Ceftolozane/tazobactam (Zerbaxa®)

National Drug Monograph
March 2015
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Ceftolozane/tazobactam is a novel combination of an antipseudomonal cephalosporin and a beta-lactamase inhibitor. Ceftolozane inhibits the formation of bacterial cell walls by binding to penicillin-binding proteins (PBP) and tazobactam irreversibly inhibits the activity of many penicillinases and cephalosporinases. It demonstrates in-vitro activity against many gram-negative organisms, including some extended-spectrum beta-lactamase producing *Enterobacteriaceae* and multidrug-resistant *Pseudomonas aeruginosa*.
Indication(s) Under Review in this document (may include off label)	Complicated Intraabdominal Infections, in combination with metronidazole Complicated Urinary Tract Infections, including Pyelonephritis
Dosage Form(s) Under Review	Zerbaxa 1.5g (1g ceftolozane + 0.5g tazobactam) reconstituted solution for injection
REMS	☐ REMS ☒ No REMS ☒ Postmarketing Requirements
Pregnancy Rating	Pregnancy Category B

Executive Summary

Efficacy	• Approval of ceftolozane/tazobactam was based upon two pivotal Phase 3 trials and two supporting Phase 2 trials evaluating adult patients with either complicated intraabdominal infections (cIAI) or complicated urinary tract infections (cUTI), including pyelonephritis. All four were designed as randomized, multicenter, double-blind, active-comparator, non-inferiority trials. • The primary efficacy endpoint in the Phase 3 cIAI trial compared cure rates in the microbiological intent-to-treat group at the test-of-cure visit between ceftolozane/tazobactam in combination with metronidazole and meropenem. The pre-specified 10% non-inferiority margin was met, 83.0% vs. 87.3%, respectively. • The package insert states decreased efficacy seen in patients with a baseline creatinine clearance <50 mL/min or patients ≥65 years of age, in the cIAI trial. • The primary efficacy endpoint used in the Phase 3 cUTI trial compared composite cure rate in the modified microbiological intent-to-treat group at the test-of-cure visit between ceftolozane/tazobactam and levofloxacin. The pre-specified 10% non-inferiority margin was met, 76.9% vs. 68.6%, respectively.
Safety	• Data are available for two Phase 2 and two Phase 3 clinical trials in cIAI and cUTI during which patients were treated between 3 and 14 days. • Common adverse events were nausea, diarrhea, headache, and pyrexia. • The prescribing information for ceftolozane/tazobactam warns of possible allergic cross-reactivity in patients with previous reactions to beta-lactam antimicrobials.
Potential Impact	• Ceftolozane/tazobactam displays in-vitro activity against *Enterobacteriaceae* and *Pseudomonas aeruginosa*. Notably, it retains activity against some MDR *Pseudomonas aeruginosa*, including carbapenem-resistant strains. • Ceftolozane/tazobactam is approved for use in the treatment of complicated intraabdominal infections (in combination with metronidazole) and complicated urinary tract infections, including pyelonephritis in adults 18 years or older.

Background

Purpose for review

Recent FDA approval: December 2014

Issues to be determined:

- ✔ Evidence of need
- ✔ Does Ceftolozane/tazobactam offer advantages over current VANF agents?
- ✔ What safety issues need to be considered?

Other therapeutic options

Formulary Alternatives	Other Considerations
Complicated Intraabdominal Infections: *Monotherapy*: Cefoxitin, Moxifloxacin, or Ertapenem *Combination therapy with Metronidazole:* Cefazolin, Cefuroxime, Cefotaxime, Ceftriaxone, Ciprofloxacin, or Levofloxacin	Based on 2010 IDSA Intraabdominal Infection guidelines for **mild to moderate severity** of disease
Complicated Intraabdominal Infections: *Monotherapy:* Piperacillin/tazobactam, Imipenem/cilastatin, or Meropenem *Combination therapy with Metronidazole:* Ceftazidime, Cefepime, Ciprofloxacin, or Levofloxacin	Based on 2010 IDSA Intraabdominal Infection guidelines for **high severity** of disease
Complicated Urinary Tract Infections: Ceftriaxone, Ceftazidime, Cefepime, Piperacillin/tazobactam, Ertapenem, Imipenem/cilastatin, Meropenem, Ciprofloxacin, Levofloxacin	Agents for cUTI broadly represent agents for the treatment of cIAI, as above (with the exception of moxifloxacin). Alternatives for cUTIs caused by multidrug resistant (MDR) organisms may include aminoglycosides or polymyxins.

