ZERBAXA®

Powder for Solution for Injection

1 g/0.5 g

Containing ceftolozane 1 g (as ceftolozane sulfate) and tazobactam 0.5 g (as tazobactam sodium)

1. INDICATIONS AND USAGE

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

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*.

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*.

Nosocomial Pneumonia, including Ventilator-associated Pneumonia

ZERBAXA is indicated for the treatment of nosocomial pneumonia, including ventilator-associated pneumonia (VAP), caused by the following Gram-negative microorganisms: *Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Klebsiella (Enterobacter) aerogenes, Klebsiella oxytoca, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa,* and *Serratia marcescens.*

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 General

Recommended Dosage

The recommended dosage regimen of ZERBAXA for injection is 1.5 gram (g) (ceftolozane 1 g and tazobactam 0.5 g) for cIAI and cUTI and 3 g (ceftolozane 2 g and tazobactam 1 g) for nosocomial pneumonia administered every 8 hours by intravenous infusion over 1 hour in patients 18 years or older and creatinine clearance (CrCL) greater than 50 mL/min. The duration of therapy should be guided by the severity and site of infection and the patient's clinical and bacteriological progress as shown in Table 1.

Table 1: Dosage of ZERBAXA 1.5 g by Infection in Patients with CrCL Greater than 50 mL/min

Infection	Dose	Frequency	Infusion Time (hours)	Duration of Treatment
Complicated Intra-abdominal Infections*	1.5 g ZERBAXA (1 g ceftolozane / 0.5 g tazobactam)	Every 8 Hours	1	4-14 days
Complicated Urinary Tract Infections, including Pyelonephritis	1.5 g ZERBAXA (1 g ceftolozane / 0.5 g tazobactam)	Every 8 Hours	1	7 days
Nosocomial Pneumonia, including Ventilator-associated Pneumonia	3 g ZERBAXA (2 g ceftolozane / 1 g tazobactam)	Every 8 Hours	1	8-14 days

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

Preparation of Solutions

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

Preparation of doses:

Constitute each vial of ZERBAXA 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 per vial. CAUTION: THE CONSTITUTED SOLUTION IS NOT FOR DIRECT INJECTION.

To prepare the required dose, withdraw the appropriate volume determined from Table 2 from the reconstituted vial(s). 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 2: 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.

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 (below 25°C) 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.

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.

2.2 Renal Impairment

Dose adjustment is required for patients whose CrCL is 50 mL/min or less. Renal dose adjustments are listed in Table 3. For patients with changing renal function, monitor CrCL at least daily and adjust the dosage of ZERBAXA accordingly [see Warnings and Precautions (4.1) and Use in Special Populations (6.5)].

Table 3: Recommended Dosage Regimens for ZERBAXA in Patients with Renal Impairment

Estimated CrCL (mL/min)	Complicated Intra-abdominal Infections and Complicated Urinary Tract Infections, including Pyelonephritis †	Nosocomial Pneumonia, including Ventilator-associated 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 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 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 Hepatic impairment

No dose adjustment is necessary in patients with hepatic impairment.

3. CONTRAINDICATIONS

ZERBAXA is contraindicated in patients with:

- Hypersensitivity to the active substances or to any of the inactive excipients;
- Hypersensitivity to any cephalosporin antibacterial agent;
- Severe hypersensitivity (e.g., anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g., penicillins or carbapenems).

4. WARNINGS AND PRECAUTIONS

4.1 Impaired renal function

The ZERBAXA dose should be adjusted based on renal function [see Dosage and Administration (2.2)].

In a subgroup analysis of a Phase 3 cIAI trial, clinical cure rates were lower in patients with baseline CrCL of 30 to ≤ 50 mL/min compared to those with CrCL>50 mL/min. 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. Patients with renal impairment at baseline should be monitored frequently for any changes in renal function during treatment and the dose of ZERBAXA should be adjusted as necessary.

4.2 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.

4.3 *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* [see Adverse Reactions (7.1)].

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.

4.4 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.

4.5 Limitation of the clinical data

Patients who were immunocompromised and patients with severe neutropenia were excluded from clinical trials.

In a trial in patients with complicated intra-abdominal infections, the most common diagnosis was appendiceal perforation or peri-appendiceal abscess (420/970 [43.3%] patients), of which 137/420 (32.6%) had diffuse peritonitis at baseline. Approximately 82% of all patients in the trial had APACHE II (Acute Physiology and Chronic Health Evaluation II) scores of <10 and 2.3% had bacteraemia at baseline. In the clinically evaluable (CE) patients, the clinical cure rates for ceftolozane/tazobactam were 95.9% in 293 patients aged less than 65 years and 87.8% in 82 patients aged 65 years or more.

Clinical efficacy data in patients with complicated lower urinary tract infection are limited. In a randomised active-controlled trial 18.2% (126/693) of microbiologically evaluable (ME) patients had complicated lower urinary tract infection (cLUTI), including 60/126 patients who were treated with ceftolozane/tazobactam. One of these 60 patients had bacteraemia at baseline.

5. DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS

No significant drug-drug interactions are anticipated between ZERBAXA and substrates, inhibitors, and inducers of cytochrome P450 enzymes (CYPs) based on *in vitro* and *in vivo* studies.

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. A clinical drug-drug interaction study was conducted and results indicated drug interactions involving CYP1A2 and CYP3A4 inhibition by ZERBAXA are not anticipated.

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

Tazobactam is a substrate for OAT1 and OAT3. *In vitro*, tazobactam inhibited human OAT1 and OAT3 transporters with IC_{50} values of 118 and 147 mcg/mL, respectively. Co-administration of ceftolozane and tazobactam with OAT1 and OAT3 substrate furosemide in a clinical study did not significantly increase furosemide plasma exposures (geometric mean ratios of 0.83 and 0.87 for C_{max} and AUC, respectively). However, active substances that inhibit OAT1 or OAT3 (e.g., probenecid) may increase tazobactam plasma concentrations. Co-administration of tazobactam with the OAT1/OAT3 inhibitor probenecid has been shown to prolong the half-life of tazobactam by 71%.

