CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206829Orig1s000

SUMMARY REVIEW

Division Director Memo

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH
Patient	Division Director Memo
NDA #	206829
Applicant Name	Cubist Pharmaceuticals, Inc.
Date of Submission	April 21, 2014
PDUFA Goal Date	December 21, 2014
Established (USAN) Name	Ceftolozane-tazobactam
Trade Name	Zerbaxa
Dosage Forms / Strength	Injection/1 gram ceftolozane and 500 mg tazobactam single use vials
Proposed Indications	1. Complicated urinary tract infections (cUTI) 2. Complicated intra-abdominal infections (cIAI)
Recommended Action:	Approval

Material Reviewed/Consulted Action Package including:	**Names of Discipline Reviewers**
Cross-Discipline Team Leader Review	Thomas Smith MD
Pharmacology Toxicology Review	James Wild PhD
Chemistry Manufacturing and Controls Review	Shrikant Pagay PhD
Medical Officer Review	Maria Allende MD Hala Shamsuddin MD
Statistical Review	Christopher Kadoorie PhD Daniel Rubin PhD
Risk Management	Joyce Weaver Pharm D
Product Quality Review	Erika Pfeiler PhD
Biopharmaceutics Review	Minerva Hughes PhD
Microbiology Review	Kerian Grande Roche PhD
Clinical Pharmacology Review	Ryan Owen PhD
Office of Scientific Investigations	Sharon Gershon Pharm D
Division of Medication Error Prevention and Analysis	Aleksander Winiarski Pharm D Jacqueline Sheppard Pharm D
Thorough QT Study Review	Interdisciplinary Review Team
Labeling Reviews	Christine Corser Pharm D

1.0 Introduction

NDA 206829, Ceftolozane-tazobactam was submitted by Cubist Pharmaceuticals, Inc. on April 21, 2014. The Applicant proposed the following indications:

1. As a single agent for the treatment of cUTIs, including pyelonephritis (b) (4) caused by the following Gram-negative microorganisms: *Escherichia coli* (b) (4) *Klebsiella pneumoniae* (b) (4) *Proteus mirabilis*, and *Pseudomonas aeruginosa*.
2. Use in combination with metronidazole for the treatment of cIAIs caused by the following Gram-negative and Gram-positive microorganisms: *E. coli* (b) (4) *K. pneumoniae* (b) (4) *P. aeruginosa, Enterobacter cloacae, K. oxytoca, P. mirabilis, Bacteroides fragilis,* (b) (4) *Streptococcus anginosus, S. constellatus,* and *S. salivarius*.

Ceftolozane-tazobactam is a new cephalosporin antibacterial drug combined with tazobactam, a beta-lactamase inhibitor. Tazobactam is currently approved in combination with piperacillin (Zosyn®) for the treatment of intra-abdominal infections, skin and skin structure infections, female pelvic infections, community-acquired pneumonia, and nosocomial pneumonia caused by susceptible isolates of designated bacteria.

2.0 Background

Ceftolozane-tazobactam was granted qualified infectious disease product (QIDP) designation for the cIAI and cUTI indications on December 5, 2012, and February 20, 2013, respectively, and fast track designation on February 20, 2013, and May 7, 2013, respectively. Under the provisions of Generating Antibiotic Incentives Now (GAIN) [Title VIII of FDASIA], new drug applications for products with a QIDP designation receive a priority review. As ceftolozane-tazobactam has QIDP designation, it received a priority review. The NDA is eligible for five additional years of marketing exclusivity under GAIN. The NDA is a PDUFA V 'Program' application as well.

This application is covered under Section 505(b)(2) of the Food Drug and Cosmetic Act as the Applicant is relying on the Agency's previous finding of safety of tazobactam, one of the components of the drug product, ceftolozane-tazobactam.

(b) (4) (b) (4) Calixa Therapeutics submitted IND 104490 for ceftolozane-tazobactam in July, 2009. Cubist acquired Calixa in December, 2009. The original development program included two identical Phase 3 trials each in cUTI and cIAI. In September 2012, the draft guidance on cIAI was issued which states that for a drug being developed for more than one indication for treatment of infections caused by similar bacterial pathogens, a single trial in cIAI and a single trial in another indication can be provided as evidence of effectiveness (e.g., one trial in cUTI and one in cIAI).[1] Cubist obtained agreement from FDA to pool the data from the ongoing Phase 3 trials into a single database for each indication. The overall sample sizes were adjusted to maintain adequate power, and the data were pooled after database lock.

The review team has completed their reviews of this application. For a detailed discussion of NDA 206829, please refer to the discipline specific reviews and the Cross-Discipline Team Leader review.

3.0 Product Quality

The Chemistry, Manufacturing and Controls (CMC) reviewer for this NDA is Shrikant Pagay, PhD. The product quality microbiology reviewer is Erika Pfeiler PhD and the biopharmaceutics reviewer is Minerva Hughes PhD.

Ceftolozane sulfate is a white to off-white powder that has limited solubility in water but has sufficient solubility in a buffer at pH 6 to dissolve in the proposed unit dose vial. There are nine process-related impurities and all are qualified at the proposed levels.

Tazobactam sodium is obtained from (b) (4). It is a white to off-white powder that is freely soluble in water. The product is sterile and the specifications include only one specified impurity. The drug master files for tazobactam acid, DMF (b) (4) and tazobactam sodium, DMF (b) (4) held by (b) (4) were referenced for CMC information. The proposed specifications for the drug substance were found to be acceptable.

The drug product, ceftolozane-tazobactam for injection, is a sterile lyophilized powder containing ceftolozane sulfate, sodium chloride, L-arginine, and citric acid. Each vial contains 1147 mg of ceftolozane sulfate which is equivalent to 1000 mg of ceftolozane and 537 mg of tazobactam sodium which is equivalent to 500 mg of tazobactam free acid. The impurities from the ceftolozane and tazobactam drug substances are also degradants in the drug product and are qualified at the proposed levels.

[1] http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm321390.pdf

The stability data provided in the application support a shelf life of 12 months. The in-use stability data for reconstituted ceftolozane-tazobactam in an infusion bag support a storage period of (b) (4) hours under ambient conditions and up to 7 days under refrigeration at 2 to 8° C.

Dr. Hughes noted no issues from a biopharmaceutics perspective and recommended approval of the NDA. Dr. Pfeiler noted that the microbiological in-use studies for the drug product support a 24-hour hold at room temperature and a 7-day hold at 2-8° C and do not support the (b) (4)-day hold proposed by the Applicant. Dr. Pfeiler recommends approval and the hold time will be addressed in labeling.

All facilities are found to be acceptable. The CMC review concluded that the information provided was generally satisfactory to assure the identity, strength, purity, and quality of the drug substances and the drug product. Because of outstanding issues including finalization of labeling and inspections of the manufacturing and testing facilities, Dr. Pagay did not recommend approval of the NDA when he completed his initial review. In an addendum dated December 18, 2014, Dr. Pagay recommended approval of the NDA.

