or tazobactam is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when administering ZERBAXA to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 1015 patients treated with ZERBAXA in the Phase 3 clinical trials, 250 (24.6%) were 65 years or older, including 113 (11.1%) 75 years or older. The incidence of adverse events in both treatment groups was higher in older subjects (65 years or older) in the trials for both indications. In the cIAI trial, cure rates in the elderly (age 65 years and older) in the ceftolozane/tazobactam plus metronidazole arm were 69/100 (69%) and in the comparator arm were 70/85 (82.4%). This finding in the elderly population was not observed in the cUTI trial.

ZERBAXA is substantially excreted by the kidney and the risk of adverse reactions to ZERBAXA may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and it may be useful to monitor renal function. Adjust dosage for elderly patients based on renal function [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)*].

8.6 Patients with Renal Impairment

Dosage adjustment is required in patients with moderate (CrCl 30 to 50 mL/min) or severe (CrCl 15 to 29 mL/min) renal impairment and in patients with ESRD on HD [*see Dosage and Administration (2.2), Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

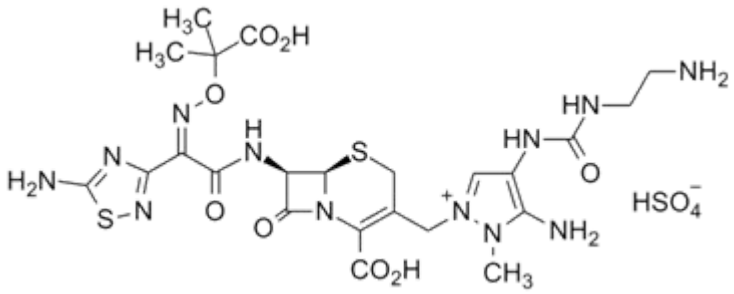
In the event of overdose, discontinue ZERBAXA and provide general supportive treatment. ZERBAXA can be removed by hemodialysis. Approximately 66% of ceftolozane, 56% of tazobactam, and 51% of the tazobactam metabolite M1 were removed by dialysis. No information is available on the use of hemodialysis to treat overdosage.

11 DESCRIPTION

ZERBAXA (ceftolozane/tazobactam) is an antibacterial combination product consisting of the cephalosporin antibacterial drug ceftolozane sulfate and the beta-lactamase inhibitor tazobactam sodium for intravenous administration.

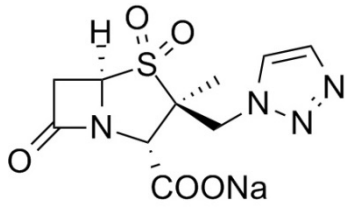
Ceftolozane sulfate is a semi-synthetic antibacterial drug of the beta-lactam class for parenteral administration. The chemical name of ceftolozane sulfate is 1*H*-Pyrazolium, 5-amino-4-[[[(2-aminoethyl)amino]carbonyl]amino]-2-[[(6*R*,7*R*)-7-[[(2*Z*)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl]-1-methyl-,sulfate (1:1). The molecular formula is $C_{23}H_{31}N_{12}O_8S_2^+ \bullet HSO_4^-$ and the molecular weight is 764.77.

Figure 1: Chemical structure of ceftolozane sulfate



Tazobactam sodium, a derivative of the penicillin nucleus, is a penicillanic acid sulfone. Its chemical name is sodium (2S,3S,5R)-3-methyl-7-oxo-3-(1H-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate-4,4-dioxide. The chemical formula is $C_{10}H_{11}N_4NaO_5S$ and the molecular weight is 322.3.

Figure 2: Chemical structure of tazobactam sodium



ZERBAXA (ceftolozane/tazobactam) for Injection is a white to yellow sterile powder consisting of ceftolozane sulfate (1.147 g/vial equivalent to 1 g of ceftolozane) and tazobactam sodium (0.537 g/vial equivalent to 0.5 g of tazobactam) packaged in glass vials. The product contains sodium chloride (487 mg/vial) as a stabilizing agent, citric acid (21 mg/vial), and L-arginine (approximately 600 mg/vial) as excipients.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ceftolozane/tazobactam is an antibacterial drug [*see Clinical Pharmacology (12.4)*].

