ZERBAXA™ (ceftolozane and tazobactam)

Powder for Infusion

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 patients with complicated intra-abdominal infections (cIAI) and required surgical intervention (e.g., laparotomy, laparoscopic surgery, or percutaneous draining of an abscess) within 24 hours of (before or after) the first dose of Zerbaxa. These cIAI are 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 patients with complicated urinary tract infections (cUTI) and pyuria with at least one of the following new or worsening symptoms (dysuria, frequency, suprapubic pain, urgency) and at least one of the following complicating factors (current bladder instrumentation, obstructive uropathy, urogenital surgery, functional or anatomical abnormality of the urogenital tract), including pyelonephritis, with or without concurrent bacteremia, caused by the following Gram-negative microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Pseudomonas aeruginosa*.

Hospital-acquired Bacterial Pneumonia or Ventilator-associated Bacterial Pneumonia (HABP / VABP)

ZERBAXA is indicated for the treatment of patients 18 years and older with hospital-acquired bacterial pneumonia or ventilator-associated bacterial pneumonia caused by the following susceptible Gram-negative microorganisms: *Enterobacter cloacae, Escherichia coli, Haemophilus influenza, 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 Hospital-acquired Bacterial Pneumonia / Ventilator-associated Bacterial Pneumonia (HABP / VABP) 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 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
Hospital-acquired Bacterial Pneumonia / Ventilator-associated Bacterial Pneumonia (HABP / VABP)	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. 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
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 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 Regimen for ZERBAXA in Patients with Renal Impairment

Estimated CrCL (mL/min)*	Complicated Intra-abdominal Infections and Complicated Urinary Tract Infections, including Pyelonephritis†	Hospital-acquired Bacterial Pneumonia / Ventilator-associated Bacterial Pneumonia (HABP / VABP) †
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)].

These types of infection may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea during or subsequent to the administration of ZERBAXA. In such circumstances, the discontinuation of therapy with ZERBAXA

and the use of supportive measures together with the administration of specific treatment for *Clostridium difficile* should be considered.

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 Immunosuppression

The experience in patients who are severely immunocompromised, receiving immunosuppressive therapy, and patients with severe neutropenia is limited since these populations were excluded from Phase 3 trials.

4.6 Non-susceptible micro-organism

The use of ceftolozane/tazobactam may promote the overgrowth of non-susceptible micro-organisms. If super infection occurs during or following treatment, appropriate measures should be taken. Ceftolozane/tazobactam is not active against bacteria that produce beta-lactamase enzymes which are not inhibited by tazobactam. See section 11.2 Mechanism of Action.

4.7 Direct antiglobulin test (Coombs test) seroconversion and potential risk of haemolytic anaemia

The development of a positive direct antiglobulin test (DAGT) may occur during treatment with ceftolozane/tazobactam. The incidence of DAGT seroconversion in patients receiving ceftolozane/tazobactam was 0.2% in the clinical trials. In clinical studies, there was no evidence of haemolysis in patients who developed a positive DAGT on treatment.

4.8 Sodium content

Ceftolozane/tazobactam contains 10.0 mmol (230 mg) of sodium per vial. The reconstituted vial with 10 mL of 0.9% sodium chloride (normal saline) for injection contains 11.5 mmol (265 mg) of sodium. This should be taken into consideration while treating patients on controlled-sodium diet.

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 Cmax 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 in renal function where appropiate) 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 occuring 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

General disorders and administration site conditions: infusion site reactions

Hospital-acquired Bacterial Pneumonia or Ventilator-associated Bacterial Pneumonia (HABP / VABP)

ZERBAXA was evaluated in a Phase 3 comparator-controlled clinical trial for Hospital-acquired Bacterial Pneumonia or Ventilator-associated Bacterial Pneumonia (HABP / VABP), 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 Hospital-acquired Bacterial Pneumonia or Ventilator-associated Bacterial Pneumonia (HABP / VABP) clinical trial.