6. USE IN SPECIFIC POPULATIONS

6.1 Pregnancy

There are no data on the use of ceftolozane and tazobactam in pregnant women. 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 3.5 (mice) and 2 (rats) times the mean daily human ceftolozane exposure at the highest recommended human dose of 2 grams every 8 hours. 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 pups at maternal doses of greater than or equal to 300 mg/kg/day. A dose of 300 mg/kg/day to rats was associated with a ceftolozane plasma exposure (AUC) value lower than the ceftolozane plasma AUC value at the highest recommended human dose of 2 grams every 8 hours.

In an embryo-fetal study in rats, tazobactam administered intravenously at doses up to 3000 mg/kg/day (approximately 10 times the highest recommended human dose of 1 gram every 8 hours 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 4 times the highest recommended human dose of 1 gram every 8 hours 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, a dose lower than the highest recommended human dose of 1 gram every 8 hours based on body surface area comparison.

6.2 Nursing Mothers

It is unknown whether ceftolozane and tazobactam are excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ZERBAXA therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

6.3 Pediatric Use

The safety and efficacy of ZERBAXA in children and adolescents below 18 years of age have not yet been established.

6.4 Geriatric Use

In a population pharmacokinetic analysis of ceftolozane and tazobactam, no clinically relevant differences in exposure were observed with regard to age. No dose adjustment of ZERBAXA based on age alone is recommended.

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)].

6.5 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) and Warnings and Precautions (4.1)].

7. ADVERSE REACTIONS

7.1 Clinical Trials Experience

Complicated Intra-abdominal Infections and Complicated Urinary Tract Infections, including Pyelonephritis

ZERBAXA was evaluated in Phase 3 comparator-controlled clinical trials of cIAI and cUTI, which included a total of 1015 patients treated with ZERBAXA (1.5 g every 8 hours, adjusted based on renal function where appropriate) 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 58% of patients enrolled in the cIAI trial were male. Table 4 lists adverse reactions occurring in 1% or greater of patients receiving ZERBAXA in Phase 3 cIAI and cUTI clinical trials.

Table 4: Adverse Reactions Occurring in 1% or Greater of Patients Receiving ZERBAXA in Phase 3 cIAI and cUTI Clinical Trials by System Organ Class, Preferred Term and Indication

Preferred Term	Complicated Intra-abdominal Infections	Complicated Urinary Tract Infections, Including Pyelonephritis

	ZERBAXA* (N=482) n (%)	Meropenem (N=497) n (%)	ZERBAXA* (N=533) n (%)	Levofloxacin (N=535) n (%)
Blood and Lymphatic System Disorders				
Anemia†	7 (1.5)	5 (1)	2 (0.4)	5 (0.9)
Thrombocytosis	9 (1.9)	5 (1)	2 (0.4)	2 (0.4)
Cardiac Disorders				
Atrial fibrillation	6 (1.2)	3 (0.6)	1 (0.2)	0
Gastrointestinal Disorders				
Abdominal pain	6 (1.2)	2 (0.4)	4 (0.8)	2 (0.4)
Constipation	9 (1.9)	6 (1.2)	21 (3.9)	17 (3.2)
Diarrhea	30 (6.2)	25 (5)	10 (1.9)	23 (4.3)
Nausea	38 (7.9)	29 (5.8)	15 (2.8)	9 (1.7)
Vomiting	16 (3.3)	20 (4)	6 (1.1)	6 (1.1)
General Disorders and Administration Site Conditions				
Infusion site reactions‡	3 (0.6)	6 (1.2)	7 (1.3)	11 (2.1)
Pyrexia§	27 (5.6)	20 (4)	9 (1.7)	5 (0.9)
Investigations				
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)
Metabolism and Nutrition Disorders				
Hypokalemia¶	16 (3.3)	10 (2)	4 (0.8)	2 (0.4)
Nervous System Disorders				
Dizziness	4 (0.8)	5 (1)	6 (1.1)	1 (0.2)
Headache	12 (2.5)	9 (1.8)	31 (5.8)	26 (4.9)
Psychiatric Disorders				
Anxiety	9 (1.9)	7 (1.4)	1 (0.2)	4 (0.7)
Insomnia	17 (3.5)	11 (2.2)	7 (1.3)	14 (2.6)

Skin and Subcutaneous Tissue Disorders				
Rash#	8 (1.7)	7 (1.4)	5 (0.9)	2 (0.4)
Vascular Disorders				
Hypotension	8 (1.7)	4 (0.8)	2 (0.4)	1 (0.2)

* The ZERBAXA for injection dose was 1.5 g intravenously every 8 hours, adjusted to match renal function where appropriate. In the cIAI trials, ZERBAXA was given in conjunction with metronidazole.
† Anemia includes the following preferred terms: anemia, hemoglobin decreased and iron deficiency anemia.
‡ Infusion site reactions includes the following preferred terms: infusion site erythema, infusion site edema, infusion site induration, infusion site pain, infusion site phlebitis, infusion site pruritus, infusion site thrombosis, infusion site infection, infusion site rash.
§ Pyrexia includes the following preferred terms: pyrexia, body temperature increased and hyperthermia.
¶ Hypokalemia includes the following preferred terms: hypokalemia and blood potassium decreased.
# Rash includes the following preferred terms: rash, rash generalized, rash maculo-papular, rash pruritic, rash macular and rash erythematosus.

Treatment discontinuation due to adverse events occurred in 2% (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 in Phase 3 cIAI and cUTI Clinical Trials

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

Infections and infestations: candidiasis including oropharyngeal and vulvovaginal, fungal urinary tract infection, *Clostridium difficile* colitis

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

Nosocomial Pneumonia, including Ventilator-associated Pneumonia

ZERBAXA was evaluated in a Phase 3 comparator-controlled clinical trial for nosocomial pneumonia, which included a total of 361 patients treated with ZERBAXA (3 g every 8 hours, adjusted based on renal function where appropriate) and 359 patients treated with comparator (meropenem 1 g every 8 hours) for up to 14 days. The mean age of treated patients was 60 years (range 18 to 98 years), across treatment arms. About 44% of the subjects were 65 years of age or older. Most patients (71%) enrolled in the trial were male. All subjects were mechanically ventilated and 92% were in an intensive care unit (ICU) at randomization. The median APACHE II score was 17. Table 5 lists adverse reactions occurring in 2% or greater of patients receiving ZERBAXA in a Phase 3 nosocomial pneumonia clinical trial.