12.2 Pharmacodynamics

As with other beta-lactam antibacterial agents, the time that the plasma concentration of ceftolozane exceeds the minimum inhibitory concentration (MIC) of the infecting organism has been shown to be the best predictor of efficacy in animal models of infection. The time above a threshold concentration has been determined to be the parameter that best predicts the efficacy of tazobactam in in vitro nonclinical models. The exposure-response analyses in Phase 2 trials support the recommended dose of ZERBAXA.

Cardiac Electrophysiology

In a randomized, positive and placebo-controlled crossover thorough QTc study, 51 healthy subjects were administered a single therapeutic dose 1.5 gram (1 g/0.5 g) and a supratherapeutic dose 4.5 gram (3 g/1.5 g) of ceftolozane/tazobactam. No significant effects of ceftolozane/tazobactam on heart rate, electrocardiogram morphology, PR, QRS, or QT interval were detected. Therefore, ZERBAXA does not affect cardiac repolarization.

12.3 Pharmacokinetics

The mean pharmacokinetic parameters of ZERBAXA in healthy adults with normal renal function after single and multiple 1-hour intravenous infusions of ZERBAXA (ceftolozane/tazobactam, 1 g/0.5 g) administered every 8 hours are summarized in Table 6. Pharmacokinetic parameters were similar for single- and multiple-dose administration.

Table 6: Mean (CV%) Plasma Pharmacokinetic Parameters of ZERBAXA (ceftolozane/tazobactam) After Single and Multiple 1 g/0.5 g Intravenous 1-hour Infusions of ZERBAXA Every 8 Hours in Healthy Adults

PK parameters	Ceftolozane/Tazobactam (1 g/0.5 g every 8 hours)			
	Ceftolozane		Tazobactam	
	Day 1 (n=9)[a]	Day 10 (n=10)	Day 1 (n=9)[a]	Day 10 (n=10)
C_{max} (mcg/mL)	69.1 (11)	74.4 (14)	18.4 (16)	18 (8)
t_{max} (h)[b]	1.02 (1.01, 1.1)	1.07 (1, 1.1)	1.02 (0.99, 1.03)	1.01 (1, 1.1)
AUC (mcg•h/mL)[c]	172 (14)	182 (15)	24.4 (18)	25 (15)
$t_{½}$ (h)	2.77 (30)	3.12 (22)	0.91 (26)[d]	1.03 (19)

[a] N = 9, one outlier subject excluded from descriptive statistics
[b] Median (minimum, maximum) presented
[c] AUC for Day 1 = AUC_{last} and AUC for Day 10 = steady state AUC ($AUC_{\tau,ss}$). Daily AUC at steady state is calculated by multiplying the Day 10 AUC values by three (e.g., 546 mcg•h/mL for ceftolozane and 75 mcg•h/mL for tazobactam)
[d] N = 8, one subject excluded from descriptive statistics as the concentration-time profile did not exhibit a terminal log-linear phase and $t_{½}$ could not be calculated

The C_{max} and AUC of ZERBAXA increase in proportion to dose. Plasma levels of ZERBAXA do not increase appreciably following multiple intravenous infusions of up to 2 g/1 g (ceftolozane/tazobactam) administered every 8 hours for up to 10 days in healthy adults with normal renal function. The elimination half-life ($t_{½}$) of ceftolozane is independent of dose.

Distribution

The binding of ceftolozane and tazobactam to human plasma proteins is approximately 16% to 21% and 30%, respectively. The mean (CV%) steady-state volume of distribution of ZERBAXA in healthy adult males (n = 51) following a single 1 g/0.5 g (ceftolozane/tazobactam) intravenous dose of ZERBAXA was 13.5 L (21%) and 18.2 L (25%) for ceftolozane and tazobactam, respectively, similar to extracellular fluid volume.

Metabolism

Ceftolozane is eliminated in the urine as unchanged parent drug and thus does not appear to be metabolized to any appreciable extent. The beta-lactam ring of tazobactam is hydrolyzed to form the pharmacologically inactive tazobactam metabolite M1.