Non-formulary Alternative	Other Considerations
Ceftazidime/avibactam (Avycaz®) 2.5gm IV Q 8 hours	Combination of avibactam, a novel beta-lactamase inhibitor and a 3rd generation antipseudomonal cephalosporin, ceftazidime. Exhibits in-vitro activity against *Enterbacteriaceae* producing *Klebsiella pneumoniae* carbapenemase (KPC). Per package insert, only limited safety and efficacy data are currently available, reserve use patients with limited or no alternative treatment options.

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to February 2015) using the search terms "ceftolozane tazobactam", and "Zerbaxa". The search was limited to studies performed in humans and published in the English language. Reference lists of review articles. All randomized controlled trials published in peer-reviewed journals were included. This search strategy revealed several Phase 1 trials in healthy human subjects, one Phase 2 cIAI trial, and one Phase 3 cIAI trial.

Review of Efficacy

The FDA approval of ceftolozane/tazobactam for the treatment of complicated intraabdominal infections (cIAI) and complicated urinary tract infections (cUTI) was based upon one pivotal Phase 3 trial and one supporting Phase 2 trial for each indication. Initially, two identical Phase 3 trials per indication had been planned and enrollment was initiated in December 2011. In September 2012, new draft Guidance for Industry for cIAI allowed for the possibility of using only a single study per indication if sponsors were developing an antimicrobial agent for more than one indication aimed at treatment of infections caused by similar pathogens. Following this, in December 2012, Cubist

obtained authorization to combine the four on-going studies into two pooled data sets, one set for each indication. The authorization to pool data sets was granted on the basis of the trials identical designs.

Complicated intraabdominal infection

The pivotal trial (combination data set: CXA-cIAI-10-08 and CXA-cIAI-10-09) for cIAI utilized a non-inferiority prospective, multicenter, double-blind, randomized, active comparator design. Complicated intraabdominal infection is defined in Table 1. Randomization occurred in a 1:1 ratio, stratified by primary site of infection and investigational site, to either 1.5g ceftolozane/tazobactam IV every 8 hours plus metronidazole 500mg IV every 8 hours or meropenem 1g IV every 8 hours plus matching saline placebo IV every 8 hours for 4 to 14 days. The primary efficacy endpoint was the difference in clinical cure rates in the microbiological intent-to-treat (MITT) population at the test-of-cure (ToC) visit. Non-inferiority of clinical cure was determined using a 10% margin of the lower bound of the 95% confidence interval. The MITT population is defined as all patients randomized with cIAI and at least 1 culture confirmed pathogen at baseline, regardless of susceptibility to study drug, which included approximately 80% of randomized subjects. Assessment for ToC was performed 26 to 30 days after initiation of the study drug. The key secondary endpoint was to compare the clinical response in the microbiologically evaluable (ME) population at the ToC visit. The ME population was defined as subjects who met the protocol definition of cIAI, adhered to all study procedures, had a clinical outcome recorded at the ToC visit, and at least 1 baseline pathogen which was susceptible to the study drug received.