Table 5: Adverse Reactions Occurring in 2% or Greater of Patients Receiving ZERBAXA in a Phase 3 Nosocomial Pneumonia Clinical Trial by System Organ Class and Preferred Term

Preferred Term	Nosocomial Pneumonia, including Ventilator-associated Pneumonia	
	ZERBAXA* N=361 n (%)	Meropenem N=359 n (%)
Gastrointestinal disorders		
Diarrhea	23 (6.4)	25 (7.0)

Vomiting	12 (3.3)	10 (2.8)
Infections and Infestations		
Clostridium difficile colitis	8 (2.2)	1 (0.3)
Investigations		
ALT increased	21 (5.8)	14 (3.9)
AST increased	19 (5.3)	14 (3.9)
Transaminases increased	11 (3.0)	10 (2.8)

*The ZERBAXA for injection dose was 3 g intravenously every 8 hours, adjusted to match renal function where appropriate.

Treatment discontinuation due to treatment-related adverse events occurred in 1.1% (4/361) of patients receiving ZERBAXA and 1.4% (5/359) of patients receiving meropenem.

Less Common Adverse Reactions in a Phase 3 Nosocomial Pneumonia Clinical Trial

The following selected adverse reactions were reported in ZERBAXA-treated subjects at a rate of less than 2%:

Infections and infestations: Clostridium difficile infection

Investigations: liver function test abnormal, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, *Clostridium* test positive, Coombs direct test positive

Laboratory Values

The development of a positive direct Coombs test may occur during treatment with ZERBAXA. The incidence of seroconversion to a positive direct Coombs test was 0.2% in patients receiving ZERBAXA and 0% in patients receiving the comparator in the cUTI and cIAI clinical trials. The incidence of seroconversion to a positive direct Coombs test was 31.2% in patients receiving ZERBAXA and 3.6% in patients receiving meropenem in the nosocomial pneumonia clinical trial. In clinical studies, there was no evidence of hemolysis in patients who developed a positive direct Coombs test in any treatment group.

8. 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.

9. CLINICAL STUDIES

9.1 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 1.5 g (ceftolozane 1 g and tazobactam 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 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 Clinically Evaluable (CE) population, which included all protocol adherent patients that received an adequate amount of study drug. The key secondary efficacy endpoint was clinical response at the TOC visit in the Intent-to-Treat (ITT) population, which included all randomized subjects regardless of whether or not the subjects went on to receive study drug.

The CE population consisted of 774 patients; the median age was 49 years and 58.7% were male. The most common diagnosis was appendiceal perforation or peri-appendiceal abscess, occurring in 47.7% of patients. Diffuse peritonitis at baseline was present in 35.9% of patients.

ZERBAXA plus metronidazole was non-inferior to meropenem with regard to clinical cure rates at the TOC visit in the CE population. Clinical cure rates at the TOC visit are displayed by patient population in Table 6. Clinical cure rates at the TOC visit by pathogen in the Microbiologically Evaluable (ME) population are presented in Table 7. The ME included all protocol adherent patients with at least 1 baseline intra-abdominal pathogen regardless of the susceptibility to study drug.

Table 6: Clinical Cure Rates in a Phase 3 Study of Complicated Intra-Abdominal Infections

Analysis Population	ZERBAXA plus metronidazole* n/N (%)	Meropenem† n/N (%)	Treatment Difference (99% CI)‡
CE Population	353/375 (94.1)	375/399 (94)	0 (-4.16, 4.3)
ITT Population	399/476 (83.8)	424/494 (85.8)	-2.2 (-7.95, 3.44)

* ZERBAXA 1.5 g IV every 8 hours + metronidazole 500 mg IV every 8 hours

† 1 g IV every 8 hours

‡ The 99% CI was calculated using the Newcombe method with minimum risk weights

Table 7: Per Pathogen Clinical Cure Rates in a Phase 3 Study of Complicated Intra-abdominal Infections (ME Population)

Organism Group Pathogen	ZERBAXA plus metronidazole n/N (%)	Meropenem n/N (%)
Aerobic Gram-negative	238/252 (94.4)	273/291 (93.8)
Escherichia coli	197/208 (94.7)	216/231 (93.5)
Escherichia coli (ESBL-producing)	14/14 (100)	18/20 (90)
Escherichia coli (CTX-M-14/15 ESBL-producing)	9/9 (100)	7/9 (77.8)
Klebsiella pneumoniae	28/30 (93.3)	22/25 (88)
Klebsiella pneumoniae (ESBL-producing)	7/8 (87.5)	3/4 (75)
Klebsiella pneumoniae (CTX-M-15 ESBL-producing)	5/5 (100)	0/1 (0)
Pseudomonas aeruginosa	26/26 (100)	27/29 (93.1)
Enterobacter cloacae	19/22 (86.4)	22/22 (100)
Klebsiella oxytoca	12/12 (100)	21/22 (95.5)
Proteus mirabilis	10/11 (90.9)	9/10 (90)
Aerobic Gram-positive	153/168 (91.1)	170/185 (91.9)
Streptococcus anginosus	25/30 (83.3)	23/23 (100)

Streptococcus constellatus	17/18 (94.4)	20/23 (87)
Streptococcus salivarius	9/10 (90)	8/8 (100)
Anaerobic Gram-negative	104/109 (95.4)	132/137 (96.4)
Bacteroides fragilis	39/41 (95.1)	56/57 (98.2)

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, while some others were not susceptible. Isolates of a specific genotype were seen in patients who were deemed to be either successes or failures.

9.2 Complicated Urinary Tract Infections, including Pyelonephritis

A total of 1068 adults hospitalized with complicated urinary tract infections (including pyelonephritis) were randomized and received study medications in a multinational, double-blind study comparing ZERBAXA (1.5 g IV every 8 hours) to levofloxacin (750 mg IV once daily) for 7 days of therapy. The primary efficacy endpoint was defined as microbiological eradication (all uropathogens found at baseline at ≥ 10^5 were reduced to <10^3 CFU/mL) at the test-of-cure (TOC) visit 7 (± 2) days after the last dose of study drug. The primary efficacy analysis population was the microbiologically evaluable (ME) population, which included protocol-adherent microbiologically modified intent-to-treat (mMITT) patients with a urine culture at the TOC visit. The key secondary efficacy endpoint was microbiological eradication at the TOC visit in the mMITT population, which included all patients who received study medication and had at least 1 baseline uropathogen.

