Brand Name: Zerbaxa

Generic Name: ceftolozane and tazobactam

Manufacturer[3]: Merck & Cubist Pharmaceuticals

Drug Class[1,2]: IV anti-infective combination of Cephalosporin (ceftolozane) & β-lactamase inhibitor (tazobactam).[2]

Uses:

Labeled Uses[1,2,3,4,5]:

- Treatment of complicated intra-abdominal infections in adults, in combination with metronidazole, caused by *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Bacteroides fragilis*, *Streptococcus anginosus*, *Streptococcus constellatus*, and *Streptococcus salivarius*
- Treatment of complicated urinary tract infections, including pyelonephritis, in adults caused by *E. coli*, *K. pneumoniae*, *P. mirabilis*, and *P. aeruginosa*

Mechanism of Action:[1,3,4]
Ceftolozane is a cephalosporin class bactericidal agent that inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins (PBPs). Tazobactam has low affinity for PBPs, but does irreversibly inhibit certain penicillinases and cephalosporinases and covalently binds to some chromosomal and plasmid-mediated bacterial beta-lactamases

Pharmacokinetics[1,2,3,4,5]:

Absorption:

	ceftolozane	tazobactam
T_{max}	1.02hrs	1.02hrs
V_d	13.5L	18.2L
$t_{½}$	2.77-3.12 hrs	0.91-1.03hrs
Clearance	4.1 to 6.73 L/hr	Not reported
Protein binding	16-20%	30%

Metabolism: Ceftolozane is not a substrate for CYP enzymes and is mainly eliminated in the urine as unchanged parent drug and thus does not appear to be metabolized to any appreciable extent. The beta-lactam ring of tazobactam is hydrolyzed to form the pharmacologically inactive tazobactam metabolite M1. (3)

Elimination: Ceftolozane is eliminated from the body by renal excretion with a half-life of approximately 3 hours. Tazobactam is eliminated by renal excretion and metabolism with a plasma half-life of approximately 1hour.

Efficacy:

Wagenlehner FM, Umeh O, Steenbergen J, Yuan G, Darouiche RO. Ceftolozane-tazobactam compared with levofloxacin in the treatment of complicated urinary-tract infections, including pyelonephritis: a randomised, double-blind, phase 3 trial (ASPECT-cUTI). Lancet. 2015 May 16;385(9981):1949-56. doi:10.1016/S0140-6736(14)62220-0. PubMed PMID: 25931244.

Study Design: Multicenter, randomized, double-blind, double-dummy, non-inferiority trial study
Description of Study: *Methods*: Hospital inpatients (n=1083) were enrolled if they were 18 years or older, had pyuria, and a diagnosis of a complicated lower-urinary-tract infection or pyelonephritis and were excluded if they had a moderate or severe hypersensitivity or allergic reaction to any beta lactam or quinolone antibacterial, had a concomitant infection at the time of randomization, received any antibiotics for the treatment of the current UTI within 48 hours before the baseline urine was obtained, had a confirmed fungal UTI, had an intractable UTI at baseline would require more than 7 days of study drug therapy, had any rapidly progressing disease or immediately life-threatening illness, any laboratory abnormalities in baseline specimens: AST, ALT, alkaline phosphatase, or total bilirubin level > 3x ULN, ANC < 500/μL, platelet count < 40,000/μL, or Hct less than 20%. Enrolled subjects were randomly assigned in a 1:1 ratio to receive intravenous 1·5 g ceftolozane-tazobactam every 8 h or intravenous high-dose (750 mg) levofloxacin once daily for 7 days. The primary endpoint was a composite of microbiological eradication and clinical cure 5-9 days after treatment in the microbiological modified intention-to-treat (MITT) population, with a non-inferiority margin of 10% *Outcome Results:* Of 1083 patients enrolled, 800 (73·9%), of whom 656 (82·0%) had pyelonephritis, were included in the microbiological MITT population. Ceftolozane-tazobactam was non-inferior to levofloxacin for composite cure (306 [76·9%] of 398 vs 275 [68·4%] of 402, 95% CI 2.3-14.6) and, as the lower bound of the two-sided 95% CI around the treatment difference was positive and greater than zero, superiority was indicated. Adverse event profiles were similar in the two treatment groups and were mainly non-serious.

Limitations: This study was sponsored the manufacturer of Zerbaxa, and some of the authors were employees of the company, which could introduce bias. The majority of subjects in this study were <65years old, white, had normal renal function or mild renal impairment, and had pyelonephritis vs. complicated lower UTI, which may limit generalizability of results to other patient populations. The authors chose the highest approved dose of levofloxacin for a longer duration than what's approved as comparator drug to account for fluoroquinolone resistance. This may not be enough to overcome resistance, though. In addition, many patients received therapy before resistance was known, yet results were still reported as mITT. The actual power in this study can't be determined because the pre-specified criteria was not met. The author's definition of treatment failure and way they included it in results was poor.