Excretion

Ceftolozane and the tazobactam metabolite M1 are eliminated by the kidneys. Following administration of a single ceftolozane/tazobactam 1 g/0.5 g intravenous dose to healthy male adults, greater than 95% of ceftolozane was excreted in the urine as unchanged parent drug. More than 80% of tazobactam was excreted as the parent compound with the remainder excreted as the tazobactam M1 metabolite. After a single dose of ZERBAXA, renal clearance of ceftolozane (3.41 – 6.69 L/h) was similar to plasma CL (4.10 to 6.73 L/h) and similar to the

glomerular filtration rate for the unbound fraction, suggesting that ceftolozane is eliminated by the kidney via glomerular filtration.

Specific Populations

Renal Impairment
ZERBAXA and the tazobactam metabolite M1 are eliminated by the kidneys.

The ceftolozane dose normalized geometric mean AUC increased up to 1.26-fold, 2.5-fold, and 5-fold in subjects with mild, moderate, and severe renal impairment, respectively, compared to healthy subjects with normal renal function. The respective tazobactam dose normalized geometric mean AUC increased approximately up to 1.3-fold, 2-fold, and 4-fold. To maintain similar systemic exposures to those with normal renal function, dosage adjustment is required [*see Dosage and Administration (2.2)*].

In subjects with ESRD on HD, approximately two-thirds of the administered ZERBAXA dose is removed by HD. The recommended dose in subjects with ESRD on HD is a single loading dose of ZERBAXA (ceftolozane/tazobactam), 500 mg/250 mg, followed by a 100 mg/50 mg maintenance dose of ZERBAXA administered every 8 hours for the remainder of the treatment period. On HD days, administer the dose at the earliest possible time following completion of HD [*see Dosage and Administration (2.2)*].

Hepatic Impairment
As ZERBAXA does not undergo hepatic metabolism, the systemic clearance of ZERBAXA is not expected to be affected by hepatic impairment.

No dose adjustment is recommended for ZERBAXA in subjects with hepatic impairment.

Geriatric Patients
In a population pharmacokinetic analysis of ZERBAXA, no clinically relevant trend in exposure was observed with regard to age.

No dose adjustment of ZERBAXA based on age is recommended.

Pediatric Patients
Safety and effectiveness in pediatric patients have not been established.

Gender
In a population pharmacokinetic analysis of ZERBAXA, no clinically relevant differences in AUC were observed for ceftolozane (116 males compared to 70 females) and tazobactam (80 males compared to 50 females).

No dose adjustment is recommended based on gender.

Race
In a population pharmacokinetic analysis of ZERBAXA, no clinically relevant differences in ZERBAXA AUC were observed in Caucasians (n = 156) compared to all other races combined (n = 30).

No dose adjustment is recommended based on race.

Drug Interactions

No drug-drug interaction was observed between ceftolozane and tazobactam in a clinical study in 16 healthy subjects. In vitro and *in vivo* data indicate that ZERBAXA is unlikely to cause clinically relevant drug-drug interactions related to CYPs and transporters at therapeutic concentrations.

Drug Metabolizing Enzymes

In vivo data indicated that ZERBAXA is not a substrate for CYPs. Thus clinically relevant drug-drug interactions involving inhibition or induction of CYPs by other drugs are unlikely to occur.

In vitro studies demonstrated that ceftolozane, tazobactam and the M1 metabolite of tazobactam did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 and did not induce CYP1A2, CYP2B6, or CYP3A4 at therapeutic plasma concentrations. In vitro induction studies in primary human hepatocytes demonstrated that ceftolozane, tazobactam, and the tazobactam metabolite M1 decreased CYP1A2 and CYP2B6 enzyme activity and mRNA levels in primary human hepatocytes as well as CYP3A4 mRNA levels at supratherapeutic plasma concentrations. Tazobactam metabolite M1 also decreased CYP3A4 activity at supratherapeutic plasma concentrations. A clinical drug-drug interaction study was conducted and results indicated drug interactions involving CYP1A2 and CYP3A4 inhibition by ZERBAXA are not anticipated.

Membrane Transporters

Ceftolozane and tazobactam were not substrates for P-gp or BCRP, and tazobactam was not a substrate for OCT2, in vitro at therapeutic concentrations.