The ME population consisted of 693 patients with cUTI, including 567 (82%) with pyelonephritis. The median age was 50 years and 73% were female. Concomitant bacteremia was identified in 50 (7.2%) patients at baseline.

ZERBAXA was superior to levofloxacin with regard to the microbiological eradication rates at the TOC visit in both the ME and mMITT populations (Table 8).

Microbiological eradication rates at the TOC visit by pathogen in the ME population are presented in Table 9.

Table 8: Microbiological Eradication Rates in a Phase 3 Study of Complicated Urinary Tract Infections

Analysis Population	ZERBAXA* n/N (%)	Levofloxacin† n/N (%)	Treatment Difference (99% CI)‡
ME	288/340 (84.7)	266/353 (75.4)	9.4 (1.54, 17.12)
mMITT	313/398 (78.6)	281/402 (69.9)	8.7 (0.77, 16.57)

* 1.5 g IV every 8 hours

† 750 mg IV once daily

‡ The 99% CI was based on the stratified Newcombe method

Table 9: Per Pathogen Microbiological Eradication Rates in a Phase 3 Study of Complicated Urinary Tract Infections (ME Population)

Organism Group Pathogen	ZERBAXA n/N (%)	Levofloxacin n/N (%)
Aerobic Gram-negative	282/322 (87.6)	255/340 (75)
Escherichia coli	232/261 (88.9)	219/284 (77.1)
Escherichia coli (ESBL-producing)	26/36 (72.2)	17/36 (47.2)
Escherichia coli (CTX-M-14/15 ESBL-producing)	19/27 (70.4)	13/25 (52)
Klebsiella pneumoniae	21/25 (84)	14/23 (60.9)
Klebsiella pneumoniae (ESBL-producing)	7/10 (70)	2/7 (28.6)
Klebsiella pneumoniae (CTX-M-15 ESBL-producing)	5/8 (62.5)	1/4 (25)
Proteus mirabilis	10/10 (100)	8/11 (72.7)
Pseudomonas aeruginosa	6/7 (85.7)	6/12 (50)

In patients with levofloxacin-resistant pathogens at baseline, ZERBAXA was superior to levofloxacin with regards to microbiological eradication rate in the ME population, 58/89 (65.2%) in the ZERBAXA treatment arm and 42/99 (42.4%) in the levofloxacin treatment arm (95% CI: 22.7 [8.47, 35.73]).

In the ME population, the microbiological eradication rate in patients with concurrent bacteremia were 21/24 (87.5%) for ZERBAXA and 20/26 (76.9%) for levofloxacin.

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, while some others were not susceptible. Isolates of a specific genotype were seen in patients who were deemed to be either successes or failures.

9.3 Nosocomial Pneumonia, including Ventilator-associated Pneumonia

A total of 726 adult patients hospitalized with ventilated nosocomial pneumonia (including hospital-acquired pneumonia and ventilator-associated pneumonia) were enrolled in a multinational, double-blind study comparing ZERBAXA 3 g (ceftolozane 2 g and tazobactam 1 g) intravenously every 8 hours to meropenem (1 g intravenously every 8 hours) for 8 to 14 days of therapy.

The primary efficacy endpoint was all-cause mortality at Day 28. 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 7 to 14 days after the end of treatment was a pre-specified key secondary endpoint. The analysis population for both the primary and key secondary endpoints was the intent-to-treat (ITT) population, which included all randomized patients.

Of the 726 patients in the ITT population the median age was 62 years and 44% of the population was greater than or equal to 65 years of age, with 22% of the population greater than or equal to 75 years of age. The majority of patients were white (83%), male (71%) and were from Eastern Europe (64%). The median APACHE II score was 17 and 33% of subjects had a baseline APACHE II score of greater than or equal to 20. All subjects were on mechanical ventilation and 519 (71%) had VAP. At randomization, the majority of subjects had been hospitalized for greater than or equal to 5 days (77%), ventilated for greater than or equal to 5 days (49%) and in an ICU (92%). Approximately 36% of patients had renal impairment at baseline and 14% had moderate or severe impairment (CrCL less than 50 mL/min). Approximately 13% of subjects had failed prior antibiotic treatment for nosocomial pneumonia and bacteremia was present at baseline in 15% of patients. Key comorbidities included chronic obstructive pulmonary disease (COPD), diabetes mellitus, and congestive heart failure at rates of 12%, 22% and 16%, respectively.

In the ITT population, ZERBAXA was non-inferior to meropenem with regard to the primary endpoint of all-cause mortality at Day 28 and key secondary endpoint of clinical cure rates at the TOC visit (Table 10).

Table 10: 28-Day All-cause Mortality and Clinical Cure Rates at TOC from a Phase 3 Study of Nosocomial Pneumonia (ITT Population)

Endpoint	ZERBAXA n/N (%)	Meropenem n/N (%)	Treatment Difference (95% CI)‡
Day 28 All-cause Mortality	87/362 (24.0)	92/364 (25.3)	1.1 (-5.13, 7.39)
VAP	63/263 (24.0)	52/256 (20.3)	-3.6 (-10.74, 3.52)
Ventilated HAP	24/99 (24.2)	40/108 (37.0)	12.8 (0.18, 24.75)
Clinical Cure at TOC Visit	197/362 (54.4)	194/364 (53.3)	1.1 (-6.17, 8.29)
VAP	147/263 (55.9)	146/256 (57.0)	-1.1 (-9.59, 7.35)
Ventilated HAP	50/99 (50.5)	48/108 (44.4)	6.1 (-7.44, 19.27)

‡ The CI for overall treatment difference was based on the stratified Newcombe method with minimum risk weights. The CI for treatment difference of each primary diagnosis was based on the unstratified Newcombe method.

In the ITT population, Day 28 all-cause mortality rates in patients with renal hyperclearance at baseline (CrCL greater than or equal to 150 mL/min) were 10/67 (14.9%) for ZERBAXA and 7/64 (10.9%) for meropenem; the clinical cure rates were 40/67 (59.7%) and 39/64 (60.9%), respectively. In those patients who failed prior antibiotic therapy for nosocomial pneumonia, Day 28 all-cause mortality rates were 12/53 (22.6%) for ZERBAXA and 18/40 (45%) for meropenem; the clinical cure rates were 26/53 (49.1%) and 15/40 (37.5%), respectively. In patients with bacteremia at baseline, Day 28 all-cause mortality rates were 23/64 (35.9%) for ZERBAXA and 13/41 (31.7%) for meropenem; clinical cure rates were 30/64 (46.9%) and 15/41 (36.6%), respectively.