Pivotal trial (combination data set: CXA-cIAI-10-08 and CXA-cIAI-10-09): Safety and Efficacy of Intravenous Ceftolozane/tazobactam and Intravenous Meropenem in Complicated Intraabdominal Infections

Table 1: Key Inclusion and Exclusion Criteria for Phase 3 cIAI Trial

Inclusions
Age ≥ 18
Complicated intraabdominal infection • Cholecystitis (with rupture or perforation), appendiceal perforation or periappendiceal abscess • Acute gastric or duodenal perforation (if operated on >24 hours after perforation) • Traumatic perforation of the intestine (if operated on >12 hours after perforation) • Peritonitis or intraabdominal abscess including liver or spleen
Collection of baseline intraabdominal culture specimen
If enrolled preoperatively, radiographic evidence of bowel perforation or intraabdominal abscess
Surgical intervention within 24 hours of initiating study drug
Evidence of systemic infection (≥1 of the following) • Fever, leukocytosis, abdominal/flank/referred pain due to cIAI, or nausea/vomiting
Exclusions
Any of the following intraabdominal infections or processes • Abdominal wall abscess • Small bowel obstruction or ischemic bowel disease without perforation • Simple appendicitis or acute suppurative cholangitis • Infected necrotizing pancreatitis, pancreatic abscess, or pelvic infection • Spontaneous bacterial peritonitis due to cirrhosis
Any surgical intervention unlikely to achieve adequate source control
Receipt of systemic antibiotics or infection with pathogen(s) known to be resistant to meropenem
Severe renal impairment or hepatic disease
Severe anemia, neutropenia, or thrombocytopenia
Life-threatening illness, including septic shock or respiratory failure
Immunocompromised

Table 2: Baseline Characteristics of the MITT Population for Phase 3 cIAI Trial

Characteristic	**Ceftolozane/Tazobactam + Metronidazole (n=389)**	**Meropenem (n=417)**

Age		
• 18-64	289 (74.2%)	332 (79.6%)
• ≥65	100 (25.7%)	85 (20.4%)
Sex, Male	218 (56.0%)	248 (59.4%)
Race, White	367 (94.3%)	388 (93.0%)
Region		
• Eastern Europe	297 (76.3%)	308 (73.8%)
• South America	36 (9.2%)	45 (10.7%)
• North America	26 (6.6%)	25 (6.0%)
Site of Infection		
• Bowel (small or large)	77 (19.7%)	80 (19.1%)
• Other site	312 (80.2%)	337 (80.8%)
Baseline Creatinine Clearance		
• ≥80 ml/min	268 (68.8%)	295 (70.7%)
• 50-70 ml/min	98 (25.1%)	109 (26.1%)
• 30-49 ml/min	23(5.9%)	13 (3.1%)
Surgical Procedure		
• Laparotomy	274 (70.4%)	271 (64.9%)
• Laparoscopy	86 (22.1%)	104 (24.9%)
APACHE Score <10 at Baseline	310 (79.6%)	347 (83.2%)
Prior Antimicrobial Use	224 (57.5%)	239 (57.3%)
Abscess Type		
• Single	186 (47.5%)	208 (50.2%)
• Multiple	33 (8.4%)	32 (7.4%)
Presence of Bacteremia	8 (2.1%)	12 (2.9%)
Polymicrobial Infection	256 (65.8%)	286 (69%)

Table 3: Efficacy Endpoints in Phase 3 cIAI Trial

Outcomes	Ceftolozane/tazobactam plus Metronidazole	Meropenem	Difference (95% CI)
Primary Efficacy Endpoint in MITT Population at ToC Visit	n = 389	n = 417	
Cure[1]	323 (83.0%)	365 (87.3%)	-4.3 (-9.2, 0.7)
Failure[2]	32 (8.2%)	34 (8.2%)	NA
Indeterminate[3]	34 (8.7%)	19 (4.6%)	NA
Secondary Efficacy Endpoint in ME Population at ToC Visit	n = 275	n = 321	
Cure	259 (94.2%)	304 (94.7%)	-0.5 (-4.5, 3.2)
Failure	16 (5.8%)	17 (5.3%)	NA

Overall quality of evidence: High (Refer to Appendix A); please note that all trials were funded by Cubist Pharmaceuticals.

[1] Complete resolution or significant improvement in signs/symptoms of the index infection, no additional antimicrobials or surgical procedures required.

[2] Death related to IAI prior to ToC, persistent/recurrent infection requiring additional intervention, need for additional antibiotics, or post-surgical wound infection.