I concur with his recommendation.

4.0 Pharmacology/Toxicology

The pharmacology/toxicology reviewer for this NDA is James Wild Ph.D. In 28-day studies in rats and dogs with ceftolozane, hyaline droplet formation was seen in proximal tubules of the renal cortex. Dose-dependent and reversible hyaline droplet formation has been observed with other cephalosporins. In the absence of other relevant pathology such as degeneration or necrosis of renal tubular epithelium or changes in clinical pathology parameters, this finding was not considered adverse in adult animals. In a non- GLP study in juvenile rats in addition to hyaline droplet formation, tubular basophilia and renal cortical fibrosis were seen. As these findings suggest the possibility of renal toxicity in juvenile animals, Dr. Wild recommended that renal function be monitored in future pediatric trials.

In rats and dogs, tazobactam produced increased liver weight and liver histopathology consistent with accumulation of glycogen and increased smooth endoplasmic reticulum. In rats, changes in serum chemistry were noted. As these changes were of low magnitude, were reversible, and not associated with degeneration or necrosis of hepatocytes, it was not considered adverse. These findings were dose-dependent and reversible. High doses of tazobactam were associated with dose-dependent decreases in hemoglobin, hematocrit, and red blood cell counts, and occasionally with increased platelet counts and percentage of lymphocytes. There was no associated bone marrow pathology.

In repeat dose combination studies with ceftolozane plus tazobactam and with each compound alone in rats (1-month) and dogs (2 weeks), no new toxicities were seen.

Dr. Wild notes that the genetic toxicity assays suggest minimal potential for genotoxicity in humans for the combination of ceftolozane and tazobactam and for each component alone.

Ceftolozane had no adverse effect on fertility in male or female rats at intravenous doses up to 1000 mg/kg/day (~3 x mean plasma exposure in healthy adults at the clinical dose of 1 g q8h). Embryo-fetal development studies performed with ceftolozane in mice and rats at doses of up to 2000 and 1000 mg/kg/day, respectively, revealed no evidence of harm to the fetus. In an embryo-fetal study in rats, tazobactam administered 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 no fetal toxicity.

Dr. Wild recommends approval of the NDA from a pharmacology/toxicology perspective. I agree with his assessment.

5.0 Clinical Microbiology

The clinical microbiology reviewer for this NDA is Kerian Grande Roche, PhD. Ceftolozane binds to penicillin-binding proteins (PBPs) and inhibits cell wall synthesis leading to cell death. The antibacterial spectrum of ceftolozane-tazobactam includes Gram-negative bacteria such as Enterobacteriaceae and *P. aeruginosa*, Gram-positive bacteria such as *Streptococcus pneumoniae* and the *S. anginosus* group, and anaerobes such as *B. fragilis*. Ceftolozane is stable to *P. aeruginosa* AmpC hydrolysis because of its low affinity for *P. aeruginosa* AmpC enzyme. Ceftolozane is not a substrate for active efflux and is not affected by the loss of outer membrane protein D (OprD) in *P. aeruginosa*.

Tazobactam has little clinically relevant *in vitro* activity against bacteria because of low affinity for PBPs. It inhibits common class A and some class C β-lactamases. Tazobactam does not inhibit carbapenemases such as *Klebsiella pneumoniae* carbapenemase (KPC) or metallo-β-lactamases such as IMP or VIM.

A range of ceftolozane and tazobactam combinations were evaluated in time-kill studies to characterize *in vitro* killing kinetics. The addition of tazobactam increased the activity of ceftolozane against the evaluated β-lactamase-expressing strains in a concentration-dependent manner. The activity of ceftolozane and ceftolozane-tazobactam was studied in murine models of infection, including sepsis, UTI, infected burn wound, pneumonia and thigh infection and pneumonia in rabbits.

In surveillance studies, the MIC90 for *E. coli* was 0.5 mcg/mL. For *P. aeruginosa*, the MIC 90 for surveillance isolates was 2 mcg/mL and for clinical isolates it was 16 mcg/mL. In the Phase 3

trials, the MIC50 and MIC90 values for ceftolozane-tazobactam for Enterobacteriaceae (including ESBL-producing strains) were 0.25 and 1 mcg/mL and 1 and 8 mcg/mL for *P. aeruginosa* respectively.

(b) (4)

Challenges with the classification and nomenclature of the > 1300 types of beta-lactamases identified so far is very well-described in the literature.[2]

Genotypic testing for ESBLs was performed in a subset of the baseline isolates from the Phase 3 cIAI and cUTI trials that met pre-specified criteria. (b) (4)

. While some isolates of a certain genotype tested susceptible to ceftolozane-tazobactam, other isolates with an identical genotype tested non-susceptible. Similarly, the clinical outcomes also varied irrespective of the identified genotype. Although these data have limitations, information regarding the clinical experience with ESBL-producing organisms might be beneficial to healthcare providers. Information about ESBL-producing *E. coli* and *K. pneumoniae* from the phase 3 cUTI and cIAI trial is included in the clinical studies section and additional information about the *in vitro* activity of ceftolozane-tazobactam is included in the Microbiology section of the package insert. As most healthcare providers will not have access to the genotype of the organism while treating patients, results of susceptibility testing will be most helpful in selecting appropriate antibacterial therapy.

I agree with Dr. Grande Roche's assessment that there are no microbiology issues precluding approval of this NDA and also with the labeling recommendations provided by Dr. Grande Roche.

6.0 Clinical Pharmacology

The clinical pharmacology reviewer for this NDA is Ryan Owen, Ph.D. The pharmacokinetics (PK) of ceftolozane are linear and dose-proportional over the range of doses studied (250 mg-3g). Following multiple-dosing there is no significant accumulation of ceftolozane or tazobactam. Some accumulation of an inactive metabolite (tazobactam M-1) is seen. The volume of distribution of both ceftolozane and tazobactam are larger than the blood volume suggesting that both distribute to the extracellular space. Protein binding is ~21% for ceftolozane and ~30% for tazobactam. Ceftolozane is not metabolized and less than 20% of tazobactam is metabolized to tazobactam M-1. Ceftolozane is excreted unchanged in the urine and both tazobactam and

[2] Bush K. Proliferation and significance of clinically relevant β-lactamases. Ann. N.Y. Acad. Sci. 2013; 84–90.

tazobactam M-1 are excreted in urine. Pharmacokinetic (PK) parameters in healthy adults are presented in Table 1.