Per pathogen clinical and microbiologic responses were assessed in the microbiologic intention to treat population (mITT), which consisted of all randomized subjects who had a baseline lower respiratory tract (LRT) pathogen that was susceptible to at least one of the study therapies, and in the microbiologically evaluable (ME) population, which included protocol-adherent mITT patients with a baseline LRT pathogen that grew at the appropriate colony-forming unit (CFU)/mL threshold. In the mITT and ME populations, *Klebsiella pneumoniae* (34.6% and 38.6%, respectively) and *Pseudomonas aeruginosa* (25% and 28.8%, respectively) were the most prevalent pathogens isolated from baseline LRT cultures. Among all Enterobacteriaceae, 157 (30.7%) in the mITT and 84 (36.1%) in the ME were ESBL-positive; among all *K. pneumoniae* isolates, 105 (20.5%) in the mITT and 57 (24.5%) in the ME were ESBL-positive. AmpC-overexpression among *P. aeruginosa* was detected in 15 (2.9%) and 9 (3.9%) of the *P. aeruginosa* isolates in the mITT and ME populations, respectively. Clinical cure rates at TOC by pathogen in the mITT and ME populations are presented in Table 11. In the mITT population clinical cure rates in patients with a Gram-negative pathogen at baseline were 157/259 (60.6%) for ZERBAXA and 137/240 (57.1%) for meropenem; results were consistent in the ME population with 85/113 (75.2%) and 78/117 (66.7%) clinical cure rates, respectively. Microbiologic response rates at TOC by pathogen in the mITT and ME populations are presented in Table 12. In the mITT population microbiologic response rates in patients with a Gram-negative pathogen at baseline were 189/259 (73%) for ZERBAXA and 163/240 (67.9%) for meropenem; results were consistent in the ME population with 79/113 (69.9%) and 73/117 (62.4%) microbiologic response rates, respectively.

Table 11: Clinical Cure Rates by Baseline Pathogen from a Phase 3 Study of Nosocomial Pneumonia (mITT and ME populations)

Baseline Pathogen Category	mITT Population		ME Population	
Baseline Pathogen	ZERBAXA	Meropenem	ZERBAXA	Meropenem

	n/N (%)	n/N (%)	n/N (%)	n/N (%)
Pseudomonas aeruginosa	36/63 (57.1)	39/65 (60.0)	23/29 (79.3)	28/38 (73.7)
AmpC Overexpressing *Pseudomonas aeruginosa*	4/9 (44.4)	3/6 (50.0)	2/4 (50.0)	3/5 (60.0)
Enterobacteriaceae	120/195 (61.5)	105/185 (56.8)	62/83 (74.7)	58/90 (64.4)
ESBL + Enterobacteriaceae	48/84 (57.1)	45/73 (61.6)	33/45 (73.3)	27/39 (69.2)
Enterobacter cloacae	10/17 (58.8)	4/16 (25.0)	4/7 (57.1)	3/8 (37.5)
Escherichia coli	32/51 (62.7)	26/42 (61.9)	17/23 (73.9)	16/23 (69.6)
ESBL + *Escherichia coli*	11/20 (55.0)	5/10 (50.0)	8/12 (66.7)	5/7 (71.4)
Klebsiella (Enterobacter) aerogenes	4/8 (50.0)	3/8 (37.5)	1/1 (100)	1/1 (100)
Klebsiella oxytoca	9/14 (64.3)	7/12 (58.3)	7/8 (87.5)	4/7 (57.1)
Klebsiella pneumoniae	53/86 (61.6)	58/91 (63.7)	32/42 (76.2)	33/48 (68.8)
ESBL + *Klebsiella pneumoniae*	31/53 (58.5)	34/52 (65.4)	22/30 (73.3)	19/27 (70.4)
Proteus mirabilis	13/24 (54.2)	11/20 (55.0)	9/11 (81.8)	7/10 (70.0)
ESBL + *Proteus mirabilis*	5/10 (50.0)	7/11 (63.6)	4/5 (80.0)	5/6 (83.3)
Serratia marcescens	9/18 (50.0)	7/12 (58.3)	4/5 (80.0)	3/6 (50.0)
Haemophilus influenzae	19/22 (86.4)	8/16 (50.0)	11/12 (91.7)	4/8 (50.0)

Table 12: Microbiologic Response Rates by Baseline Pathogen from a Phase 3 Study of Nosocomial Pneumonia (mITT and ME populations)

Baseline Pathogen Category Baseline Pathogen	mITT Population		ME Population	
	ZERBAXA n/N (%)	Meropenem n/N (%)	ZERBAXA n/N (%)	Meropenem n/N (%)
Pseudomonas aeruginosa	47/63 (74.6)	41/65 (63.1)	23/29 (79.3)	21/38 (55.3)
AmpC Overexpressing *Pseudomonas aeruginosa*	6/9 (66.7)	1/6 (16.7)	2/4 (50.0)	1/5 (20.0)
Enterobacteriaceae	145/195 (74.4)	129/185 (69.7)	57/83 (68.7)	59/90 (65.6)
ESBL + Enterobacteriaceae	56/84 (66.7)	52/73 (71.2)	30/45 (66.7)	27/39 (69.2)
Enterobacter cloacae	11/17 (64.7)	8/16 (50.0)	4/7 (57.1)	6/8 (75.0)
Escherichia coli	43/51 (84.3)	33/42 (78.6)	18/23 (78.3)	17/23 (73.9)

ESBL + *Escherichia coli*	18/20 (90.0)	8/10 (80.0)	10/12 (83.3)	6/7 (85.7)
Klebsiella (Enterobacter) aerogenes	6/8 (75.0)	6/8 (75.0)	1/1 (100)	1/1 (100)
Klebsiella oxytoca	13/14 (92.9)	8/12 (66.7)	7/8 (87.5)	4/7 (57.1)
Klebsiella pneumoniae	63/86 (73.3)	65/91 (71.4)	30/42 (71.4)	32/48 (66.7)
ESBL + *Klebsiella pneumoniae*	33/53 (62.3)	38/52 (73.1)	20/30 (66.7)	18/27 (66.7)
Proteus mirabilis	18/24 (75.0)	14/20 (70.0)	7/11 (63.6)	7/10 (70.0)
ESBL + *Proteus mirabilis*	7/10 (70.0)	7/11 (63.6)	3/5 (60.0)	5/6 (83.3)
Serratia marcescens	11/18 (61.1)	9/12 (75.0)	2/5 (40.0)	3/6 (50.0)
Haemophilus influenzae	20/22 (90.9)	11/16 (68.8)	11/12 (91.7)	4/8 (50.0)

In the mITT population, per subject microbiologic cure was achieved in 193/264 (73.1%) of ZERBAXA-treated patients and in 168/247 (68.0%) of meropenem-treated patients. Similar results were achieved in the ME population in 81/115 (70.4%) and 74/118 (62.7%) patients, respectively.

