AUSTRALIAN PRODUCT INFORMATION

ZERBAXA®

(ceftolozane/tazobactam)
Powder for Injection

1 NAME OF THE MEDICINE

Ceftolozane sulfate/tazobactam sodium

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1000 mg of ceftolozane (as ceftolozane sulfate) and 500 mg tazobactam (as tazobactam sodium).

Ceftolozane sulfate is a white to off white hygroscopic powder that is freely soluble in water and 0.05M sodium perchlorate, insoluble in isopropyl alcohol, acetonitrile, dichloromethane and methyl-*tert*-butyl ether and slightly soluble in *N*-methylpyrrolidone. The pH of a 20 mg/mL (2%) aqueous solution is 1.92. The pKa is 9.3, 3.2, and 1.9. Ceftolozane sulfate is a single stereoisomer with the 6*R,* 7*R* configuration.

Tazobactam sodium is a white to off-white, hygroscopic powder, that is freely soluble in water and slightly soluble in ethanol and acetone. The pH of an aqueous solution of the drug substance is 5.0-7.0. The specific optical rotation is between +138.0° and 152.0°.

For the full list of excipients, see **Section 6.1 List of excipients**.

3 PHARMACEUTICAL FORM

ZERBAXA (ceftolozane sulfate/tazobactam sodium) is a white to yellow powder for solution.

ZERBAXA (ceftolozane/tazobactam) solutions range from clear, colourless solutions to solutions that are clear and slightly yellow.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ZERBAXA (ceftolozane/tazobactam) is indicated for the treatment of adult and paediatric (birth to less than 18 years of age) patients with the following infections caused by designated susceptible microorganisms:

- Complicated intra-abdominal infections in combination with metronidazole
- Complicated urinary tract infections, including pyelonephritis

ZERBAXA (ceftolozane/tazobactam) is also indicated for the treatment of the following infection in adults (18 years or older):

- Nosocomial pneumonia, including ventilator-associated pneumonia (VAP)

Consideration should be given to published therapeutic guidelines on the appropriate use of antibacterial agents.

4.2 DOSE AND METHOD OF ADMINISTRATION

Each vial is for single use in one patient only. Discard any residue.

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

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to use whenever solution and container permit. ZERBAXA (ceftolozane/tazobactam) infusions range from clear, colourless solutions to solutions that are clear and slightly yellow. Variations in colour within this range do not affect the potency of the product.

Method of administration

ZERBAXA (ceftolozane/tazobactam) is intended for intravenous infusion. The sterile powder in the vial can be reconstituted with either sterile water for injection or 0.9% sodium chloride for injection (normal saline). **CAUTION: THE RECONSTITUTED SOLUTION IS NOT FOR DIRECT INJECTION.**

ZERBAXA (ceftolozane/tazobactam) must not be mixed with other medicinal products except those mentioned in **Preparation of Doses,** below.

ZERBAXA (ceftolozane/tazobactam) should not be infused simultaneously with other medications via the same intravenous line.

The reconstituted solution should range from clear and colourless to clear and slightly yellow. Variations in colour within this range do not reflect the potency of the medicinal product.

The recommended infusion time is 1 hour for ZERBAXA (1000 mg ceftolozane / 500 mg tazobactam).

Preparation of doses

Constitute each vial of ZERBAXA (ceftolozane/tazobactam) with 10 mL of sterile water for injection or 0.9% Sodium Chloride for injection (normal saline) and gently shake to dissolve. The final volume is approximately 11.4 mL per vial. The resultant concentration is approximately 132 mg/mL.

To prepare the required dose, withdraw the appropriate volume determined from Table 1 from the reconstituted vial(s). Add the withdrawn volume to an infusion bag containing 100 mL of 0.9% Sodium Chloride for Injection (normal saline) or 5% Glucose Injection.

Table 1: Preparation of Select Doses

ZERBAXA (ceftolozane and tazobactam) Dose	**Volume to Withdraw from Reconstituted Vial(s)**
2000 mg and 1000 mg	Two vials of 11.4 mL each (entire contents from two vials)
1500 mg and 750 mg	11.4 mL from one vial (entire contents) and 5.7 mL from a second vial
1000 mg and 500 mg	11.4 mL (entire contents from one vial)
500 mg and 250 mg	5.7 mL
300 mg and 150 mg	3.5 mL

250 mg and 125 mg	2.9 mL
100 mg and 50 mg	1.2 mL

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to use whenever solution and container permit. Variations in colour within this range do not affect the potency of the product.

Dosage Regimen

Adult Patients

The recommended dose regimen of ZERBAXA (ceftolozane/tazobactam) for injection in patients 18 years or older and creatinine clearance (CrCL) greater than 50 mL/min is shown in the following Table by infection type.

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 2.

Table 2: Dosage of ZERBAXA (ceftolozane/tazobactam) by type of infection in Adult Patients (18 years or older) with a creatinine clearance (CrCL) greater than 50 mL/min

Type of Infection	Dose	Frequency	Infusion Time	Duration of treatment
Complicated intra-abdominal infections*	1000 mg ceftolozane / 500 mg tazobactam	Every 8 hours	1 hour	4-14 days
Complicated urinary tract infections, including pyelonephritis	1000 mg ceftolozane / 500mg tazobactam	Every 8 hours	1 hour	7 days
Nosocomial Pneumonia, including Ventilator-associated Pneumonia	(2000 mg ceftolozane / 1000 mg tazobactam)	Every 8 Hours	1 hour	8-14 days

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

Paediatric Patients

The recommended dosage regimen of ZERBAXA (ceftolozane/tazobactam) for injection in paediatric patients from birth to less than 18 years of age with cIAI and cUTI who have an estimated glomerular filtration rate (eGFR) greater than 50 mL/min/1.73 m^2 is described in Table 3. ZERBAXA (ceftolozane/tazobactam) is administered every 8 hours by intravenous infusion over 1 hour. The duration of treatment should be guided by the severity and site of infection and the patient's clinical and bacteriological progress as shown in Table 3.

ZERBAXA (ceftolozane/tazobactam) is not recommended in paediatric patients with cIAI and cUTI who have an eGFR of 50 mL/min/1.73m^2 or less (see Section 5.2 Pharmacokinetic Properties).

There is insufficient information to recommend a dosage regimen for paediatric patients with nosocomial pneumonia (see Section 5.2 Pharmacokinetic Properties).

Table 3: Dosage of ZERBAXA (ceftolozane/tazobactam) by infection in Paediatric Patients (birth * to less 18 years of age) with eGFR[+] greater than 50 mL/min/1.73m^2**

Infection	Dose	Frequency	Infusion time	Duration of treatment
Complicated Intra-abdominal Infections*	30 mg/kg up to a maximum dose of 1.5 g**	Every 8 hours	1 hour	5 to 14 days
Complicated Urinary Tract Infections including Pyelonephritis	30 mg/kg up to a maximum dose of 1.5 g**	Every 8 hours	1 hour	7 to 14 days

[+] eGFR using an age-appropriate equation for use in the paediatric population.

* Used in conjunction with metronidazole (see Section 5.1 Pharmacodynamic Properties).

** Paediatric patients weighing greater than 50 kg should not exceed a maximum dose of 1.5 g.

*** Defined as > 32 weeks gestational age and ≥ 7 days postnatal.

Duration of treatment

The usual duration of treatment for indications is in the range of 4 to 14 days. However, the duration of treatment should be guided by the severity of the infection, the infection site, the infecting pathogen(s) and the patient's clinical and bacteriological response.