[3] Study data not available for evaluation of efficacy for any reason, including death prior to ToC deemed unrelated to infection or subjects lost to follow-up.

Table 4: Key MITT Subgroups Failing to Meet Non-inferiority Criteria with Respect to Primary Efficacy Outcome in Phase 3 cIAI Trial

MITT Subgroup of Primary Efficacy Outcome	Ceftolozane/tazobactam plus Metronidazole	Meropenem	Difference[1]
Age ≥65	69/100 (69%)	70/85 (82%)	-13
APACHE Score >10	54/78 (69%)	56/70 (80%)	-11
Creatinine Clearance <50mL/min	11/23 (47%)	9/13 (69%)	-22

[1] No statistical analysis performed for these subgroup differences.

Summary: In a primarily white, Eastern European population of middle-aged subjects with complicated intraabdominal infections, administration of intravenous ceftolozane/tazobactam 1.5g every 8 hours (plus metronidazole 500mg IV every 8 hours) for 4 to 14 days was non-inferior compared to meropenem at achieving clinical cure. Package insert warns of the potential for decreased efficacy seen in patients with a baseline creatinine clearance <50 mL/min or those patients ≥65 years of age.

Complicated urinary tract infection

The pivotal trial (combination data set: CXA-cUTI-10-04 and CXA-cUTI-10-05) for cUTI utilized a non-inferiority prospective, multicenter, double-blind, double-dummy, randomized, active comparator design. Complicated urinary tract infections, including pyelonephritis, are defined in Table 1. The study randomized a total of 1083 patients in a 1:1 ratio, stratified by geographical region, to either 1.5g ceftolozane/tazobactam IV every 8 hours or levofloxacin 750mg IV every 24 hours for 7 days. The primary efficacy endpoint was the difference in the composite microbiological and clinical cure rates in the microbiological modified intent-to-treat (mMITT) population at the ToC visit. Non-inferiority of clinical cure was determined using a 10% margin of the lower bound of the 95% confidence interval. The mMITT population is defined as all patients randomized with cUTI, who received at least 1 dose of study drug, and had at least 1 qualified uropathogen from the pre-treatment urine culture. Assessment for ToC was performed 5 to 9 days after initiation of the study drug. The key secondary endpoint was to compare the composite microbiological and clinical cure in the microbiologically evaluable (ME) population at the ToC visit. The ME population was defined as subjects who met the protocol definition of cUTI, adhered to all study procedures, had a clinical outcome recorded at the ToC visit, and with an appropriately collected and interpretable urine culture at both baseline and ToC visit.

Pivotal trial (combination data set: CXA-cUTI-10-04 and CXA-cUTI-10-05): Safety and Efficacy of Intravenous Ceftolozane/tazobactam and Intravenous Levofloxacin in Complicated Urinary Tract Infections, including Pyelonephritis

Table 1: Key Inclusion and Exclusion Criteria for Phase 3 cUTI Trial

Inclusions
Age ≥ 18
Baseline urine specimen with pyuria and culture
Clinical signs and/or symptoms of complicated urinary tract infection or pyelonephritis • Dysuria, frequency, or urgency • Fever, rigors, chills, or warmth • Suprapubic pain, flank pain, or tenderness • Nausea or vomiting PLUS at least 1 complicating factor • Males with a documented history of urinary retention • Indwelling urinary catheter scheduled to be removed during therapy and before EoT • Obstructive uropathy scheduled to be relieved during therapy and before EoT • Functional/anatomical abnormality of GU tract with voiding disturbance (≥100mL urine)
Exclusions
Concomitant infection or receipt of systemic antibiotics (except agents with gram-positive activity only)
Intractable urinary tract infection or complete, permanent obstruction of the urinary tract
Fungal urinary tract infection
Permanent or unremovable indwelling bladder catheter, urinary stent, or nephrostomy tube
Suspected or confirmed perinephric abscess, intrarenal abscess, or prostatitis
Presence of severe renal impairment