In a subset of Enterobacteriaceae isolates from both arms of the trial that met pre-specified criteria for beta-lactam susceptibility, genotypic testing identified certain ESBL groups (e.g., TEM, SHV, CTX-M, OXA) in 157/511 (30.7%). Cure rates in this subset were similar to the overall trial results.

10. CLINICAL PHARMACOLOGY

10.1 Therapeutic Class

Ceftolozane-tazobactam is a beta-lactam and beta-lactamase inhibitor.

10.2 Mechanism of Action

ZERBAXA is an antibacterial drug.

Microbiology

Mechanism of Action

Ceftolozane belongs to the cephalosporin class of antimicrobials. Ceftolozane exerts bactericidal activity through binding to important penicillin-binding proteins (PBPs), resulting in inhibition of bacterial cell wall

synthesis and subsequent cell death. Ceftolozane is an inhibitor of PBPs of *P. aeruginosa* (e.g., PBP1b, PBP1c and PBP3) and *E. coli* (e.g., PBP3).

Tazobactam is a beta-lactam structurally related to penicillin. It is an inhibitor of many Molecular Class A beta-lactamases, including CTX M, SHV, and TEM enzymes [see Resistance].

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 also 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).

In the 2017 PACTS (Program to Assess Ceftolozane/Tazobactam Susceptibility) surveillance study the overall ceftolozane/tazobactam susceptibility of 3937 Enterobacteriaceae isolates collected from all sources from US hospitals was 95.6% and against extended spectrum beta-lactamase (ESBL), non-carbapenem resistant Enterobacteriaceae isolates the percent ceftolozane/tazobactam susceptibility was 93.5%. The overall ceftolozane/tazobactam susceptibility of 910 *P. aeruginosa* isolates collected from US hospitals was 97.7%. When ceftolozane/tazobactam was tested against isolates non-susceptible to ceftazidime, meropenem or piperacillin/tazobactam, the percent susceptibility to ceftolozane/tazobactam was 87.2%, 91.3% and 89.5%, respectively.

Resistance

Mechanisms of bacterial resistance to ceftolozane and tazobactam include:

- Production of beta-lactamases that can hydrolyse ceftolozane and which are not inhibited by tazobactam (see below)
- Modification of PBPs

Tazobactam does not inhibit all Class A enzymes.
In addition, tazobactam does not inhibit the following types of beta-lactamase:

- Serine-based carbapenemases (e.g., *Klebsiella pneumoniae* carbapenemases [KPCs])
- Metallo-beta-lactamases (e.g., New Delhi metallo-beta-lactamase [NDM])
- Ambler Class D beta-lactamases (OXA-carbapenemases)

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

Cross-Resistance

Isolates resistant to other cephalosporins may be susceptible to ceftolozane and tazobactam, although cross-resistance may occur.

Interaction with Other Antimicrobials

In vitro synergy studies suggest no antagonism between ceftolozane and tazobactam 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

Nosocomial Pneumonia, including Ventilator-associated Pneumonia

Gram-negative bacteria

Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Klebsiella (Enterobacter) aerogenes
Klebsiella oxytoca
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa
Serratia marcescens

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 ceftolozane and tazobactam against isolates of similar genus or organism group. However, the efficacy of ZERBAXA in treating clinical infections due to these bacteria has not been established in adequate and well controlled clinical trials.

Gram-negative bacteria
Citrobacter koseri
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Serratia liquefaciens

Gram-positive bacteria
Streptococcus agalactiae
Streptococcus intermedius

Table 13-A*: 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	≥ 22^	19-21^	≤ 18^
Pseudomonas aeruginosa	≤ 4/4	8/4	≥ 16/4	≥ 21	17-20	≤ 16
Haemophilus influenzae (nosocomial pneumonia,	≤ 0.5/4	---	---	---	---	---

including VAP)†						
Streptococcus anginosus *Streptococcus constellatus* and *Streptococcus salivarius* (cIAI and cUTI, including pyelonephritis)*	≤ 8/4	16/4	≥ 32/4	---	---	---
Bacteroides fragilis (cIAI and cUTI, including pyelonephritis)*	≤ 8/4	16/4	≥ 32/4	---	---	---

*based on CLSI Breakpoints

^based on MSD Disk-MIC Analysis

S=susceptible, I = intermediate, R = resistant

*Based on 1.5 g IV every 8 hours

† Based on 3 g IV every 8 hours

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. Standard ceftolozane and tazobactam powder should provide the following range of MIC values provided in Table 13-B. For the diffusion technique using the 30 mcg ceftolozane / 10 mcg tazobactam disk, the criteria provided in Table 13-B should be achieved.

Table 13-B: Acceptable Quality Control Ranges for Ceftolozane/Tazobactam

Quality Control Organism	Minimum Inhibitory Concentrations (mcg/mL)	Disk Diffusion Zone Diameters (mm)
Escherichia coli	0.12/4-0.5/4	24-32

ATCC 25922		
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.

10.3 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.

For tazobactam the PD index associated with efficacy was determined to be the percentage of the dose interval during which the plasma concentration of tazobactam exceeds a threshold value (%T>threshold). The time above a threshold concentration has been determined to be the parameter that best predicts the efficacy of tazobactam in *in vitro* and *in vivo* nonclinical models.

The exposure-response analyses in efficacy and safety clinical trials for cIAI, cUTI, and nosocomial pneumonia support the recommended dose regimens of ZERBAXA.