Special population
Patients with renal impairment

Ceftolozane/tazobactam is eliminated primarily by the kidneys.

In adult patients with moderate or severe renal impairment (CrCL is 50mL/min or less), and in adult patients with end stage renal disease on haemodialysis, the dose should be adjusted as listed in Table4.

In patients with mild renal impairment (estimated CrCL greater than 50 mL/min), no dose adjustment is necessary (see **Section 5.2 Pharmacokinetic Properties**).**Table 4: Recommended Dosage Regimens for ZERBAXA (ceftolozane/tazobactam) in Adult 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**
> 50	No dose adjustment necessary	No dose adjustment necessary
30 to 50	500 mg ceftolozane / 250 mg tazobactam intravenously every 8 hours	1000 mg ceftolozane / 500 mg tazobactam intravenously every 8 hours
15 to 29	250 mg ceftolozane / 125 mg tazobactam intravenously every 8 hours	500 mg ceftolozane / 250 mg tazobactam intravenously every 8 hours

End stage renal disease on haemodialysis***	A single loading dose of 500 mg ceftolozane / 250 mg tazobactam followed after 8 hours by a 100 mg ceftolozane / 50 mg tazobactam maintenance dose administered every 8 hours for the remainder of the treatment period (on haemodialysis days, the dose should be administered at the earliest possible time following completion of dialysis)	A single loading dose of 1500 mg ceftolozane / 750 mg tazobactam followed after 8 hours by a 300 mg ceftolozane / 150 mg tazobactam maintenance dose administered every 8 hours for the remainder of the treatment period (on haemodialysis days, the dose should be administered at the earliest possible time following completion of dialysis)

*CrCL estimated using Cockcroft-Gault formula

**All doses of ZERBAXA (ceftolozane/tazobactam) are administered over 1 hour and are recommended for all indications.

***Dosing recommendations in ESRD for patients with NP and VAP are based solely on clinical trial population pharmacokinetic computer modelling.

ZERBAXA (ceftolozane/tazobactam) is not recommended in paediatric patients who have an eGFR of 50 mL/min/1.73m^2 or less (see Section 5.2 Pharmacokinetic Properties).

Patients with hepatic impairment
No dose adjustment is necessary in patients with hepatic impairment (see **Section 5.2 Pharmacokinetic Properties**).

Elderly (≥ 65 years of age)
No dose adjustment is necessary for the elderly based on age alone (see **Section 5.2 Pharmacokinetic Properties**).

Gender
No dose adjustment is necessary based on gender (see **Section 5.2 Pharmacokinetic Properties**).

Ethnicity
No dose adjustment is necessary based on race (see **Section 5.2 Pharmacokinetic Properties**).

Paediatric population
The safety and efficacy of ceftolozane/tazobactam in children and adolescents below 18 years of age have not yet been established for the treatment of nosocomial pneumonia, including ventilator-associated pneumonia (VAP) .

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substances or to any of the excipients listed under **Section 6.1 List of Excipients.**

Known serious hypersensitivity to ceftolozane/tazobactam, or members of the cephalosporin class, or other members of the beta-lactam class.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions are possible.

Patients who have a history of hypersensitivity to cephalosporins, penicillins or other beta-lactam antibacterials may also be hypersensitive to ceftolozane/tazobactam. ZERBAXA (ceftolozane/tazobactam) is contraindicated in patients with a history of hypersensitivity to

piperacillin/tazobactam or members of the cephalosporin class (see **Section 4.3 Contraindications**). ZERBAXA (ceftolozane/tazobactam) should be used with caution in patients with a history of any other type of hypersensitivity reaction to penicillins or any other type of beta-lactam antibacterial agent. If a severe allergic reaction occurs during treatment with ZERBAXA (ceftolozane/tazobactam), the medicinal product should be discontinued and appropriate measures taken. Serious acute hypersensitivity (anaphylactic reactions) requires immediate emergency treatments.

Neurotoxicity

There have been reports of neurotoxicity associated with cephalosporin treatment. Symptoms of neurotoxicity include encephalopathy, seizures and/or myoclonus. Risk factors for developing neurotoxicity with cephalosporin treatment include being elderly, renal impairment, central nervous system disorders and intravenous administration. Withdrawal of the medicine should be considered if there are signs of neurotoxicity.

Effect on renal function

A decline in renal function has been seen in patients receiving ceftolozane/tazobactam.

Use in renal impairment

Adult Patients

Ceftolozane, tazobactam, and the tazobactam metabolite M1 are eliminated by the kidneys.

In clinical trials of adult cIAI and cUTI, the efficacy of ceftolozane/tazobactam was lower in patients with moderate renal impairment compared with those with normal or mildly impaired renal function at baseline. The ceftolozane/tazobactam dose should be adjusted based on renal function (see **Section 4.2 Dose and Method of Administration, Table 4**). Patients with renal impairment at baseline should be monitored frequently for any changes in renal function during treatment and the dose of ceftolozane/tazobactam should be adjusted as necessary.

To maintain similar systemic exposures to those with normal renal function, dosage adjustment is required (see **Section 5.2 Pharmacokinetic Properties** and **Section 4.2 Dose and Method of Administration**).

In subjects with end stage renal disease on hemodialysis, approximately two-thirds of the administered ceftolozane/tazobactam dose is removed by haemodialysis. The recommended dose in subjects with end stage renal disease on haemodialysis is a single loading dose of 500 mg / 250 mg ceftolozane/tazobactam followed by a 100 mg / 50 mg maintenance dose of ceftolozane/tazobactam administered every 8 hours for the remainder of the treatment period. With haemodialysis, the dose should be administered immediately following completion of dialysis (see **Section 4.2 Dose and Method of Administration**).

Paediatric Patients

No dose adjustment has been established in paediatric patients aged birth to less than 18 years of age with an eGFR of 50 mL/min/1.73m^2 or less (see Section 5.2 Pharmacokinetic Properties).

Limitations of the clinical data

Patients who were immunocompromised, patients with severe neutropenia, and patients with end stage renal disease on haemodialysis (ESRD) were excluded from clinical trials.

***Clostridioides difficile*-associated diarrhoea**

Antibacterial-associated colitis and pseudomembranous colitis have been reported with ZERBAXA (ceftolozane/tazobactam) (see **Section 4.8 Adverse Effects (Undesirable Effects)**). 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 diarrhoea during or subsequent to the administration of ZERBAXA (ceftolozane/tazobactam). In such circumstances, the discontinuation of therapy with ZERBAXA(ceftolozane/tazobactam) and the use of supportive measures together with the administration of specific treatment for *Clostridioides difficile* should be considered.

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.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics. When SCAR is suspected, ZERBAXA (ceftolozane/tazobactam) should be discontinued immediately and an alternative treatment should be considered.

Gender

No dose adjustment is recommended based on gender (see **Section 5.2 Pharmacokinetic Properties** and **Section 4.2 Dose and Method of Administration**).

Ethnicity

No dose adjustment is recommended based on ethnicity (see **Section 5.2 Pharmacokinetic Properties** and **Section 4.2 Dose and Method of Administration**).

Use in hepatic impairment

No dose adjustment is recommended for ceftolozane/tazobactam in subjects with hepatic impairment (see **Section 4.2 Dose and Method of Administration**).

Use in the elderly

No dose adjustment of ceftolozane/tazobactam based on age alone is recommended. Ceftolozane/tazobactam is substantially excreted by the kidney and the risk of adverse reactions 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 and adjust dosage based on renal function (see **Section 5.2 Pharmacokinetic Properties** and **Section 4.2 Dose and Method of Administration**).