Conclusion: The study showed that treatment with ceftolozane-tazobactam led to better responses than high-dose levofloxacin in patients with complicated lower-urinary-tract infections or pyelonephritis. Zerbaxa may be a possibility for treating pyelonephritis in patients that have similar characteristics as the sample in the study when the pathogen is resistant to first-line treatments and susceptible to zerbaxa, or when first-line options are contraindicated. Even though it has an approved indication for complicated lower urinary tract infection in adults, clinical efficacy data for this diagnosis is limited. The benefit to use zerbaxa must outweigh the cost compared less expensive options.

Joseph Solomkin, Ellie Hershberger, Benjamin Miller, Myra Popejoy, Ian Friedland, Judith Steenbergen, Minjung Yoon, Sylva Collins, Guojun Yuan, Philip S. Barie, Christian Eckmann; Ceftolozane/Tazobactam Plus Metronidazole for Complicated Intra-abdominal Infections in an Era of Multidrug Resistance: Results From a Randomized, Double-Blind, Phase 3 Trial (ASPECT-cIAI). *Clin Infect Dis* 2015; 60 (10): 1462-1471. doi: 10.1093/cid/civ097

Study Design: multicenter, prospective, randomized, double-blind, placebo-controlled trial

Description of Study: *Methods*: Hospitalized patients (n=993) with complicated intra-abdominal infections (cIAI) received either 1.5g ceftolozane/tazobactam plus 500 mg metronidazole every 8 hours (n= 487) or 1g meropenem every 8 hours IV (n=506) for 4–14 days. The inclusion criteria were patients ≥18 years of age, with clinical evidence of cIAI. The exclusion criteria were cIAI managed by staged abdominal repair in which the fascia was not closed; low likelihood of adequate source control at surgery; creatinine clearance <30 mL/minute; or use of systemic

antimicrobial therapy for IAI for >24 hours prior to the first dose of study drug (unless this treatment failed). The objectives were to demonstrate statistical noninferiority in clinical cure rates at the test-of-cure visit (24–32 days from start of therapy) in the microbiological intent-to-treat (primary) and microbiologically evaluable (secondary) populations using a noninferiority margin of 10%. Microbiological outcomes and safety were also evaluated. *Outcome Results*: Ceftolozane/tazobactam plus metronidazole was noninferior to meropenem in the primary (83.0% [323/389] vs 87.3% [364/417]; weighted difference, −4.2%; 95% confidence interval [CI], −8.91 to .54) and secondary (94.2% [259/275] vs 94.7% [304/321]; weighted difference, −1.0%; 95% CI, −4.52 to 2.59) endpoints. In patients with ESBL-producing Enterobacteriaceae, clinical cure rates were 95.8% (23/24) and 88.5% (23/26) in the ceftolozane/tazobactam plus metronidazole and meropenem groups, respectively, and 100% (13/13) and 72.7% (8/11) in patients with CTX-M-14/15 ESBLs. The frequency of adverse events (AEs) was similar in both treatment groups (44.0% vs 42.7%); the most common AEs in either group were nausea and diarrhea.

Limitations: This study was sponsored by the manufacturer of Zerbaxa, and some of the authors were employees of the company, which could introduce bias. Clinical cure rate was highest in patients with the appendix as the site of infection, patients with APACHE scores <10, and mild renal impairment, which was the majority of patients. It is unclear if the same benefit would occur in other patients with different characteristics.

Conclusion: Treatment with ceftolozane/tazobactam plus metronidazole was noninferior to meropenem in adult patients with cIAI, including infections caused by multidrug-resistant pathogens. In this study, zerbaxa really only showed superior benefit compared to meropenem for patients with ESBL-producing Enterobacteriaceae and ceftolozane + metronidazole ESBL's. Zerbaxa for abdominal infections appears to be a possible option for abdominal infections (particularly originating in the appendix) and in patients with characteristics similar to the majority of patients in this study with ESBL-producing Enterobacteriaceae and ceftolozane + metronidazole ESBL's, or as an alternative when first line agents are contraindicated.