Table 1. Mean (CV%) PK Parameters of Ceftolozane-tazobactam after Single and Multiple Doses in Healthy Adults

	Ceftolozane-tazobactam (1g/0.5 g every 8 hours)			
	Ceftolozane		Tazobactam	
PK parameters	Day 1 (n=9)[a]	Day 10 (n=10)	Day 1 (n=9)[a]	Day 10 (n=10)
C_{max} (mcg/mL)	69.1 (11)	74.4 (14)	18.4 (16)	18 (8)
t_{max} (h) (median (min, max)	1.02 (1.01, 1.1)	1.07 (1, 1.1)	1.02 (0.99, 1.03)	1.01 (1, 1.1)
AUC (mcg•h/mL)	172 (14)	182 (15)	24.4 (18)	25 (15)
$t_{½}$ (h)	2.77 (30)	3.12 (22)	0.91 (26)	1.03 (19)

[a] n = 9, one outlier subject excluded from descriptive statistics

The proposed dosing regimen for ceftolozane-tazobactam is 1.5 g (1.0 g/0.5 g) administered intravenously (IV) over 1 hour q 8 h in adult patients with creatinine clearance (CrCl) >50 mL/min. The dosing regimen needs to be adjusted in patients with CrCl ≤50 mL/min as outlined in Table 2. Although the Phase 3 cIAI trial, met its primary endpoint, Dr. Owen notes that a higher dose of ceftolozane-tazobactam may have resulted in better outcomes. Although, the clinical pharmacology recommendation was to conduct dose-ranging studies in Phase 2, only a single dose was evaluated. In this Phase 2 trial, the point estimates for clinical cure favored the comparator (meropenem).

Table 2: Dosing recommendations in patients with renal impairment

Estimated CrCL (mL/min)	Recommended Dosage Regimen
30 to 50	Ceftolozane-tazobactam (500 mg/250 mg) intravenously every 8 hours
15 to 29	Ceftolozane-tazobactam (250 mg/125 mg) intravenously every 8 hours
End stage renal disease (ESRD) on hemodialysis (HD)	A single loading dose of ceftolozane-tazobactam (500 mg/250 mg) followed by a maintenance dose of (100 mg/50 mg) IV every 8 hours (on hemodialysis days, administer dose at the earliest possible time following completion of dialysis)

No dose adjustment is necessary for hepatic impairment. In a clinical cocktail drug-drug interaction study using probe substrates for OAT1/3, CYP1A2 and CYP3A4, no clinically relevant changes in the PK of the probe drugs were seen.

Susceptibility Test Interpretive Criteria:

The Applicant proposed similar susceptibility test interpretive criteria for both Enterobacteriaceae and *P. aeruginosa* (susceptible ≤ 8, intermediate 16, and resistant >32).

The susceptibility test interpretive criteria were determined based on the MIC distribution from clinical and surveillance data, nonclinical PK/PD information and clinical outcome data at various minimum inhibitory concentrations (MICs) from the Phase 3 trials. As no PK data were collected in the Phase 3 trials, exposure-response analysis could not be performed.

Based on the MIC distributions of the clinical isolates and surveillance data, the epidemiologic cut-off values for Enterobacteriaceae were determined to be 2 mcg/mL and 4 mcg/mL for *P. aeruginosa*.

In mouse neutropenic thigh models using strains of *E. coli. K. pneumoniae* and *P. aeruginosa*, the %T>MIC was identified as the PK/PD parameter that most closely correlates with efficacy for ceftolozane. The magnitude of the %T>MIC associated with stasis and 1- and 2-log10 kill was evaluated for beta-lactamase negative Enterobacteriaceae and *P. aeruginosa* using total drug concentration (since protein binding of ceftolozane was negligible in mice). The median %T>MIC associated with stasis, 1-log10 kill, and 2-log10 kill were (b) (4), and 42.8%, respectively. (b) (4) . Dr. Owen considered a cidal (2-log 10 kill) target of 40% T>MIC given the severity of the cIAI indication and the lower cure rates seen in the cIAI trials. The 1-log10 kill target of (b) (4) is also lower than the traditional cidal cephalosporin target of 50%T> MIC.

Using the *in vitro* hollow fiber model, the relevant PK/PD parameter for tazobactam was determined to be the %T>threshold concentration. Since the %T>threshold concentration required for efficacy is strain-dependent, and the types of beta-lactamase enzymes that are expressed by bacterial strains can vary considerably, a unifying relationship that would account for these variables was sought. A translational relationship was proposed of one half of the MIC to ceftolozane/tazobactam representing the critical threshold concentration. Using the *in vitro* hollow fiber model, data from several strains were plotted. From this relationship, a percent time of 65.9% above a threshold concentration was defined as the static target for tazobactam.

Using a PTA of 90%, the conventional threshold for setting interpretive criteria, a %T>MIC target of (b) (4) (as proposed by the Applicant) would support a susceptible breakpoint of (b) (4) for Enterobacteriaceae whereas a target of 40% as recommended by Dr. Owen would support a susceptible breakpoint of 4 mcg/mL. A gated approach was used to co-model ceftolozane and tazobactam in which simulated patients are tested for achieving 1) the tazobactam target and (if not achieved) 2) the ceftolozane target. Applying the conventional PTA threshold of 90% to this analysis would support a susceptible breakpoint of up to 1 mcg/mL. For *P. aeruginosa*, a target of (b) (4) (as proposed by the Applicant) would support a susceptible breakpoint of (b) (4) whereas a target of 40% as recommended by Dr. Owen would support a susceptible breakpoint of 4 mcg/mL as shown in Table 3.

Table 3: Probability of target attainment analyses

MIC	**Probability of achieving free drug % T> MIC**	
	(b) (4) ≥ 40	≥ 50
1	100	99
2	99.2	97.7
4	97.6	90.8
8	83.5	65.4
16	37.6	21.2
≥32	1.90	0.50

Modified from submission to NDA on 12/2/2014

For Enterobacteriaceae, the clinical data can support a susceptible breakpoint of 4 mcg/mL. The number of isolates with an MIC > 4 mcg/mL is small and the cure rates were also lower at MICs > 4 mcg/mL. For *P. aeruginosa*, the clinical data are very limited at MIC values of > 1 mcg/mL as shown in the table below:

Table 4: Clinical outcome by MIC for *P. aeruginosa*

MIC	Total Isolates	Cure (%)	Failure (%)	Indeterminate (%)
0.5	18	13 (72.2)	0 (0)	5 (27.8)
1	22	17 (77.3)	1 (4.5)	4 (18.2)
2	1	1 (100)	0	0
4	3	1 (33.3)	2 (66.7)	0
8	1	0	1 (100)	0
16	1	1 (100)	0	0
32	0	0	0	0
64	0	0	0	0
>64	2	2 (100)	0	0

Modified from table 2.2.4.1-7, clinical pharmacology review

The following table summarizes the basis for Dr. Owen's recommendations for susceptible breakpoints for Enterobacteriaceae and *P. aeruginosa*:

Table 5: Summary of evidence for establishing susceptible breakpoints

Evidence	**Enterobacteriaceae mcg/mL**	***P. aeruginosa* mcg/mL**
Epidemiological Cutoff	2	4
Nonclinical PK/PD – ceftolozane only 40% T>MIC target	4	4
Nonclinical PK/PD – co-model 40%T>MIC target	1	NA
Clinical Cutoff	4	1*
Proposed Susceptible Breakpoint	**2**	**4**

*very limited clinical data at MIC > 1 mcg/mL; modified from tables 2.2.4.1-8 and -9, clinical pharmacology review