Paediatric use

Complicated Intra-abdominal Infections (cIAI) and Complicated Urinary Tract Infections (cUTI), including Pyelonephritis

The safety and effectiveness of ZERBAXA (ceftolozane/tazobactam) for the treatment of cIAI and cUTI have been established in paediatric patients aged birth to less than 18 years old. Use of ZERBAXA (ceftolozane/tazobactam) in these age groups is supported by evidence from adequate and well-controlled studies of ZERBAXA (ceftolozane/tazobactam) in adults with cUTI and cIAI and additional pharmacokinetic and safety data from paediatric trials (see Section 5 Pharmacological Properties).

The safety profile of ZERBAXA (ceftolozane/tazobactam) in paediatric patients was similar to adults with cIAI and cUTI treated with ZERBAXA (ceftolozane/tazobactam) (see Section 4.8 Adverse Effects (Undesirable effects)).

There is insufficient information to recommend dosage adjustment for paediatric patients younger than 18 years of age with cIAI and cUTI with an eGFR of 50 mL/min/1.73m^2 or less (see Section 4.2 Dose and Method of Administration and 5.2 Pharmacokinetic Properties).

ZERBAXA (ceftolozane/tazobactam) is not recommended in paediatric patients who have an eGFR of 50 mL/min/1.73m^2 or less. Paediatric patients born at term or pre-term may not have an eGFR of 50 mL/min/1.73m^2 or greater at birth or within the first few months of life.

Nosocomial Pneumonia, including Ventilator-associated Pneumonia

The safety and effectiveness of ZERBAXA (ceftolozane/tazobactam) in paediatric patients aged birth to less than 18 years old have not been established for the treatment of nosocomial pneumonia, including VAP.

Effects on laboratory tests

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

Co-administration of ceftolozane/tazobactam with OAT1 and OAT3 substrate furosemide does not increase furosemide plasma concentration. However, drugs that inhibit OAT1 or OAT3 (e.g., probenecid, diclofenac, cimetidine) may increase tazobactam plasma concentrations. No other significant drug-drug interactions involving membrane transporters are anticipated.

ZERBAXA (ceftolozane/tazobactam) must not be mixed with other medicinal products for infusion, except those mentioned in **Section 4.2 Dose and Method of Administration, Preparation of doses**.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effects of ceftolozane and tazobactam on fertility in humans have not been studied. 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).

Use in pregnancy

Category B1

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

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. The plasma exposure (AUC) associated with a NOAEL dose of 100 mg/kg/day in rats is approximately 0.2 fold 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 the 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.

Use in lactation

It is unknown whether ceftolozane and tazobactam are excreted in human breast milk. Women who are breast-feeding should be treated only if the expected benefit outweighs the possible risks to the woman and child.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of ZERBAXA (ceftolozane/tazobactam) on the ability to drive and use machines have been performed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and also may not reflect rates observed in practice.

Adult Patients

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

ZERBAXA (ceftolozane/tazobactam) was evaluated in Phase 3 comparator-controlled clinical trials of cIAI and cUTI, which included a total of 1015 patients treated with ZERBAXA (ceftolozane/tazobactam, 1500 mg 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 most patients (58%) enrolled in the cIAI trial were male. Most patients (>70%) in both trials were enrolled in Eastern Europe and were White. Table 5 lists adverse reactions occurring in 1% or greater of patients receiving ZERBAXA (ceftolozane/tazobactam) in Phase 3 cIAI and cUTI clinical trials.

The most common adverse reactions (5% or greater in either indication) occurring in patients receiving ZERBAXA (ceftolozane/tazobactam) were nausea, diarrhoea, headache, and pyrexia.

Table 5: Adverse Reactions Occurring in 1% or Greater of Adult Patients Receiving ZERBAXA (ceftolozane/tazobactam) in Phase 3 cIAI and cUTI Clinical Trials

Preferred Term	Complicated Intra-abdominal Infections		Complicated Urinary Tract Infections, Including Pyelonephritis	
	ZERBAXA[a] (N=482) n (%)	Meropenem (N=497) n(%)	ZERBAXA[a] (N=533) n(%)	Levofloxacin (N=535) n(%)
Nausea	38 (7.9)	29 (5.8)	15 (2.8)	9 (1.7)
Headache	12 (2.5)	9 (1.8)	31 (5.8)	26 (4.9)
Diarrhoea	30 (6.2)	25 (5)	10 (1.9)	23 (4.3)
Pyrexia	27 (5.6)	20 (4)	9 (1.7)	5 (0.9)
Constipation	9 (1.9)	6 (1.2)	21 (3.9)	17 (3.2)
Insomnia	17 (3.5)	11 (2.2)	7 (1.3)	14 (2.6)
Vomiting	16 (3.3)	20 (4)	6 (1.1)	6 (1.1)
Hypokalemia	16 (3.3)	10 (2)	4 (0.8)	2 (0.4)
ALT increased	7 (1.5)	5 (1)	9 (1.7)	5 (0.9)
AST increased	5 (1)	3 (0.6)	9 (1.7)	5 (0.9)
Anaemia	7 (1.5)	5 (1)	2 (0.4)	5 (0.9)
Thrombocytosis	9 (1.9)	5 (1)	2 (0.4)	2 (0.4)
Abdominal pain	6 (1.2)	2 (0.4)	4 (0.8)	2 (0.4)
Anxiety	9 (1.9)	7 (1.4)	1 (0.2)	4 (0.7)
Dizziness	4 (0.8)	5 (1)	6 (1.1)	1 (0.2)
Hypotension	8 (1.7)	4 (0.8)	2 (0.4)	1 (0.2)
Atrial fibrillation	6 (1.2)	3 (0.6)	1 (0.2)	0
Rash	8 (1.7)	7 (1.4)	5 (0.9)	2 (0.4)
Infusion site reactions	3 (0.6)	6 (1.2)	7 (1.3)	11 (2.1)

[a] The ZERBAXA (ceftolozane/tazobactam) for injection dose was 1000 mg/500 mg intravenously every 8 hours, adjusted to match renal function where appropriate. In the cIAI trials, ZERBAXA (ceftolozane/tazobactam) was given in conjunction with metronidazole.

Treatment discontinuation due to adverse events occurred in 2.0% (20/1015) of patients receiving ZERBAXA (ceftolozane/tazobactam) 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 (ceftolozane/tazobactam) 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 (ceftolozane/tazobactam) 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 (ceftolozane/tazobactam)-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: c*andidiasis, including oropharyngeal and vulvovaginal, fungal urinary tract infection, *Clostridioides 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: d*yspnoea

Skin and subcutaneous tissue disorders: urticaria, severe cutaneous adverse reactions (SCAR), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported with beta-lactam antibiotics.

Vascular disorders: venous thrombosis

Nosocomial Pneumonia, including Ventilator-associated Pneumonia

ZERBAXA (ceftolozane/tazobactam) was evaluated in a Phase 3 comparator-controlled clinical trial for nosocomial pneumonia, which included a total of 361 patients treated with ZERBAXA (ceftolozane/tazobactam) (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

6 lists adverse reactions occurring in 2% or greater of patients receiving ZERBAXA (ceftolozane/tazobactam) in a Phase 3 nosocomial pneumonia clinical trial.