Table 5: Adverse Reactions Occurring in 2% or Greater of Patients Receiving ZERBAXA in a Phase 3 Hospital-acquired Bacterial Pneumonia or Ventilator-associated Bacterial Pneumonia (HABP / VABP) Clinical Trial by System Organ Class and Preferred Term

Preferred Term	Hospital-acquired Bacterial Pneumonia or Ventilator-associated Bacterial Pneumonia (HABP / VABP)	
	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 Hospital-acquired Bacterial Pneumonia or Ventilator-associated Bacterial Pneumonia (HABP / VABP) 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 Hospital-acquired Bacterial Pneumonia or Ventilator-associated Bacterial Pneumonia (HABP / VABP) 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.

The highest single dose of Zerbaxa received in clinical trials was 3.0 g / 1.5 g of ceftolozane/tazobactam. At this dosage, no adverse pharmacological effects have been observed.

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 $\geq 10^5$ 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 Hospital-acquired Bacterial Pneumonia / Ventilator-associated Bacterial Pneumonia (HABP / VABP)

A total of 726 adult patients hospitalized with Hospital-acquired Bacterial Pneumonia / Ventilator-associated Bacterial Pneumonia (HABP / VABP) 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 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. All-cause mortality at Day 28 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 VABP. 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 Hospital-acquired Bacterial Pneumonia / Ventilator-associated Bacterial Pneumonia (HABP / VABP) 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 clinical cure rates at the TOC visit and key secondary endpoint of all-cause mortality at Day 28 (Table 10).

Table 10: Clinical Cure at TOC and 28-Day All-cause Mortality Rates from a Phase 3 Study of Hospital-acquired Bacterial Pneumonia or Ventilator-associated Bacterial Pneumonia (HABP / VABP) (ITT Population)

Endpoint	ZERBAXA n/N (%)	Meropenem n/N (%)	Treatment Difference (97.5% CI)‡
Clinical Cure at TOC Visit	197/362 (54.4)	194/364 (53.3)	1.1 (-7.20, 9.31)
VABP	147/263 (55.9)	146/256 (57.0)	-1.1 (-10.79, 8.55)
Ventilated HABP	50/99 (50.5)	48/108 (44.4)	6.1 (-9.31, 21.06)
Day 28 All-cause Mortality	87/362 (24.0)	92/364 (25.3)	1.1 (-6.03, 8.28)
VABP	63/263 (24.0)	52/256 (20.3)	-3.6 (-11.75, 4.55)
Ventilated HABP	24/99 (24.2)	40/108 (37.0)	12.8 (-1.63, 26.37)

‡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, the clinical cure rates in patients with renal hyperclearance at baseline (CrCL greater than or equal to 150 mL/min) were 40/67 (59.7%) for ZERBAXA and 39/64 (60.9%) for meropenem; Day 28 all-cause mortality rates were 10/67 (14.9%) and 7/64 (10.9%), respectively. In those patients who failed prior antibiotic therapy for Hospital-acquired Bacterial Pneumonia or Ventilator-associated Bacterial Pneumonia (HABP / VABP), the clinical cure rates were 26/53 (49.1%) for ZERBAXA and 15/40 (37.5%) for meropenem; Day 28 all-cause mortality rates were 12/53 (22.6%) and 18/40 (45%), respectively. In patients with bacteremia at baseline, clinical cure rates were 30/64 (46.9%) for ZERBAXA and 15/41 (36.6%) for meropenem; Day 28 all-cause mortality rates were 23/64 (35.9%) and 13/41 (31.7%), 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 Hospital-acquired Bacterial Pneumonia or Ventilator-associated Bacterial Pneumonia (HABP / VABP) (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	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 Hospital-acquired Bacterial Pneumonia or Ventilator-associated Bacterial Pneumonia (HABP / VABP) (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 surveillance study (PACTS, Program to Assess Ceftolozane/Tazobactam Susceptibility) the overall ceftolozane/tazobactam susceptibility of 3948 Enterobacteriaceae isolates collected from all sources from European hospitals was 88% and against extended spectrum beta-lactamase (ESBL), non-carbapenem resistant Enterobacteriaceae isolates the percent ceftolozane/tazobactam susceptibility was 74.3%. The overall ceftolozane/tazobactam susceptibility of 878 *P. aeruginosa* isolates collected from European hospitals was 88.2%. When ceftolozane/tazobactam was tested against isolates non-susceptible to ceftazidime, meropenem or piperacillin/tazobactam, the percent

susceptibility to ceftolozane/tazobactam was 52.4%, 61.4% and 58.4%, 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