Cardiac Electrophysiology

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

10.4 Pharmacokinetics

General Introduction

The mean pharmacokinetic parameters of ZERBAXA (ceftolozane and tazobactam) in healthy adults with normal renal function after multiple 1-hour intravenous infusions of ZERBAXA 1.5 g (ceftolozane 1 g and tazobactam 0.5 g) or 3 g (ceftolozane 2 g and tazobactam 1 g) administered every 8 hours are summarized in Table 14. Ceftolozane and tazobactam pharmacokinetics are similar following single- and multiple-dose administration. The C_{max} and AUC of ceftolozane and tazobactam increase in proportion to dose. The elimination half-life ($t_{½}$) of ceftolozane or tazobactam is independent of dose.

Table 14: Mean (CV%) Steady-State Plasma Pharmacokinetic Parameters of ZERBAXA (ceftolozane and tazobactam) After Multiple Intravenous 1-hour Infusions of ZERBAXA 1.5 g (ceftolozane 1 g and tazobactam 0.5 g) or 3 g (ceftolozane 2 g and tazobactam 1 g) Every 8 Hours in Healthy Adults

PK parameters	ZERBAXA 1.5 g (ceftolozane 1 g and tazobactam 0.5 g)		ZERBAXA 3 g (ceftolozane 2 g and tazobactam 1 g)	
	Ceftolozane (n=10)	Tazobactam (n=10)	Ceftolozane (n=7)	Tazobactam (n=7)
C_{max} (mcg/mL)	74.4 (14)	18.0 (8)	112 (13)	25.8 (15)
t_{max} (h)†	1.07 (1.00, 1.10)	1.01 (1.00, 1.10)	1.0 (1.0, 1.0)	1.0 (0.5, 1.0)
$AUC_{0-8,ss}$ (mcg• h/mL)‡	182 (15)	25.0 (15)	300 (9.8)	40.5 (13)
$t_{½}$ (h)	3.12 (22)	1.03 (19)	2.8 (14)	1.0 (18)

† Median (minimum, maximum)

‡ Steady-state AUC for 8 hour dosing interval. Daily AUC at steady-state is calculated by multiplying the $AUC_{0-8,ss}$ values by three (e.g., 546 mcg• h/mL for ceftolozane and 75 mcg• h/mL for tazobactam at the ceftolozane 1 g and tazobactam 0.5 g dosing regimen)

The mean steady-state population pharmacokinetic parameters of ZERBAXA in patients with cIAI and cUTI receiving 1 hour intravenous infusion of ZERBAXA 1.5 g (ceftolozane 1 g and tazobactam 0.5 g) or patients with nosocomial pneumonia receiving 1 hour intravenous infusion of ZERBAXA 3 g (ceftolozane 2 g and tazobactam 1 g) every 8 hours are summarized in Table 15.

Table 15: Mean (CV%) Steady-State Plasma Population Pharmacokinetic Parameters of ZERBAXA (ceftolozane and tazobactam) After Multiple Intravenous 1 hour Infusions of ZERBAXA 1.5 g (ceftolozane 1 g and tazobactam 0.5 g) or 3 g (ceftolozane 2 g and tazobactam 1 g) Every 8 Hours in Patients with CrCL greater than 50 mL/min

PK parameters	ZERBAXA 1.5 g (ceftolozane 1 g and tazobactam 0.5 g) in cIAI and cUTI Patients		ZERBAXA 3 g (ceftolozane 2 g and tazobactam 1 g) in Nosocomial Pneumonia Patients	
	Ceftolozane (n=317)	Tazobactam (n=244)	Ceftolozane (n=247)	Tazobactam (n=247)

C_{max} (mcg/mL)	65.7 (41)	17.8 (51)	105 (44)	26.4 (49)
$AUC_{0-8,ss}$ (mcg• h/mL)	186 (40)	35.8 (160)	392 (60)	73.3 (104)
$t_{½}$ (h)	2.7 (32)	1.8 (83)	3.9 (50)	3.2 (61)

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 intravenous dose of ZERBAXA 1.5 g (ceftolozane 1 g and tazobactam 0.5 g) was 13.5 L (21%) and 18.2 L (25%) for ceftolozane and tazobactam, respectively, similar to extracellular fluid volume.

Following 1 hour intravenous infusions of ZERBAXA 3 g (ceftolozane 2 g and tazobactam 1 g) or adjusted based on renal function every 8 hours in ventilated patients with confirmed or suspected pneumonia (N=22), ceftolozane and tazobactam concentrations in pulmonary epithelial lining fluid were greater than 8 mcg/mL and 1 mcg/mL, respectively, over 100% of the dosing interval. Mean pulmonary epithelial-to-free plasma AUC ratios of ceftolozane and tazobactam were approximately 50% and 62%, respectively and are similar to those in healthy subjects (approximately 61% and 63%, respectively) receiving ZERBAXA 1.5 g (ceftolozane 1 g and tazobactam 0.5 g).

Metabolism

Ceftolozane is mainly 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.

Elimination

Ceftolozane, tazobactam, and the tazobactam metabolite M1 are eliminated by the kidneys. Following administration of a single 1 g / 0.5 g IV dose of ceftolozane/tazobactam to healthy male adults greater than 95% of ceftolozane was excreted in the urine as unchanged parent substance. More than 80% of tazobactam was excreted as the parent compound with the remaining amount 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 clearance (4.10 - 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.

The mean terminal elimination half-life of ceftolozane and tazobactam in healthy adults with normal renal function is approximately 3 hours and 1 hour, respectively.

Special Populations

Renal Impairment

Ceftolozane, tazobactam, 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 ceftolozane/tazobactam dose is removed by HD. The recommended dose in cIAI or cUTI subjects with ESRD on HD is a single loading dose of ZERBAXA 750 mg (ceftolozane 500 mg and tazobactam 250 mg), followed by a ZERBAXA 150 mg (ceftolozane 100 mg and tazobactam 50 mg) maintenance dose administered every 8 hours for the remainder of the treatment period. The recommended dose in nosocomial pneumonia subjects with ESRD on HD is a single loading dose of ZERBAXA 2.25 g (ceftolozane 1.5 g and tazobactam 0.75 g), followed by a ZERBAXA 450 mg (ceftolozane 300 mg and tazobactam 150 mg) maintenance dose administered every 8 hours for the remainder of the treatment period. With HD, the dose should be administered immediately following completion of dialysis [see Dosage and Administration (2.2)].