Table 6: Adverse Reactions Occurring in 2% or Greater of Adult Patients Receiving ZERBAXA (ceftolozane/tazobactam) 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		
Clostridioides 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 (ceftolozane/tazobactam) 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 (ceftolozane/tazobactam) 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: Clostridioides difficile infection

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

Paediatric Patients

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

ZERBAXA (ceftolozane/tazobactam) was evaluated in two blinded, randomized, active-controlled clinical studies in paediatric patients from birth to less than 18 years of age, one in cIAI and the other in cUTI, which included a total of 170 paediatric patients treated with ZERBAXA (ceftolozane/tazobactam) and 54 paediatric patients treated with the comparator. The ZERBAXA (ceftolozane/tazobactam) dosing regimen was the same in each trial (see Section 4.2 Dose and Method of Administration). Patients were randomized 3:1 to receive ZERBAXA (ceftolozane/tazobactam) plus metronidazole or meropenem plus placebo in the cIAI study and ZERBAXA (ceftolozane/tazobactam) or meropenem in the cUTI study (see Section 5 Pharmacological Properties). In these paediatric patients, the type of adverse reactions were generally comparable to those observed in adults. Table 7 lists adverse reactions occurring in 4% or greater of paediatric patients receiving ZERBAXA (ceftolozane/tazobactam) in either the paediatric cIAI or cUTI clinical trial.

Table 7: Adverse Reactions Occurring in 4% or Greater of Paediatric Patients (birth to less than 18 years of age) Receiving ZERBAXA (ceftolozane/tazobactam) in either the cIAI or cUTI Clinical Trial

Adverse Reaction	Complicated Intra-abdominal Infections		Complicated Urinary Tract Infections, Including Pyelonephritis	
	ZERBAXA* (N=70) n (%)	Meropenem (N=21) n (%)	ZERBAXA (N=100) n (%)	Meropenem (N=33) n (%)
Thrombocytosis[1]	11 (16)	3 (14)	9 (9)	3 (9)
Diarrhea	12 (17)	5 (24)	7 (7)	3 (9)
Pyrexia[2]	9 (13)	3 (14)	7 (7)	1 (3)
Leukopenia[3]	3 (4)	0 (0)	8 (8)	0 (0)
Abdominal pain[4]	8 (11)	0 (0)	2 (2)	1 (3)
AST increased	5 (7)	1 (5)	4 (4)	2 (6)
Vomiting	7 (10)	1 (5)	1 (1)	1 (3)
ALT increased	4 (6)	1 (5)	4 (4)	2 (6)
Anemia	5 (7)	0 (0)	2 (2)	0 (0)
Phlebitis[5]	4 (6)	0 (0)	1 (1)	1 (3)
Hypertension	3(4)	0 (0)	0 (0)	1 (3)
Gastritis	3 (4)	0 (0)	0 (0)	0 (0)
Hypokalemia[6]	3 (4)	0 (0)	0 (0)	0 (0)
Bradypnea[7]	3 (4)	0 (0)	0 (0)	0 (0)

*In the cIAI trials, ZERBAXA (ceftolozane/tazobactam) was given in conjunction with metronidazole.
[1] Includes platelet count increased.
[2] Includes hyperthermia.
[3] Includes neutropenia and neutrophil count decreased.
[4] Includes upper abdominal pain.
[5] Includes superficial phlebitis.
[6] Includes blood potassium decreased.
[7] Includes respiratory rate decreased.

Post-marketing experience

There have been post marketing reports of neurotoxicity (including seizures, encephalopathy, myoclonus) associated with cephalosporin treatment.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

In the event of overdose, ZERBAXA (ceftolozane/tazobactam) should be discontinued and general supportive treatment should be given. ZERBAXA (ceftolozane/tazobactam) can be removed by haemodialysis. Approximately 66% of ceftolozane, 56% of tazobactam, and 51% of the M1 metabolite of tazobactam were removed by approximately 3-4 hour period of haemodialysis. However, no information is available on the use of haemodialysis to treat overdosage.

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

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: antibacterials for systemic use, combination of cephalosporins and beta-lactamase inhibitors, ATC code: J01DI54.

Mechanism of action

ZERBAXA (ceftolozane/tazobactam) is an antibacterial drug product composed of a cephalosporin and a beta-lactamase inhibitor.

Ceftolozane belongs to the cephalosporin class of antimicrobials. Ceftolozane exerts bactericidal activity through binding to important penicillin-binding proteins (PBPs), resulting in inhibition of cell-wall synthesis and subsequent cell death. Ceftolozane has a high affinity to *Pseudomonas aeruginosa* PBPs [PBP1b (IC_{50} 0.07 mg/L), PBP1c (IC_{50} 0.64 mg/L), PBP2 (IC_{50} 1.36 mg/L), PBP3 (IC_{50} 0.02 mg/L) and PBP4 (IC_{50} 0.29 mg/L)] and *Escherichia coli* PBP3 (IC_{50} 0.03 mg/L).

Tazobactam, a beta-lactam structurally related to penicillins, is a potent, irreversible inhibitor of Class A broad-spectrum and extended-spectrum beta-lactamases and Class C cephalosporinases, which commonly cause resistance to penicillins and cephalosporins. Tazobactam extends the antimicrobial spectrum of ceftolozane to include beta-lactamase-producing bacteria.

ZERBAXA (ceftolozane/tazobactam) is stable to common mechanisms of resistance found in Gram-negative bacteria, including production of broad spectrum beta-lactamases (TEM-1, TEM-2, SHV-1), extended spectrum beta-lactamases (TEM-3, SHV-2, CTX-M-14, CTX-M-15), chromosomal pseudomonal AmpC, oxacillinases (OXA -2, OXA -5, OXA -23), loss of outer membrane porin (OprD) and upregulation of efflux pumps (MexXY, MexAB). These mechanisms of resistance can reduce the activity of penicillins, cephalosporins, and carbapenems in *Pseudomonas aeruginosa* and Enterobacteriaceae, including *Escherichia coli* and *Klebsiella pneumoniae*.

In vitro ZERBAXA (ceftolozane/tazobactam) showed little potential to antagonise or be antagonised by other antibacterial agents.

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.

Mechanisms of resistance

ZERBAXA (ceftolozane/tazobactam) has a low potential for development of resistance in *Pseudomonas aeruginosa* and Enterobacteriaceae including ESBL-producing strains.

Bacterial resistance mechanisms that affect ZERBAXA (ceftolozane/tazobactam) include drug inactivation by serine carbapenamases, such as KPC, and metallo-beta lactamases.

Isolates resistant to other cephalosporins may be susceptible to ZERBAXA (ceftolozane/tazobactam) although cross-resistance may occur.

Susceptibility testing breakpoints

Ceftolozane and tazobactam susceptibility testing is performed with a fixed 4 mcg /mL concentration of tazobactam. Minimum inhibitory concentrations (MIC) values should be interpreted according to the criteria shown in Table 8. Disk diffusion testing should be determined using 30 mcg ceftolozane/10 mcg tazobactam disks and results interpreted according to criteria provided in Table 8.

Table 8: Susceptibility interpretative criteria for Ceftolozane/Tazobactam

	Minimum Inhibitory Concentrations (mcg/mL)			**Disk Diffusion Zone Diameter (mm)**		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Enterobacterales	≤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, including VAP)†	≤0.5/4	---	---	---	---	---
*Streptococcus spp. Viridans Group (cIAI and cUTI, including pyelonephritis)**	≤8/4	16/4	≥32/4	-	-	-
*Bacteroides fragilis (cIAI and cUTI, including pyelonephritis)**	≤8/4	16/4	≥32/4	-	-	-

S= susceptible, I=intermediate, R=resistant

†Based on ceftolozane/tazobactam 2000/1000mg IV every 8 hours. Doses were modified according to renal function.