Tazobactam is a known substrate for OAT1 and OAT3. Co-administration of tazobactam with the OAT1/OAT3 inhibitor probenecid has been shown to prolong the half-life of tazobactam by 71%. Co-administration of ZERBAXA with drugs that inhibit OAT1 and/or OAT3 may increase tazobactam plasma concentrations.

In vitro data indicate that ceftolozane did not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, MRP, BSEP, OAT1, OAT3, MATE1, or MATE2-K in vitro at therapeutic plasma concentrations.

In vitro data indicate that neither tazobactam nor the tazobactam metabolite M1 inhibit P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, or BSEP transporters at therapeutic plasma concentrations. In vitro, tazobactam inhibited human OAT1 and OAT3 transporters with IC_{50} values of 118 and 147 mcg/mL, respectively. A clinical drug-drug interaction study was

conducted and results indicated clinically relevant drug interactions involving OAT1/OAT3 inhibition by ZERBAXA are not anticipated.

12.4 Microbiology

Mechanism of Action

Ceftolozane belongs to the cephalosporin class of antibacterial drugs. The bactericidal action of ceftolozane results from inhibition of cell wall biosynthesis, and is mediated through binding to penicillin-binding proteins (PBPs). Ceftolozane is an inhibitor of PBPs of *P. aeruginosa* (e.g., PBP1b, PBP1c, and PBP3) and *E. coli* (e.g., PBP3).

Tazobactam sodium has little clinically relevant in vitro activity against bacteria due to its reduced affinity to penicillin-binding proteins. It is an irreversible inhibitor of some beta-lactamases (e.g., certain penicillinases and cephalosporinases), and can bind covalently to some chromosomal and plasmid-mediated bacterial beta-lactamases.

Resistance

Mechanisms of beta-lactam resistance may include the production of beta-lactamases, modification of PBPs by gene acquisition or target alteration, up-regulation of efflux pumps, and loss of outer membrane porin.

Clinical isolates may produce multiple beta-lactamases, express varying levels of beta-lactamases, or have amino acid sequence variations, and other resistance mechanisms that have not been identified.

Culture and susceptibility information and local epidemiology should be considered in selecting or modifying antibacterial therapy.

ZERBAXA demonstrated in vitro activity against Enterobacteriaceae in the presence of some extended-spectrum beta-lactamases (ESBLs) and other beta-lactamases of the following groups: TEM, SHV, CTX-M, and OXA. ZERBAXA is not active against bacteria that produce serine carbapenamases [*K. pneumoniae* carbapenemase (KPC)], and metallo-beta lactamases.

In ZERBAXA clinical trials, some isolates of *E. coli* and *K. pneumoniae,* that produced beta-lactamases, were susceptible to ZERBAXA (minimum inhibitory concentration $\leq$ 2 mcg/mL). These isolates produced one or more beta-lactamases of the following enzyme groups: CTX-M, OXA, TEM, or SHV.

Some of these beta-lactamases were also produced by isolates of *E. coli* and *K. pneumoniae* that were not susceptible to ZERBAXA (minimum inhibitory concentration > 2 mcg/mL). These isolates produced one or more beta-lactamases of the following enzyme groups: CTX-M, OXA, TEM, or SHV.

ZERBAXA demonstrated in vitro activity against *P. aeruginosa* isolates tested that had chromosomal AmpC, loss of outer membrane porin (OprD), or up-regulation of efflux pumps (MexXY, MexAB).

Cross-Resistance

Isolates resistant to other cephalosporins may be susceptible to ZERBAXA, although cross-resistance may occur.

Interaction with Other Antimicrobials

In vitro synergy studies suggest no antagonism between ZERBAXA and other antibacterial drugs (e.g., meropenem, amikacin, aztreonam, levofloxacin, tigecycline rifampin, linezolid, daptomycin, vancomycin, and metronidazole).

List of Microorganisms

ZERBAXA has been shown to be active against the following bacteria, both in vitro and in clinical infections [*see Indications and Usage (1)*].