Chandorkar G, Xiao A, Mouksassi MS, Hershberger E, Krishna G. Population pharmacokinetics of ceftolozane/tazobactam in healthy volunteers, subjects with varying degrees of renal function and patients with bacterial infections. J Clin Pharmacol. 2015 Feb;55(2):230-9. doi: 10.1002/jcph.395. PubMed PMID: 25196976;PubMed Central PMCID: PMC4303958.
https://www.researchgate.net/publication/265389189_Population_Pharmacokinetics_of_CeftolozaneTazobactam_in_Healthy_Volunteers_Subjects_With_Varying_Degrees_of_Renal_Function_and_Patients_With_Bacterial_Infections

Study Design: Multicenter, double-blind, randomized, placebo-controlled, parallel group study

Description of Study: *Methods*: A pharmacokinetic analysis was performed on ceftolozane and tazobactam plasma concentration–time data from adult subjects enrolled in 10 studies. Serum concentration data were analyzed from 184 healthy volunteers, three studies in subjects with varying degrees of renal impairment (n=42), and two phase 2 studies in patients with bacterial infections (73 patients with cUTIs and 77 patients with cIAIs). Healthy volunteers received various single or multiple doses of ceftolozane alone or ceftolozane/tazobactam with sampling periods up to 24 hours following infusion. Subjects with mild (CrCl 50 to <90 mL/min) or moderate (CrCl 30 to <50 mL/min) renal impairment received a single dose of ceftolozane/tazobactam 1000/500 mg, with sampling up to 36 hours. Subjects with severe renal impairment (CrCl 15 to <30 mL/ min) received a single dose of ceftolozane/tazobactam 500/250 mg, with sampling up to 48 hours. In the phase 2 trials, cUTI patients received ceftolozane alone 1000 mg every 8 hours, and cIAI patients received ceftolozane/tazobactam 1000/500 mg every 8hours. *Outcome Results:* Variability between the subjects had more influence on relative clearance than the effect of infection. For both ceftolozane and tazobactam, clearance was lower with severe and moderate renal impairment compared with normal and mild renal impairment. Other aspects, such as age, body weight, sex, ethnicity, and presence of infection, had no clinically significant effects on clearance.

Limitations: This study was sponsored by Cubist Pharmaceuticals, the manufacturer of Zerbaxa, and some of the authors were employees of the company, which could introduce bias. Other types of infections weren't included, and it may be important to identify any additional covariates to extrapolate the results to other infections. This article doesn't prove this drug to be useful for clinical application, beyond the fact that renal impairment can affect the drug's clearance.

Conclusion: There appears to be a possible conflict of interest which could lead to biased results, but the main downfall with this article is that it can't be specified which dose to give to a patient based on their renal impairment from this study alone. More studies need to be performed focusing on doses that achieve clinical effect corresponding to various renal impairments.

Contraindications[1,2,3,4,5]:

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

Precautions[1,2,3,4,5]:

- Hypersensitivity: Hypersensitivity and anaphylaxis (serious and sometimes fatal) have been reported in patients receiving beta-lactam drugs. Question patient about previous hypersensitivity reactions to other cephalosporins, penicillins or other beta-lactams. Cross-sensitivity has been established. If administered, use with caution and if anaphylaxis occurs, discontinue and institute appropriate supportive therapy.
- Superinfection: Use may result in fungal or bacterial superinfection, including *C. difficile*-associated diarrhea (CDAD) and pseudomembranous colitis; CDAD has been observed >2 months postantibiotic treatment.
- Renal impairment: Exposure to ceftolozane is increased with increasing degrees of renal impairment; monitor creatinine clearance at least daily in patients with changing renal function and adjust the dose. In clinical trials, cure rates were lower in patients with a baseline CrCl of 30 to 50 mL/minute.
- Development of Drug-Resistant Bacteria: Prescribing ZERBAXA in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Adverse Effects[1,2,,4,5]:

1% to 10%:

- Cardiovascular: Hypotension (≤2%), atrial fibrillation (≤1%)
- Central nervous system: Headache (3% to 6%), insomnia (complicated intra-abdominal infections: 4%; complicated UTIs: 1%), anxiety (≤2%), dizziness (≤1%)
- Dermatologic: Skin rash (≤2%)
- Endocrine: Hypokalemia (complicated intra-abdominal infections: 3%; complicated UTIs: <1%)
- Gastrointestinal: Nausea (3% to 8%), diarrhea (complicated intra-abdominal infections: 6%; complicated UTIs: 2%), constipation (2% to 4%), vomiting (complicated intra-abdominal infections: 3%, complicated UTIs: 1%), abdominal pain (≤1%)
- Hematologic & oncologic: Anemia (≤2%), thrombocythemia (≤2%)
- Hepatic: Increased serum ALT (2%), increased serum AST (1% to 2%)
- Miscellaneous: Fever (complicated intra-abdominal infections: 6%; complicated UTIs: 2%)

<1%, postmarketing, and/or case reports: Abdominal distention, angina pectoris, candidiasis, *Clostridium difficile* associated diarrhea, dyspepsia, dyspnea, flatulence, fungal urinary tract infection, gastritis, hyperglycemia, hypomagnesemia, hypophosphatemia, increased gamma-glutamyl transferase, increased serum alkaline phosphatase, infusion site reaction, nonhemorrhagic stroke, oropharyngeal candidiasis, paralytic ileus, positive direct Coombs test, renal failure, renal insufficiency, tachycardia, urticaria, venous thrombosis, vulvovaginal candidiasis

Drug Interactions[1,2,,4,5]:

Cholera vaccine, live: Concurrent use of live cholera vaccine and systemic antibiotics may result in reduced immune response to the cholera vaccine.