Augmented renal clearance

Following a single 1 hour intravenous infusion of ZERBAXA 3 g (ceftolozane 2 g and tazobactam 1 g) to critically ill patients with CrCL greater than or equal to 180 mL/min (N=10), mean terminal half-life values of ceftolozane and tazobactam were 2.6 hours and 1.5 hours, respectively. Free plasma ceftolozane concentrations were greater than 8 mcg/mL over 70% of an 8-hour period; free tazobactam concentrations were greater than 1 mcg/mL over 60% of an 8-hour period. No dose adjustment of ZERBAXA is recommended for nosocomial pneumonia patients with augmented renal clearance [see Clinical Studies (9.3)].

Hepatic impairment

As ceftolozane/tazobactam does not undergo hepatic metabolism, the systemic clearance of ceftolozane/tazobactam is not expected to be affected by hepatic impairment. No dose adjustment is recommended for ZERBAXA in subjects with hepatic impairment [see Dosage and Administration (2.3)].

Elderly

In a population pharmacokinetic analysis of ceftolozane/tazobactam, no clinically relevant differences in AUC were observed with regard to age. No dose adjustment of ZERBAXA based on age alone is

recommended. Dosage adjustment for ZERBAXA in elderly patients should be based on renal function [see Dosage and Administration (2.2)].

Paediatric patients

Safety and efficacy in paediatric patients have not been established.

Gender

In a population pharmacokinetic analysis of ceftolozane/tazobactam, no clinically relevant differences in AUC were observed for ceftolozane and tazobactam. No dose adjustment is recommended based on gender.

Race

In a population pharmacokinetic analysis of ceftolozane/tazobactam, no clinically relevant differences in ceftolozane/tazobactam AUC were observed in Caucasians compared to other races. No dose adjustment is recommended based on race.

10.5 Drug Interaction Studies

See Drug Interactions and Other Forms of Interactions (5).

11. ANIMAL TOXICOLOGY

11.1 Carcinogenesis

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

11.2 Mutagenesis

ZERBAXA was not genotoxic *in vivo*. 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, but only at highly toxic concentrations.

Ceftolozane was negative for genotoxicity in the *in vitro* microbial mutagenicity (Ames) assay, the *in vitro* chromosomal aberration assay in Chinese hamster lung fibroblast cells, the *in vitro* mouse lymphoma

assay, the *in vitro* HPRT assay in Chinese hamster ovary cells, the *in vivo* mouse micronucleus assay, and the *in vivo* unscheduled DNA synthesis (UDS) assay.

Tazobactam was negative for genotoxicity in an *in vitro* microbial mutagenicity (Ames) assay, an *in vitro* chromosomal aberration assay in Chinese hamster lung cells, a mammalian point-mutation (Chinese hamster ovary cell HPRT) assay, an *in vivo* rat chromosomal aberration assay, an *in vivo* mouse bone marrow micronucleus assay, and a UDS assay. Tazobactam was positive for genotoxicity in an *in vitro* mouse lymphoma assay at ≥ 3000 mcg/mL.

11.3 Reproduction

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 1.4 times the mean daily human ceftolozane exposure value at the highest recommended human dose of 2 grams every 8 hours.

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 2 times the highest recommended human dose of 1 gram every 8 hours based on body surface comparison).

11.4 Development

See Pregnancy (6.1).

12. NAME OF THE DRUG

ZERBAXA (ceftolozane and tazobactam)

13. PHARMACEUTICAL FORM

ZERBAXA 1.5 g (ceftolozane and tazobactam) for injection is supplied as a white to yellow sterile powder for reconstitution in single dose vials; each vial contains ceftolozane 1 g (equivalent to 1.147 g of ceftolozane sulfate) and tazobactam 0.5 g (equivalent to 0.537 g of tazobactam sodium).

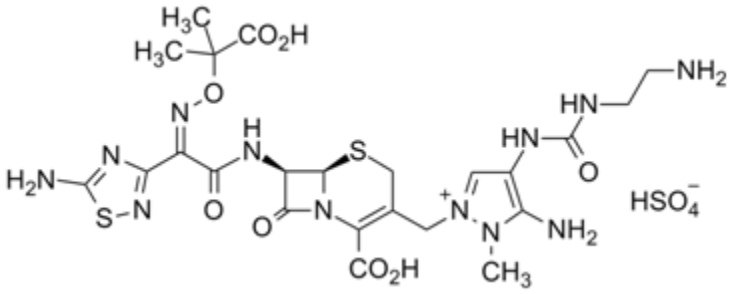
14. PHARMACEUTICAL PARTICULARS

14.1 Chemistry

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

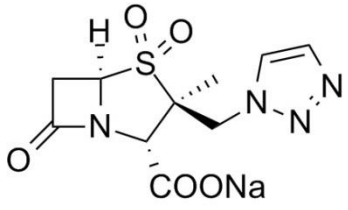
Ceftolozane sulfate is a semi-synthetic antibacterial drug of the beta-lactam class for parenteral administration. The chemical name of ceftolozane sulfate is 1*H*-Pyrazolium, 5-amino-4-[[[(2-aminoethyl)amino]carbonyl]amino]-2-[[(6*R*,7*R*)-7-[[(2*Z*)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[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 1.5 g (ceftolozane and tazobactam) for injection is a white to yellow sterile powder for reconstitution consisting of ceftolozane 1 g (equivalent to 1.147 g ceftolozane sulfate) and tazobactam 0.5 g (equivalent to 0.537 g tazobactam sodium) per vial packaged in single-dose 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.

14.2 Composition

Active Ingredient

ZERBAXA 1.5 g (ceftolozane and tazobactam) for injection is a white to yellow sterile powder for reconstitution consisting of ceftolozane 1 g (equivalent to 1.147 g ceftolozane sulfate) and tazobactam 0.5 g (equivalent to 0.537 g tazobactam sodium) per vial packaged in single-dose glass vials.

Inactive Ingredients (List of excipients)

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.

14.3 Storage

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

For storage conditions after reconstitution or dilution of the medicinal product [see Dosage and Administration (2.1)].

14.4 Incompatibilities

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.

14.5 Availability (a.k.a. Nature and Contents of Container)

ZERBAXA is supplied in pack size of 10 glass vials per carton.

Product Owner:
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