Complicated Intra-abdominal Infections

Gram-negative bacteria

Enterobacter cloacae

Escherichia coli

Klebsiella oxytoca

Klebsiella pneumoniae

Proteus mirabilis

Pseudomonas aeruginosa

Gram-positive bacteria

Streptococcus anginosus

Streptococcus constellatus

Streptococcus salivarius

Anaerobic bacteria

Bacteroides fragilis

Complicated Urinary Tract Infections, Including Pyelonephritis

Gram-negative bacteria

Escherichia coli

Klebsiella pneumoniae

Proteus mirabilis

Pseudomonas aeruginosa

The following in vitro data are available, but their clinical significance is unknown. At least 90% of the following microorganisms exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to 2 mcg/mL for ceftolozane/tazobactam. The safety and effectiveness of ZERBAXA in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Gram-negative bacteria

Acinetobacter baumannii

Burkholderia cepacia

Citrobacter freundii

Citrobacter koseri

Enterobacter aerogenes

Enterobacter cloacae

Haemophilus influenzae

Moraxella catarrhalis

Morganella morganii

Pantoea agglomerans

Proteus vulgaris

Providencia rettgeri

Providencia stuartii

Serratia liquefacians

Serratia marcescens

Gram-positive bacteria

Streptococcus agalactiae

Streptococcus intermedius

Streptococcus pyogenes

Streptococcus pneumoniae

Anaerobic bacteria

Fusobacterium spp.

Prevotella spp.

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide the results of in vitro susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and

community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

Dilution Techniques

Quantitative methods are used to determine antimicrobial MICs. Ceftolozane/tazobactam susceptibility testing is performed with a fixed 4 mcg/mL concentration of tazobactam. These MICs provide estimates of the susceptibility of bacteria to antibacterial compounds. The MICs should be determined using a standardized test method (broth, and/or agar).[1,4] The MIC values should be interpreted according to the criteria in Table 7.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method.[2,4] This procedure uses paper disks impregnated with 30 mcg of ceftolozane and 10 mcg of tazobactam to test the susceptibility of microorganisms to ceftolozane/tazobactam. The disk diffusion should be interpreted according to the criteria in Table 7.

Anaerobic Techniques

For anaerobic bacteria, the susceptibility to ceftolozane/tazobactam can be determined by standardized test method.[3] The MIC values obtained should be interpreted according to criteria provided in Table 7.

Table 7: Susceptibility Interpretive Criteria for Ceftolozane/Tazobactam

Pathogen	**Minimum Inhibitory Concentrations (mcg/mL)**			**Disk Diffusion Zone Diameter (mm)**		
	S	I	R	**S**	I	R
Enterobacteriaceae	≤2/4	4/4	≥8/4	---	---	---
Pseudomonas aeruginosa	≤4/4	8/4	≥16/4	≥21	17-20	≤16
Streptococcus anginosus *Streptococcus constellatus and* *Streptococcus salivarius*	≤8/4	16/4	≥32/4	---	---	---
B. fragilis	≤8/4	16/4	≥32/4	---	---	---

S = susceptible, I = intermediate, R = resistant

A report of "Susceptible" indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentration usually achievable at the site of infection. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report

of "Resistant" indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentrations usually achievable at the infection site; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test.[1,2,3,4] Standard ceftolozane/tazobactam powder should provide the following range of MIC values provided in Table 8. For the diffusion technique using the 30 mcg ceftolozane/10 mcg tazobactam disk, the criteria provided in Table 8 should be achieved.[4]

Table 8: Acceptable Quality Control Ranges for Ceftolozane/Tazobactam

Quality Control Organism	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion Zone Diameters (mm)
Escherichia coli ATCC 25922	0.12/4-0.5/4	24-32
Escherichia coli[a] ATCC 35218	0.06/4-0.25/4	25-31
Pseudomonas aeruginosa ATCC 27853	0.25/4-1/4	25-31
Staphylococcus aureus ATCC 25923	Not Applicable	10-18
Staphylococcus aureus ATCC 29213	16/4-64/4	Not Applicable
Haemophilus influenzae[b] ATCC 49247	0.5/4-2/4	23-29
Klebsiella pneumoniae[a] ATCC 700603	0.5/4-2/4	17-25
Streptococcus pneumoniae ATCC 49619	0.25/4-1/4	21-29
Bacteroides fragilis ATCC 25285 (agar and broth)	0.12/4-1/4	Not Applicable
Bacteroides thetaiotaomicron ATCC 29741 (agar)	16/4-128/4	Not Applicable
Bacteroides thetaiotaomicron ATCC 29741 (broth)	16/4-64/4	Not Applicable

ATCC = American Type Culture Collection

[a] Store *E. coli* ATCC 35218 and *K. pneumoniae* ATCC 700603 stock cultures at -60°C or below and prepare working stock cultures weekly.