Hospital-acquired Bacterial Pneumonia or Ventilator-associated Bacterial Pneumonia (HABP / VABP)
Gram-negative bacteria
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Klebsiella oxytoca
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa
Serratia marcescens

Clinical efficacy has not been established against the following pathogens although *in vitro* studies suggest that they would be susceptible to ZERBAXA in the absence of acquired mechanisms of resistance.

Gram-negative bacteria
Burkholderia cepacia
Citrobacter freundii
Citrobacter koseri
Moraxella catarrhalis
Morganella morganii
Pantoea agglomerans
Proteus vulgaris
Providencia rettgeri
Providencia stuartii

Serratia liquefaciens
Klebsiella (Enterobacter) aerogenes

Gram-positive bacteria
Streptococcus agalactiae
Streptococcus intermedius
Streptococcus pyogenes
Streptococcus pneumoniae

Anaerobic bacteria:
Fusobacterium spp.
Prevotella spp.

In vitro data indicate that the following species are not susceptible to ceftolozane/tazobactam:
Staphylococcus aureus
Enterococcus faecalis
Enterococcus faecium

Table 13: Susceptibility Testing Breakpoints

		Minimum Inhibitory Concentrations (mg/L)		**Disk Diffusion** Zone Diameters (mm)	
Pathogen	**Type of Infection**	**Susceptible**	**Resistant**	**Susceptible**	**Resistant**

*Enterobacterales**	• Complicated intra-abdominal infections* • Complicated urinary tract infections* • Acute pyelonephritis* • Hospital-acquired Bacterial Pneumonia or Ventilator-associated Bacterial Pneumonia (HABP / VABP) †	≤2	>2	≥22	<22
*P. aeruginosa**	• Complicated intra-abdominal infections* • Complicated urinary tract infections* • Acute pyelonephritis* • Hospital-acquired Bacterial Pneumonia or Ventilator-associated Bacterial Pneumonia (HABP /	≤4	>4	≥24	<24

	VABP) †				
H. influenzae†	• Hospital-acquired Bacterial Pneumonia or Ventilator-associated Bacterial Pneumonia (HABP / VABP) †	≤0.5	> 0.5	≥23	<23

S = susceptible, R = resistant

*Based on 1.5 g IV every 8 hours

†Based on 3 g IV every 8 hours

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 Hospital-acquired Bacterial Pneumonia or Ventilator-associated Bacterial Pneumonia (HABP / VABP) 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 Cmax and AUC of ceftolozane and tazobactam increase in proportion to dose. The elimination half-life (t1/2) 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)
Cmax (mcg/mL)	74.4 (14)	18.0 (8)	112 (13)	25.8 (15)
tmax (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)
AUC0-8,ss (mcg•h/mL)‡	182 (15)	25.0 (15)	300 (9.8)	40.5 (13)
t½ (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 AUC0-8,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 Hospital-acquired Bacterial Pneumonia or Ventilator-associated Bacterial Pneumonia (HABP / VABP) 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 Hospital-acquired Bacterial Pneumonia or

			Ventilator-associated Bacterial Pneumonia (HABP / VABP)Patients	
	Ceftolozane (n=317)	Tazobactam (n=244)	Ceftolozane (n=247)	Tazobactam (n=247)
Cmax (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 Hospital-acquired Bacterial Pneumonia or Ventilator-associated Bacterial Pneumonia (HABP / VABP) 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 Hospital-acquired Bacterial Pneumonia or Ventilator-associated Bacterial Pneumonia (HABP / VABP)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 (7.1).