The Applicant does not agree with Dr. Owen's recommendations for a susceptible breakpoint of 4 mcg/mL for *P. aeruginosa*. The Applicant's justification for a susceptible breakpoint of (b) (4) is based on a %T>MIC target of (b) (4) and (b) (4)

However, as shown in Table 4, clinical data at MICs > 1 mcg/mL are very limited with only 0-3 patients treated with ceftolozane-tazobactam at each MIC value > 1 mcg/mL. If the interpretive criteria are based on clinical data alone, a susceptible breakpoint of 1 mcg/mL can be supported. However, given that the PK/PD data show that the probability of target attainment is >90% at MICs of 2 and 4 mcg/mL, some degree of extrapolation is acceptable. In addition, the PTA show that using the Applicant's chosen target of (b) (4) This poses a safety risk in patients being treated with ceftolozane-tazobactam, particularly in patients with cIAI. The overall clinical outcomes in ceftolozane-tazobactam treated patients in both the Phase 2 and Phase 3 cIAI trials was lower than that seen in the meropenem arm. As noted in the statistics review by Dr. Kadoorie, subgroup analyses based on prognostic variables of interest showed a trend towards less favorable outcomes in the ceftolozane/tazobactam plus metronidazole arm in patients with higher risk profiles at baseline, further raising concern about the performance of ceftolozane-tazobactam in the treatment of cIAI.

While I agree that based on the Applicant's PTA analysis alone, a susceptible breakpoint of (b) (4) for *P. aeruginosa*, can be justified, I agree with Dr. Owen's assessment that based on the totality of information provided, a susceptible breakpoint of 4 mcg/mL is justified.

Dr. Owen recommends approval of the NDA and I agree with his recommendation.

7.0 Clinical Efficacy and Safety

The clinical reviewers for this NDA are Maria Allende, MD and Hala Shamsuddin MD. Dr. Allende reviewed the efficacy for the cIAI indication and Dr. Shamsuddin for the cUTI indication. The statistical reviewers for this NDA are Christopher Kadoorie PhD and Daniel Rubin PhD. Dr. Kadoorie reviewed the efficacy for the cIAI indication and Dr. Rubin for the cUTI indication.

Efficacy

Complicated intra-abdominal infections

Phase 2 trial

Study CXA-cIAI-10-01 was a multicenter, randomized, double-blind trial that compared ceftolozane-tazobactam plus metronidazole to meropenem in the treatment of cIAI. Adult patients with cIAI were randomized 2:1 to receive ceftolozane-tazobactam, 1.5 g iv q8h plus

metronidazole 500 mg iv q8h (at the discretion of the investigator in patients with upper gastrointestinal infection or cholecystitis), or meropenem, 1 g iv q8h, plus matching saline placebo iv q8h for 4 to 7 days. No inference testing was planned for this trial.

The primary endpoint was clinical response at the test of cure (TOC) visit 7 to 14 days post-therapy in the microbiological modified ITT (mMITT) and microbiologically evaluable (ME) populations. The mMITT population was defined as all randomized patients who received study drug and had at least one qualifying pathogen at baseline; the ME population was a subset of the ITT population who met the protocol definition of cIAI, had at least one baseline pathogen susceptible to study drug, received adequate amounts of study drug, and had sufficient information available to make a non-confounded clinical outcome assessment at the TOC visit.

A total of 122 patients were randomized, 83 to the ceftolozane-tazobactam arm and 39 to the meropenem arm. The mMITT population included 61 patients in the ceftolozane-tazobactam arm and 25 in the meropenem arm. Appendiceal perforation or periappendiceal abscess was the most common diagnosis. *E. coli* was the most common pathogen isolated. The clinical response in the mMITT population was 83.6% (51/61) in the ceftolozane-tazobactam arm and 96% (24/25) in the meropenem arm.

Phase 3 Trial

Patients were randomly assigned (1:1) to receive ceftolozane-tazobactam, 1.5 gm iv q8h, plus metronidazole, 500 mg iv q8h, or meropenem, 1g iv q8h for 4-10 days. A dummy saline infusion was used to maintain the study blind. Up to 14 days of therapy was allowed in limited circumstances (multiple abscesses, diffuse peritonitis from a source other than appendix, failure of prior therapy and a source other than appendix, or hospital-acquired infection). Concomitant systemic antibacterial therapy with daptomycin, vancomycin, or linezolid was allowed for methicillin-resistant *Staphylococcus aureus* or enterococcal infections.

The primary endpoint was clinical cure at the TOC visit 24 to 32 days following treatment initiation. Clinical cure at the TOC visit in the ME population was a pre-specified secondary endpoint. Clinical cure was defined as complete resolution or significant improvement in signs and symptoms of the index infection, such that no additional antibacterial therapy or surgical or drainage procedure was required. Clinical failure was defined as any of the following:

- death related to cIAI at any time point before the TOC visit
- persistent or recurrent infection that required additional intervention
- need for additional antibacterial therapy for symptoms of cIAI before the TOC visit
- post-surgical wound infection requiring additional antimicrobial therapy or drainage

Repeat percutaneous aspiration of an abscess within 72 hours of the original aspiration, without worsening clinical signs and symptoms, or exploratory or diagnostic procedures with no evidence of ongoing infection were not considered failures. Indeterminate outcomes included lack of study data for evaluation of efficacy for any reason, including death during the study period unrelated to the index infection, and circumstances that precluded classification as cure or failure, such as loss to follow-up.

The primary analysis population was the microbiological intent-to-treat (MITT) population, defined as all randomized patients with a pathogen identified at baseline, regardless of susceptibility to study drug. The ME population, included patients who met the protocol definition of cIAI, had a baseline pathogen identified that was susceptible to study drug, adhered to study procedures, and had a clinical outcome at the TOC visit.

Adequate control of the source of infection was required for inclusion in the clinically evaluable or ME populations. An independent surgical review panel (SRP), consisting of 3 surgeons, 2 interventional radiologists, and a chairperson evaluated the adequacy of the initial surgical intervention in achieving source control in patients whose clinical outcomes were assessed as failures by the investigator and in patients who had a clinical outcome of "cure" who had a second, unplanned intra-abdominal intervention.

Of the 993 patients randomized, 806 patients were included in the MITT population (81.2% of the randomized patients), 389 in the ceftolozane-tazobactam plus metronidazole arm and 417 in the meropenem arm. Baseline characteristics were generally similar between the two arms. A higher percentage of patients in the ceftolozane-tazobactam arm were 65 years of age or older, had creatinine clearance < 50 mL/min, APACHE scores ≥10, had a non-appendiceal site of infection, and underwent laparotomy. Only 51 patients were enrolled from North America, including 33 from the U.S. The most common diagnosis was appendiceal perforation or periappendiceal abscess. The most common pathogen isolated at baseline was *E. coli* (65.1%), followed by *B. fragilis* (13.8%). Most infections were polymicrobial (67.6%). Bacteremia was present at baseline in 2.5%.

