PRODUCT INFORMATION

NAME OF THE MEDICINE

ZERBAXA® (ceftolozane/tazobactam) Powder for Injection

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.

The structural formula is presented in Figure 1 below.

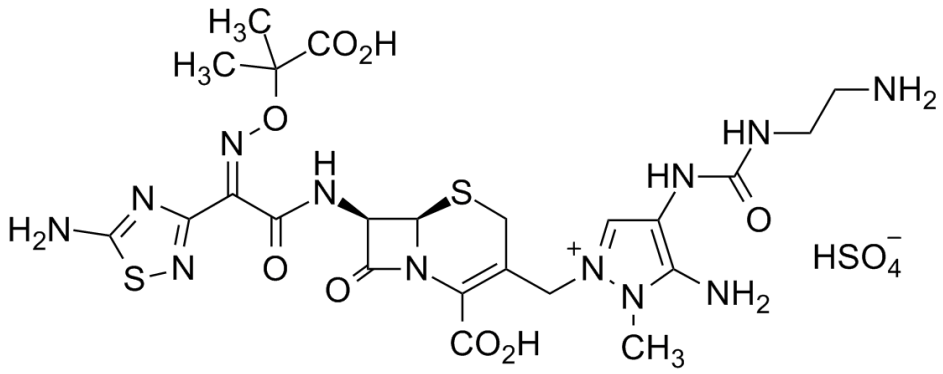

Figure 1: Ceftolozane Sulfate Structural Formula

CAS No. 936111-69-2

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.

The structural formula is shown in Figure 2 below.

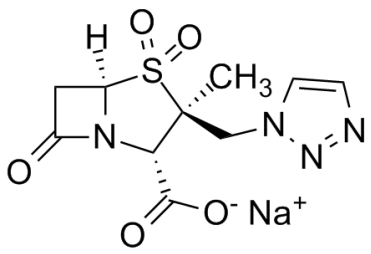

Figure 2: Tazobactam Sodium Structural Formula

CAS No. 89785-84-2

DESCRIPTION

Ceftolozane sulfate/tazobactam sodium (Zerbaxa) is a white to yellow powder for solution. Each vial contains 1000 mg of ceftolozane (as ceftolozane sulfate) and 500mg 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°.

After reconstitution with 10 mL diluent, the concentrations are 100 mg/mL ceftolozane equivalent and 50 mg/mL tazobactam equivalent. Zerbaxa (ceftolozane/tazobactam) solutions range from clear, colourless solutions to solutions that are clear and slightly yellow.

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

PHARMACOLOGY

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.

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 1. Disk diffusion testing should be determined using 30 mcg ceftolozane/10 mcg tazobactam disks and results interpreted according to criteria provided in Table 1.

Table 1 Susceptibility interpretative criteria for Ceftolozane/Tazobactam

	Minimum Inhibitory Concentrations (mcg/mL)			**Disk Diffusion Zone Diameter (mm)**		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Enterobacteriaceae	≤2/4	4/4	≥8/4	≥21	18-20	≤17
Pseudomonas aeruginosa	≤4/4	8/4	≥16/4	≥21	17-20	≤ 16
Streptococcus spp. Viridans Group	≤8/4	16/4	≥32/4	-	-	-
Bacteroides fragilis	≤8/4	16/4	≥32/4	-	-	-

S= susceptible, I=intermediate, R=resistant

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 CLINICAL TRIALS section.

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

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
Enterobacter aerogenes
Haemophilus influenzae
Moraxella catarrhalis
Morganella morganii
Pantoea agglomerans
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Serratia liquefacians
Serratia marcescens

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 Phase 2 trials support the recommended dose of Zerbaxa (cetolozane/tazobactam).

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. 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.

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 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 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 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 DOSAGE AND ADMINISTRATION) and timing of dose relative to haemodialysis treatment in ESRD patients on haemodialysis is required (see PRECAUTIONS, DOSAGE AND ADMINISTRATION).

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 DOSAGE AND ADMINISTRATION).

Elderly
In a population pharmacokinetic analysis of ceftolozane/tazobactam, no clinically relevant trend in exposure was observed with regard to age. No dose adjustment of ceftolozane/tazobactam based on age alone is recommended.

Paediatric patients
Safety and effectiveness in pediatric patients (< 18 years of age) have not been established.