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

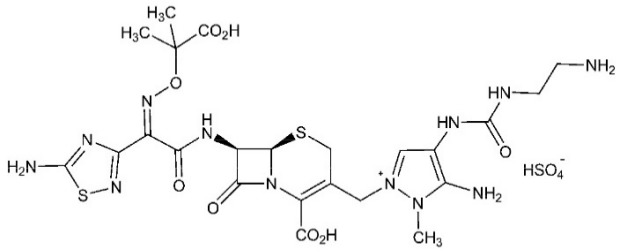
14.1 Chemistry

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.

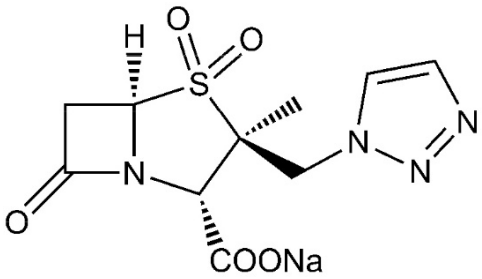
Ceftolozane sulfate is a semi-synthetic antibacterial drug of the beta-lactam class for parenteral administration. The chemical name of ceftolozane sulfate is 1*H*-Pyrazolium, 5-amino-4-[[[(2-aminoethyl)amino]carbonyl]amino]-2-[[(6*R*,7*R*)-7-[[(2*Z*)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-[(1-carboxy-1-methylethoxy)imino]acetyl]amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo[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.

In use stability

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 Shelf Life

36 months

14.6 Availability (Presentation)

Box, 10 vials @ 1.5 g

Reg. No.: DKI1937700380A1

HARUS DENGAN RESEP DOKTER

Registered by:

PT Organon Pharma Indonesia Tbk

Pasuruan, Jawa Timur

Distributed by:

PT Merck Sharp & Dohme Indonesia

Jakarta, Indonesia

Manufactured and Packaged by:

Steri-Pharma, LLC, New York, USA

Released by:

FAREVA Mirabel, Clermont-Ferrand, France

CCDS-MK7625A-IV-092020

Version 3

MSD

ZERBAXA (ceftolozane and tazobactam)

[Serbuk untuk Infus]

Harap membaca leaflet ini dengan seksama sebelum anda mulai minum obat, walaupun anda telah menggunakan obat ini sebelumnya. Beberapa informasi dalam leaflet sebelumnya dapat berubah.
Ingatlah bahwa dokter anda hanya meresepkan obat ini hanya untuk anda. Jangan berikan kepada orang lain.

1. APAKAH *ZERBAXA* ITU ?

Zerbaxa 1.5 g mengandung bahan aktif berikut per vial : ceftolozane 1 g dan tazobactam 0.5 g. Untuk dosis di atas 1,5 g, dua vial Zerbaxa digunakan.
Zerbaxa juga mengandung bahan tidak aktif : sodium chloride, citric acid, dan L-arginine.
Zerbaxa merupakan serbuk berwarna putih kekuningan dalam wadah kaca (vial). Serbuk dicampur dengan cairan steril hingga berwarna jernih, tidak berwarna hingga larutan kuning untuk infus.
ZERBAXA merupakan agen antibakteri yang bekerja dengan membunuh bakteri tertentu yang dapat menyebabkan infeksi serius.

2. MENGAPA DOKTER SAYA MERESEPKAN *ZERBAXA* ?

ZERBAXA adalah antibiotik yang diresepkan untuk mengobati orang dewasa yang berusia 18 tahun atau lebih dengan:

- Infeksi bakteri yang berat dalam saluran pencernaan dan saluran kemih, termasuk kondisi yang disebut “ pyelonephritis ” (sejenis tipe infeksi saluran kemih yang mempengaruhi satu atau kedua ginjal).
- *Hospital-acquired Bacterial Pneumonia (HABP)* (infeksi paru-paru yang dapat terjadi saat di rumah sakit atau pada pasien yang baru dirawat di rumah sakit), atau *Ventilator-associated Bacterial Pneumonia (VABP)* (infeksi paru-paru yang dapat terjadi saat menggunakan intubasi endotrakeal).