During the trial, two study sites (1009-4227 and 1008-4024) were closed because of concerns about GCP noncompliance and a potential risk to data integrity. Cubist notified FDA of these closures in May, 2013 and the 23 patients enrolled at these two sites were excluded from the analyses. A sensitivity analysis of the primary efficacy endpoint including the 19 patients in the MITT population from these two sites did not change the overall efficacy assessment.

In the MITT population, ceftolozane-tazobactam plus metronidazole was noninferior to meropenem. The trial met the pre-specified noninferiority margin of -10%. The treatment difference was -4.3 [95% confidence intervals (CI), -9.2, 0.7].

Table 6: Clinical response rates at the TOC visit in the MITT and ME populations

	Ceftolozane-tazobactam plus metronidazole n (%)	Meropenem n(%)	Treatment difference (95% CI)
MITT	**N = 389**	**N = 417**	-4.3 (-9.2, 0.7)
Cure	323 (83.0)	364 (87.3)	
Failure	32 (8.2)	34 (8.2)	
Indeterminate	34 (8.7)	19 (4.6)	
ME	**N = 275**	**N = 321**	-0.5 (-4.5, 3.2)
Cure	259 (94.2)	304 (94.7)	
Failure	16 (5.8)	17 (5.3)	

95% CI calculated as unstratified Wilson Score Cis; Source: Table 6, Dr. Kadoories's statistics review

More patients in the ceftolozane-tazobactam plus metronidazole arm had indeterminate outcomes compared to the meropenem arm [34/389 (8.7%) vs. 19/417 (4.6%)]. The most common reasons for an indeterminate outcome were discontinuation of study drug because of an adverse event (10 patients in the ceftolozane-tazobactam plus metronidazole arm and 4 patients in the meropenem arm) and subject withdrawal (9 patients in the ceftolozane-tazobactam plus metronidazole arm and 5 patients in the meropenem arm).

Clinical cure rates in patients enrolled in North America were 17/26 (65.4%) for patients in the ceftolozane-tazobactam plus metronidazole arm and 19/25 (76.0%) in the meropenem arm.

Clinical cure rates were lower in both arms for patients with moderate renal impairment (creatinine clearance 30-≤50 mL/min) compared to those with CrCl of > 50 mL/min. A greater decrease was seen in patients in the ceftolozane-tazobactam plus metronidazole arm compared to the meropenem arm. Patients with severe renal impairment were excluded from the trial. The all-cause mortality in patients with baseline CrCl 30-≤50 mL/min was 4/23 (17.4%) in the ceftolozane-tazobactam plus metronidazole arm and 1/13 (7.7%) in the meropenem arm.

Table 7: Clinical Cure Rates in a Phase 3 Trial of cIAI by Baseline Renal Function (MITT Population)

Baseline Renal Function	Ceftolozane-tazobactam plus metronidazole n/N (%)	Meropenem n/N (%)
Normal/mild impairment (CrCl ≥50 mL/min)	312/366 (85.2)	355/404 (87.9)
Moderate impairment (CrCl 30-≤50 mL/min)	11/23 (47.8)	9/13 (69.2)

Dr. Kadoorie performed subgroup analyses based on prognostic variables of interest which showed a trend towards less favorable outcomes in the ceftolozane/tazobactam plus metronidazole arm in patients with higher risk profiles at baseline (e.g. age ≥ 65 years, region of

N. America/W. Europe/Rest of World, non-appendiceal site of infection, APACHE II Score > 10, creatinine clearance < 50 mL/min. or multiple abscesses).

Multivariate regression analyses in the MITT population were conducted by the Applicant and Dr. Kadoorie. The risk factors included treatment, age (< 65, ≥ 65), prior antibiotics (Yes, No), CrCl (< 50, ≥ 50 mL/min), primary site of infection (bowel, other), APACHE II Score (< 10, ≥ 10), number of abscesses (≤ 1, > 1), peritonitis (local, diffuse, none), site of infection (appendix, non-appendix), region (N. America, S. America, E. Europe, W. Europe and Rest of World). A second model considered the same risk factors as the above model above except that it excluded the Region variable. These multivariate logistic regression analyses were exploratory and did not attempt to draw inferences. The most significant factor appeared to be CrCl which may possibly be driving the findings. The influence of other risk factors did not appear to be conclusive. Information regarding the decreased efficacy and numerically higher mortality in the ceftolozane-tazobactam plus metronidazole arm will be included in the Warnings and Precautions section of the labeling with a recommendation to monitor renal function closely.

There were 185 patients >65 years of age. Clinical cure rates were 69/100 (69.0%) for patients treated with ceftolozane-tazobactam plus metronidazole and 70/85 (82.4%) for patients treated with meropenem. The reduction in cure rates was more pronounced in the ceftolozane-tazobactam plus metronidazole arm compared to the meropenem arm. This information will be included in the Geriatric Use subsection of the labeling.

Complicated Urinary Tract Infections

Phase 2 trial

Study CXA-101-03 was a multicenter, randomized, double-blind trial that compared ceftolozane alone 1 gram iv q8h to ceftazidime 1 gram iv q 8h for 7-10 days in the treatment of cUTI. The primary endpoint was microbiological eradication rate at the TOC visit 6 to 9 days post-therapy in the microbiological modified ITT (mMITT) and microbiologically evaluable (ME) populations. The mMITT population was defined as all randomized patients who received study drug and had at least one qualifying pathogen at baseline; the ME population was defined as the patients who met the protocol definition of cUTI, had at least one baseline pathogen, received at least five days of study drug, and had an appropriately collected, interpretable urine culture at the TOC visit. This trial was not powered for formal statistical inference.

A total of 129 patients were randomized, 86 to receive ceftolozane and 43 to receive ceftazidime. Approximately 33% of the patients had pyelonephritis. The mMITT population consisted of 65 patients who received ceftolozane and 38 who received ceftazidime. *E. coli* was the most common pathogen isolated (66.2% and 71.1% in the ceftolozane and ceftazidime arms

respectively). In the mMITT population, microbiologic eradication rates were 83.1% (54/65) and 76.3% (29/38) for the ceftolozane and ceftazidime arms, respectively.

Phase 3 Trial

A total of 1083 patients were randomized 1:1 at 209 study centers. Approximately 75% of the study population was enrolled in Eastern Europe. Randomization was initially stratified by study site and later amended to stratification by region. Patients were hospitalized for the duration of the IV therapy, with the exception of a few sites, where clinically stable patients could be discharged after completion of at least 3 days of treatment and if continued IV administration could be set up.

A total of 543 patients were randomized to receive ceftolozane-tazobactam 1.5 g IV q 8 hours plus one dummy infusion and 540 patients were randomized to receive 750 mg IV levofloxacin arm plus three dummy infusions. In the mMITT population, baseline demographic characteristics were generally similar between the two arms; ~ 74% of the patients were female, 75% were < 65 years of age and approximately 82% had pyelonephritis.