Gender
In a population pharmacokinetic analysis of ceftolozane/tazobactam, no clinically relevant differences in AUC were observed for ceftolozane (116 males compared to 70 females) and tazobactam (80 males compared to 50 females). No dose adjustment is recommended based on gender (see DOSAGE AND ADMINISTRATION).

Ethnicity
In a population pharmacokinetic analysis of ceftolozane/tazobactam, no clinically relevant differences in ceftolozane/tazobactam AUC were observed in Caucasians (n = 156) compared to all other ethnic groups combined (n = 30). No dose adjustment is recommended based on ethnicity.

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

Complicated intra-abdominal infections

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 2. Clinical cure rates at the TOC visit by pathogen in the microbiologically evaluable (ME) population are presented in Table 3.

Table 2: Clinical cure rates in a Phase 3 study of complicated intra-abdominal infections

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

Organism group Pathogen	**Ceftolozane/tazobactam 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 (90.0)
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)

Complicated urinary tract infections, including pyelonephritis

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 4). Microbiological eradication rates at the TOC visit by pathogen in the ME population are presented in Table 5.

Table 4: Microbiological Eradication rates in a Phase 3 study of complicated urinary tract infections

Analysis population	**Ceftolozane/tazobactam[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 5: Per pathogen microbiological eradication rates in a Phase 3 study of complicated urinary tract infections (ME population)

Organism group Pathogen	**Ceftolozane/tazobactam 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, ceftolozane/tazobactam was superior to levofloxacin with regards to microbiological eradication rate in the ME population, 58/89 (65.2%) in the 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 ceftolozane/tazobactam and 20/26 (76.9%) for levofloxacin.

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

The clinical response rates of 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 6.

Table 6: Clinical cure rates by ESBL status from the Phase 3 clinical trials (ME population)

Pathogen	Ceftolozane/tazobactam[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] Ceftolozane/tazobactam 1000 mg/500 mg IV every 8 hours. In the complicated intra-abdominal infection studies, 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 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.

INDICATIONS

Zerbaxa (ceftolozane/tazobactam) is indicated for the treatment of the following infections in adults suspected or proven to be caused by designated susceptible microorganisms:

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

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

CONTRAINDICATIONS

Hypersensitivity to the active substances or to any of the excipients listed under DESCRIPTION.

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

PRECAUTIONS

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 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.

***Clostridium difficile*-associated diarrhoea**
Antibacterial-associated colitis and pseudomembranous colitis have been reported with Zerbaxa (ceftolozane/tazobactam) (see ADVERSE 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 *Clostridium 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.

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 3 times the mean daily human ceftolozane exposure value in healthy adults at the clinical dose of 1g thrice daily.

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

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 foetus.

Embryo-foetal 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 foetus. The mean plasma exposure (AUC) values associated with these doses are approximately 7 (mice) and 4 (rats) times the mean daily human exposure in healthy adults at the clinical dose of 1 gram thrice daily. It is not known if ceftolozane crosses the placenta in animals.

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

In an embryo-foetal study in rats, tazobactam administered intravenously at doses up to 3000 mg/kg/day (approximately 19 times the recommended human dose based on body surface area comparison) produced maternal toxicity (decreased food consumption and body weight gain) but was not associated with foetal toxicity. In rats, tazobactam was shown to cross the placenta. Concentrations in the foetus 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 8 times the recommended human dose based on body surface area comparison). No effects on the development, function, learning or fertility of F1 pups were noted, but postnatal body weights for F1 pups delivered to dams receiving 320 and 1280 mg/kg/day tazobactam were significantly reduced 21 days after delivery. F2 generation foetuses were normal for all doses of tazobactam. The NOAEL for reduced F1 body weights was considered to be 40 mg/kg/day (approximately 0.3 times the recommended human dose based on body surface area comparison).

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.

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

To maintain similar systemic exposures to those with normal renal function, dosage adjustment is required (see PHARMACOLOGY, DOSAGE AND 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 DOSAGE AND ADMINISTRATION).

Hepatic impairment
No dose adjustment is recommended for ceftolozane/tazobactam in subjects with hepatic impairment (see DOSAGE AND ADMINISTRATION).

Elderly Patients
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 PHARMACOLOGY, DOSAGE AND ADMINISTRATION).

Paediatric patients
The safety and effectiveness of ceftolozane/tazobactam in children and adolescents below 18 years of age has not yet been established.

Gender
No dose adjustment is recommended based on gender (see PHARMACOLOGY, DOSAGE AND ADMINISTRATION).