[b] This strain may lose its plasmid and develop susceptibility to beta-lactam antimicrobial agents after repeated transfers onto culture media. Minimize by removing new culture from storage at least monthly or whenever the strain begins to show increased zone diameters to ampicillin, piperacillin, or ticarcillin.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in animals have not been conducted with ZERBAXA, ceftolozane, or tazobactam.

ZERBAXA was negative for genotoxicity in an in vitro mouse lymphoma assay and an in vivo rat bone-marrow micronucleus assay. In an in vitro chromosomal aberration assay in Chinese hamster ovary cells, ZERBAXA was positive for structural aberrations.

Ceftolozane was negative for genotoxicity in an in vitro microbial mutagenicity (Ames) assay, an in vitro chromosomal aberration assay in Chinese hamster lung fibroblast cells, an in vivo mouse micronucleus assay, and an in vivo unscheduled DNA synthesis (UDS) assay. Ceftolozane was positive for mutagenicity in an in vitro mouse lymphoma assay.

Tazobactam was negative for genotoxicity in an in vitro microbial mutagenicity (Ames) assay, an in vitro chromosomal aberration assay in Chinese hamster lung fibroblast cells, a mammalian point-mutation (Chinese hamster ovary cell HPRT) assay, an in vivo rat bone-marrow micronucleus assay, and an in vivo UDS assay. In another mammalian (mouse lymphoma cell) gene-mutation assay, tazobactam was positive for genotoxicity.

Ceftolozane had no adverse effect on fertility in male or female rats at intravenous doses up to 1000 mg/kg/day. The mean plasma exposure (AUC) value at this dose is approximately 3 times the mean daily human ceftolozane exposure value in healthy adults at the clinical dose of 1 gram thrice daily.

In a rat fertility study with intraperitoneal tazobactam twice-daily, male and female fertility parameters were not affected at doses less than or equal to 640 mg/kg/day (approximately 4 times the recommended clinical daily dose based on body surface comparison).

14 CLINICAL STUDIES

14.1 Complicated Intra-abdominal Infections

A total of 979 adults hospitalized with cIAI were randomized and received study medications in a multinational, double-blind study comparing ZERBAXA (ceftolozane/tazobactam 1 g/0.5 g intravenously every 8 hours) plus metronidazole (500 mg intravenously every 8 hours) to meropenem (1 g intravenously every 8 hours) for 4 to 14 days of therapy. Complicated intra-abdominal infections included appendicitis, cholecystitis, diverticulitis, gastric/duodenal perforation, perforation of the intestine, and other causes of intra-abdominal abscesses and peritonitis. The majority of patients (75%) were from Eastern Europe; 6.3% were from the United States.

The primary efficacy endpoint was clinical response, defined as complete resolution or significant improvement in signs and symptoms of the index infection at the test-of-cure (TOC) visit which occurred 24 to 32 days after the first dose of study drug. The primary efficacy analysis population was the microbiological intent-to-treat (MITT) population, which included all patients who had at least 1 baseline intra-abdominal pathogen regardless of the susceptibility to study drug. The key secondary efficacy endpoint was clinical response at the TOC visit in the microbiologically evaluable (ME) population, which included all protocol-adherent MITT patients.

The MITT population consisted of 806 patients; the median age was 52 years and 57.8% were male. The most common diagnosis was appendiceal perforation or peri-appendiceal abscess, occurring in 47% of patients. Diffuse peritonitis at baseline was present in 34.2% of patients.

ZERBAXA plus metronidazole was non-inferior to meropenem with regard to clinical cure rates at the TOC visit in the MITT population. Clinical cure rates at the TOC visit are displayed by patient population in Table 9. Clinical cure rates at the TOC visit by pathogen in the MITT population are presented in Table 10.