Table 2: Baseline Characteristics of the mMITT Population for Phase 3 cUTI Trial

Characteristic	**Ceftolozane/Tazobactam (n=398)**	**Levofloxacin (n=402)**
Age • Mean (range)	49.1 (18-90)	48.1 (18-87)

• 18 – 45 years of age	165 (41.4%)	182 (45.3%)
Sex, Female	293 (73.6%)	299 (74.4%)
Race, White	340 (85.4%)	346 (86.1%)
Region		
• Eastern Europe	304 (76.4%)	304 (75.6%)
• North America	15 (3.7%)	10 (2.5%)
Baseline Creatinine Clearance		
• ≥80 ml/min	247 (62.1%)	274 (68.2%)
• 50-70 ml/min	116 (29.1%)	100 (24.9%)
Diagnosis		
• Pyelonephritis	328 (82.4%)	328 (81.6%)
• cUTI, excluding pyelonephritis	70 (17.6%)	74 (18.4%)
Presence of bacteremia	29 (7.3%)	33 (8.2%)
Signs and symptoms of pyelonephritis	328 (82.4%)	328 (81.6%)
• Fever, rigors, chills	258 (78.7%)	267 (81.4%)
• Flank pain	313 (95.4%)	312 (95.1%)
• CV or suprapubic tenderness	298 (90.9%)	297 (90.5%)
• Nausea or vomiting	175 (53.4%)	171 (52.1%)
Signs and symptoms of cUTI	70 (17.6%)	74 (18.4%)
• Dysuria/frequency/urgency	64 (91.4%)	69 (93.2%)
• Fever, rigors, chills	17 (24.3%)	16 (21.6%)
• Suprapubic or flank pain	61 (87.1%)	70 (94.6%)
• Nausea or vomiting	19 (27.1%)	9 (12.2%)
Baseline Urinary Pathogens		
• Gram Negative Aerobes	378 (95.0%)	386 (96.0%)
• *Enterobacteriaceae*	369 (92.7%)	370 (92.0%)
• *E. coli*	305 (76.6%)	324 (80.6%)
• *K. pneumoniae*	33 (8.3%)	25 (6.2%)
• *P. mirabilis*	12 (3.0%)	12 (3.0%)
• *Enterobacter spp.*	10 (2.5%)	9 (2.2%)
• *P. aeruginosa*	8 (2.0%)	15 (3.7%)
• Gram Positive Aerobes	25 (6.3%)	23 (5.7

Table 3: Efficacy Endpoints in Phase 3 cUTI Trial

Outcomes	Ceftolozane/Tazobactam	Levofloxacin	Difference (95% CI)
Primary Efficacy Endpoint in mMITT Population at ToC Visit	n = 398	n = 402	
Composite Cure[1]	306 (76.9%)	275 (68.6%)	8.5 (2.31, 14.57)
Failure[2]	66 (16.6%)	103 (25.6%)	NA
Indeterminate[3]	26 (6.5%)	24 (6.0%)	NA
Secondary Efficacy Endpoint in ME Population at ToC Visit	n = 341	n = 353	Difference (95% CI)
Composite Cure	284 (76.9%)	266 (68.6%)	8.0 (1.95, 13.97)
Failure	57 (16.6%)	87 (25.6%)	NA
Subgroup Analysis: Baseline Susceptibility of Pathogen to Levofloxacin (LVX)	n = 341	n = 353	Difference (95% CI)
Clinical Cure[4] (LVX-resistant)	90/100 (90.0%)	86/112 (76.8%)	13.2 (3.2, 23.2)
Composite Cure (LVX-resistant)	60/100 (60.0%)	44/112 (39.3%)	20.7 (7.2, 33.2)
Clinical Cure (LVX-susceptible)	276/298 (92.6%)	270/290 (93.1%)	-0.5 (-4.8, 3.8)

Composite Cure (LVX-susceptible)	231/272(84.9%)	210/259 (81.8%)	3.8 (-2.6, 10.3)

Overall quality of evidence: High (Refer to Appendix A); please note that all trials were funded by Cubist Pharmaceuticals.