*Based on ceftolozane/tazobactam 1000/500mg IV every 8 hours. Doses were modified according to renal function.

Susceptibility
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert microbiology advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Susceptibility of specific pathogens to ZERBAXA (ceftolozane/tazobactam)
The following pathogens were recovered from clinical trials and reported susceptible to ZERBAXA (ceftolozane/tazobactam) in *in vitro* testing. For clinical efficacy against these pathogens, please see **Section 5.1 Pharmacodynamic Properties, Clinical trials**.

Complicated intra-abdominal infections

Gram-negative bacteria
Enterobacter cloacae
Escherichia coli
Escherichia coli (CTX-M-14 ESBL-producing strains including those also expressing TEM-1)
Escherichia coli (CTX-M-15 ESBL-producing strains including those also expressing one or both of the following: OXA-1/30, TEM 1)
Klebsiella oxytoca
Klebsiella pneumoniae
Klebsiella pneumoniae (CTX-M-15 ESBL-producing strains including those also expressing one or more of the following: OXA-1/30, TEM-1, SHV-1, SHV-11, SHV-32)
Proteus mirabilis
Pseudomonas aeruginosa

Gram-positive bacteria
Streptococcus anginosus
Streptococcus constellatus
Streptococcus salivarius

Gram-negative anaerobes
Bacteroides fragilis
*Bacteroides ovatus**
*Bacteroides thetaiotaomicron**
*Bacteroides vulgatus**

* in combination with metronidazole

Complicated Urinary Tract Infections, including pyelonephritis
Gram-negative bacteria
Escherichia coli
Escherichia coli (fluoroquinolone-resistant strains)
Escherichia coli (CTX-M-14 ESBL-producing strains including those also expressing TEM-1)
Escherichia coli (CTX-M-15 ESBL-producing strains including those also expressing one or more of the following: CTX-M-27, OXA-1/30, TEM-1, TEM-176)
Klebsiella pneumoniae
Klebsiella pneumoniae (fluoroquinolone-resistant strains)
Klebsiella pneumoniae (CTX-M-15 ESBL-producing strains including those also expressing one or more of the following: OXA-1/30, OXA-10, SHV-1, SHV-11, TEM-1)
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

Antibacterial activity against other relevant pathogens
Clinical efficacy has not been established against the following pathogens although *in vitro* studies suggest that they would be susceptible to ZERBAXA (ceftolozane/tazobactam) 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

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

Anaerobic microorganisms
Fusobacterium spp
Prevotella spp

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

Pharmacokinetic/pharmacodynamic relationship(s)
Similar to other beta-lactam antimicrobial agents, the time that the plasma concentration of ceftolozane exceeds the minimum inhibitory concentration (MIC) of the infecting organism has been shown to be the best predictor of efficacy in animal models of infection. The PK-PD analyses in adult efficacy and safety clinical trials for cIAI and cUTI, and nosocomial pneumonia support the recommended dose regimens of ZERBAXA (ceftolozane/tazobactam).

Clinical trials

ZERBAXA (ceftolozane/tazobactam) demonstrated clinical and microbiological efficacy against ESBL-producing *E. coli* (CTX-M-14/15 producing isolates) and *K. pneumoniae* (CTX-M-15 producing isolates) in two well-controlled randomized Phase 3 studies in complicated

intra-abdominal infections and complicated urinary tract infections, including pyelonephritis. ZERBAXA (ceftolozane/tazobactam) demonstrated clinical and microbiological efficacy against *E. coli* and *K. pneumoniae* strains with resistance to fluoroquinolones, including strains with amino acid substitutions in GyrA and ParC.

Data from clinical studies

Adult Patients

Complicated intra-abdominal infections

ZERBAXA (ceftolozane/tazobactam) plus metronidazole showed non-inferiority to meropenem with regard to clinical cure rates at the test-of-cure (TOC) visit in both the clinically evaluable (CE) and intent-to treat (ITT) populations. Clinical cure rates at the TOC visit are displayed by patient population in Table 9. Clinical cure rates at the TOC visit by pathogen in the microbiologically evaluable (ME) population are presented in Table 10.

Table 9: Clinical cure rates in a Phase 3 study of complicated intra-abdominal infections

Analysis population	**ZERBAXA (ceftolozane/tazobactam) plus metronidazole[a] n/N (%)**	**Meropenem[b] n/N (%)**	**Treatment difference (95% CI)[c]**
CE	353/375 (94.1)	375/399 (94.0)	0 (-4.16, 4.30)
ITT	399/476 (83.8)	424/494 (85.8)	-2.2 (-7.95, 3.44)

[a] ZERBAXA (ceftolozane/tazobactam) 1000 mg/500 mg IV every 8 hours + metronidazole 500 mg IV every 8 hours
[b] 1 g IV every 8 hours
[c] The 95% CI was calculated using the Newcombe method with minimum risk weights

Table 10: Per pathogen clinical cure rates in a Phase 3 study of complicated intra-abdominal infections (ME population)

Organism group Pathogen	**ZERBAXAplus 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 (90.0)
Escherichia coli (CTX-M-14/15 ESBL-producing)	9/9 (100)	7/9 (77.8)
Klebsiella pneumonia	28/30 (93.3)	22/25 (88.0)
Klebsiella pneumoniae (ESBL-producing)	7/8 (87.5)	3/4 (75.0)
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 (90.0)
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 (87.0)
Streptococcus salivarius	9/10 (90.0)	8/8 (100)

Anaerobic gram-negative	104/109 (95.4)	132/137 (96.4)
Bacteroides fragilis	39/41 (95.1)	56/57 (98.2)

Paediatric Patients

The paediatric cIAI trial was a randomized, double-blind, multi-center, active controlled trial conducted in hospitalized patients from birth to less than 18 years (NCT03217136). Patients were randomized in a 3:1 ratio to either intravenous (IV) ZERBAXA (ceftolozane/tazobactam) (see 4.2 Dose and Method of Administration) plus metronidazole (10 mg/kg IV every 8 hours), or meropenem (20 mg/kg IV every 8 hours) plus placebo. Patients received IV study treatment for a minimum of 3 days before an optional switch to oral step-down therapy at the discretion of the investigator to complete a total of 5 to 14 days of antibacterial therapy.

The modified intent-to-treat (MITT) population consisted of 91 patients (N=70 in the ZERBAXA (ceftolozane/tazobactam) plus metronidazole group; N=21 in the meropenem plus placebo group) who were randomized and received at least one dose of study treatment. The median age of patients was 8.2 years and 8.5 years in the ZERBAXA (ceftolozane/tazobactam) plus metronidazole and meropenem plus placebo groups, respectively. In the ZERBAXA (ceftolozane/tazobactam) plus metronidazole group, enrollment by age group was as follows: 12 to <18 y: n=16, 6 to <12 y: n=30, 2 to <6 y: n=22, 3 months to <2 y: n=1, birth to <3 months: n=1. Patients treated with ZERBAXA (ceftolozane/tazobactam) plus metronidazole were predominantly male (67%) and White (87%). Patients treated with meropenem plus placebo were predominantly female (71%) and White (91%). Most patients in the MITT population had a diagnosis of complicated appendicitis at baseline (ZERBAXA (ceftolozane/tazobactam) plus metronidazole: 91.4%; meropenem plus placebo: 100%). The median (range) duration of IV study treatment was comparable between patients in the ZERBAXA (ceftolozane/tazobactam) plus metronidazole (6.3 [0.3 to 14.0] days) and meropenem plus placebo (6.0 [2.3 to 8.8] days) groups.