Ethnicity
No dose adjustment is recommended based on ethnicity (see PHARMACOLOGY, DOSAGE AND ADMINISTRATION).

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 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 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.

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

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

INTERACTIONS WITH OTHER MEDICINES

No significant drug-drug interactions are anticipated between 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 tazobactam 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 DOSAGE AND ADMINISTRATION – PREPARATION OF DOSES.

ADVERSE 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.

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

The most common adverse reactions (5% or greater in either indication) occurring in patients receiving Zerbaxa (ceftolozane/tazobactam) were nausea, diarrhoea, headache, and pyrexia. Table 7 lists adverse reactions occurring in 1% or greater of patients receiving Zerbaxa (ceftolozane/tazobactam) in Phase 3 clinical trials.

Table 7: Adverse Reactions Occurring in 1% or Greater of Patients Receiving Zerbaxa (ceftolozane/tazobactam) in Phase 3 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 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

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: 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: dyspnoea

Skin and subcutaneous tissue disorders: urticaria

Vascular disorders: venous thrombosis

DOSAGE AND 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 the vial 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. The resultant concentration is approximately 132 mg/mL.

For preparation of the 1000 mg ceftolozane / 500 mg tazobactam dose: Withdraw the entire contents (approximately 11.4 mL) of the reconstituted vial using a syringe and add it to an infusion bag containing 100 mL of 0.9% Sodium Chloride for Injection (normal saline) or 5% Glucose Injection.

For preparation of the 500 mg ceftolozane / 250 mg tazobactam dose: Withdraw approximately 5.7 mL of the contents of the reconstituted vial and add it to an infusion bag containing 100 mL of 0.9% Sodium Chloride for Injection (normal saline) or 5% Glucose Injection.

For preparation of the 250 mg ceftolozane / 125 mg tazobactam dose: Withdraw approximately 2.9 mL of the contents of the reconstituted vial and add it to an infusion bag containing 100 mL of 0.9% Sodium Chloride for Injection (normal saline) or 5% Glucose Injection.

For preparation of the 100 mg ceftolozane / 50 mg tazobactam dose: Withdraw approximately 1.2 mL of the contents of the reconstituted vial and add it to an infusion bag containing 100 mL of 0.9% Sodium Chloride for Injection (normal saline) or 5% Glucose Injection.

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
The recommended dose regimen of Zerbaxa (ceftolozane/tazobactam) 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 (see Table 8).

Table 8: Dose of Zerbaxa (ceftolozane/tazobactam) by type of infection in patients with a creatinine clearance (CrCL) > 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

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

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 patients with moderate or severe renal impairment, and in patients with end stage renal disease on haemodialysis, the dose should be adjusted as listed in Table 9.

In patients with mild renal impairment (estimated CrCL > 50 mL/min), no dose adjustment is necessary, see PHARMACOLOGY).

Table 9: Dosage of Zerbaxa (ceftolozane/tazobactam) in patients with renal impairment

Estimated CrCL (mL/min)*	**Recommended Dose Regimen for Zerbaxa (ceftolozane/tazobactam)****
> 50	No dose adjustment necessary
30 to 50	500 mg ceftolozane / 250 mg tazobactam intravenously every 8 hours
15 to 29	250 mg ceftolozane / 125 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)

*CrCL estimated using Cockcroft-Gault formula
**All doses of Zerbaxa (ceftolozane/tazobactam) are administered over 1 hour and are recommended for both indications.

Patients with hepatic impairment
No dose adjustment is necessary in patients with hepatic impairment (see PHARMACOLOGY).

Elderly (≥ 65 years of age)
No dose adjustment is necessary for the elderly based on age alone (see PHARMACOLOGY).

Gender
No dose adjustment is necessary based on gender (see PHARMACOLOGY).

Ethnicity
No dose adjustment is necessary based on race (see PHARMACOLOGY).

Paediatric population
The safety and efficacy of ceftolozane/tazobactam in children and adolescents below 18 years of age have not yet been established. No data are available.

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 Poison Information Centre on 131126 (Australia) or 0800 764 766 (New Zealand).

PRESENTATION AND STORAGE CONDITIONS

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.

Store in a refrigerator (2°C – 8°C).
Store in the original packaging to protect from light.

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

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.

This medicinal product must not be mixed with other medicinal products except those mentioned in DOSAGE AND ADMINISTRATION.

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

NAME AND ADDRESS OF THE SPONSOR

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POISION SCHEDULE OF THE MEDICINE
S4

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG)
4 November 2015

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