Table 9: Clinical Cure Rates in a Phase 3 Trial of Complicated Intra-Abdominal Infections

Analysis Population	ZERBAXA plus metronidazole[a] n/N (%)	Meropenem[b] n/N (%)	Treatment Difference (95% CI)[c]
MITT	323/389 (83)	364/417 (87.3)	-4.3 (-9.2, 0.7)
ME	259/275 (94.2)	304/321 (94.7)	-0.5 (-4.5, 3.2)

[a] ZERBAXA 1 g/0.5 g intravenously every 8 hours + metronidazole 500 mg intravenously every 8 hours
[b] 1 gram intravenously every 8 hours
[c] The 95% confidence interval (CI) was calculated as an unstratified Wilson Score CI.

Table 10: Clinical Cure Rates by Pathogen in a Phase 3 Trial of Complicated Intra-abdominal Infections (MITT Population)

Organism Group Pathogen	ZERBAXA plus metronidazole n/N (%)	Meropenem n/N (%)
Aerobic Gram-negative		
Escherichia coli	216/255 (84.7)	238/270 (88.1)
Klebsiella pneumoniae	31/41 (75.6)	27/35 (77.1)
Pseudomonas aeruginosa	30/38 (79)	30/34 (88.2)
Enterobacter cloacae	21/26 (80.8)	24/25 (96)
Klebsiella oxytoca	14/16 (87.5)	24/25 (96)
Proteus mirabilis	11/12 (91.7)	9/10 (90)
Aerobic Gram-positive		
Streptococcus anginosus	26/36 (72.2)	24/27 (88.9)
Streptococcus constellatus	18/24 (75)	20/25 (80)

Organism Group Pathogen	ZERBAXA plus metronidazole n/N (%)	Meropenem n/N (%)
Streptococcus salivarius	9/11 (81.8)	9/11 (81.8)
Anaerobic Gram-negative		
Bacteroides fragilis	42/47 (89.4)	59/64 (92.2)
Bacteroides ovatus	38/45 (84.4)	44/46 (95.7)
Bacteroides thetaiotaomicron	21/25 (84)	40/46 (87)
Bacteroides vulgatus	12/15 (80)	24/26 (92.3)

In a subset of the *E. coli* and *K. pneumoniae* isolates from both arms of the cIAI Phase 3 trial that met pre-specified criteria for beta-lactam susceptibility, genotypic testing identified certain ESBL groups (e.g., TEM, SHV, CTX-M, OXA) in 53/601 (9%). Cure rates in this subset were similar to the overall trial results. In vitro susceptibility testing showed that some of these isolates were susceptible to ZERBAXA (MIC $\leq$ 2 mcg/mL), while some others were not susceptible (MIC > 2 mcg/mL). Isolates of a specific genotype were seen in patients who were deemed to be either successes or failures.

14.2 Complicated Urinary Tract Infections, including Pyelonephritis

A total of 1068 adults hospitalized with cUTI (including pyelonephritis) were randomized and received study medications in a multinational, double-blind study comparing ZERBAXA (ceftolozane/tazobactam 1 g/0.5 g intravenously every 8 hours) to levofloxacin (750 mg intravenously once daily) for 7 days of therapy. The primary efficacy endpoint was defined as complete resolution or marked improvement of the clinical symptoms and microbiological eradication (all uropathogens found at baseline at $\geq 10^5$ were reduced to $<10^4$ CFU/mL) at the test-of-cure (TOC) visit 7 ($\pm$ 2) days after the last dose of study drug. The primary efficacy analysis population was the microbiologically modified intent-to-treat (mMITT) population, which included all patients who received study medication and had at least 1 baseline uropathogen. The key secondary efficacy endpoint was the composite microbiological and clinical cure response at the TOC visit in the microbiologically evaluable (ME) population, which included protocol-adherent mMITT patients with a urine culture at the TOC visit.

The mMITT population consisted of 800 patients with cUTI, including 656 (82%) with pyelonephritis. The median age was 50.5 years and 74% were female. Concomitant bacteremia was identified in 62 (7.8%) patients at baseline; 608 (76%) patients were enrolled in Eastern Europe and 14 (1.8%) patients were enrolled in the United States.

ZERBAXA demonstrated efficacy with regard to the composite endpoint of microbiological and clinical cure at the TOC visit in both the mMITT and ME populations (Table 11). Composite microbiological and clinical cure rates at the TOC visit by pathogen in the mMITT population are presented in Table 12.