ZERBAXA terdiri dari 2 zat aktif :

- Ceftolozane (suatu antibiotik golongan “sefalosporin”) membunuh bakteri tertentu yang dapat menyebabkan infeksi.
- Tazobactam (suatu “penghambat beta laktamase”) yang menghambat aksi enzim tertentu yang disebut beta laktamase. Enzim beta laktamase ini membuat bakteri resisten terhadap ceftolozane dengan memecah antibiotik sebelum dapat bekerja. Dengan menghambat aksi mereka, tazobactam membuat ceftolozane lebih efektif dalam membunuh bakteri.

Kedua antibiotik bekerja sama untuk membunuh bakteri tertentu dan mengobati infeksi.

Obat antibakteri, termasuk ZERBAXA, hanya digunakan untuk mengobati infeksi bakteri. Tidak untuk mengobati infeksi virus (Misal: flu). Bakteri dapat menjadi resisten terhadap antibiotik dari waktu ke waktu. Dokter Anda yang akan memutuskan jika harus memberikan ZERBAXA untuk mengobati infeksi Anda.

3. BAGAIMANA CARA SAYA MENGGUNAKAN *ZERBAXA* ?

Dokter Anda atau ahli kesehatan lainnya akan memberikan ZERBAXA.

3.1. Cara Penggunaan

Dosis tergantung pada jenis infeksi yang Anda miliki, dimana infeksi tersebut ada di tubuh Anda dan seberapa serius infeksi tersebut. Dokter Anda akan memutuskan dosis yang Anda butuhkan.

Dosis yang disarankan untuk ZERBAXA adalah 1.5 g (terdiri dari 1 g ceftolozane dan 0.5 g tazobactam) atau 3 g (terdiri dari 2 g ceftolozane dan 1 g tazobactam) setiap 8 jam, yang diberikan ke salah satu pembuluh darah Anda (langsung ke dalam aliran darah) secara infus intravena (IV) selama lebih dari 1 jam. Pengobatan dengan ZERBAXA biasanya selama 4 sampai 14 hari, tergantung dengan tingkat keparahan dan lokasi infeksi dan bagaimana tubuh Anda merespon pengobatan.

Pasien dengan masalah ginjal

Dokter Anda mungkin perlu mengurangi dosis ZERBAXA atau memutuskan seberapa sering ZERBAXA diberikan kepada Anda. Dokter Anda mungkin juga ingin memeriksa darah Anda untuk memastikan Anda dapat menerima dosis yang tepat.

3.2 Apa yang harus saya lakukan jika terjadi kelebihan dosis ?

Karena produk ini diberikan oleh dokter atau ahli kesehatan lainnya, sangat tidak mungkin jika Anda diberikan ZERBAXA terlalu banyak. Namun, apabila anda memiliki keluhan, Anda harus segera memberitahu dokter Anda atau ahli kesehatan lainnya.

3.3 Apa yang harus saya lakukan jika saya terlupa satu dosis ?

Jika Anda berpikir terlupa satu dosis ZERBAXA, sampaikan ke dokter Anda atau ahli kesehatan lainnya segera.

3.4 Gejala apa yang akan terjadi jika saya berhenti menggunakan ZERBAXA ?

ZERBAXA harus diberikan secara tepat seperti yang diarahkan. Lupa dosis atau tidak menyelesaikan terapi dapat memperburuk gejala. Penggunaan ZERBAXA yang tidak tepat dapat meningkatkan kemungkinan bakteri akan mengembangkan resistensi dan mungkin tidak dapat diobati dengan ZERBAXA atau anti bakteri lainnya di waktu yang akan datang.

Jika Anda memiliki pertanyaan lebih lanjut mengenai penggunaan obat ini, tanyakan dokter Anda atau ahli kesehatan lainnya.