The primary objective of the study was to evaluate the safety and tolerability of ZERBAXA (ceftolozane/tazobactam). Efficacy assessments were not powered for formal hypothesis testing of between-treatment group comparisons. At the TOC visit, which occurred 7 to 14 days after the last dose of study drug, a favorable clinical response was defined as complete resolution or marked improvement in signs and symptoms of the cIAI or return to pre-infection signs and symptoms such that no further antibiotic therapy (IV or oral) or surgical or drainage procedure was required for treatment of the cIAI. A summary of clinical response rates in the MITT and clinically evaluable (CE) populations at the TOC visit are presented in Table 11. The CE included all protocol adherent MITT patients with a clinical outcome at the visit of interest.

Table 11: Clinical Response Rates in a Paediatric Study of Complicated Intra-Abdominal Infections

Analysis Population	**ZERBAXA plus metronidazole** **n/N (%)**	**Meropenem** **n/N (%)**	**Treatment Difference (95% CI)***
MITT Population	56/70 (80.0)	21/21 (100.0)	-19.1 (-30.2, -2.9)
CE Population	52/58 (89.7)	19/19 (100.0)	-10.7 (-21.5, 6.8)

*The Miettinen & Nurminen method stratified by age group with Cochran-Mantel-Haenszel weights was used.

Complicated urinary tract infections, including pyelonephritis

Adult Patients

ZERBAXA (ceftolozane/tazobactam) was superior to levofloxacin with regard to the microbiological eradication rates at the test-of-cure (TOC) visit in both the microbiologically modified intent-to-treat (mMITT) and microbiologically evaluable (ME) populations (Table 12). Microbiological eradication rates at the TOC visit by pathogen in the ME population are presented in Table 13.

Table 12: Microbiological Eradication rates in a Phase 3 study of complicated urinary tract infections

Analysis population	**ZERBAXA[a] n/N (%)**	**Levofloxacin[b] n/N (%)**	**Treatment difference (99% CI)[c]**
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)

[a] 1000 mg/500 mg IV every 8 hours
[b] 750 mg IV once daily
[c] The 99% CI was based on the stratified Newcombe method

Table 13: 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 (ceftolozane/tazobactam) was superior to levofloxacin with regards to microbiological eradication rate in the ME population, 58/89 (65.2%) in the ZERBAXA (ceftolozane/tazobactam) 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 (ceftolozane/tazobactam) and 20/26 (76.9%) for levofloxacin.

Paediatric Patients

The cUTI paediatric trial was a randomized, double-blind multi-center, active controlled trial conducted in hospitalized patients from birth to less than 18 years (NCT03230838). Eligible patients were randomized in a 3:1 ratio to IV ZERBAXA (ceftolozane/tazobactam) or

meropenem, respectively. Patients received IV study treatment for a minimum of 3 days before an optional switch to oral step-down therapy at the discretion of the investigator to complete a total of 7 to 14 days of antibacterial therapy.

The microbiologic modified intent-to-treat (mMITT) population consisted of 95 patients (N=71 in the ZERBAXA (ceftolozane/tazobactam) group; N=24 in the meropenem group) who were randomized and received at least one dose of study treatment and had an eligible uropathogen isolated from a baseline urine culture.

The median age of patients was 2.7 years and 1.6 years in the ZERBAXA (ceftolozane/tazobactam) and meropenem groups, respectively. In the ZERBAXA (ceftolozane/tazobactam) group, enrollment by age group was as follows: 12 to <18 y: n=10, 6 to <12 y: n=13, 2 to <6 y: n=14, 3 months to <2 y: n=20, birth to <3 months: n=14. Patients treated with ZERBAXA (ceftolozane/tazobactam) were predominantly female (56%) and White (99%). Patients treated with meropenem were predominantly female (63%) and White (100%). Most patients in the mMITT population had a diagnosis of pyelonephritis (ZERBAXA: 84.5%; meropenem: 79.2%). The most common baseline qualifying gram-negative uropathogens were *Escherichia coli* (ZERBAXA: 74.6%; meropenem: 87.5%), *Klebsiella pneumoniae* (8.5%; 4.2%), and *Pseudomonas aeruginosa* (7.0%; 8.3%).

The primary objective of the study was to evaluate the safety and tolerability of ZERBAXA (ceftolozane/tazobactam). Efficacy assessments were not powered for formal hypothesis testing of between treatment group comparisons. At the TOC visit, which occurred 7 to 14 days after the last dose of study drug, a favorable clinical response was defined as complete resolution or marked improvement in signs and symptoms of the cUTI or return to pre-infection signs and symptoms, such that no further antibiotic therapy (IV or oral) was required for the treatment of the cUTI. A favorable microbiological response at the TOC was defined as eradication (all uropathogens found at baseline at $\geq 10^5$ were reduced to $<10^4$ CFU/mL) of baseline uropathogens from the urine culture. A summary of clinical and microbiologic response rates in the mMITT population at the TOC visit is presented in Table 14.

Table 14 Clinical and Microbiological Response Rates in a Paediatric Study of Complicated Urinary Tract Infections

mMITT Population	**ZERBAXA (ceftolozane/tazobactam) n/N (%)**	**Meropenem n/N (%)**	**Treatment Difference (95% CI)***
Clinical Response Rate	63/71 (88.7)	23/24 (95.8)	-7.3 (-18.0, 10.1)
Microbiologic Response Rate	60/71 (84.5)	21/24 (87.5)	-3.0 (-17.1, 17.4)

*The Miettinen & Nurminen method stratified by age group with Cochran-Mantel-Haenszel weights was used.

ESBL-producing strains of gram-negative pathogens in Phase 3 studies

The clinical response rates of ZERBAXA (ceftolozane/tazobactam) and comparators against *E. coli* and *K. pneumoniae* strains producing CTX-M-14/15 ESBLs in the Phase 3 clinical trials are shown in Table 15.

Table 15: Clinical cure rates by ESBL status from the Phase 3 clinical trials (ME population)

Pathogen	ZERBAXA[a] n/N (%)	All comparators[b] n/N (%)
Escherichia coli	452/470 (96.2)	483/515 (93.8)
Escherichia coli (ESBL-producing)	49/50 (98.0)	48/56 (87.5)
Escherichia coli (CTX-M-14/15 ESBL-producing)	35/36 (97.2)	28/34 (82.4)
Klebsiella pneumoniae	51/55 (92.7)	41/48 (85.4)
Klebsiella pneumoniae (ESBL-producing)	17/18 (94.4)	8/11 (72.7)
Klebsiella pneumoniae (CTX-M-15 ESBL-producing)	13/13 (100)	2/5 (40.0)

[a] ZERBAXA (ceftolozane/tazobactam) 1000 mg/500 mg IV every 8 hours. In the complicated intra-abdominal infection studies, ZERBAXA (ceftolozane/tazobactam) was combined with metronidazole.
[b] Comparators included meropenem 1 g IV every 8 hours in the Phase 3 complicated intra-abdominal infection trial and levofloxacin 750 mg IV every 24 hours in the Phase 3 complicated urinary tract infection trials

Cardiac electrophysiology

In a randomized, positive and placebo-controlled crossover thorough QTc study, 51 healthy adult subjects were administered a single therapeutic dose (1000 mg/500 mg) and a supratherapeutic dose (3.0 g / 1.5 g) of ceftolozane/tazobactam. No significant effects of ZERBAXA (ceftolozane/tazobactam) on heart rate, electrocardiogram morphology, PR, QRS, or QT interval were detected. Therefore, ZERBAXA (ceftolozane/tazobactam) does not affect cardiac repolarization.