Clinical and microbiologic assessments were done at EOT (within 24 hours after last dose of study drug), at the TOC visit (7 +/-2 days after the last dose of study drug) and the Late Follow Up visit (21 to 42 days after last dose of study drug). The primary efficacy endpoint was a responder endpoint requiring both microbiological eradication and clinical cure at the TOC visit. The primary analysis population was the mMITT population, which was defined as all randomized patients who received any amount of study drug and had at least 1 qualifying causative uropathogen from a pretreatment baseline urine specimen. The key secondary analysis was the composite microbiological eradication and clinical cure rate in the ME population at the TOC visit.

In the mMITT population, ceftolozane-tazobactam was noninferior to levofloxacin for the primary endpoint of microbiological and clinical cure at the TOC visit. The trial met the pre-specified NI margin of 10% as shown in Table 8. In both treatment arms, clinical cure rates were higher for patients with pyelonephritis compared to those with complicated lower UTI.

Table 8: Composite Microbiological and Clinical Cure Rates in the mMITT Population

mMITT Population	Ceftolozane-tazobactam N = 398 n(%)	Levofloxacin N = 402 n(%)	Treatment difference (95% CI)
Success	306 (76.9)	275 (68.4)	8.5 (2.3, 14.6)
Failure	66 (16.6)	103 (25.6)	
Indeterminate	26 (6.5)	24 (6.0)	

Source; CDTL memo, Table 8

As the lower bound of the 95% CI is greater than zero, (b) (4) A total of 212 (26.5%) patients in the mMITT population had baseline isolates that were resistant to levofloxacin. (b) (4) the finding will be described in the Clinical Studies section of labeling. Cure rates by levofloxacin susceptibility in the mMITT population are shown in Table 9.

Table 9: Composite Microbiological and Clinical Cure Rates by Levofloxacin Resistance

Baseline pathogen	Ceftolozane-tazobactam n/N (%)	Levofloxacin n/N (%)
Levofloxacin-resistant	60/100 (60.0)	44/112 (39.3)
Not levofloxacin resistant	246/298 (82.6)	231/290 (79.7)

Source: Table 1, Dr. Rubin's statistics review

According to the protocol, if an organism was resistant to one or both study drugs, the investigator was to determine whether the patient would remain on study drug based on the patient's clinical response "and not solely on the *in vitro* susceptibility results." Patients with satisfactory clinical responses could remain on study therapy despite the presence of *in vitro* resistance.

Dr. Rubin performed additional analyses based on levofloxacin susceptibility of the baseline pathogen. Patients with baseline pathogens resistant to levofloxacin differed from the group without levofloxacin resistance in terms of baseline characteristics including age, sex, subtype of the disease, complicating factors, and infecting pathogens. In the levofloxacin resistant subgroup, there were more males, older patients (≥ 65 years), complicated lower UTI as disease type, males with urinary retention and functional abnormality than in the subgroup with levofloxacin susceptible isolates. Dr. Rubin also noted that persistence of infection was the most common

reason for failure in levofloxacin treated subjects with levofloxacin resistant pathogens. Dr. Rubin performed additional analyses of symptom improvement in patients with levofloxacin resistant pathogens and found that symptom improvement was relatively similar in the two treatment arms.

Of the 62 patients with bacteremia at baseline, cure rates were 23/29 (79.3%) for patients treated with ceftolozane-tazobactam and 19/33 (57.6%) for patients treated with levofloxacin. Only 14 patients (1.8%) in the mMITT population were enrolled from the U.S. Cure rates were lower in both arms for patients with CrCl 30-50 mL/min. A total of 199 patients were ≥65 years of age. Composite cure rates in patients were >65 years of age were 70/100 (70.0%) in the ceftolozane-tazobactam arm and 53/99 (53.5%) in the levofloxacin arm.

As seen in the cIAI trial, in patients with impaired renal function, the decrease was greater in patients in the ceftolozane-tazobactam arm than in the levofloxacin arm (Table 10). This was seen both in the mMITT population and in the subgroup of patients with only levofloxacin susceptible baseline isolates. Patients with severe renal impairment were excluded from the trial.

Table 10: Composite clinical and microbiological outcome at TOC (mMITT population)

Creatinine clearance	Ceftolozane-tazobactam	Levofloxacin
Overall		
>50 mL/min	285/363 (78.5%)	258/374 (69.0%)
≤50 mL/min	21/34 (61.8%)	17/28 (60.7%)
Susceptible to Levofloxacin		
>50 mL/min	231/275 (84.0%)	215/272 (79.0%)
≤50 mL/min	15/22 (68.2%)	16/18 (88.9%)

The composite microbiological and clinical response rates at the TOC visit for the baseline uropathogens are shown in Table 11.

Table 11: Composite microbiological and clinical response rates at the TOC visit by baseline uropathogens

Pathogen	Ceftolozane-tazobactam n/N (%)	Levofloxacin n/N (%)
Escherichia coli	247/305 (81.0)	228/324 (70.4)
Klebsiella pneumoniae	22/33 (66.7)	12/25 (48.0)
Proteus mirabilis	11/12 (91.7)	6/12 (50.0)
Pseudomonas aeruginosa	6/8 (75.0)	7/15 (46.7)

Drs. Allende and Kadoorie concluded that adequate evidence has been provided to support the indication of cIAI. Drs. Shamsuddin and Rubin concluded that adequate evidence has been provided to support the indication of cUTI. Dr. Smith, the cross-discipline team leader concurs with their recommendations for approval of ceftolozane/tazobactam for the treatment of cIAI and cUTI. I agree with their assessment.

Safety

Maria Allende, M.D., reviewed the safety findings in the cIAI trials and in the overall safety database. Hala Shamsuddin, M.D., reviewed the safety findings from the cUTI trials.

The safety database included nine Phase 1 studies, two Phase 2 trials, and two Phase 3 trials. A total of 1276 subjects received ceftolozane-tazobactam and 173 subjects received ceftolozane alone.

In the Phase 1 studies, there was one report of a Serious Adverse Event (SAE) of thrombosis of an arteriovenous fistula requiring hospitalization for heparinization and catheter replacement in a renal impairment study. Two subjects who received ceftolozane-tazobactam discontinued the drug due to vomiting and pyrexia. The most common Treatment Emergent Adverse Event (TEAE) in subjects receiving ceftolozane or ceftolozane-tazobactam were infusion site reactions and headache.

In the Phase 2 trials, three deaths were reported in the cIAI trial and none in the cUTI trial; all three occurred in ceftolozane-tazobactam treated patients. The causes of deaths included urosepsis, pulmonary embolism following deep vein thrombosis three weeks after end of therapy, and renal failure with cardiopulmonary arrest in a patient who had received two doses of ceftolozane-tazobactam. Dr. Allende reviewed the narratives and case report forms of the patients who died and concurred with the Applicant that the deaths were not related to study drug.

In the cIAI trial, SAEs were more common in the ceftolozane-tazobactam arm [14/82 (17.1%)] compared to 2/39 (5.1%) in the meropenem arm. Most SAEs appeared to be related to the

underlying cIAI or surgical procedure. In the cUTI trial, there was only one SAE (relapse of pyelonephritis in a patient receiving ceftolozane).