4. APA YANG HARUS SAYA TAHU SEBELUM SAYA DIBERIKAN *ZERBAXA*?

4.1. Siapa yang tidak boleh diberikan ZERBAXA ?

Anda tidak boleh diberikan ZERBAXA jika Anda:

- Alergi terhadap: ceftolozane, tazobactam, atau salah satu bahan dari obat ini
- Alergi dengan obat yang mengandung golongan sefalosporin

- Pernah memiliki reaksi alergi yang parah (misalnya pengelupasan kulit yang parah, pembengkakan wajah, tangan, kaki, bibir, lidah atau tenggorokan; atau kesulitan menelan atau bernafas) terhadap antibiotik beta-laktam (misalnya penisilin atau carbapenems).

4.2 Apa yang harus saya katakan kepada dokter saya sebelum dan saat menggunakan ZERBAXA ?

Katakan kepada dokter Anda atau ahli kesehatan lainnya sebelum menggunakan ZERBAXA:

- Jika Anda memiliki masalah ginjal.
- Jika Anda tahu alergi terhadap sefalosporin, penisilin, atau antibiotik lainnya.
- Jika Anda baru saja mengalami diare atau jika diare terjadi saat menggunakan ZERBAXA
- Jika Anda memiliki infeksi lain, sedang menggunakan obat untuk mengobati infeksi, atau memiliki kadar sel darah putih yang rendah (neutropenia)

4.3 Hamil

Katakan kepada dokter Anda jika Anda sedang hamil atau berencana untuk hamil.

Dokter Anda akan memberi saran jika Anda harus menggunakan ZERBAXA selama kehamilan.

4.4 Menyusui

Katakan kepada dokter Anda jika Anda sedang menyusui atau berencana untuk menyusui.

Dokter Anda akan mendiskusikan kemungkinan resiko dan manfaat menggunakan ZERBAXA selama Anda menyusui.

4.5 Anak-Anak

Obat ini tidak boleh diberikan kepada anak-anak dibawah umur 18 tahun karena belum ada

informasi yang cukup mengenai penggunaan obat pada usia grup tersebut.

4.6. Dapatkah saya menggunakan ZERBAXA bersamaan dengan obat lain, suplemen makanan, produk herbal atau makanan ?

Katakan kepada dokter Anda mengenai semua obat yang Anda gunakan, termasuk obat resep dan obat tanpa resep, vitamin, dan suplemen herbal.

Mengetahui obat-obatan yang Anda gunakan. Menyimpan daftar obat dan tunjukkan daftar tersebut kepada dokter Anda atau apoteker saat Anda mendapatkan obat baru.

Hal ini merupakan hal yang penting untuk dikatakan kepada dokter Anda jika Anda menggunakan:

- Probenecid (obat yang digunakan untuk mengobati asam urat).
  Obat ini dapat meningkatkan waktu yang diperlukan tazobactam untuk keluar dari tubuh Anda.

5. APA EFEK YANG TIDAK DIINGINKAN DARI *ZERBAXA* ?

Semua obat memiliki efek yang tidak diinginkan, yang disebut efek samping.

Pasien dirawat karena infeksi bakteri yang berat dalam saluran pencernaan dan saluran kemih.

Efek samping yang umum (dapat terjadi hingga 1 dari 10 orang) meliputi:

- Sakit kepala
- Sakit perut
- Sembelit
- Diare
- Mual
- Muntah
- Peningkatan enzim hati (dari uji darah)
- Ruam
- Demam (suhu tinggi)

- Penurunan tekanan darah
- Penurunan kadar kalium (dari uji darah)
- Peningkatan jumlah jenis tertentu sel darah yang dikenal sebagai trombosit
- Pusing
- Gelisah
- Susah tidur
- Masalah lokal (misalnya kemerahan tidak normal pada kulit, peradangan, nyeri, gatal atau ruam) saat pemberian obat melalui pembuluh darah (reaksi efek pemberian infus)

Efek samping yang tidak umum terjadi (dapat terjadi hingga 1 dari 100 orang) termasuk:

- Radang usus besar karena bakteri *C.difficile*
- Radang lambung
- Perut kembung
- Gangguan pencernaan
- Gas berlebihan di lambung atau usus
- Obstruksi usus
- Infeksi jamur dalam mulut (sariawan)
- Infeksi jamur pada organ kewanitaan
- Infeksi jamur saluran kemih
- Peningkatan kadar gula (glukosa) (dari uji darah)
- Penurunan kadar magnesium (dari uji darah)
- Penurunan kadar fosfat (dari uji darah)
- Stroke iskemik (stroke yang disebabkan berkurangnya aliran darah di otak)
- Iritasi atau peradangan pembuluh darah, di tempat suntikan
- Trombosis vena (pembekuan darah di pembuluh darah)
- Jumlah sel darah merah yang rendah
- Fibrilasi atrium (kondisi dimana detak jantung cepat dan tidak teratur)
- Detak jantung cepat
- Angina pektoris (nyeri dada atau rasa sesak, tekanan atau berat di dada)
- Ruam gatal atau bengkak pada kulit (gatal-gatal)
- Masalah ginjal
- Penyakit ginjal
- Nafas pendek

- Uji Coombs positif (tes darah yang mencari antibodi yang dapat melawan sel darah merah Anda)

Pasien dirawat karena infeksi paru-paru *Hospital-acquired Bacterial Pneumonia / Ventilator-associated Bacterial Pneumonia (HABP / VABP)*

Efek samping yang umum (dapat terjadi hingga 1 dari 10 orang) meliputi:

- Radang usus besar karena bakteri *C. difficile*
- Diare
- Mual
- Peningkatan enzim hati (dari tes darah)

Efek samping yang tidak umum terjadi (dapat terjadi hingga 1 dari 100 orang) termasuk:

- Infeksi karena bakteri *C. difficile*
- Uji *C. difficile* positif (dari uji feses)
- Uji Coombs positif (tes darah yang mencari antibodi yang dapat melawan sel darah merah Anda)

Efek samping lainnya mungkin jarang terjadi, dan dengan setiap resep obat, beberapa efek samping dapat menjadi serius.

Minta kepada dokter Anda atau ahli kesehatan lainnya untuk informasi lebih lanjut. Mereka memiliki daftar efek samping yang lebih lengkap. Katakan kepada dokter Anda atau ahli kesehatan lainnya segera mengenai efek samping dan gejala lain yang tidak biasa.

6. BERAPA LAMA SAYA HARUS MENYIMPAN OBAT SAYA?

Obat ini diberikan oleh dokter atau ahli kesehatan lainnya, sehingga Anda tidak perlu menyimpan ZERBAXA.

7. BAGAIMANA SAYA HARUS MENYIMPAN *ZERBAXA*?

Karena obat ini diberikan oleh dokter atau ahli kesehatan lainnya, mereka akan menyimpan ZERBAXA sesuai yang disarankan.

ZERBAXA vial harus disimpan dalam dalam keadaan dingin pada suhu 2° sampai 8°C (36 ° sampai 46°F) dan terlindung dari cahaya.

Simpan ZERBAXA dan obat-obatan lainnya secara aman jauh dari jangkauan anak-anak.

8. BAGAIMANA SAYA DAPAT MEMPELAJARI LEBIH MENGENAI *ZERBAXA* DAN KEADAAN SAYA?

Anda dapat mendapatkan informasi lebih lanjut dari dokter Anda atau ahli kesehatan lainnya.

Reg. No.: DKI1937700380A1

Kemasan :

Dus, 10 vial @ 1.5 g

HARUS DENGAN RESEP DOKTER

Didaftarkan oleh :

PT Organon Pharma Indonesia Tbk

Pasuruan, Jawa Timur

Didistribusikan oleh:

PT Merck Sharp & Dohme Indonesia

Jakarta, Indonesia

Diproduksi dan Dikemas oleh :

Steri-Pharma LLC, Syracuse, USA

Dirilis oleh :

FAREVA Mirabel, Clermont-Ferrand, France

CCPPI-MK7625A-IV-092020

Version 1.1