[1] Composite of clinical cure (resolution of signs and symptoms of infection) and microbiological eradication (culture negative for baseline uropathogen).

[2] Death related to cUTI prior to ToC, persistent signs/symptoms of infection, persistence of culture positive for baseline pathogen, or need for additional antibiotics.

[3] Study data not available for evaluation of efficacy for any reason, including death prior to ToC deemed unrelated to infection or subjects lost to follow-up.

[4] Clinical cure is defined as resolution of signs and symptoms of infection at ToC visit.

Summary: In a primarily white, Eastern European population of middle-aged female subjects with complicated urinary tract infections including pyelonephritis, administration of intravenous ceftolozane/tazobactam 1.5g every 8 hours for 3 to 9 days was non-inferior compared to levofloxacin at achieving composite cure.

Potential Off-Label Use

- Other infections typically involving Gram-negatives including pneumonia and diabetic foot infection
- According to clinicaltrials.gov, the pharmaceutical company has registered a Phase 3 clinical trial for ventilated nosocomial pneumonia using a higher dose of ceftolozane/tazobactam (i.e. 3g IV Q8)[4]

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	• None
Contraindications	• Known serious hypersensitivity to ceftolozane/tazobactam piperacillin/tazobactam, or other members of the beta-lactam class
Warnings/Precautions	• Reduced efficacy in patients with baseline creatinine clearance ≤50 mL/min • Hypersensitivity reactions • *Clostridium difficile*-associated diarrhea • Development of drug-resistant bacteria

Safety Considerations

This safety assessment is based on upon data from one Phase 2 and Phase 3 study of cIAI and one Phase 3 study of cUTI. The Phase 3 trials of cIAI and cUTI included 1015 patients treated with ceftolozane/tazobactam and 1032 patient treated with comparator agents, meropenem or levofloxacin. The mean age was 49 with about 25% of patients aged ≥65. Most patients in both trials (>70%) were White and from Eastern Europe. In the cUTI trial 75% were female and in the cIAI trial 58% were male.

Adverse Reactions

Common adverse reactions	Incidence ≥5%: nausea, headache, diarrhea, pyrexia
Death/Serious adverse reactions	*Combination Data from Phase 2 and Phase 3 cIAI Trials* All-cause Mortality: 2.5% (14/564) vs. 1.5% (8/536) in the comparator arm. Cause of death varied, including worsening and/or complications of infection, surgery, and underlying conditions (none were considered drug-related) *Data from Phase 3 cUTI Trial* All-cause Mortality: 0.2% (1/533) vs. 0% (0/535) in the comparator arm. Cause of death was bladder cancer occurring 38 days after end of study therapy. *Combination data from Phase 3 cIAI and cUTI Trials* Serious Adverse Events: 5.3% (54/1015) vs. 5.2% (54/1032) in comparator arm. Treatment-related: 3 (0.3%) vs. 1 (0.1%) in comparator arm, all *C. difficile* colitis
Discontinuations due to adverse reactions	*Combination data from Phase 3 cIAI and cUTI Trials* 2% (20/1015) vs. 1.9% (20/1032) in the comparator arm - No significant differences except discontinuations due to renal impairment 0.5% (5/1015) vs. 0% (0/1032) in the comparator arm

Drug Interactions

Drug-Drug Interactions

- No significant drug-drug interactions have been observed or are anticipated between ceftolozane/tazobactam and the substrates, inhibitors, or inducers of cytochrome P450 enzymes
- Tazobactam is a known substrate of OAT1 and OAT3; co-administration with the OAT inhibitor probenecid has been shown to prolong tazobactam half-life by 71%, although clinical implications are unknown at this time

Risk Evaluation

As of 02/06/2015

Comments

Sentinel event advisories

- None

Look-alike/sound-alike error potentials

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Ceftolozane/ tazobactam	None	None	None	Cefazolin Ceftaroline Ceftazidime Ceftazidime/avibactam Piperacillin/tazobactam
Zerbaxa	None	None	None	Zavesca Zebeta Zyprexa

Other Considerations

Postmarketing requirements for adults:

- Conduct a five-year, prospective study after the introduction of ceftolozane/tazobactam to determine if decreased susceptibility is occurring in the target population of bacteria that are in the approved labeling.