Four subjects had TEAEs leading to discontinuation of study drug, three ceftolozane-tazobactam treated and one treated with ceftazidime. In the cIAI trial, the most commonly reported TEAEs in the ceftolozane-tazobactam arm were pyrexia (14.7%), anemia (6.1%), and nausea (6.1%). In the cUTI trial, the most commonly reported TEAEs in ceftolozane-treated patients were constipation (9.4%), sleep disorder (7.1%), headache (5.9%), and nausea (5.9%).

In the two Phase 3 trials combined, 1015 patients received ceftolozane-tazobactam, 482 in the cIAI trial and 533 in the cUTI trial. The median duration of exposure to ceftolozane-tazobactam was 6.7 days. The maximum duration of exposure was 14 days.

In the Phase 3 trials, there were 12 deaths in ceftolozane-tazobactam treated patients (11 in the cIAI trial and one in the cUTI trial) and eight deaths in patients treated with meropenem (cIAI trial). In the Phase 3 cIAI trial, there were more deaths in the ceftolozane-tazobactam arm (11, 2.3%) than in the meropenem arm (8, 1.6%). In the Phase 2 and 3 cIAI trials combined, the mortality rates were 14/564 (2.5%) in ceftolozane-tazobactam treated patients and 8/536 (1.5%) in meropenem-treated patients.

The causes of death in ceftolozane-tazobactam treated patients included cardiac causes, multi-organ failure, sudden death, septic shock, pseudomonal lung infection, acute renal failure, and ischemic stroke. In the Phase 3 cIAI trial, seven patients died while on study therapy (four in the ceftolozane-tazobactam and three in the meropenem arms), and 12 died more than 24 hours after the last dose of study drug (seven in the ceftolozane-tazobactam arm and five in the meropenem arm). The one death in the cUTI trial occurred 38 days after end of therapy from worsening of bladder cancer.

Dr. Allende reviewed the narratives and case report forms of patients who died and concurred with the Applicant that the deaths were not related to study drug; most were related to age and underlying co-morbidities. Dr. Allende noted that lack of efficacy of the study drug was a plausible contributing factor in some patients. In the cIAI trial, in the subgroup of patients with creatinine clearance 30-50 mL/min, mortality was higher in patients treated with ceftolozane-tazobactam (4/23, 17.4%) than in patients treated with meropenem (1/13, 7.7%). Dr. Allende also notes that among patients who died, certain baseline characteristics were more common in the ceftolozane-tazobactam arm compared to meropenem, e.g. age ≥ 65 years, involvement of large bowel, renal impairment, need for laparotomy and APACHE score (Table 57, clinical review).

In both trials, the incidence of TEAEs and SAEs was similar in both arms. In the cIAI trial, TEAEs, SAEs, discontinuations due to TEAEs, and deaths due to TEAEs were more common

than that reported in the cUTI trial, which is consistent with cIAI patients being sicker and likely to have more co-morbidities than patients with cUTI.

SAEs were reported by 54 (5.3%) patients treated with ceftolozane-tazobactam and 54 (5.2%) treated with comparators. Most SAEs were single events and were most commonly reported in the Infections and Infestations SOC (pneumonia, bacteremia, abscess, sepsis, and pyelonephritis).

In the ceftolozane-tazobactam arm, 20/1015 (2.0%) patients discontinued study drug due to TEAEs and 20/1032 (1.9%) discontinued in the comparator arm. Renal impairment (including the terms renal impairment, renal failure, and renal failure acute) leading to discontinuation of study drug was reported in five patients in the ceftolozane-tazobactam arm and in no patients receiving comparators. Renal impairment was the only TEAE leading to study drug discontinuation in more than one patient. All five patients had at least mild renal impairment at baseline.

The most commonly reported TEAEs in ceftolozane-tazobactam treated patients were nausea (5.2%), headache (4.2%), diarrhea (3.9%), pyrexia (3.3%), and constipation (3.0%).

Dr. Allende performed a standardized MedDRA query for thrombotic and embolic events (which includes stroke, myocardial infarction, venous and arterial thrombosis or embolism). Venous thromboses (portal vein thrombosis, deep venous thrombosis, pelvic vein thrombosis) were reported in four patients in the ceftolozane/tazobactam arm (all in the cIAI trial) and none in the meropenem arm. While the underlying illness may have contributed to these adverse events, Dr. Allende could not rule out an association with ceftolozane-tazobactam. Venous thrombosis will be included in the Adverse Reaction section of labeling.

Dr. Allende's review of the SDTM data with Empirica Study (Oracle, Inc.) identified five patients in the ceftolozane-tazobactam arm and four in the meropenem arm who met the criteria for Hy's Law at post-baseline measurements. Four of the ceftolozane-tazobactam treated patients had elevated values at baseline. The fifth patient with gangrenous cholecystitis and abscess had elevated liver enzymes on day 1 [ALT 114 (0-41 U/L), AST 210 (0-27 U/L), bilirubin 94.1 (0-18.1 mmol/L), and alkaline phosphatase 229 (40-135 U/L)]. The values improved by day 3 and were normal at the end of therapy. She received 11 days of ceftolozane-tazobactam plus metronidazole.

A thorough QT (TQT) study showed that ceftolozane-tazobactam did not prolong the QT interval. The TQT study was reviewed by the interdisciplinary review team (IRT). The IRT recommended that language regarding the TQT study be included in Section 12.2 (Pharmacodynamics) of labeling.

No significant differences were seen between the treatment groups with respect to clinical laboratory evaluations. Transient elevations in serum transaminases were observed with similar frequency in the two arms; they were more common in the cIAI trial and occurred on therapy. A few more outliers with higher ALT or AST (>5 times ULN) and bilirubin (>2 times ULN) values were seen in the ceftolozane-tazobactam arm compared to the meropenem arm; all improved during the course of the study.

8.0 Labeling

Labeling recommendation from Aleksander Winiarski, Pharm D and Jacqueline Sheppard, Pharm D from the Division of Medication Error Prevention and Analysis and Christine Corser Pharm D, from the Office of Prescription Drug Promotion (OPDP) have been incorporated in labeling.

9.0 Pediatrics

Under the Pediatric Research and Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless the requirement is waived, deferred or inapplicable. The applicant submitted the agreed initial Pediatric Study Plan (iPSP) and a request for deferral of pediatric studies with the NDA. The pediatric plan and deferral request were presented to the Pediatric Review Committee (PeRC) on October 22, 2014. The PeRC agreed with the deferral request as the product is ready for approval in adults. The proposed pediatric studies will be postmarketing requirements.