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 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 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 (ceftolozane/tazobactam) 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 with a predefined margin of 12.5% (Table 16).

Table 16: Clinical Cure at TOC and 28-Day All-cause Mortality Rates from a Phase 3 Study of Nosocomial Pneumonia (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)
VAP	147/263 (55.9)	146/256 (57.0)	-1.1 (-10.79, 8.55)
Ventilated HAP	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)
VAP	63/263 (24.0)	52/256 (20.3)	-3.6 (-11.75, 4.55)
Ventilated HAP	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 (ceftolozane/tazobactam) 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 nosocomial pneumonia, the clinical cure rates were 26/53 (49.1%) for ZERBAXA (ceftolozane/tazobactam) 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 (ceftolozane/tazobactam) 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. In the mITT and ME populations, the most prevalent pathogens isolated from baseline LRT cultures were *Klebsiella pneumoniae* (34.6% and 38.6%, respectively) and *Pseudomonas aeruginosa* (25% and 28.8%, respectively).

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 17. In the mITT population clinical cure rates in patients with a Gram-negative pathogen at baseline were 157/259 (60.6%) for ZERBAXA (ceftolozane/tazobactam) 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 18. In the mITT population microbiologic response rates in patients with a Gram-negative pathogen at baseline were 189/259 (73%) for ZERBAXA (ceftolozane/tazobactam) 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 17: Clinical Cure 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	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)

*Microbiologic intention to treat population
†Microbiologically evaluable

Table 18: 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)

*Microbiologic intention to treat population
†Microbiologically evaluable

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 Enterobacterales 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%).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

The C_{max} and AUC of ceftolozane/tazobactam increase approximately in proportion to dose within ceftolozane single-dose range of 250 mg to 3 g and tazobactam single-dose range of 500 mg to 1.5 g. Ceftolozane and tazobactam pharmacokinetics are similar following single- and multiple-dose administration. No appreciable accumulation of ceftolozane/tazobactam is observed following multiple 1-hour IV infusions of ceftolozane/tazobactam 1000 mg/500 mg administered every 8 hours for up to 10 days in healthy adults with normal renal function.

Distribution

The binding of ceftolozane and tazobactam to human plasma proteins is low (approximately 16% to 21% and 30%, respectively). The mean (CV%) steady-state volume of distribution of ceftolozane/tazobactam in healthy adult males (n = 51) following a single 1000 mg/500 mg IV dose 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 adult patients with confirmed or suspected pneumonia (N=22), mean minimum ceftolozane and tazobactam epithelial lung lining fluid concentrations at the end of the dosing interval were 8.2 mcg/mL and 1.0 mcg/mL, respectively. Mean pulmonary epithelial-to-free plasma AUC ratios of ceftolozane and tazobactam respectively were approximately 50% and 62% for the ventilated patients,

compared to approximately 61% and 63%for healthy adult individuals administered ceftolozane 1 g and tazobactam 0.5 g.

Metabolism

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

Excretion

Ceftolozane, tazobactam, and the tazobactam metabolite M1 are eliminated by the kidneys. Following administration of a single IV dose of ceftolozane/tazobactam 1000 mg/500 mg to healthy male adults greater than 95% of ceftolozane was excreted in the urine as unchanged parent drug. More than 80% of tazobactam was excreted as the parent compound with the remainder excreted as the tazobactam M1 metabolite. After a single dose of ceftolozane/tazobactam 1000 mg/500 mg, renal clearance of ceftolozane (3.41 - 6.69 L/h) was similar to plasma clearance (4.10 to 6.73 L/h) and similar to the glomerular filtration rate for the unbound fraction, suggesting that ceftolozane is eliminated by the kidney via glomerular filtration.

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. The elimination half-life ($t_{½}$) of ceftolozane or tazobactam is independent of dose.

Specific 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 adult 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. In adult subjects with end stage renal disease (ESRD) on haemodialysis, the exposure to ceftolozane, tazobactam and its M1 metabolite are substantially increased when not on dialysis. Approximately two-thirds of the administered ceftolozane/tazobactam dose is removed by haemodialysis. To maintain similar systemic exposures to those with normal renal function, dosage adjustment in all renal impairment patients with ≤ 50 mL/min CrCL (see **Section 4.2 Dose and Method of Administration**) and timing of dose relative to haemodialysis treatment in ESRD patients on haemodialysis is required (see **Section 4.4 Special Warnings and Precautions for Use** and **Section 4.2 Dose and Method of Administration**).

Augmented renal clearance
Following a single 1 hour intravenous infusion of ZERBAXA 3 g (ceftolozane 2 g and tazobactam 1 g) to critically ill adult 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 (ceftolozane/tazobactam) is recommended for nosocomial pneumonia patients with augmented renal clearance (see **Section 5.1 Pharmacodynamic Properties, Clinical trials)**.

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 ceftolozane/tazobactam in subjects with hepatic impairment (see **Section 4.2 Dose and Method of Administration**).

Elderly
In a population pharmacokinetic analysis of ceftolozane/tazobactam, no clinically relevant differences in exposure were observed with regard to age. No dose adjustment of ceftolozane/tazobactam based on age alone is recommended. Dosage adjustment for ZERBAXA (ceftolozane/tazobactam) in elderly patients should be based on renal function (see **Section 4.2 Dose and Method of Administration)**.

Paediatric patients
The pharmacokinetics of ceftolozane and tazobactam in paediatric patients (birth to less than 18 years of age) were evaluated from 3 clinical studies: patients with proven or suspected gram-negative infection, cIAI, and cUTI. Ceftolozane exposures were numerically higher in paediatric patients with cUTI compared to paediatric patients with cIAI, however, such a difference was not observed for tazobactam (Table 19 and Table 20) (see Section 5.1 Pharmacodynamic Properties, Clinical trials).

In patients with cIAI (Table 19) and cUTI (Table 20) total body clearance of both ceftolozane and tazobactam increased with age, with values in adolescents approaching those in the adult population, whereas elimination half-life tended to decrease with a decrease of age. While ceftolozane exposures in paediatric patients with cIAI and cUTI overlapped with the range of exposures seen in adults, in general they were lower than mean exposures in adults. Tazobactam exposures were comparable between paediatric and adult patients except for patients aged birth to <3 months (Group 5) with cUTI, who had higher exposures.

Population pharmacokinetic analyses and target attainment simulations in paediatric patients with cIAI and cUTI demonstrated that the recommended paediatric dosing regimens for patients from birth to less than 18 years with an eGFR greater than 50 mL/min/1.73 m^2 result in no clinically relevant differences in systemic exposure to those in adult patients given ZERBAXA (ceftolozane/tazobactam) 1.5 grams.

There is insufficient information to assess the exposure of ZERBAXA (ceftolozane/tazobactam) in the paediatric patients with an eGFR ≤ 50 mL/min/1.73m^2.