Microbiology:

Ceftolozane/tazobactam is a novel cephalosporin/β-lactamase inhibitor. The gram-positive activity of ceftolozane/tazobactam includes the majority of streptococci, though activity against *Streptococcus pneumoniae* varied according the corresponding penicillin susceptibility of the isolate. However, ceftolozane/tazobactam is poorly active against both staphylococci and enterococci. Ceftolozane/tazobactam has activity against *Enterobacteriaceae* and *Pseudomonas aeruginosa*. Ceftolozane/tazobactam has demonstrated in-vitro activity against *Pseudomonas aeruginosa*, including some MDR and carbapenem-resistant strains, and the majority of *Enterobacteriaceae*, including some ESBL-producing CTX-M strains. Tazobactam lacks inhibitory activity against serine carbapenemases, such as KPCs, or metallo-β-lactamases, such as IMP or VIM. Ceftolozane/tazobactam has in-vitro activity against select anaerobic organisms including *Bacteroides fragilis, Clostridium perfringens, Fusobacterium spp., and Prevotella spp.*, but has limited activity against non-fragilis species of *Bacteroides*. This gap in anaerobic coverage warranted the addition of metronidazole to ceftolozane/tazobactam in the cIAI trials.

Dosing and Administration

The recommended dose of ceftolozane/tazobactam for both complicated intraabdominal and urinary tract infections, including pyelonephritis is 1.5g administered every 8 hours by intravenous infusion over 1 hour in patients 18 years or older with normal renal function or mild renal impairment. The indicated duration of therapy for cIAI is 4-14 days and for cUTI is 7 days, but duration of therapy decisions should be guided by the severity and site of infection as well as the patient's clinical and bacteriological progress.

Dose Adjustment in Renal Impairment

Estimated creatinine clearance	**Dose**
> 50 mL/min	1.5g IV every 8 hours
30–50 mL/min	750mg IV every 8 hours
10–29 mL/min	375mg IV every 8 hours
End-Stage Renal Disease (ESRD) on chronic hemodialysis	**Loading dose:** 750mg IV x1

	Maintenance dose: 150mg IV every 8 hours

Special Populations (Adults)

	Comments
Elderly	• No dose adjustment based on age is recommended • The incidence of adverse events in treatment groups for both studied indications was higher in subjects age 65 and older • Cure rates in cIAI were lower in patients age 65 and older • Elderly patients are more likely to have decreased baseline renal function, increased vigilance warranted; see "**Renal Impairment**"
Pregnancy	• Pregnancy Category B • Pregnant women were excluded from clinical studies • Weigh potential risks and benefits to infant and mother before use
Lactation	• Unknown if ceftolozane/tazobactam excreted in human breast milk. • Nursing mothers were excluded from clinical studies • Weigh potential risks and benefits to infant and mother before use
Renal Impairment	• Ceftolozane mean AUC increased by 1.25, 2.5, and 5-fold in subjects with mild, moderate, and severe renal impairment, respectively • Two-thirds of administered dose is removed by hemodialysis • Dosage adjustments are required in patients with moderate to severe renal impairment and in patients with ESRD on hemodialysis
Hepatic Impairment	• Does not undergo significant hepatic metabolism
Pharmacogenetics/genomics	• No data identified

Projected Place in Therapy

- Ceftolozane/tazobactam is approved for use in the treatment of complicated intraabdominal infections (in combination with metronidazole) and complicated urinary tract infections, including pyelonephritis in adults 18 years of age and older.
- Ceftolozane/tazobactam may have a role in the treatment of infections caused by multidrug-resistant *Pseudomonas aeruginosa* with limited therapeutic options; however, susceptibility testing is highly recommended in these cases.

References

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.