Probenecid: May increase the serum concentration of Cephalosporins. *Risk C: Monitor therapy*

Sodium picosulfate; Magnesium oxide; Anhydrous citric acid: Prior or concomitant use of antibiotics with sodium picosulfate; magnesium oxide; anhydrous citric acid may reduce efficacy of the bowel preparation as conversion of sodium picosulfate to its active metabolite bis-(p-hydroxy-phenyl)-pyridyl-2-methane (BHPM) is mediated by colonic bacteria. If possible, avoid coadministration

BCG (Intravesical): Antibiotics may diminish the therapeutic effect of BCG (Intravesical). *Risk X: Avoid combination*

BCG Vaccine (Immunization): Antibiotics may diminish the therapeutic effect of BCG Vaccine (Immunization). *Risk C: Monitor therapy*

Typhoid Vaccine: Antibiotics may diminish the therapeutic effect of Typhoid Vaccine. Only the live attenuated Ty21a strain is affected. Management: Vaccination with live attenuated typhoid vaccine (Ty21a) should be avoided in patients being treated with systemic antibacterial agents. Use of this vaccine should be postponed until at least 3 days after cessation of antibacterial agents. *Risk D: Consider therapy modification*

Lactobacillus and Estriol: Antibiotics may diminish the therapeutic effect of Lactobacillus and Estriol. *Risk C: Monitor therapy*

Vitamin K Antagonists (eg, warfarin): Cephalosporins may enhance the anticoagulant effect of Vitamin K Antagonists. *Risk C: Monitor therapy*

Dosing/Administration[1,2,3,4,5]:

Adult/ Geriatric Dosing

Intra-abdominal infections (complicated): IV: 1.5 g every 8 hours for 4 to 14 days in combination with metronidazole

Urinary tract infections (complicated, includes pyelonephritis): IV: 1.5 g every 8 hours for 7 days

Pediatrics

Safety and efficacy have not been established in pediatric patients

Renal impairment

CrCl >50 mL/minute: No dosage adjustment necessary.

CrCl 30 to 50 mL/minute: 750 mg every 8 hours

CrCl 15 to 29 mL/minute: 375 mg every 8 hours

CrCl <15 mL/minute not on dialysis: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied)

End-stage renal disease (ESRD) requiring intermittent hemodialysis (IHD): Dialyzable (~66%).
Initial: 750 mg for one dose, followed by 150 mg every 8 hours. Administer dose immediately after dialysis on dialysis days.

Hepatic impairment
No dosage adjustment necessary.

Use in special circumstances:

Overdosage: [3] In the event of overdose, discontinue ZERBAXA and provide general supportive treatment. ZERBAXA can be removed by hemodialysis. Approximately 66% of ceftolozane, 56% of tazobactam, and 51% of the tazobactam metabolite M1 were removed by dialysis. No information is available on the use of hemodialysis to treat overdosage.

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

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

Overall Conclusion:

Drug resistance is currently an issue due to the over-use of antibiotics. There is a demand for antibiotics that can cover multidrug resistant pathogens. Zerbaxa adds to the available options for the treatment of multidrug-resistant pathogens (including ESBL pathogens), but it doesn't serve as the solution in every situation. Currently, there is limited data for treatment of other serious infections caused by these pathogens, although other studies are in process.

Zerbaxa is approved for use in the treatment of complicated intra-abdominal infections (in combination with metronidazole) and complicated urinary tract infections, including pyelonephritis in adults 18 years of age and older. Even though zerbaxa is approved for these indications, studies that got zerbaxa approval for these indications had narrow spectrum of characteristics for the majority of their subjects. This drug does require dose adjustments in patients with creatinine clearance (CrCl) of less than 50 mL/min, but it has a relatively safe adverse event profile and limited drug interaction profile.

When initiating therapy with this drug, it is necessary to inspect cultures and verify susceptibilities. Prescribing zerbaxa in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases risks the development of drug-resistant bacteria. Since there is limited published data for the treatment of other disease states caused by MDR bacteria, potential roles include empiric therapy where infection by a resistant Gram-negative organism (ESBL) is suspected when therapeutic options are limited, or as part of combination therapy (with metronidazole) where a polymicrobial infection is suspected. Zerbaxa may be a possible alternate therapy to third-generation cephalosporins after treatment failure or for infections with Gram-negative bacilli producing ESBLs.

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Prepared by: Heather Smith, Doctor of Pharmacy Candidate