10.0 Other Regulatory Issues

Clinical Site Inspections

The Office of Scientific Investigations conducted inspections of six clinical investigator sites (three each for the Phase 3 cUTI and the cIAI trial) and of the Applicant. The sites chosen for inspection had high enrollment and/or a high treatment effect favoring the active drug arm. The sites inspected were in Lithuania, Poland, Romania, Estonia, Latvia, and Colombia. No regulatory violations were found during the inspections of the site in Romania and Estonia. Both inspections were classified as preliminary no action indicated (NAI). Three observational Form FDA 483's were issued, one each for failure to follow the investigational plan (Site 6380), failure to maintain accurate records (Site 7404), and failure to include risk information in the informed consent document (Site 6602). Review by OSI does not confirm this as a regulatory violation.

No regulatory violations were found during the inspection of the Applicant site and the inspection was classified as NAI. A non-compliant site was identified during the inspection. Cubist had investigated and terminated the site due to data falsification. The investigation found that Cubist had reported the termination of this site to FDA.

Dr. Gershon concluded that the regulatory violations noted during inspections are unlikely to significantly impact the primary efficacy or safety analysis and that the data may be considered reliable.

Dr. Gershon also noted that as all the final EIRs were not available at the time this clinical inspection summary was written, the observations noted are based on preliminary EIRs or email communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIRs.

Advisory Committee Meeting

This NDA was not discussed by the Anti-Infective Drugs Advisory Committee.

11.0 Risk Management

Joyce Weaver, Pharm D, was the reviewer from the Division of Risk Management. Dr. Weaver concluded that the risks that have emerged to date can be addressed in labeling and a REMS is not required at this time. I agree with Dr. Weaver's assessment. Safety findings with ceftolozane-tazobactam have been adequately addressed in labeling and will be monitored in routine pharmacovigilance.

Post Marketing Commitments (PMCs) and Post Marketing Requirements (PMRs)

The applicant has agreed to the following PMRs:

PEDIATRIC POSTMARKETING REQUIREMENTS:

1. Conduct a randomized, double blind, multicenter, comparative study to establish the safety and tolerability profile of ceftolozane/tazobactam compared to that of meropenem in hospitalized children from birth to <18 years with cUTI. The dose for this study will be determined upon review of the data to be submitted by December 2016 from a single-dose, multicenter, non-comparative study assessing the pharmacokinetics (PK) of ceftolozane/tazobactam in pediatric patients ages 0 to <18 years that was initiated in June 2014.

2. A randomized, double blind, multicenter, comparative study to establish the safety and tolerability profile of ceftolozane/tazobactam compared to that of meropenem in hospitalized children from birth to <18 years with cIAI. The dose for this study will be

determined upon review of the data to be submitted by December 2016 from the a single- dose, multicenter, non-comparative study to assessing the PK pharmacokinetics (PK) of ceftolozane/tazobactam in pediatric patients ages 0 to <18 years that was initiated in June 2014.

POSTMARKETING REQUIREMENTS UNDER 505(o):

1. Conduct a prospective study over a five-year period after the introduction of ceftolozane-tazobactam to the market to determine if decreased susceptibility to ceftolozane-tazobactam is occurring in the target population of bacteria that are in the approved ceftolozane-tazobactam label.

12.0 Recommended Regulatory Action

I agree with the review team that the Applicant has provided adequate information to support the safety and effectiveness of ceftolozane-tazobactam for the treatment of adults with complicated urinary tract infections and complicated intra-abdominal infections. In an adequate and well-controlled Phase 3 trial in each indication, ceftolozane-tazobactam was noninferior to the comparator regimen. The main safety concerns are adequately addressed in the Warnings and Precautions and Adverse Reactions sections of the package insert. I recommend approval of this NDA.

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/s/

SUMATHI NAMBIAR
12/19/2014

Memo to File

Date	(electronic stamp)
From	Sumathi Nambiar MD MPH
Patient	Division Director Memo
NDA #	206829
Applicant Name	Cubist Pharmaceuticals, Inc.
Date of Submission	April 21, 2014
PDUFA Goal Date	December 21, 2014
Established (USAN) Name	Ceftolozane-tazobactam
Trade Name	Zerbaxa
Dosage Forms / Strength	Injection/1 gram ceftolozane and 500 mg tazobactam single use vials
Proposed Indications	1. Complicated urinary tract infections (cUTI) 2. Complicated intra-abdominal infections (cIAI)

Material Reviewed/Consulted Action Package including:	**Names of Discipline Reviewers**
Cross-Discipline Team Leader Review	Thomas Smith MD
Pharmacology Toxicology Review	James Wild PhD
Chemistry Manufacturing and Controls Review	Shrikant Pagay PhD
Medical Officer Review	Maria Allende MD Hala Shamsuddin MD
Statistical Review	Christopher Kadoorie PhD Daniel Rubin PhD
Risk Management	Joyce Weaver Pharm D
Product Quality Review	Erika Pfeiler PhD
Biopharmaceutics Review	Minerva Hughes PhD
Microbiology Review	Kerian Grande-Roche PhD
Clinical Pharmacology Review	Ryan Owen PhD
Office of Scientific Investigations	Sharon Gershon Pharm D
Division of Medication Error Prevention and Analysis	Aleksander Winiarski Pharm D Jacqueline Sheppard Pharm D
Thorough QT Study Review	Interdisciplinary Review Team
Labeling Reviews	Christine Corser Pharm D

NDA 206829, Ceftolozane-tazobactam was submitted by Cubist Pharmaceuticals, Inc. on April 21, 2014. The Applicant proposed the following indications:

1. As a single agent for the treatment of cUTIs, including pyelonephritis (b) (4) caused by the following Gram-negative microorganisms: *Escherichia coli* (b) (4) *Klebsiella pneumoniae* (b) (4) *Proteus mirabilis*, and *Pseudomonas aeruginosa*.
2. Use in combination with metronidazole for the treatment of cIAIs caused by the following Gram-negative and Gram-positive microorganisms: *E. coli* (b) (4) *K. pneumoniae* (b) (4) *P. aeruginosa, Enterobacter cloacae, K. oxytoca, P. mirabilis, Bacteroides fragilis,* (b) (4) *Streptococcus anginosus, S. constellatus,* and *S. salivarius*.

All primary reviews and the CDTL review have been completed. However, a final recommendation regarding the acceptability of the facilities is not yet available. Although, the CMC review concluded that the information provided was generally satisfactory to assure the identity, strength, purity, and quality of the drug substances and the drug product, because of the outstanding inspections of the manufacturing and testing facilities at the time the review was required to be completed [under the requirements of the Program (PDUFA V applications], Dr. Pagay did not recommend approval of the NDA.

Although, I agree with the review team that the Applicant has provided adequate information to support the safety and effectiveness of ceftolozane-tazobactam for the treatment of adults with complicated urinary tract infections and complicated intra-abdominal infections, I am unable to make a final recommendation on the regulatory action for this NDA as the status of the facilities is still under review. Additionally, labeling discussions are still ongoing with the Applicant with regard to susceptibility test interpretive criteria and inclusion of a warning regarding the lower cure rates in patients with creatinine clearance < 50 mL/min.

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/s/

SUMATHI NAMBIAR
12/11/2014