In the mMITT population, the composite cure rate in ZERBAXA-treated patients with concurrent bacteremia at baseline was 23/29 (79.3%).

Although a statistically significant difference was observed in the ZERBAXA arm compared to the levofloxacin arm with respect to the primary endpoint, it was likely attributable to the 212/800 (26.5%) patients with baseline organisms non-susceptible to levofloxacin. Among patients infected with a levofloxacin-susceptible organism at baseline, the response rates were similar (Table 11).

Table 11: Composite Microbiological and Clinical Cure Rates in a Phase 3 Trial of Complicated Urinary Tract Infections

Analysis Population	ZERBAXA[a] n/N (%)	Levofloxacin[b] n/N (%)	Treatment Difference (95% CI)[c]
mMITT	306/398 (76.9)	275/402 (68.4)	8.5 (2.3, 14.6)
Levofloxacin resistant baseline pathogen(s)	60/100 (60)	44/112 (39.3)	
No levofloxacin resistant baseline pathogen(s)	246/298 (82.6)	231/290 (79.7)	
ME	284/341 (83.3)	266/353 (75.4)	8.0 (2.0, 14.0)

[a] 1 g/0.5 g (ceftolozane/tazobactam) intravenously every 8 hours
[b] 750 mg intravenously once daily
[c] The 95% confidence interval was based on the stratified Newcombe method.

Table 12: Composite Microbiological and Clinical Cure Rates in a Phase 3 Trial of Complicated Urinary Tract Infections, in Subgroups Defined by Baseline Pathogen (mMITT Population)

Pathogen	ZERBAXA n/N (%)	Levofloxacin n/N (%)
Escherichia coli	247/305 (81)	228/324 (70.4)
Klebsiella pneumoniae	22/33 (66.7)	12/25 (48)
Proteus mirabilis	11/12 (91.7)	6/12 (50)
Pseudomonas aeruginosa	6/8 (75)	7/15 (46.7)

In a subset of the *E. coli* and *K. pneumoniae* isolates from both arms of the cUTI Phase 3 trial that met pre-specified criteria for beta-lactam susceptibility, genotypic testing identified certain ESBL groups (e.g., TEM, SHV, CTX-M, OXA) in 104/687 (15%). Cure rates in this subset were similar to the overall trial results. In vitro susceptibility testing showed that some of these isolates were susceptible to ZERBAXA (MIC $\leq$ 2 mcg/mL), while some others were not susceptible (MIC > 2 mcg/mL). Isolates of a specific genotype were seen in patients who were deemed to be either successes or failures.

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – Ninth Edition.* CLSI document M07-A9, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.
2. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard – Eleventh Edition.* CLSI document M02-A11, Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA 2012.
3. Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard – Eighth Edition*. CLSI document M11-A8. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.
4. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-fourth Informational Supplement*. CLSI document M100-S24. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2014.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ZERBAXA (ceftolozane/tazobactam) for Injection is supplied in single-use 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. Vials are supplied in cartons containing 10 vials. (NDC 67919-030-01)

16.2 Storage and Handling

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

The reconstituted solution, once diluted, may be stored for 24 hours at room temperature or for 7 days under refrigeration at 2 to 8°C (36 to 46°F).

17 PATIENT COUNSELING INFORMATION

Serious Allergic Reactions

Advise patient that allergic reactions, including serious allergic reactions, could occur and that serious reactions require immediate treatment. Ask patient about any previous hypersensitivity reactions to ZERBAXA, other beta-lactams (including cephalosporins) or other allergens [*see Warnings and Precautions (5.2)*].

Potentially Serious Diarrhea

Advise patient that diarrhea is a common problem caused by antibacterial drugs. 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, tell patient to contact his or her healthcare provider [*see Warnings and Precautions (5.3)*].

Antibacterial Resistance

Counsel patient that antibacterial drugs including ZERBAXA should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When ZERBAXA is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ZERBAXA or other antibacterial drugs in the future [*see Warnings and Precautions (5.4)*].

Distributed by:
Cubist Pharmaceuticals U.S.
Lexington, MA 02421 USA