Table 19: Mean (SD) Steady-State Plasma Population Pharmacokinetic Parameters of ZERBAXA (ceftolozane and tazobactam) in Paediatric cIAI Patients*

Patient Characteristics	**Group 1 (12 to <18 years)**	**Group 2 (7 to <12 years)**	**Group 3 (2 to <7 years)**
	N=16	N=27	N=23
Ceftolozane			
C_{eoi} (mcg/mL)	51.1 (21)	53.7 (17)	43.9 (14)
AUC_{0-8} (mcg•h/mL)	123 (46)	117 (30)	99 (25)
Clearance (L/h)	123 (46)	117 (30)	99 (25)
V_{ss} (L)	9.55 (4.7)	5.91 (2.2)	3.76 (1.2)

Patient Characteristics	Group 1 (12 to <18 years)	Group 2 (7 to <12 years)	Group 3 (2 to <7 years)
Tazobactam			
C_{eoi} (mcg/mL)	21.7 (9.7)	21.4 (6.5)	17.5 (6.1)
AUC_{0-8} (mcg•h/mL)	31.7 (16)	30.4 (7)	24 (6.4)
Clearance (L/h)	18.9 (7.5)	11.2 (4.1)	7.79 (2.5)
V_{ss} (L)	18.8 (11)	10.9 (6.4)	7.17 (3.9)

AUC_{0-8}, area under the curve in the dosing interval 0 to 8 hours at steady-state; C_{eoi}, concentration at the end of infusion; CL, elimination clearance; SD, standard deviation; VSS, steady-state volume of distribution.

*One patient was enrolled in Group 4 (3 months to <2 years) in the C/T arm but discontinued before the day of PK sample collection; one participant was enrolled for Group 5 (Birth to <3 months) in the C/T arm with steady-state ceftolozane PK parameter values: AUC_{0-8}=173 mcg*h/mL; C_{eoi}=43.4 mcg/mL; and with tazobactam PK parameter values: AUC_{0-8}=69.9 mcg*h/mL; C_{eoi}=30.5 mcg/mL.

Table 20: Mean (SD) Steady-State Plasma Population Pharmacokinetic Parameters of ZERBAXA (ceftolozane and tazobactam) in Paediatric cUTI Patients

Patient Characteristics	Group 1 (12 to <18 years)	Group 2 (7 to <12 years)	Group 3 (2 to <7 years)	Group 4 (3 months to <2 years)	Group 5 (Birth to <3 months)
	N=14	N=15	N=24	N=22	N=14
Ceftolozane					
C_{eoi} (µg/mL)	68.7 (21)	62.1 (22)	59.6 (23)	50.3 (20)	43.1 (12)
AUC_{0-8} (mcg•h/mL)	177 (65)	146 (55)	135 (50)	129 (57)	144 (38)
Clearance (L/h)	6.3 (2.2)	5.1 (2.1)	2.8 (1.2)	1.5 (0.6)	0.8 (0.3)
V_{ss} (L)	15.8 (5.5)	11.4 (5.6)	5.8 (2.2)	3.7 (2.5)	2.5 (1)
Tazobactam					
C_{eoi} (µg/mL)	22.9 (7.6)	20.5 (6.8)	19 (6.3)	18.9 (8)	25.9 (9.6)
AUC_{0-8} (mcg•h/mL)	35 (12)	27.6 (10)	26.1 (7.7)	28.6 (13)	44.6 (15)
Clearance (L/h)	15.7 (4.5)	13.3 (5.3)	7.17 (3.5)	3.53 (1.7)	1.32 (0.81)
V_{ss} (L)	16 (6.6)	10.6 (8.9)	5.97 (3.7)	3.72 (3.4)	1.54 (0.81)

AUC_{0-8}, area under the curve in the dosing interval 0 to 8 hours at steady-state; C_{eoi}, concentration at the end of infusion; CL, elimination clearance; SD, standard deviation; V_{SS}, steady-state volume of distribution.

For ZERBAXA (ceftolozane/tazobactam) dosage recommendation in paediatric cIAI and cUTI patients, refer to table 2 (see Section 4.2 Dose and Method of Administration).

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 (see **Section 4.2 Dose and Method of Administration**).

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

ZERBAXA (ceftolozane/tazobactam) was not genotoxic *in vivo*. ZERBAXA (ceftolozane/tazobactam) 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 (ceftolozane/tazobactam) was positive for structural aberrations, but only at highly toxic concentrations.

Ceftolozane was negative for genotoxicity in an *in vitro* microbial mutagenicity (Ames) assay, an *in vitro* chromosomal aberration assay in Chinese hamster lung fibroblast cells, an *in vitro* mouse lymphoma assay, an *in vitro* HPRT point mutation assay in Chinese hamster ovary cells, an *in vivo* mouse micronucleus assay, and an *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 HPRT point mutation assay in Chinese hamster ovary cells, 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.

Carcinogenicity

Carcinogenicity studies with ceftolozane, tazobactam, or ZERBAXA (ceftolozane/tazobactam) have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each vial contains the following inactive ingredients: sodium chloride, arginine and citric acid.

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except those mentioned in **Section 4.2 Dose and Method of Administration.**

6.3 SHELF LIFE

The expiry date can be found on the packaging. In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG).

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (2°C - 8°C).

Store in the original packaging to protect from light.

To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2°C - 8°C for not more than 24 hours.

6.5 NATURE AND CONTENTS OF CONTAINER

Single-use 20 mL vial (Type I clear glass) with stopper (bromobutyl rubber) and flip-off seal.

Pack sizes of 10 vials.

The vials contain a white to yellow powder.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Ceftolozane sulfate

Ceftolozane sulfate is a semisynthetic antibiotic and is described chemically as 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 empirical formula of ceftolozane sulfate is $C_{23}H_{31}N_{12}O_8S_2^+ \bullet HSO_4^-$ with a molecular weight of 764.77.

Tazobactam Sodium

Tazobactam sodium is described chemically as Sodium(2*S,*3*S,*5*R*)-3-methyl-7-oxy-3-(1*H*-1,2,3-triazol-1-ylmethyl)-4-thia-1-azabicyclo-[3.2.0]heptane-2-carboxylate-4,4-dioxide.

The empirical formula of tazobactam sodium is $C_{10}H_{11}N_4NaO_5S$ with a molecular weight of 322.28.

Chemical structure

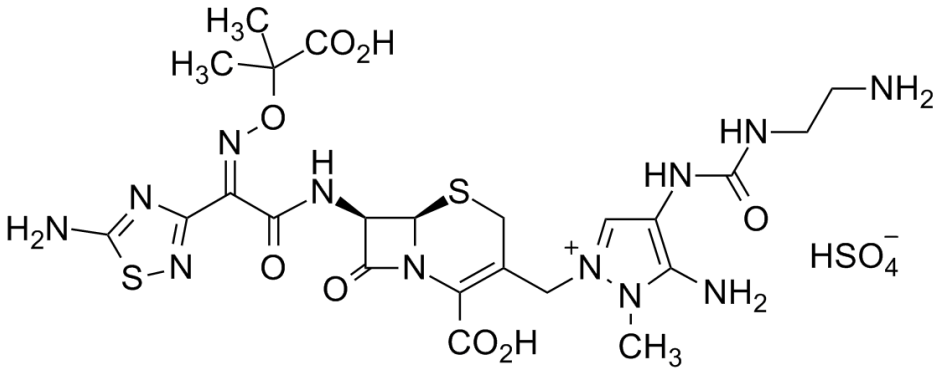

Figure 1: Ceftolozane Sulfate Structural Formula

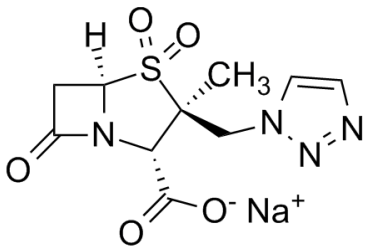

Figure 2: Tazobactam Sodium Structural Formula

CAS number

Ceftolozane Sulfate

936111-69-2

Tazobactam Sodium

89785-84-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (S4)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

4 November 2015

10 DATE OF REVISION

24 June 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Addition of paediatric indication for complicated intra-abdominal infections and complicated urinary tract infections. Editorial revisions also made throughout document.

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